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Personalizacja leczenia w ACTH-zależnym zespole Cushinga - ocena skuteczności i bezpieczeństwa nowoczesnych terapii farmakologicznych

Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu w dyscyplinie nauki medyczne

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SPIS TREŚCI

1. WYKAZ STOSOWANYCH SKRÓTÓW

Skrót	*Pełna nazwa w języku angielskim* Pełna nazwa w języku polskim
ACTH	*adrenocorticotropic hormone* hormon adrenokortykotropowy
AI	*adrenal insufficiency* niedoczynność kory nadnerczy
CD	*Cushing disease* choroba Cushinga
CS	*Cushing syndrome* zespół Cushinga
P450scc	*cholesterol side-chain cleavage enzyme* enzym rozszczepiający łańcuch boczny cholesterolu
P450c11β	*11β-hydroxylase* 11β-hydroksylaza
P450c11AS	*aldosterone synthase* syntaza aldosteronu
P450c17	*17α-hydroxylase/17,20-lyase* 17α-hydroksylaza/17,20-liaza
D2R	*dopamine 2 receptor* receptor dopaminy typu 2
EAS	*ectopic ACTH syndrome* zespół ektopowego wydzielania ACTH
LAR	*long-acting release* o przedłużonym uwalnianiu
LNSC	*late-night salivary cortisol* późnowieczorne stężenie kortyzolu w ślinie
SCS	*severe Cushing syndrome* ciężki zespół Cushinga
SSTR5	*somatostatin receptor type 5* receptor dla somatostatyny typu 5
UFC	*urinary free cortisol* dobowe wydalanie wolnego kortyzolu z moczem

2. STRESZCZENIE

Zespół Cushinga (ang. *Cushing syndrome*, CS) stanowi istotne wyzwanie diagnostyczne i terapeutyczne w praktyce endokrynologicznej. Leczeniem z wyboru CS pozostaje resekcja chirurgiczna guza odpowiedzialnego za nadmierną sekrecję kortyzolu. W ostatnich latach, dzięki opracowaniu nowych leków, możliwości terapeutyczne w zakresie leczenia i kontroli hiperkortyzolemii istotnie się poszerzyły, co pozwoliło ugruntować farmakoterapię jako skuteczną opcję terapeutyczną drugiego rzutu, szczególnie u pacjentów z przetrwałą lub nawrotową postacią choroby. Dane dotyczące skuteczności i bezpieczeństwa terapii osilodrostatem czy pasyreotydem u pacjentów z chorobą Cushinga (ang. *Cushing disease*, CD) pochodzą jednak głównie z badań klinicznych. Farmakoterapia znajduje również zastosowanie jako leczenie pomostowe przed planowanym zabiegiem chirurgicznym (zwłaszcza w przypadkach ciężkiego CS [ang. *severe CS*, SCS]) oraz w sytuacjach, gdy leczenie operacyjne nie jest możliwe lub istnieją przeciwwskazania do jego wykonania.

Biorąc pod uwagę zróżnicowaną etiologię CS oraz szerokie spektrum nasilenia hiperkortyzolemii, obrazu klinicznego i powikłań choroby, leczenie farmakologiczne u poszczególnych pacjentów wymaga znacznej indywidualizacji. W doborze farmakoterapii należy uwzględnić szybkość działania oraz skuteczność leku w celu osiągnięcia zadowalającej kontroli hiperkortyzolemii, ryzyko wystąpienia działań niepożądanych oraz łatwość stosowania, aby zapewnić adherencję pacjenta wobec terapii i uzyskać satysfakcjonujące efekty. Kontrola wzrostu guza przysadki stanowi dodatkowy czynnik, który należy uwzględnić przy wyborze leczenia u wybranej grupy pacjentów z CD. Dostępne opcje terapeutyczne oraz ich kombinacje umożliwiają opracowanie zindywidualizowanych terapii, co pozwala osiągnąć optymalne długoterminowe wyniki leczenia, przekładające się na poprawę jakości życia oraz zmniejszenie śmiertelności pacjentów z CS.

Niniejsza rozprawa doktorska obejmuje cykl czterech powiązanych tematycznie publikacji naukowych oceniających skuteczność i bezpieczeństwo nowoczesnych terapii farmakologicznych oraz schematów terapeutycznych u pacjentów z ACTH-zależną hiperkortyzolemią w rzeczywistych warunkach klinicznych.

Serię publikacji otwiera artykuł *Cushing's Disease: Long-Term Effectiveness and Safety of Osilodrostat in a Polish Group of Patients with Persistent Hypercortisolemia in the Experience of a Single Center*. W ramach retrospektywnej analizy oceniono długoterminowe efekty terapii osilodrostatem u sześciu pacjentów z nawrotową lub przetrwałą CD, którzy początkowo uczestniczyli w badaniu klinicznym LINC4, a następnie kontynuowali leczenie osilodrostatem

finansowanym w ramach Ratunkowego Dostępu do Technologii Lekowych. Terapia osilodrostatem pozwoliła na pełną kontrolę hiperkortyzolemii u wszystkich pacjentów oraz istotną poprawę parametrów metabolicznych i sercowo-naczyniowych. Mediana czasu do uzyskania normalizacji średniego dobowego wydalania wolnego kortyzolu z moczem (ang. *urinary free cortisol*, mUFC) wynosiła 5 tygodni przy medianie dawki osilodrostatu 5 mg dwa razy dziennie. W pracy szczegółowej analizie poddano również przypadki trzech pacjentów, u których w trakcie leczenia osilodrostatem wystąpiły specyficzne działania niepożądane, wymagające wdrożenia określonego, indywidualnego postępowania w celu ich ustąpienia.

Kolejny artykuł *Cushing's syndrome: a combined treatment with etomidate and osilodrostat in severe life-threatening hypercortisolemia* stanowi opis przypadku. Po raz pierwszy w literaturze przedstawiono w nim możliwość leczenia SCS przy użyciu skojarzonej terapii etomidatem i osilodrostatem. Podejście to zostało następnie rozszerzone i przeanalizowane w pracy oryginalnej *Is there still a place for etomidate in the management of Cushing's syndrome? The experience of a single center of low-dose etomidate and combined etomidate-osilodrostat treatment in severe hypercortisolemia*. Celem tej strategii terapeutycznej było szybkie uzyskanie stabilnej kontroli hiperkortyzolemii dzięki terapii niskimi dawkami etomidatu, a następnie jej utrzymanie za pomocą monoterapii osilodrostatem. Wykazano, że terapia skojarzona osilodrostatem i etomidatem była dobrze tolerowana oraz charakteryzowała się wysoką skutecznością w kontroli SCS. W powyższej pracy oryginalnej oceniono również skuteczność i bezpieczeństwo niskodawkowej terapii etomidatem u pacjentów z powikłanym, zagrażającym życiu SCS. U wszystkich pacjentów uzyskano szybką kontrolę hiperkortyzolemii, osiągając docelowe stężenie kortyzolu w surowicy w medianie czasu 30 godzin. Niskodawkowa terapia etomidatem okazała się nie tylko wysoce skuteczna, ale i bezpieczna z możliwością jej prowadzenia poza oddziałem intensywnej terapii.

Cykl zamyka artykuł *Real-World Experience with Pasireotide-LAR in Cushing's Disease: Single-Center 12-Month Observational Study*. Dokonano w nim retrospektywej analizy prospektywnie gromadzonych danych pacjentów z przetrwałą lub nawrotową CD, leczonych co najmniej 12 miesięcy pasyreotydem o przedłużonym uwalnianiu (ang. *long-acting release*, LAR). Ocenie poddano skuteczność w zakresie kontroli hiperkortyzolemii, wpływ terapii na parametry kardiometaboliczne oraz jej bezpieczeństwo. W analizowanej grupie stwierdzono istotną redukcję mUFC podczas terapii pasyreotydem LAR, największy w początkowych miesiącach leczenia. Późnowieczorne stężenia kortyzolu w ślinie (ang. *late-night sailvary cortisol*, LNSC) wykazywały zmienność w trakcie obserwacji, z największą redukcją w pierwszych miesiącach terapii, jednak bez istotności statystycznej. Pasyreotyd LAR

charakteryzował się dobrą tolerancją, a najczęstszym działaniem niepożądanym obserwowanym u wszystkich pacjentów była hiperglikemia lub pogorszenie kontroli stwierdzanych uprzednio zaburzeń gospodarki węglowodanowej.

3. SUMMARY

Treatment Personalization in ACTH-Dependent Cushing's Syndrome: Evaluation of the Effectiveness and Safety of Modern Pharmacological Therapies

Cushing syndrome (CS) represents a significant diagnostic and therapeutic challenge in endocrinological practice. Surgical resection of the tumor responsible for excessive cortisol secretion remains the treatment of choice for CS. In recent years, however, the development of novel pharmacological agents has substantially expanded therapeutic options for the treatment and control of hypercortisolemia, establishing pharmacotherapy as an effective second-line treatment, particularly in patients with persistent or recurrent disease. Data on the efficacy and safety of therapies such as osilodrostat or pasireotide in patients with Cushing disease (CD) are derived mainly from clinical trials. Pharmacotherapy is also used as bridging treatment prior to planned surgery (especially in cases of severe CS [SCS]) and in situations where surgical treatment is not feasible or contraindicated.

Given the heterogeneous etiology of CS and the wide spectrum of hypercortisolemia severity, clinical presentation, and disease-related complications, pharmacological treatment requires a high degree of individualization. The selection of therapy should take into account the speed of onset and efficacy of the drug in achieving adequate control of hypercortisolemia, the risk of adverse events, and ease of use to ensure patient adherence and satisfactory therapeutic outcomes. Control of pituitary tumor growth constitutes an additional factor to be considered when selecting treatment in a subset of patients with CD. Available therapeutic options and their combinations allow for the development of individualized treatment strategies, enabling optimal long-term outcomes, improvement in quality of life, and reduction in mortality among patients with CS.

This doctoral dissertation comprises a series of four thematically related scientific publications evaluating the efficacy and safety of modern pharmacological therapies and treatment regimens in patients with ACTH-dependent hypercortisolemia under real-world clinical conditions.

The series opens with the article *Cushing's Disease: Long-Term Effectiveness and Safety of Osilodrostat in a Polish Group of Patients with Persistent Hypercortisolemia in the Experience of a Single Center*. This retrospective analysis assessed the long-term effects of osilodrostat therapy in six patients with recurrent or persistent CD who initially participated in the LINC4 clinical trial and subsequently continued osilodrostat treatment funded through the Emergency

Access to Drug Technologies program. Osilodrostat therapy achieved complete control of hypercortisolemia in all patients and resulted in significant improvement in metabolic and cardiovascular parameters. The median time to normalization of mean urinary free cortisol (mUFC) excretion was 5 weeks at a median osilodrostat dose of 5 mg twice daily. The study also provides a detailed analysis of three patients who developed specific adverse events during osilodrostat therapy, requiring individualized management to achieve resolution.

The next article, *Cushing's syndrome: a combined treatment with etomidate and osilodrostat in severe life-threatening hypercortisolemia*, is a case report. It presents, for the first time in the literature, the use of combined etomidate and osilodrostat therapy for the treatment of SCS. This approach was subsequently expanded and analyzed in the original study *Is there still a place for etomidate in the management of Cushing's syndrome? The experience of a single center of low-dose etomidate and combined etomidate–osilodrostat treatment in severe hypercortisolemia*". The aim of this therapeutic strategy was to achieve rapid and stable control of hypercortisolemia using low-dose etomidate therapy, followed by maintenance with osilodrostat monotherapy. The combined osilodrostat–etomidate therapy was shown to be well tolerated and highly effective in controlling SCS. The same study also evaluated the efficacy and safety of low-dose etomidate therapy in patients with complicated, life-threatening SCS. Rapid control of hypercortisolemia was achieved in all patients, with target serum cortisol concentrations reached within a median time of 30 hours. Low-dose etomidate therapy proved to be not only highly effective but also safe, with the possibility of administration outside the intensive care unit.

The series concludes with the article *Real-World Experience with Pasireotide-LAR in Cushing's Disease: Single-Center 12-Month Observational Study*. This retrospective analysis of prospectively collected data included patients with persistent or recurrent CD treated with long-acting release pasireotide (pasireotide LAR) for at least 12 months. The study evaluated efficacy in controlling hypercortisolemia, the impact of therapy on cardiometabolic parameters, and safety. A significant reduction in mUFC was observed during pasireotide LAR therapy, with the greatest decrease occurring in the initial months of treatment. Late-night salivary cortisol (LNSC) levels showed variability during follow-up, with the greatest reduction observed in the early months of therapy, although without statistical significance. Pasireotide LAR was generally well tolerated, and the most common adverse event observed in all patients was hyperglycemia or worsening of pre-existing disturbances in glucose metabolism.

4. WSTĘP

4.1 Epidemiologia i definicja jednostki chorobowej

Endogenny zespół Cushinga (CS, ang. *Cushing syndrome*) jest bardzo rzadką chorobą endokrynologiczną związaną z patologiczną nadprodukcją kortyzolu przez korę nadnerczy (1,2). Szacowana zapadalność na CS wynosi od 2–3 do 8 przypadków na milion osób rocznie (2). Większość przypadków CS (około 80-85%%) wynika z nadmiernej produkcji hormonu adrenokortykotropowego (ACTH, ang. *adrenocorticotropic hormone*), co określa się jako ACTH-zależny CS (1,2). Guzy neuroendokrynne przysadki wydzielające ACTH (klasycznie określane jako choroba Cushinga [CD, ang. *Cushing disease*]) odpowiadają za około 85–90% ACTH-zależnych postaci CS i stanowią jednocześnie najczęstszą przyczynę zespołu (3). W pozostałych 10–15% ACTH-zależnych postaci CS przyczyną są pozaprzysadkowe guzy neuroendokrynne ektopowo wydzielające ACTH (EAS, ang. *ectopic ACTH syndrome*) (1,4). ACTH-niezależna postać CS, wynikająca z autonomicznej produkcji kortyzolu przez nadnercza, najczęściej na skutek łagodnego gruczolaka kory nadnerczy, stanowi około 20% wszystkich przypadków CS (1,2).

4.2 Obraz kliniczny i powikłania hiperkortyzolemii

Manifestacja kliniczna CS jest zróżnicowana i zależy od czasu trwania hiperkortyzolemii, jej nasilenia, wieku pacjenta, chorób współistniejących oraz indywidualnej wrażliwości receptora glikokortykosteroidowego (5–8). Hiperkortyzolemia prowadzi między innymi do zmian w redystrybucji tkanki tłuszczowej z dominującą otyłością centralną i towarzyszącym zanikiem oraz osłabieniem mięśni proksymalnych, zaburzeń metabolicznych, w tym insulinooporności, cukrzycy oraz dyslipidemii, a także nadciśnienia tętniczego. Ekspozycja na nadmiar kortyzolu wiąże się ponadto ze zwiększoną podatnością na zakażenia, zaburzenia zakrzepowo-zatorowe, sprzyja utracie masy kostnej oraz rozwojowi zaburzeń neuropsychiatrycznych (1,2,5–8).

Szerokie spektrum powikłań narządowych znacząco przyczynia się do zwiększenia śmiertelności wśród pacjentów z CS, która jest około trzykrotnie wyższa w porównaniu z populacją ogólną (9–11). Najczęstszymi przyczynami zgonu u pacjentów z aktywną hiperkortyzolemią są powikłania sercowo-naczyniowe (w tym zawał mięśnia sercowego i udar mózgu), powikłania zakrzepowo-zatorowe oraz zakażenia (9,11).

Wyzwaniem terapeutycznym dla endokrynologów pozostaje ciężki CS (ang. *severe CS*, SCS), obarczony licznymi powikłaniami i związany z wysoką śmiertelnością (4,12). SCS charakteryzuje się znacznym nasileniem hiperkortyzolemii (przygodne stężenie kortyzolu

w surowicy > 41 μg/dl, dobowe wydalanie wolnego kortyzolu z moczem przekraczające pięciokrotnie górną granicę normy) i/lub współistnieniem ciężkiej hipokaliemii (< 3,0 mmol/l), przy jednoczesnym występowaniu co najmniej jednego z ostrych powikłań sercowo-naczyniowych, zakaźnych lub metabolicznych związanych z hiperkortyzolemią (12).

4.3 Leczenie zespołu Cushinga

Optymalizacja długoterminowych wyników leczenia CS wymaga wczesnego i trafnego rozpoznania, właściwego doboru terapii oraz kompleksowego prowadzenia choroby podstawowej i współistniejących schorzeń przez doświadczonych klinicystów.

4.3.1. Leczenie operacyjne

Leczeniem z wyboru u pacjentów z CS pozostaje całkowita resekcja guza będącego pierwotnym źródłem choroby (1,2). W przypadku pacjentów z CD zabieg obejmuje selektywną, transfenoidalną adenomektomię, której skuteczność, przy przeprowadzeniu zabiegu przez doświadczonego neurochirurga, wynosi około 80% u pacjentów z mikrogruczolakami oraz 60% u pacjentów z makrogruczolakami przysadki wydzielającymi ACTH (3,13). U pacjentów z EAS skuteczność chirurgicznego usunięcia guza wydzielającego ACTH i biochemicznej remisji hiperkortyzolemii waha się w zakresie 30-60% i zależna jest między innymi od typu nowotworu neuroendokrynnego i precyzyjnego ustalenia jego lokalizacji, obecności przerzutów oraz stopnia nasilenia hiperkortyzolemii (4,14). Laparoskopowa adrenalektomia stanowi natomiast standard leczenia CS wywołanego przez jednostronne, łagodne gruczolaki nadnerczy produkujące kortyzol (15).

4.3.2. Leczenie farmakologiczne

W przypadku nawrotu hiperkortyzolemii lub braku możliwości przeprowadzenia radykalnej resekcji guza odpowiedzialnego za CS, potencjalnymi opcjami terapeutycznymi są leczenie farmakologiczne, radioterapia oraz obustronna adrenalektomia (1–3,16). W ostatnich latach dzięki dostępności nowych leków, farmakoterapia wyłoniła się jako opcja leczenia drugiego rzutu (17,18). Środki farmakologiczne stosowanie w terapii CS obejmują inhibitory steroidogenezy nadnerczowej, leki działające na poziomie przysadki (u pacjentów z CD) oraz antagonistów receptorów glikokortykoidowych (19). Farmakoterapia znajduje również zastosowanie u pacjentów, u których leczenie chirurgiczne jest przeciwwskazane lub nieakceptowane, a także jako leczenie pomostowe, mające na celu kontrolę hiperkortyzolemii w okresie oczekiwania na wdrożenie innych procedur terapeutycznych (1,3,19,20).

4.3.2.1 Doustne inhibitory steroidogenezy nadnerczowej

Spośród dostępnych metod farmakoterapii CS najczęściej stosowaną w praktyce klinicznej grupę stanowią doustne inhibitory steroidogenezy nadnerczowej, do których należą ketokonazol, lewoketokonazol, metyrapon oraz osilodrostat (19,21,22).

4.3.2.1.1 Ketokonazol i lewoketokonazol

Ketokonazol, syntetyczna pochodna imidazolu, jest lekiem przeciwgrzybiczym, który hamuje kluczowe enzymy steroidogenezy w korze nadnerczy, w tym enzym rozszczepiający łańcuch boczny cholesterolu (P450scc), 17α-hydroksylazę/17,20-liazę (P450c17) oraz 11β-hydroksylazę (P450c11β) (19,22,23). W CS ketokonazol stosuje się w dawkach 200–1200 mg na dobę; jednak ze względu na krótki okres półtrwania (3,3 h) lek ten wymaga podawania 2–3 razy dziennie (21). Brakuje danych z prospektywnych badań oceniających skuteczność ketokonazolu w leczeniu CS; w największym retrospektywnym badaniu obejmującym 200 pacjentów z CD normalizację dobowego wydalania wolnego kortyzolu z moczem (ang. *urinary free cortisol*, UFC) uzyskano u 49,3% pacjentów (24). Główne ograniczenia stosowania ketokonazolu obejmują hepatotoksyczność, hamowanie wydzielania androgenów u mężczyzn oraz działania niepożądane ze strony przewodu pokarmowego (19,22,23). Problemem jest również jego ograniczona skuteczność ketokonazolu w leczeniu długoterminowym, gdyż utrata efektu terapeutycznego po początkowej odpowiedzi dotyczy nawet do 23% pacjentów (22).

Lewoketokonazol, będący enancjomerem 2S,4R ketokonazolu, charakteryzuje się dłuższym okresem półtrwania niż ketokonazol (4–6 h), co umożliwia jego podawanie dwa razy dziennie w dawce 300–1200 mg na dobę (19,21,22). W randomizowanym badaniu III fazy z fazą odstawienia leczenia LOGICS (NCT03277690) kontrolę mUFC uzyskano u 50% pacjentów leczonych lewoketokonazolem w porównaniu z 5% w grupie placebo (25).

Ketokonazol i lewoketokonazol w chwili obecnej są niedostępne w Polsce.

4.3.2.1.2 Metyrapon

Metyrapon jest pochodną pirydyny, która względnie selektywnie hamuje P450c11β, wykazując przy tym słabsze działanie inhibicyjne wobec syntazy aldosteronu (P450c11AS) (19,22,23). Ze względu na krótki okres półtrwania (około 2 h) lek ten wymaga wielokrotnego podawania w ciągu dnia, nawet 4–6 razy na dobę, w dawkach 500–6000 mg na dobę (21–23). Skuteczność metyraponu w leczeniu CS oceniono w prospektywnym, jednoramiennym, otwartym badaniu III fazy PROMPT (NCT02297945) (26). Do badania włączono 50 pacjentów

z CS, którzy otrzymywali metyrapon przez maksymalnie 36 tygodni, w tym przez 12 tygodni w okresie podstawowym z możliwością modyfikacji dawki. Główny punkt końcowy, tj. normalizację mUFC w 12. tygodniu leczenia, osiągnięto u 47% pacjentów przy medianie dawki 1500 mg na dobę (26). W badaniach retrospektywnych normalizację mUFC osiągano średnio u 71% pacjentów z CS, przy medianie dawki wynoszącej 1750 mg na dobę oraz medianie czasu terapii równej 5,5 miesiąca (27).

Typowe działania niepożądane leczenia metyraponem wynikają ze wzrostu stężenia prekursorów o aktywności mineralokortykosteroidowej oraz androgenów i obejmują nadciśnienie tętnicze, hipokaliemię, obrzęki oraz hirsutyzm; do częściej obserwowanych działań niepożądanych należą również zmęczenie, zawroty głowy, bóle stawów oraz nudności (19,22). Podobnie jak w przypadku ketokonazolu, długotrwałe leczenie metyraponem może prowadzić do utraty początkowego efektu terapeutycznego u nawet 18,7% pacjentów (19,28).

4.3.2.1.3 Osilodrostat

Osilodrostat to doustny inhibitor steroidogenezy nadnerczowej, który w ostatnich latach stał się nową opcją terapeutyczną w terapii CS (29,30). Jego mechanizm działania polega na silnej inhibicji P450c11β – enzymu katalizującego końcowy etap syntezy kortyzolu – oraz dodatkowym hamowaniu P450c11AS, co prowadzi do zmniejszenia produkcji aldosteronu (31,32).

Wysoką skuteczność oraz korzystny profil bezpieczeństwa osilodrostatu potwierdzono w badaniach klinicznych II i III fazy, w których wykazano szybką i trwałą kontrolę hiperkortyzolemii, z równoczesną poprawą parametrów metabolicznych, czynników ryzyka sercowo-naczyniowego oraz jakości życia pacjentów (18,31,p.20,33). W randomizowanym, podwójnie zaślepionym, kontrolowanym placebo, wieloośrodkowym badaniu rejestracyjnym III fazy LINC4 (NCT02697734) oceniano skuteczność i bezpieczeństwo osilodrostatu u 73 dorosłych pacjentów z utrzymującą się lub nawrotową postacią CD (18). Normalizację mUFC w 12. tygodniu leczenia uzyskano u 77% pacjentów leczonych osilodrostatem w porównaniu z 8% w grupie placebo, a mediana czasu do uzyskania pierwszej kontroli mUFC wyniosła 35 dni (18). Odsetek pacjentów osiągających normalizację mUFC w 36. tygodniu badania, po 24-tygodniowym leczeniu osilodrostatem w otwartej fazie, wyniósł 81% (18).

Najczęstszymi działaniami niepożądanymi podczas terapii osilodrostatem są spadek apetytu, bóle stawów, zawroty głowy oraz nudności (18,33,34), w dużej mierze wynikające z zespołu odstawienia glikokortykosteroidów (35). Wysoka skuteczność osilodrostatu wiąże się jednak z relatywnie częstym występowaniem niedoczynności kory nadnerczy (ang. *adrenal*

insufficiency, AI), obserwowanej u około 27% leczonych pacjentów (18,31,33,34). AI w trakcie leczenia osilodrostatem najczęściej obserwuje się we wczesnej fazie terapii podczas dostosowywania dawki leku (18,33), chociaż może również wystąpić u pacjentów stosujących stabilny, długoterminowy schemat dawkowania (36,37). Podobnie jak w przypadku metyraponu, osilodrostat, ze względu na wysoce selektywne hamowanie P450c11β, może prowadzić do działań niepożądanych związanych z akumulacją prekursorów o aktywności mineralokortykosteroidowej oraz androgenów (18,31,33), które zazwyczaj ustępują w trakcie trwania terapii (38–40). Niemniej jednak dostępne dane wskazują, że osilodrostat powoduje mniejszy wzrost stężeń prekursorów steroidogenezy (41,42), a związane z nimi działania niepożądane występują rzadziej i mają łagodniejszy przebieg niż podczas terapii metyraponem (43).

Zalecana dawka początkowa osilodrostatu, zgodnie z charakterystyką produktu leczniczego, wynosi 2 mg podawane dwa razy dziennie, z możliwością zwiększenia dawki do maksymalnie 60 mg na dobę (44,45). Osilodrostat charakteryzuje się również dłuższym okresem półtrwania (4 godziny) w porównaniu z metyraponem i ketokonazolem (30), co umożliwia jego podawanie dwa razy dziennie i może poprawiać przestrzeganie zaleceń terapeutycznych przez pacjentów (21,22).

4.3.2.2 Leki działające na poziomie przysadki

Do leków działających na poziomie przysadki, mających zastosowanie w farmakoterapii pacjentów z CD, należy pasyreotyd i kabergolina (19,46).

4.3.2.2.1 Pasyreotyd

Pasyreotyd jest ligandem receptora somatostatynowego drugiej generacji, wykazującym wysokie powinowactwo do podtypu 5 receptora somatostatynowego (ang. *somatostatin receptor type 5*, SSTR5), który to cechuje się najwyższym poziomem ekspresji w guzach kortykotropowych przysadki (19,46,47). W podwójnie zaślepionym badaniu III fazy (NCT00434148) u pacjentów z CD, w trakcie terapii pasyreotydem, normalizację mUFC osiągnięto u 36% uczestników w 6. miesiącu leczenia oraz u 31% uczestników w 12. miesiącu leczenia (48). Pasyreotyd w postaci o przedłużonym uwalnianiu (ang. *long-acting release*, LAR) stanowi zmodyfikowaną, długodziałającą formę leku, podawaną domięśniowo raz w miesiącu, o porównywalnym profilu skuteczności i bezpieczeństwa do postaci krótkodziałającej (17,49). W badaniu klinicznym III fazy (NCT01374906) po 7. miesiącach leczenia normalizację mUFC uzyskano u 41% pacjentów z CD (17). Głównym działaniem

niepożądanym pasyreotydu są zaburzenia gospodarki węglowodanowej, które wynikają z hamowania wydzielania insuliny przez pobudzenie SSTR5 w trzustce oraz niekorzystnego wpływu na sekrecję hormonów inkretynowych (47,50).

4.3.2.2.2 Kabergolina

Kabergolina jest pochodną ergoliny, silnym agonistą receptora dopaminowego typu 2 (ang. *dopamine 2 receptor*, D2R) i powszechnie stosowana jest w leczeniu hiperprolaktynemii (51). D2R wykazują wysoką ekspresję w obrębie przedniego płata przysadki, gdzie uczestniczą głównie w regulacji wydzielania prolaktyny przez laktotrofy (52). Wykazano również, że D2R mogą ulegać ekspresji w obrębie komórek guzów kortykotropowych, z których część może charakteryzować się wysoką wrażliwością na leczenie agonistami dopaminy (53). Na leczenie kabergoliną odpowiada około 20–25% pacjentów z CD, przy stosowanych dawkach mieszczących się w zakresie 0,5–7 mg tygodniowo (54,55).

4.3.3 Postępowanie w ciężkim zespole Cushinga

SCS wymaga pilnej interwencji medycznej; kluczowe znaczenie w terapii ma szybka normalizacja stężenia kortyzolu przy użyciu inhibitorów steroidogenezy nadnerczowej, równocześnie z wdrożeniem działań profilaktycznych i leczniczych ukierunkowanych na powikłania indukowane hiperkortyzolemią oraz prowadzeniem kompleksowej diagnostyki w celu ustalenia pierwotnego źródła choroby (4,12). Preferowanymi inhibitorami steroidogenezy nadnerczowej w terapii SCS są leki o szybkim początku działania, takie jak metyrapon, osilodrostat i ketokonazol (4,56,57). W najcięższych postaciach SCS w celu kontroli hiperkortyzolemii można rozważyć wykorzystanie etomidatu (4,12,58).

4.3.3.1 Etomidat

Etomidat jest pochodną imidazolu, krótko działającym lekiem dożylnym o właściwościach anestetycznych, którego jednym z działań niepożądanych jest zahamowanie czynności kory nadnerczy poprzez odwracalną blokadę P450c11β, P450c17, P450scc oraz P450c11AS (19,58–60). Supresja steroidogenezy nadnerczowej istotnie ogranicza zastosowanie etomidatu w praktyce anestezjologicznej, jednak jednocześnie stwarza możliwość jego wykorzystania poza wskazaniami rejestracyjnymi u pacjentów z SCS (12,58,59). Etomidat umożliwia wysoce skuteczną i szybką kontrolę hiperkortyzolemii, a normalizacja stężenia kortyzolu może zostać osiągnięta już w ciągu kilkunastu godzin (61–63). Ponadto etomidat jest jedynym inhibitorem steroidogenezy nadnerczowej podawanym pozajelitowo, co pozwala na jego zastosowanie

u pacjentów, u których leki doustne są niewskazane lub niemożliwe do podania, np. u osób nieprzytomnych lub z nasilonymi zaburzeniami neuropsychiatrycznymi indukowanymi SCS (12,58,59).

4.3.3.2 Leczenie skojarzone

W wybranych przypadkach leki stosowane w terapii hiperkortyzolemii mogą być podawane w skojarzeniu (57,64–66). Takie podejście, polegające na jednoczesnym stosowaniu preparatów o synergistycznym i/lub komplementarnym mechanizmie działania, zwiększa skuteczność redukcji stężenia kortyzolu, a dzięki możliwości zastosowania niższych dawek niż w monoterapii, potencjalnie ogranicza ryzyko działań niepożądanych (19,22). Pośród inhibitorów steroidogenezy nadnerczowej, w literaturze najczęściej wskazuje się na możliwość skojarzonego zastosowania metyraponu i ketokonazolu (57,64). U pacjentów z CD istnieje również możliwość leczenia skojarzonego inhibitorem steroidogenezy nadnerczowej i lekiem działającym na poziomie przysadki (65,67,68).

4.4 Uzasadnienie wyboru tematu pracy i połączenia przedstawionych publikacji w cykl

Prace wchodzące w skład przedłożonego cyklu publikacji w sposób spójny koncentrują się na farmakoterapii z zastosowaniem nowych leków lub schematów terapeutycznych u pacjentów z ACTH-zależną hiperkortyzolemią, oceniając ich skuteczność i bezpieczeństwo w rzeczywistych warunkach klinicznych.

Publikacja *Cushing's Disease: Long-Term Effectiveness and Safety of Osilodrostat in a Polish Group of Patients with Persistent Hypercortisolemia in the Experience of a Single Center* stanowi pracę oryginalną, w której retrospektywnie analizowano efekt długoterminowej terapii osilodorostatem u pacjentów z nawrotową lub przetrwałą CD. W pracy opisano również trzy przypadki kliniczne, które ilustrują skuteczność osilodrostatu w terapii hiperkortyzolemii o zróżnicowanym nasileniu, a także działania niepożądane leku o szczególnym znaczeniu oraz sposoby postępowania w przypadku ich wystąpienia. Takie ujęcie pozwala zobrazować potencjalne sytuacje kliniczne, z którymi lekarze endokrynolodzy mogą się zmierzyć się podczas terapii osilodrostatem. Publikacja *Cushing's syndrome: a combined treatment with etomidate and osilodrostat in severe life-threatening hypercortisolemia*, stanowi pierwszy w literaturze opis przypadku pacjentki z SCS, u której w terapii wykorzystano leczenie skojarzone etomidatetm i osilodrostatem. W publikacji *Is there still a place for etomidate in the management of Cushing's syndrome? The experience of a single center of low-dose etomidate and combined etomidate-osilodrostat treatment in severe hypercortisolemia*

oceniano skuteczność i bezpieczeństwo niskodawkowej terapii etomidatem u pacjentów z powikłanym, zagrażającym życiu SCS. Ponadto u części z analizowanych przypadków dalszej analizie poddano schemat terapeutyczny leczenia skojarzonego etomidatem i osilodrostatem. Publikacja *Real-World Experience with Pasireotide-LAR in Cushing's Disease: Single-Center 12-Month Observational Study* jest pracą oryginalną, w której retrospektywnie przeanalizowano skuteczność i bezpieczeństwo terapii pasyreotydem LAR u pacjentów z przetrwałą lub nawrotową CD.

Podsumowując, niniejszy cykl publikacji przedstawia aktualne możliwości farmakoterapii u pacjentów z ACTH-zależną hiperkortyzolemią, ze szczególnym uwzględnieniem ich skuteczności i bezpieczeństwa. Prace te podkreślają konieczność indywidualnego doboru strategii terapeutycznej, co ma kluczowe znaczenie dla poprawy skuteczności leczenia, rokowania oraz jakości życia pacjentów z CS. Przedstawione wyniki mogą stanowić istotne i praktyczne źródło wiedzy dla lekarzy podejmujących leczenie pacjentów z CS

5. ZAŁOŻENIA I CEL PRACY

Celem niniejszej rozprawy doktorskiej jest przedstawienie skuteczności oraz bezpieczeństwa nowoczesnych terapii farmakologicznych stosowanych u pacjentów z ACTH-zależną hiperkortyzolemią, ze szczególnym uwzględnieniem ich wykorzystania w warunkach rzeczywistej praktyki klinicznej. W ramach pracy przeprowadzono analizę leczenia osilodrostatem i pasyreotydem LAR u pacjentów z chorobą Cushinga oraz oceniono rolę etomidatu — zarówno w monoterapii, jak i w terapii skojarzonej — w ciężkich, zagrażających życiu przypadkach hiperkortyzolemii.

Niniejsza rozprawa doktorska ma na celu przedstawienie doświadczeń klinicznych wynikających ze stosowania powyższych terapii, identyfikację potencjalnych działań niepożądanych oraz wzbogacenie istniejących strategii postępowania terapeutycznego. Szczególny nacisk położono na konieczność indywidualizacji leczenia z uwzględnieniem profilu klinicznego pacjenta, chorób współistniejących, dynamiki choroby oraz tolerancji farmakoterapii.

Ostatecznym zamierzeniem rozprawy jest poszerzenie wiedzy dotyczącej efektów nowoczesnych metod leczenia w praktyce klinicznej, ugruntowanie ich miejsca w aktualnych schematach terapeutycznych oraz wskazanie potencjalnych korzyści wynikających z właściwego doboru terapii. Przedstawione dane mogą być wykorzystane w praktyce klinicznej oraz stanowić pomoc w wyborze najodpowiedniejszego leczenia farmakologicznego hiperkortyzolemii, co potencjalnie wpłynie na poprawę rokowania oraz jakości życia pacjentów z zespołem Cushinga.

6. KOPIE OPUBLIKOWANYCH PRAC

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Cushing's Disease: Long-Term Effectiveness and Safety of Osilodrostat in a Polish Group of Patients with Persistent Hypercortisolemia in the Experience of a Single Center

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Abstract: Osilodrostat is a potent oral steroidogenesis inhibitor that has emerged as the new medical agent for patients with Cushing's disease (CD) requiring long-term medical therapy for hypercortisolemia control. Its efficacy and safety have been assessed in clinical trials; however, real-world evidence is still scarce. This study aimed to investigate the long-term treatment (156 weeks) clinical and biochemical effect of osilodrostat in six patients with CD at a single center in Poland, initially participating in the LINC4 study. At week 36, all six patients met the key secondary endpoint of the LINC4 trial, achieving normalization of median urinary free cortisol. Osilodrostat treatment allowed for complete disease control in all patients and none of the patients was excluded due to the lack of treatment effectiveness in 156 weeks of follow-up. All patients demonstrated significant improvement from baseline on most metabolic and cardiovascular parameters, which was most evident at week 36 and sustained throughout the study period. This study supports and strengthens the role of osilodrostat as an effective long-term medical treatment in patients with CD. We also present three patient case histories in detail to highlight the clinical situations that endocrinologists might face during osilodrostat therapy.

Keywords: adrenal steroidogenesis inhibitors; cortisol; Cushing's disease; Cushing's syndrome; medical therapy; osilodrostat

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1. Introduction

Endogenous Cushing's syndrome (CS) is a very rare endocrine condition with an estimated annual incidence of 0.2–5 per million per year. The most common cause of CS, accounting for approximately 70% of all cases, is an adrenocorticotropin (ACTH)-secreting pituitary neuroendocrine tumor (Pit-NET), traditionally defined as Cushing's disease (CD) [1]. Sustained hypercortisolemia is linked with significantly impaired quality of life, morbidity, and mortality [2–8]; therefore, normalization of cortisol overproduction while avoiding permanent hormone deficiency and drug dependence is the ideal goal of CD treatment. While the therapy of choice for CD is transsphenoidal surgery (TSS), some patients require additional treatment, including pharmacological agents, radiotherapy, radiosurgery or bilateral adrenalectomy [9,10]. Pharmacotherapy is especially indicated when neurosurgery is unsuccessful, contraindicated, not feasible or not accepted, as well as in recurrent cases and as bridging therapy, while awaiting other procedures [9–11]. Medical treatment options include inhibitors of steroidogenesis, pituitary-targeted drugs, and glucocorticoid receptor antagonists [10,12–14].

Osilodrostat is a particularly potent oral inhibitor of 11β-hydroxylase (CYP11B1), which catalyzes the final step of cortisol synthesis and represents a novel approach to achieving eucortisolism in patients with CD [15,16]. In the phase III LINC3 study (NCT02180217), evaluating the efficacy and safety of osilodrostat, normalization of mean urinary free cortisol (mUFC) was achieved in 66.4% of patients at the end of the trial [17]. In the phase III LINC4 study (NCT02697734), with an initial placebo-controlled phase, osilodrostat has been shown to be significantly superior to placebo at normalizing mUFC at week 12 (77% vs. 8%) and led to sustained mUFC levels below the upper limit of normal (ULN) in 68.5% of patients in 48 weeks of observation [18]. In the recently published results from the LINC4 study extension (NCT02180217), 72.4% of patients maintained mUFC values below the upper limit of normal (ULN) at their extension end-of-treatment visit (up to 96 weeks) [19].

Data from the clinical practice on patients with CD treated with osilodrostat are limited. Hence, this study aimed to present the clinical and biochemical response of long-term (156 weeks) treatment with osilodrostat in six patients with persistent or recurrent CD at a single center in Poland, with the results of three patients depicted in detail. In contrast to the large clinical studies, our paper is mainly focused on presenting our center's experience of CD treatment with osilodrostat in real-life settings.

2. Materials and Methods

2.1. Study Design

The study group included 6 adult patients (4 women and 2 men, aged 35.7 ± 12.8 years) with persistent or recurrent CD (all patients underwent at least one TSS) with uncontrolled hypercortisolemia and who were not suitable for re-operation, enrolled in the phase III LINC4 study at the Department of Internal Medicine, Endocrinology and Diabetes, Medical University of Warsaw, Poland between September 2018 and January 2019. Patients' baseline characteristics are summarized in Table 1.

Patients must have had an active disease evidenced by mUFC of three 24 h UFC samples above 1.3× the ULN, morning plasma ACTH concentration above or within the reference range (WRR), and a confirmed pituitary source of ACTH excess. The LINC 4 study protocol comprised an initial, randomized, double-blind period (12 weeks) to compare the efficacy of osilodrostat against a placebo and a subsequent 36-week, open-label period complemented by an optional extension (48 weeks) to evaluate the sustained effect of osilodrostat and long-term safety. During the first 12 weeks, patients were randomized in a double-blinded manner to receive osilodorostat 2 mg twice a day (BID) or a matching placebo in accordance with the study protocol. In that phase, dose adjustments were made based on mUFC, rate of mUFC decrease, and drug tolerability. The dose could be increased approximately every 3 weeks with an escalation sequence of 2–5–10–20 mg BID. All 6 patients restarted the open-label period (weeks 13–48) on osilodrostat 2 mg BID and then continued treatment as a part of the extension phase (weeks 48–96). The investigators determined dose adjustments during open-label and extension periods based on mUFC, mean late-night salivary cortisol (mLNSC), clinical presentation, and drug tolerability. The maximum dose of osilodrostat in double-blinded and open-label/extension periods was 20 and 30 mg BID, respectively. The primary endpoint of the LINC4 study was to determine whether osilodrostat was superior to placebo in normalizing mUFC at week 12. The key secondary endpoint was the proportion of patients achieving mUFC normalization at week 36 (after 24 weeks of open-label treatment). Complete biochemical response was defined as mUFC < ULN, and partial biochemical response as mUFC > ULN but ≥50% reduction from baseline. A detailed description of the study has already been presented [18]. After completing their participation in the clinical trial, all patients continued treatment with osilodrostat financed by the National Health Fund.

Table 1. Baseline patient characteristics.

Characteristics	All Patients, $n = 6$
Age, years	
Median (range)	32.5 (24–62)
Mean (SD)	35.7 (12.8)
Sex, *n*	
Female	4
Male	2
Previous treatment, *n* (%)	
Pituitary surgery	6
Medical therapy	5
Comorbidities, *n* (%)	
Hypertension	5
Abnormal weight	
Overweight	4
Obesity	1
Impaired glucose metabolism	
IFG	1
IGT	2
DM	2
Dyslipidemia	5
Decreased BMD	5
Physical manifestation of hypercortisolemia, n	
Central obesity	6
Dorsal fat pad	5
Supraclavicular fat pads	6
Facial rubor	3
Proximal muscle atrophy	4
Striae	6
Ecchymoses	2
Hirsutism (in females, $n = 4$)	2
mUFC, nmol/24h	
Median (range)	480.0 (220.5–3316.4)
Mean (SD)	900.3 (1839)
mLNSC, nmol/L	
Median (range)	11.4 (3.60–28.85)
Mean (SD)	11.4 (5.35)

IFG—impaired fasting glucose; IGT—impaired glucose tolerance; DM—diabetes mellitus; BMD—bone mineral density; mUFC—mean urinary free cortisol; mLNSC—mean late-night salivary cortisol.

2.2. Clinical Evaluation

The clinical evaluation, performed at baseline and every study visit, included assessment of physical features of CD, signs and symptoms of adrenal insufficiency (AI) and the measurement of weight, body mass index (BMI), waist circumference, blood pressure (BP), and heart rate by standard methods. Electrocardiogram (ECG) with calculated corrected QT (QTcF) intervals was performed pre-dose and 1.5 h post-dose at each visit.

2.3. Laboratory Assessment

After the patients' enrollment in the LINC4 trial, biochemical and hormonal parameters were assessed by the central laboratory designated by the study protocol.

UFC (RR: 11.0–138 nmol/24 h), LNSC (RR: 10–11 PM: ≤2.5 nmol/L), and total serum cortisol (TSC, RR: 8–10 AM: 127–567 nmol/L) were measured by liquid chromatography-tandem mass spectrometry and plasma ACTH by immunoassay (RR: 7–10 AM: 1.3–11.1 pmol/L). mUFC was calculated from two or three 24 h UFC measurements and mLNSC from two LNSC measurements, collected on three or two consecutive days before visits. Metabolic factors, including fasting plasma glucose (FPG), lipids, glycated hemoglobin (HbA1c) and liver parameters (alanine transaminase (ALT) and aspartate transaminase (AST)) were measured by standard methods. After completing the clinical trial, biochemical and hormonal

assessments were performed in the laboratory of the Endocrinology Department of the Medical University of Warsaw.

2.4. Tumor Imaging

Pituitary imaging was performed using a 1.5-T magnetic resonance imaging (MRI) with gadolinium enhancement with 2.5 mm slice thickness at baseline, weeks 26, 48, 72 and 96, and 144.

2.5. Statistic Analysis

Data are presented as mean and standard deviation (SD) or median and range. The Wilcoxon signed-rank test was used for the comparisons between baseline and particular points of observation. All calculations were completed using IBM® SPSS® Statistics 25. The p-values < 0.05 were considered as statistically significant.

3. Results

3.1. Effectiveness and Hormonal Parameters Analysis

At the baseline, in the six patients included in the study, median mUFC and mLNSC values were 480.0 nmol/24 h (3.48× ULN) and 11.40 nmol/L (4.57× ULN), respectively. At week 36 (after 24 weeks of the open-label phase), all six patients met the key secondary endpoint of the LINC4 trial, achieving a mUFC < ULN, at a median osilodrostat dose of 4 mg BID (range: 1–20 mg BID). At that time, the median mUFC was 75.15 nmol/24 h (WRR, range: 34.97–94.60 nmol/24 h; $p = 0.031$) and the median mLNSC was 2.11 nmol/L (WRR, range: 0.8–5.35 nmol/L; $p = 0.031$); four (66.7%) of the analyzed patients had both mUFC and mLNSC < ULN. Median time and osilodrostat dose to first mUFC < ULN (from study restart at week 12) was 5 weeks (range: 2–20 weeks) and 5 mg BID (range: 2–20 mg BID), respectively. Median time and osilodrostat dose to first mUFC and mLNSC < ULN (from study restart at week 12) was 9.5 weeks (range: 2–48 weeks) and 5 mg BID (range: 2–25 mg BID), respectively. The minimum and maximum osilodrostat dose required, at least temporarily, to achieve and maintain eucortisolemia during the whole observation period was 1 mg every 3 days (patient 4) and 30 mg BID (patient 1 and 2), respectively. At 96 weeks' follow-up, the median mLNSC (1.58 nmol/L, WRR) significantly decreased by 82.75% ($p = 0.031$) compared to baseline (11.43 nmol/L, 4.57x ULN); four of the six patients had an mLNSC < ULN at that time. At 156 weeks' follow-up, the median mUFC (50.83 nmol/24 h, WRR, range: 17.2-110,6 nmol/24 h) decreased by 92.99% ($p = 0.031$) compared to baseline (480.0 nmol/24 h, 3.48x ULN, range: 220.53–3316.40 nmol/24 h), and morning TSC (281.50 nmol/L, WRR, range: 116.0–420.0 nmol/L) decreased by 33.64% ($p = 0.031$) compared to baseline (448.5 nmol/L, WRR, range: 290–420 nmol/L). However, the median morning TSC was within the reference range through the whole study period. All six patients achieved and maintained a complete treatment response, and none of the patients was excluded due to the lack of treatment effectiveness in 156 weeks of follow-up.

The median ACTH concentration significantly increased during the whole study period, and at 156 weeks' follow-up (91.6 pmol/L, 8.25x ULN) it was 9.5-fold higher ($p = 0.031$) compared to baseline. Data are summarized in Table 2. Figure 1 presents mUFC, Figure 2 mLNSC, and Figure 3 ACTH evolution according to osilodrostat dose during the study observation for every patient. Figure 4 presents median mUFC (a) and median mLNSC (b) evolution according to median osilodrostat dose during the study observation of all patients.

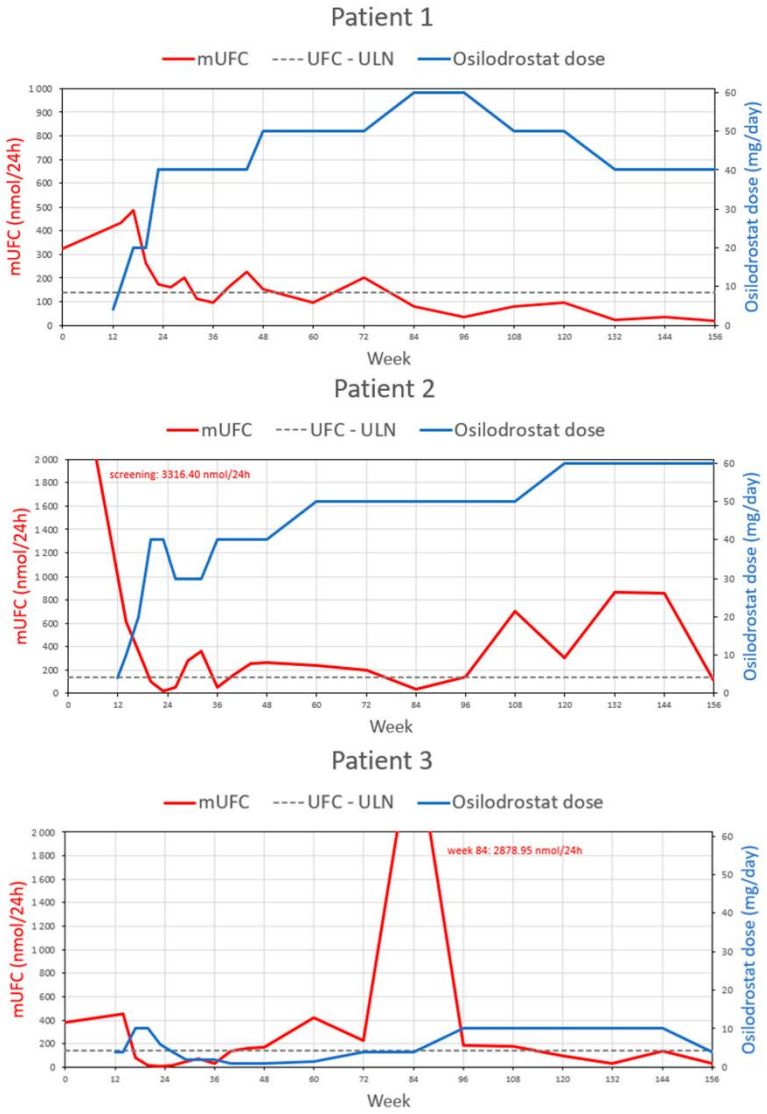


Figure 1. *Cont.*

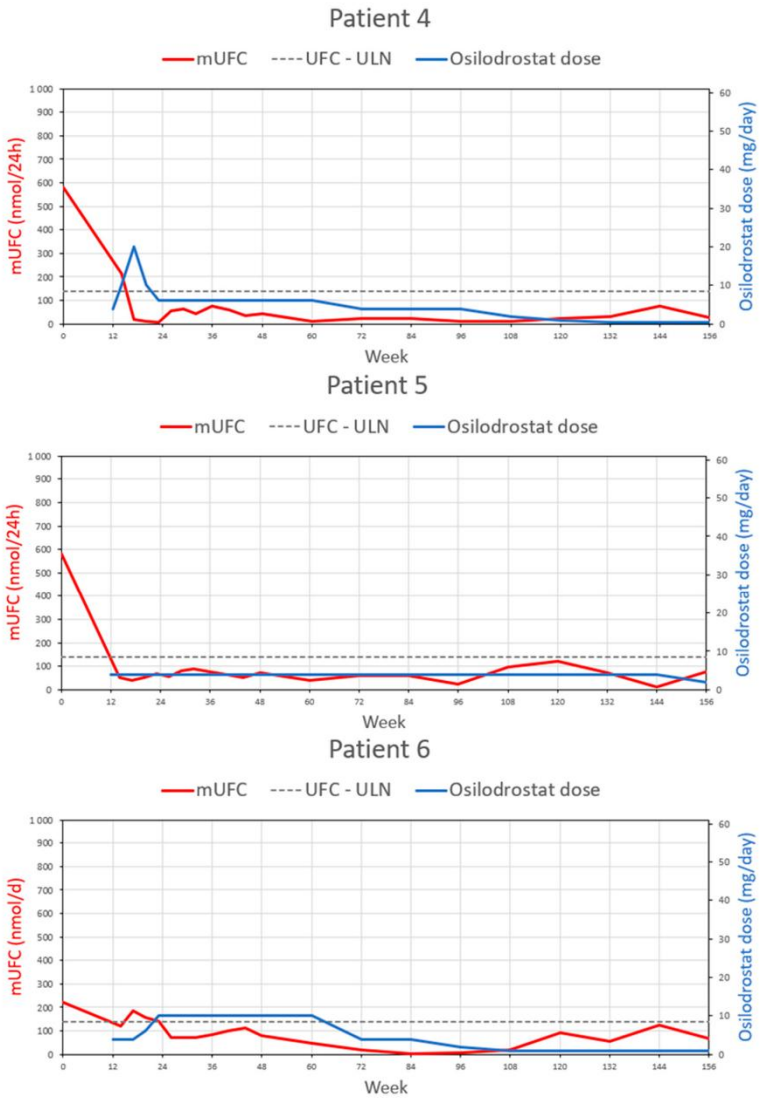


Figure 1. mUFC evolution according to osilodrostat dose during 156 weeks' observation for every patient.

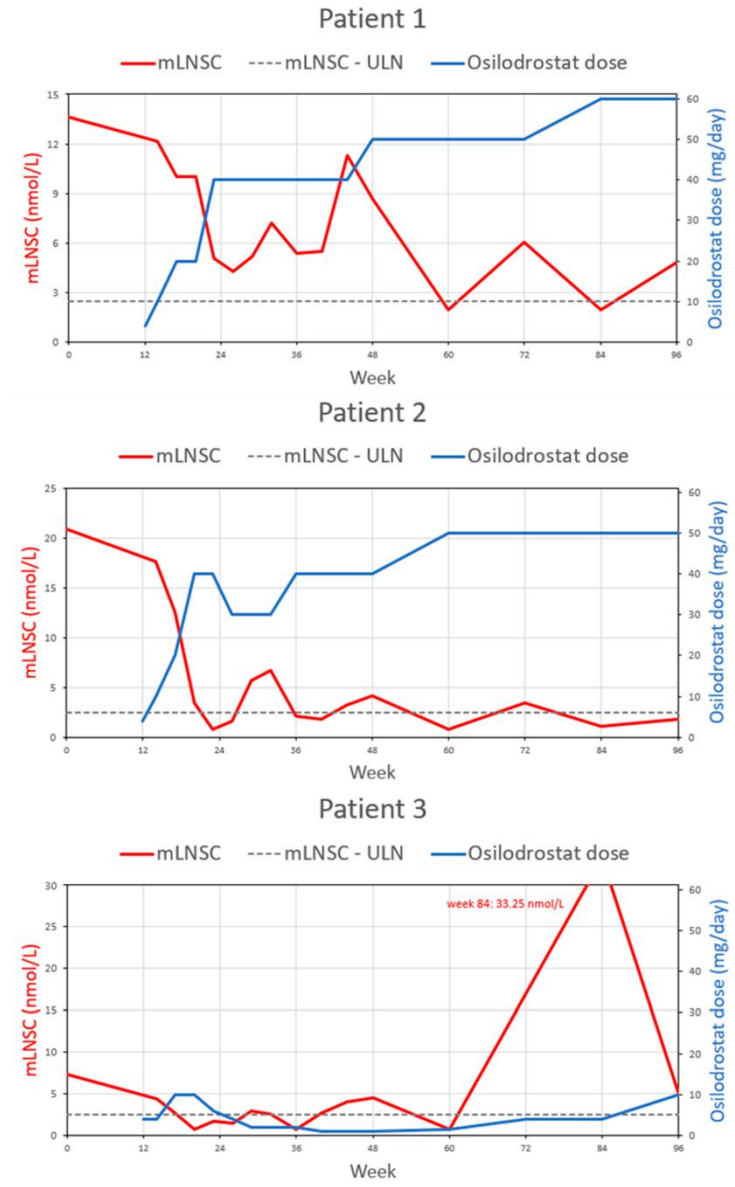


Figure 2. *Cont.*

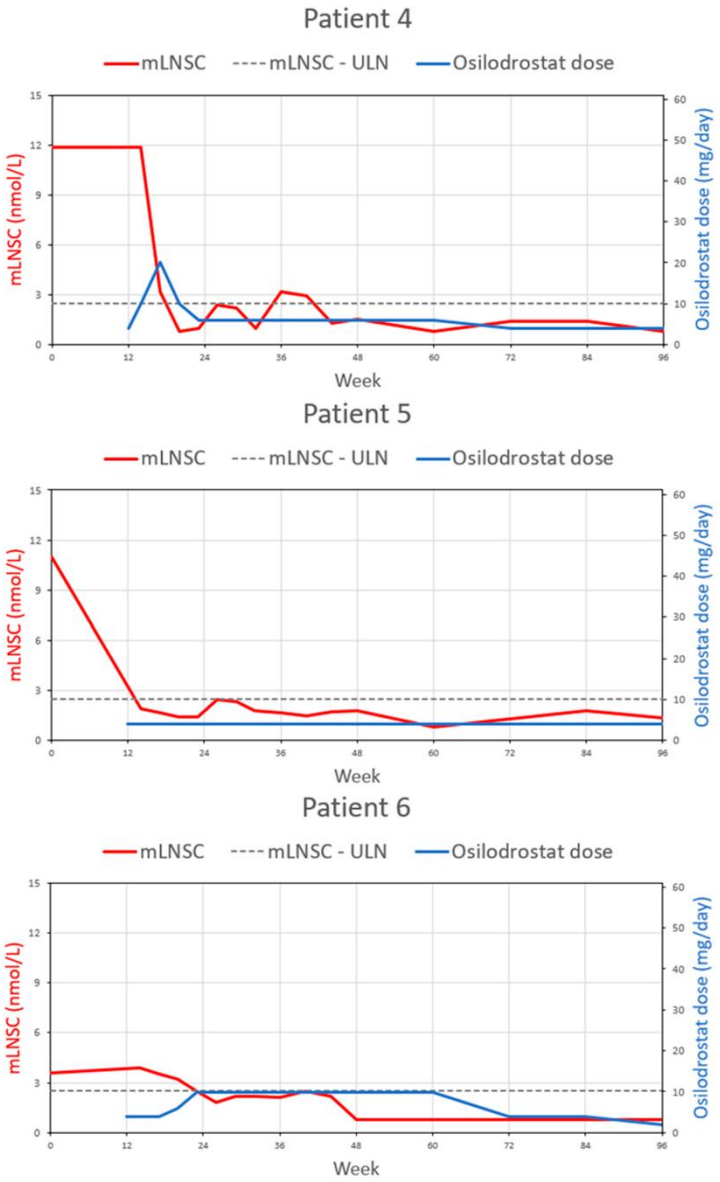


Figure 2. mLNSC evolution according to osilodrostat dose during the 96 weeks' observation for every patient.

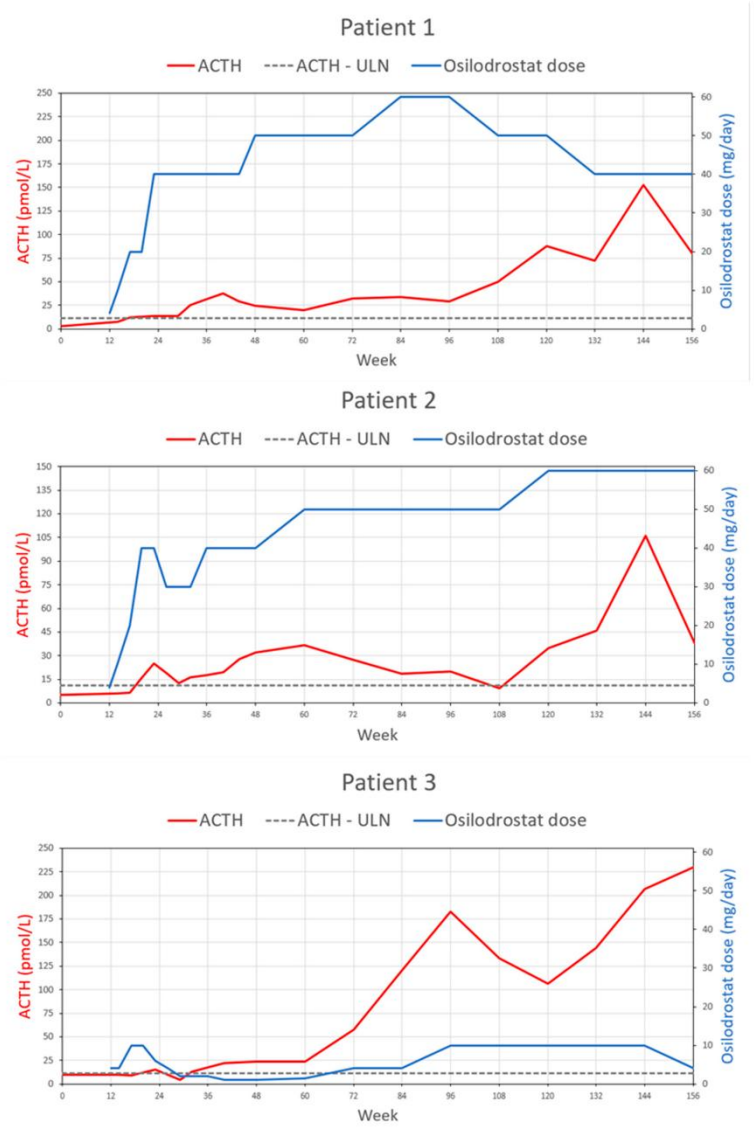


Figure 3. *Cont.*

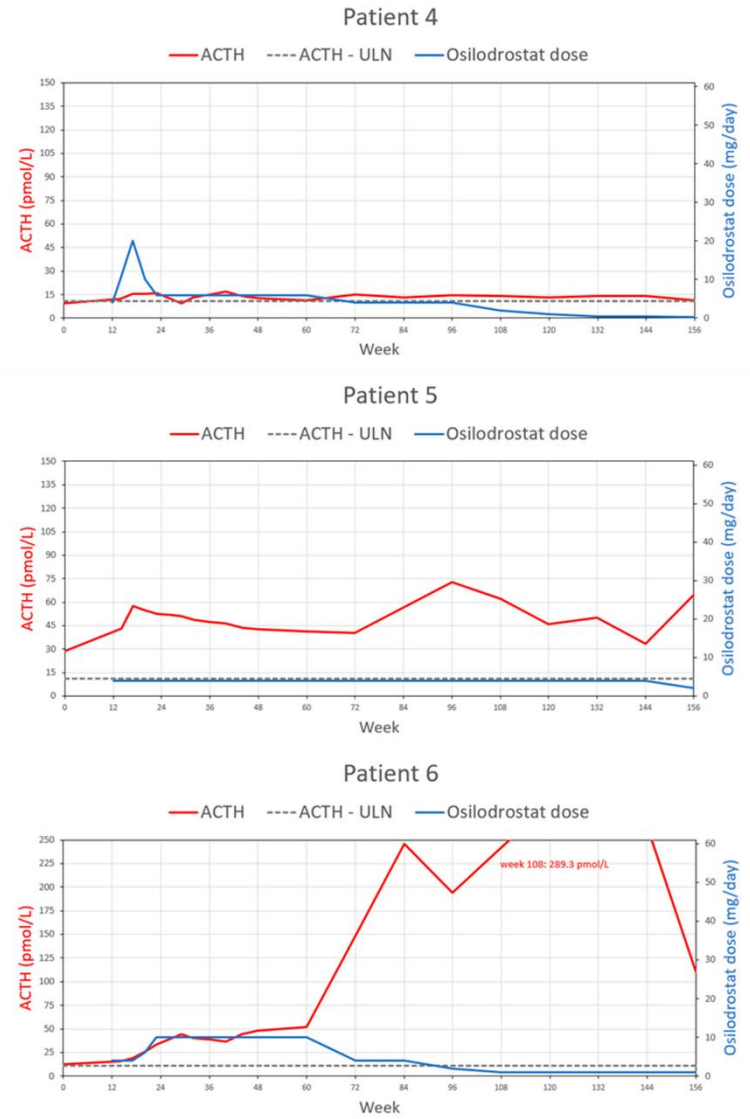
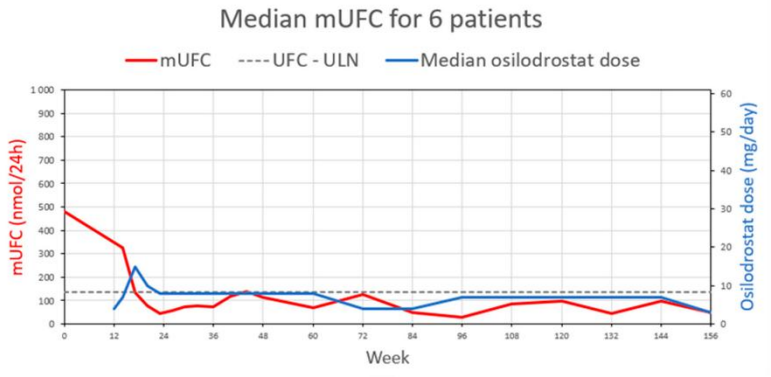
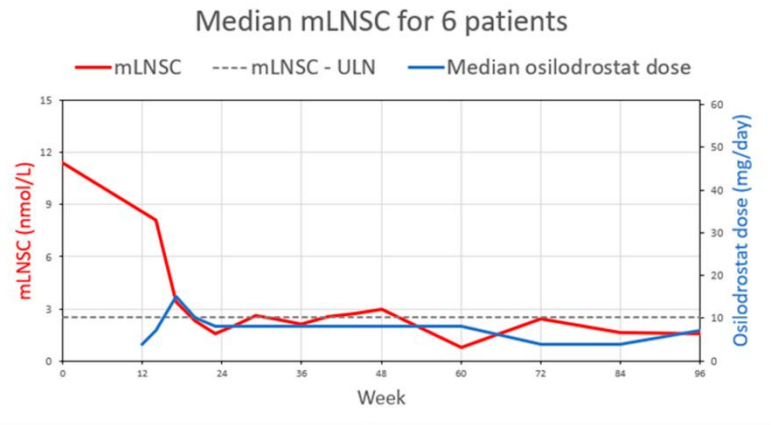


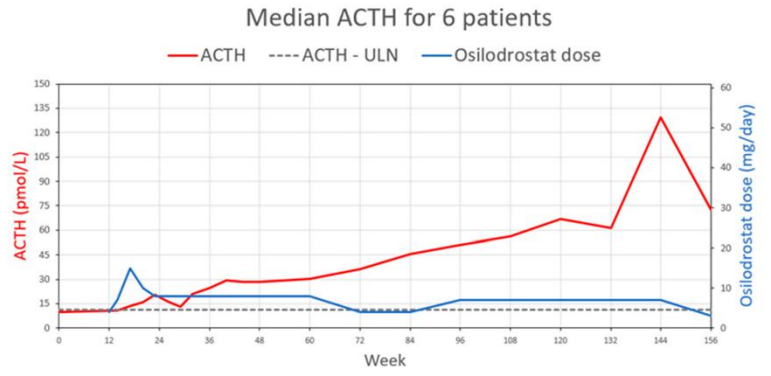
Figure 3. ACTH evolution according to osilodrostat dose during 156 weeks' observation for every patient.



(**a**)



(**b**)



(**c**)

Figure 4. Median mUFC (**a**), median mLNSC (**b**), and median ACTH (**c**) evolution according to median osilodrostat dose during the study observation of all patients.

Table 2. Median mUFC, mLNSC, TSC, and ACTH concentrations and their changes from baseline at each checkpoint during observation.

Follow-Up	Median (Range)	Δ% from Baseline	*p*-Value
mUFC (nmol/24 h)			
Baseline	480.02 (220.53–3 316.40)	-	-
Week 36	75.15 (34.97–94.60)	−87.60	0.031
Week 72	127.83 (17.80–223.70)	−90.73	0.031
Week 96	30.26 (8.90–182.40)	−95.77	0.031
Week 132	44.48 (22.40–868.30)	−89.32	0.031
Week 156	50.83 (17.20–110.60)	−92.99	0.031
mLNSC (nmol/L)			
Baseline	11.43 (3.60–20.85)	-	-
Week 36	2.11 (0.80–5.35)	−77.05	0.031
Week 72	2.43 (0.80–6.05)	−83.45	0.031
Week 96	1.58 (0.80–5.10)	−82.75	0.031
TSC (nmol/L)			
Baseline	448.5 (290.0 673.0)	-	-
Week 36	268.0 (196.0 367.0)	41.75	0.063
Week 72	263.0 (102.0–511.0)	−49.73	0.156
Week 96	331.0 (86.0 820.0)	56.42	0.438
Week 132	307.5 (75.0–392.0)	−42.26	0.031
Week 156	281.5 (116.0 420.0)	33.64	0.031
ACTH (pmol/L)			
Baseline	9.65 (2.90–28.60)	-	-
Week 36	29.45 (17.10–46.20)	+161.23	0.031
Week 72	37.00 (13.30–245.80)	+362.09	0.031
Week 96	56.30 (9.50–242.00)	+677.09	0.031
Week 132	129.55 (14.20–264.60)	+1933.44	0.031
Week 156	91.60 (11.10–200.00)	+651.29	0.031

mUFC—mean urinary free cortisol; mLNSC—mean late night salivary cortisol; TSC—total serum cortisol; ACTH—adrenocorticotropic hormone.

3.2. *Effect on Metabolic, Cardiovascular and Liver Parameters*

At the baseline, mean (SD) weight, BMI, and waist circumference measurements of the analyzed group were 69.88 (12.34) kg, 26.74 (3.11) kg/m^2, and 93.67 cm (3.59), respectively. BMI was WRR (18.5–24.9 kg/m^2) in 1/6 patients, 4/6 patients were overweight (BMI: 25 29.9 kg/m^2), and 1/6 patients had obesity (BMI: ≥30 kg/m^2). During observation, weight, BMI, and waist circumference gradually decreased in all patients; mean (SD) weight, BMI, and waist circumference at the end of the observation were 63.75 (11.79) kg, 24.41 (3.13) kg/m^2, and 84.83 cm (9.06), respectively. BMI was WRR in 4/6 patients, and 2/6 were overweight. The fastest decrease in body weight, BMI, and waist circumference was observed during the first 36 weeks; however, the lowest values were achieved during the last follow-up. One patient, after initial improvement, had a significant increase in body weight between weeks 60 and 96 of the study, which was associated with primary disease progression. Mean (SD) TC decreased from 5.58 (1.05) mmol/L at baseline to 4.02 mmol/L (0.69) at week 96; mean (SD) TAG decreased from 1.94 (1.21) mmol/L at baseline to 1.55 (0.86) at week 96. One of the three patients taking antilipidemic drugs at baseline discontinued the treatment. At the baseline, 2/6 patients were classified as diabetic, 2/6 had IGT, and 1/6 had IFG. Mean (SD) FPG decreased from 5.12 (1.23) mmol/L at baseline to 4.43 mmol/L (0.43) at week 96; mean (SD) HbA1c decreased from 5.5% (0.61) at baseline to 5.35% (0.56) at week 156. The fastest improvement in metabolic parameters was observed during the first 36 weeks; however, the lowest values were achieved during the last follow-up, excluding TG (week 72) and HbA1c% (week 132).

At the baseline, mean (SD) SBP and DBP were 125.0 (8.25) mmHg and 79.23 (7.20) mmHg, respectively. Five of the six patients had hypertension prior to the study and were taking antihypertensive drugs. At the end of the observation, mean (SD) SBP and DBP were 121.17 (3.71) mmHg and 83.33 (7.09) mmHg, respectively. However, considering 5/6 patients were under antihypertensive treatment at baseline, osilodrostat therapy allowed for the reduction of the dose or the number of antihypertensive drugs in four of them. Mean (SD) QTcF did not significantly change during the observation: at baseline it was 394.17 (18.04) ms, and at week 156, 404 (17.01) ms.

Mean (SD) ALT and AST activity decreased during the whole study period: ALT at baseline was 29.33 (15.51) U/L, and at week 156, 15.33 (4.55) U/L; AST baseline was 23.33 (7.87) U/L, and at week 156, 18.33 (2.66) U/L. The fastest decrease in ALT and AST activity was observed during the first 36 weeks; however, the lowest values were achieved during the last follow-up.

Data are summarized in Table 3.

Table 3. Metabolic, cardiovascular, and liver parameters at baseline and their changes from baseline at checkpoints during observation.

Parameter (Mean, SD)	Baseline	Week 36	Δ%	Week 72	Δ%	Week 96	Δ%	Week 132	Δ%	Week 156	Δ%
Weight (kg)	69.88 (13.52)	64.72 (8.38)	−6.49 (7.47)	64.68 (9.40)	−6.75 (6.79)	64.20 (10.04)	−7.48 (8.52)	64.92 (9.68)	−6.51 (5.80)	63.75 (11.79)	−8.66 (4.52)
BMI (kg/m^2)	26.74 (3.40)	24.87 (2.30)	−6.49 (7.47)	24.83 (2.55)	−6.75 (6.79)	24.64 (2.83)	−7.48 (8.52)	24.90 (2.46)	−6.51 (5.80)	24.41 (3.13)	−8.67 (4.52)
Waist circumference (cm)	93.67 (3.93)	89.92 (4.03)	−3.99 (2.32)	88.67 (9.27)	−5.49 (6.88)	89.92 (9.78)	−7.34 (7.38)	86.40 (9.71)	−8.79 (7.96)	84.83 (9.06)	−9.50 (7.79)
SBP (mmHg)	125.00 (8.25)	115.67 (8.60)	−7.25 (7.61)	113.00 (12.18)	−9.29 (11.46)	119.17 (16.23)	−4.30 (14.63)	130.33 (16.75)	+4.56 (14.51)	121.17 (3.71)	−2.76 (6.18)
DBP (mmHg)	79.17 (7.20)	76.25 (7.24)	−3.11 (12.57)	76.50 (6.72)	−2.75 (12.28)	80.17 (11.44)	+2.01 (17.20)	83.00 (14.14)	+4.93 (15.59)	83.33 (7.09)	+1.99 (11.07)
QTcF (ms)	394.17 (18.04)	407.83 (4.96)	+3.62 (4.13)	412.41 (27.30)	+4.73 (7.07)	411.08 (21.10)	+4.46 (7.12)	410.00 (21.77)	+4.05 (4.18)	404.17 (17.01)	+2.65 (4.96)
FPG (mmol/L)	5.12 (1.23)	4.53 (0.48)	−8.43 (16.49)	4.47 (0.67)	−11.22 (7.70)	4.33 (0.43)	−12.87 (13.09)	-	-	-	-
HbAlc (%)	5.55 (0.61)	5.35 (0.49)	−3.01 (5.95)	5.40 (0.57)	−2.19 (6.08))	5.33 (0.45)	−3.29 (5.50)	5.32 (0.59)	−3.84 (4.27)	5.35 (0.56)	−3.26 (2.00)
TC (mmol/L)	5.58 (1.05)	4.38 (1.59)	−20.43 (24.89)	4.55 (0.69)	−14.75 (25.26)	4.02 (0.69)	−25.73 (18.51)	-	-	-	-
TG (mmol/L)	1.94 (1.21)	1.53 (1.70)	−25.16 (35.60)	1.31 (0.72)	−19.84 (42.82)	1.55 (0.86)	−1.87 (52.12)	-	-	-	-
ALT (U/L)	29.33 (15.51)	17.08 (4.41)	−23.59 (48.42)	22.83 (12.48)	−9.55 (83.47)	24.50 (15.83)	−14.61 (92.09)	18.50 (6.29)	−14.33 (50.99)	15.33 (4.55)	−30.27 (40.88)
AST (U/L)	23.33 (7.87)	18.42 (2.80)	−11.75 (36.55)	20.17 (4.79)	−5.81 (34.70)	23.08 (10.39)	−7.20 (54.01)	19.83 (7.25)	−11.25 (26.28)	18.33 (2.66)	−15.06 (25.58)

BMI—body mass index; SBP—systolic blood pressure; DBP—diastolic blood pressure; QTcF—corrected QT interval; FPG—fasting plasma glucose; HbA1c—glycated hemoglobin; TC—total cholesterol; TG—triglycerides; ALT—alanine transaminase, AST—aspartate transaminase.

3.3. Treatment Tolerability and Adverse Events

Treatment with osilodrostat was generally well tolerated. During 156 weeks of observation, every patient experienced at least one adverse event (AE) suspected to be related to osilodrostat. Overall, all six patients experienced the AE of increased ACTH concentration. Five of the six patients (83.33%) presented with AI; there was no need to discontinue osilodrostat in any of these patients, and the dose was temporarily adjusted. A transient increase in 11-deoxycorticosterone (DOC) was observed in all patients, mainly after initiating osilodrostat treatment or during dose escalation. However, only two of the patients presented with the clinical effect of DOC accumulation (hypertension and hypokalemia in patient two and hypokalemia in patient four). All four female patients had a periodic increase in testosterone level, but only one presented with induced mild hirsutism, which resolved with time on continued treatment. Arthralgia, myalgia, or fatigue occurred in

three of the six patients (50%), nausea, decreased appetite or hypokalemia in two patients (33.33%), and headache or hypertension in one patient (16.67%).

3.4. Description of Specific Cases

- Patient #1

The first patient we would like to detail is a 28-year-old woman with persistent CD, complicated by obesity, decreased bone mineral density (BMD), impaired glucose tolerance, and arterial hypertension. Diagnostics found an onset in adolescence (at 16 years of age) when a non-intentional weight gain of 10 kg in six months with central and facial redistribution of body fat occurred, accompanied by acne and purple striae on the thighs and lateral surfaces of the trunk. At that time, the body weight centile chart corresponded to the 97th percentile, while height was between the 50th and 75th percentiles. The hormonal evaluation confirmed ACTH-dependent hypercortisolemia and an MRI visualized a 3 × 5 mm lesion of weak contrast enhancement in the posterior part of the pituitary gland. The patient was diagnosed with CD and, in June 2011, underwent a successful, uncomplicated TSS with biochemical and clinical remission, requiring six months of hydrocortisone replacement. Pathology examination identified densely granulated corticotroph adenoma with Ki-67 > 3%. About two years after the neurosurgery, the patient noticed weight gain, discoloration of the skin all over her body and reported secondary amenorrhea. The hormonal evaluation revealed CD recurrence. A follow-up MRI did not visualize a lesion compatible with a pituitary adenoma. In September 2013, the patient underwent an unsuccessful surgical exploration of the sella turcica without biochemical remission in a postoperative assessment.

Due to the persistent uncontrolled hypercortisolemia, the patient required medical therapy. In 2015–2016, the patient was treated with long-acting release (LAR) pasireotide. However, therapy had to be discontinued because of the induced hyperglycemia. In the following years, 2016 and 2017, the patient was treated with levoketoconazole, but the therapy was discontinued due to asymptomatic QT interval prolongation on ECG. In 2017–2018, the patient was switched to ketoconazole in combination with cabergoline; however, she reported continued weight gain, increased stretch marks on the abdominal skin, and persistent amenorrhea. Ketoconazole therapy had to be stopped due to its unavailability in Poland, while cabergoline was discontinued because of low effectiveness. Considering comorbid arterial hypertension and the patient's reported deterioration of visual acuity, she was assessed ophthalmologically and diagnosed with grade I vascular retinopathy.

Due to the lack of clinical and biochemical control of the primary disease and gradually increasing complications of hypercortisolemia, the patient was offered to participate in the phase III LINC-4 trial. At the time of enrollment (September 2018), the hormonal tests were as follows: morning TSC—290.0 nmol/L (WRR), morning ACTH—2.9. pmol/L (WRR), mUFC—322.8 nmol/day (2.3× ULN), mLNSC—13.65 nmol/L (5.5× ULN). According to randomization, the patient was allocated to a placebo group and started an osilodrostat of 2 mg BID in the 12th week of the study. On the 14th week, laboratory assessment revealed TSC 546 nmol/L (WRR), mLNSC 12.15 nmol/L (5× ULN), and mUFC 433.4 nmol/d (3× ULN); therefore, the dose was increased to 5 mg BID, then in week 17 and 23 to 10 and 20 mg BID, respectively, which was maintained through the end of the week 47 of the study. The first significant decrease in hypercortisolemia severity was obtained at week 23: TSC 257 nmol/L (WRR), mLNSC 5.1 nmol/L (2× ULN), mUFC 174.85 nmol/d (1.3× ULN), and treatment was continued at a daily dose of 40 mg. The normalization of mUFC (113.55 nmol/d; WRR) and mLNSC (1.95 nmol/L; WRR) was achieved on the 32nd and 60th weeks of the study, respectively. In subsequent weeks, according to the results of hormonal tests and the patient's clinical assessment, doses were modified appropriately and oscillated between 40 and 60 mg. After 156 weeks of treatment, a significant decrease in mUFC to 17.2 nmol/d (WRR) was achieved.

The patient tolerated the treatment well. There were no signs of adrenal insufficiency, except at week 132, when in the hormonal evaluation a significant reduction in morning

TSC was found (75 nmol/L, <lower limit of normal). The dose of osilodrostat was reduced to 20 mg BID and continued after that until week 156 of the study. The patient episodically reported a mild degree of fatigue and mild intermittent headaches. The ECG demonstrated a mild prolongation of the QTc interval, which did not significantly progress in the following weeks of the study with treatment at a maximum daily dose of 60 mg. After the introduction of osilodrostat, testosterone levels increased significantly during dose escalation (maximum at week 48: 12.21 nmol/L—7.8x ULN, 3.67-fold increase compared to baseline); however, the patient did not present clinically significant hyperandrogenism (Ferriman and Gallwey score rated between 0 and 2 during the whole 156 weeks' observation).

During the treatment with osilodrostat, the patient's waist circumference decreased, and moderate weight reduction occurred, with the complete normalization of fat redistribution in the neck and supraclavicular regions and resolution of other cushingoid features—atrophy of proximal muscle groups and central obesity.

- Patient #2

The second example of a patient whose clinical case we would like to detail is a 33-year-old male whose diagnostics started in September 2014 due to rapid unintentional weight gain with central fat redistribution, facial plethora, and purple striae. CS was suspected, and the baseline hormonal evaluation confirmed ACTH-dependent hypercortisolemia: positive corticotropin-releasing hormone (CRH) stimulation test, anterior pituitary lesion measuring 3 × 2.5 × 2 mm visualized in MRI, and positive bilateral inferior petrosal sinus sampling combined with CRH stimulation were compatible with CD. Other hormonal findings included thyrotropic and gonadotropic insufficiency. In November 2014, the patient underwent successful, uncomplicated TSS and required transient hydrocortisone substitution. In regular subsequent follow-ups, there was no recurrence of hypercortisolemia. Similarly, no tumor regrowth was found on the control MRI.

In February 2018, the patient reported a weight gain of 20 kg over the past few months and noticeably high blood pressure in in-home measurements. The hormonal evaluation revealed ACTH-dependent hypercortisolemia and a positive result of the combined LDDST and desmopressin test (CDDT) indicated the recurrence of CD. An MRI revealed a 2 mm focus of weak contrast enhancement on the left side of the anterior pituitary gland. In August 2018, the patient underwent a second TSS; however, the suppression of cortisol secretion was not achieved, compatible with persistent CD. Over the subsequent three months, the clinical features of hypercortisolemia dramatically intensified, including weight gain of another 10 kg, easy skin wounding, pustular skin lesions, and new purple striae. Based on an oral glucose tolerance test (OGTT), the patient was diagnosed with impaired FPG, and treatment with metformin was introduced. Hypotensive treatment with ramipril was also continued. Due to the refractory CD, the patient was offered to participate in the phase III LINC-4 trial. At the time of enrollment (December 2018), the hormonal tests were as follows: morning TSC—500 nmol/L (WRR), morning ACTH—5.3 pmol/L (WRR), mUFC—3316.4 nmol/day (24× ULN), mLNSC—20.85 nmol/L (8.35× ULN). According to randomization, the patient was allocated to the osilodrostat group. Based on the study protocol, he initially received osilodrostat at a dose of 2 mg BID, which then was adjusted every 4 weeks with an escalation sequence of 5–10 mg BID until week 12 when the dose was restarted. Throughout the open-label phase of the study, the dose of osilodrostat was systematically increased from the initial 2 mg to 30 mg BID according to the results of hormonal evaluations and the investigators' clinical assessments. Several periods require particular comments during treatment. Significant improvement in hypercortisolemia severity was achieved after just 12 weeks of the treatment. In the hormonal evaluation performed on week 14, mUFC reduced nearly 5.5-fold from the baseline (611.95 nmol/L; 4× ULN). A normalization of mUFC and mLNSC was achieved in weeks 20 and 26 of the study, respectively, with a dose of osilodrostat of 20 mg BID. However, at week 26, rapid reduction in hypercortisolemia severity was found in hormonal evaluation (mUFC 52.45 nmol/day, LNSC 1.55 nmol/L, TSC 157 nmol/L), and as a result the dose of osilodrostat was reduced to 15 mg BID, although that time patient did not report any features of adrenal insufficiency.

Noteworthy is the favorable metabolic effect as early as the 14th week—a decrease of 10 kg in body weight and an improvement in metabolism parameters—producing a reduction in TC and FPG. However, treatment with metformin was also continued at that time. During the first 8 weeks of the study, a mild transient increase in ALT (67 U/L) activity was observed, which did not worsen during the subsequent increase in the daily dose, even to a maximum of 60 mg during the open-label phase of the trial.

The patient tolerated the treatment well. At week 56, the patient reported headache, persistent fatigue, and muscle and joint pain. Considering the reported symptoms of AI, the dose of osilodrostat was reduced, but then based on the increased mUFC from two subsequent visits and the absence of symptoms of AI, the dose was increased again to 25 mg BID on week 64, which the patient tolerated well. A relevant increase in blood pressure was observed in week 108 of the study along with mild hypokalemia. Laboratory tests at that time revealed significantly elevated DOC concentration: 5447 pmol/L (12× ULN, RR: <454 pmol/L). The dose of ramipril taken was increased, and spironolactone was included. However, during following weeks the hypertension control worsened as the DOC concentration increased even more (during osilodrostat up-titration to maximum dose of 60 mg)—at week 132 it was 14 253 pmol/L (31.4× ULN)—meaning further antihypertensive and mineralocorticoid receptor blockade treatment intensification was required, which resulted in satisfactory BP control at week 156. DOC concentration at that the end of the observation declined to 3693 pmol/L (8.15× ULN).

Treatment with osilodrostat resulted in spectacular improvements both biochemically and clinically. After 156 weeks of treatment, a pleasing decrease in mUFC to 110.6 nmol/d (WRR) was demonstrated. Therapy with osilodrostat also resulted in excellent enhancement in clinical features of hypercortisolemia—fat redistribution and muscle atrophy disappeared, and the severity of striae decreased.

- Patient #3

The next patient presented is a 23-year-old woman with hypercortisolemia symptoms appearing during pregnancy, when she experienced significant weight gain (approximately 20 kg) with purple striae and developed gestational hypertension. Postpartum, secondary amenorrhea appeared, striae intensified, and the patient presented with hirsutism, acne, and a tendency to easy bruising. Furthermore, there was a central body fat redistribution and moderate muscle atrophy with weakness. The patient was referred to the department of endocrinology, and in December 2013, she was diagnosed with ACTH-dependent hypercortisolemia. Additional comorbidities included diabetes mellitus and osteoporosis. An MRI revealed a hypointense focal pituitary lesion measuring 6x4 mm. Pending surgery, bridging therapy with ketoconazole was implemented, and TSS was successfully performed in January 2014.

After four years of remission, from January 2018, the patient showed signs of CD recurrence, e.g., weight gain with central fat distribution, generalized weakness, muscle fatigue, hirsutism, acne, purple striae, tachycardia, and hypertension. The hormonal evaluation confirmed ACTH-dependent hypercortisolemia, and positive high-dose DST and CDDT were compatible with CD. An MRI revealed a small (1.5 mm) hypointense lesion on the left side of the anterior pituitary. In September 2018, the patient underwent a second TSS; however, the postoperative hormonal evaluation showed persistent hypercortisolemia. Due to the refractory CD, the patient was offered to participate in the phase III LINC-4 trial. At the time of enrollment (November 2018), the hormonal tests were as follows: morning TSC—328.0 nmol/L (WRR), ACTH—10.0 pmol/L (WRR), mUFC—380.03 nmol/24 h (2.75× ULN), mLNSC—7.35 nmol/L (2.94× ULN). According to randomization, the patient was allocated to the placebo group and started on osilodrostat of 2 mg BID in the 12th week of the study. Initially, we observed a significant improvement in clinical symptoms and biochemical control of the disease; mUFC and mLNSC had normalized only after 5 and 8 weeks, respectively. The response to the treatment was highly satisfactory, and the patient periodically required a dose reduction to 1 mg daily. At week 36 of the study, her body weight had decreased by 6 kg. At that time, mUFC and mLNSC were 34.97 nmol/24 h and

0.80 nmol/L, respectively. However, a pituitary MRI performed at week 48 showed tumor size progression (9 × 5 × 8 mm). ACTH at that time was 24 pmol/L (2.16× ULN).

From week 60, the patient noticed a gradual increase in body weight, which was assumed to be associated with the course of the primary disease, evidenced by an increase in mUFC (421,60 nmol/24 h, 3.06× ULN); therefore, the osilodrostat dose was increased. Unfortunately, conducting unscheduled visits with more detailed diagnostics was much more difficult in Poland at that time due to the ongoing COVID-19 pandemic. Due to epidemiological reasons, the visit in week 72 could only be conducted remotely. In the 84th week of the study, the physical examination showed weight gain (67 kg, BMI: 26.8 kg/m^2) with central fat distribution, dorsal and supraclavicular fat pads, new abdominal purple striae, generalized hyperpigmentation, and an increase in BP. There was a sudden increase in mUFC (2878.75 nmol/24 h, 20.86× ULN), mLNSC (33.25 nmol/L, 13.3× ULN), and morning TSC (1046 nmol/L, 1.85× ULN). ACTH (182.7 pmol/L, 16.46× ULN) had significantly increased—by approximately 18.3-fold compared to baseline. Pituitary MRI revealed a further enlargement of the tumor (12 × 8 × 14 mm) extending to the left sinus cavernous, adjacent to the left internal carotid artery, without chiasmatic compression. The patient reported no headaches or visual disturbances.

Due to the corticotroph tumor progression (CTP), the patient was discussed during a multidisciplinary pituitary tumor board and qualified for the next operation. However, it was decided to continue osilodrostat treatment at an increased dose (5 mg BID) to control hypercortisolemia. The patient underwent a third TSS in October 2020 (week 100), however, it was possible to only partially remove the tumor. Morning TSC on the first postoperative day (511.18 nmol/L, WRR) showed persistent CD, and it was decided to continue osilodrostat. Pathology examination identified corticotroph adenoma with a high proliferation index (Ki-67 > 10%). A controlled pituitary MRI, performed in week 120, showed even further tumor progression: 14.5 × 8.5 × 15.5 mm. In June 2021 (week 136), the patient underwent a single-session *Gamma Knife* stereotactic radiosurgery for the residual tumor at a dose of 20 Gy. From the onset of CTP, osilodrostat was maintained at 5 mg BID, which allowed the disease to be controlled (mUFC < ULN) from week 120. At week 156 (at the end of this study observation), the patient reported fatigue and decreased appetite; low mUFC (33.05 nmol/24 h, WRR) indicated AI, and the osilodrostat was reduced to 2 mg BID. The MRI showed a slight regression of tumor remnant (11.5 × 7 × 13 mm). The patient remains eucortisolemic to date on a small dose of osilodrostat.

4. Discussion

CD remains a major diagnostic and therapeutic challenge. Uncontrolled, chronic hypercortisolemia is associated with significant morbidity, including metabolic complications comprising glucose metabolism impairment and dyslipidemia, arterial hypertension, hypercoagulability, increased risk of infections, and psychoneurological complications, which overall results in impaired quality of life, increased mortality, and reduced life expectancy compared to that of the general population. The goal of the treatment is to reverse signs and symptoms of hypercortisolemia by achieving cortisol normalization, improving quality of life, alleviating the burden of morbidity, and reducing mortality.

TSS is a treatment of choice in CD with a promising remission rate (70–90%); however, long-term recurrence rates reach up to 35% [10,15]. Pharmacotherapy has had a secondary role in managing patients with CD, but thanks to the development of several novel drugs, it has become more relevant. The spectrum of available medications in CD includes adrenal steroidogenesis inhibitors, glucocorticoid receptor antagonists, and pituitary-directed drugs; however, they exhibit specific limitations [10,12–14]. In light of the unmet medication need for the optimal medical treatment of patients with CD, osilodrostat (a potent inhibitor of 11-β-hydroxylase synthase enzyme) has emerged. In clinical trials, osilodrostat provided rapid onset and long-term control of cortisol production, sustained control of biochemical parameters, and improved clinical signs and physical manifestations of hypercortisolemia and patient-reported outcomes.

Smaller studies depicting the cases of patients in real-life clinical settings can be valuable supplements to large clinical trials. This report documents the course of osilodrostat therapy in a group of six Polish patients previously taking part in the LINC4 study and indicates its effectiveness as a long-term treatment option for patients with CD. The results of our observational study are consistent with those obtained during the clinical trials. Osilodrostat allowed for achieving biochemical control, resolution of clinical symptoms of hypercortisolemia, and improvement in the quality of life of all patients in the study. By week 36, mUFC < ULN was achieved in all patients at a median osilodrostat dose of 4 mg BID. At the end of the observation, mUFC normalization was sustained in all patients at a median osilodrostat dose of 3 mg/day. At week 96 (LOV for mLNSC), 4/6 patients had mLNSC < ULN. In all patients, the highest mUFC and mLNSC level reduction was observed in the first 36 weeks of the treatment ($p = 0.031$). Since mUFC and mLNSC seem to be equal in assessing the efficacy of pharmacological treatment of CD and the best prognosis is associated with normalization of both parameters [20], complete biochemical control (defined as both parameters < ULN) at week 96 was achieved in 4/6 patients. However, all patients presented with normalization of mUFC and mLNSC at least temporarily, and after week 96, assessing mLNSC was no longer possible. There was no apparent relationship between baseline mUFC or mLNSC and the osilodrostat dose required for mUFC or mLNSC normalization, and the dose range to maintain disease control was 1 mg every three days to 30 mg BID.

All patients demonstrated significant improvement from baseline in most metabolic parameters, including weight, BMI, waist circumference, TC, TG, FPG and HbA1c, and this was most evident at week 36 and then sustained throughout the study period. The osilodrostat allowed for discontinuation of antilipidemic drugs in one of the three and hypoglycemic treatment (metformin) in two of three (one diabetic and one with IGT) patients taking the drugs at baseline. Improvement in BP control was most evident early in osilodrostat treatment: the most significant decrease in mean SBP and mean DBP was achieved at weeks 72 and 36, respectively. However, from week 96, a slight increase in mean SBP and mean DBP was observed, and a maximum mean SBP and mean DBP during the study were observed at weeks 132 and 156, respectively. This change was probably because, in 4/5 patients under antihypertensive treatment at baseline, osilodrostat allowed for the dose or number of the drugs to be reduced. On the other hand, one hypertensive patient at baseline presented high BP between weeks 108 and 144 of the study due to the osilodrostat dose escalation and the DOC accumulation effect, requiring intensifying antihypertensive treatment (including implementation of mineralocorticosteroid blockage). However, mean SBP and BDP remained WRR during the whole study period. Of course, the analysis of BP, lipid parameters, FPG, and HbA1c in the presented patients has limited value, mainly since the patients were taking antihypertensive, antilipidemic, and/or hypoglycemic drugs before osilodrostat initiation. Clinically significant QTcF prolongation ($\geq$450 ms) did not occur in any of the patients.

The three cases presented in detail confirm high osilodrostat effectiveness in CD management and highlight the specific clinical situations that physicians may have to face during osilodrostat therapy. In the first case, osilodrostat was the "last chance" medical treatment, considering the necessity to discontinue the pasireotide and levoketoconazole because of their side effects and unsuccessful combination therapy with ketoconazole and cabergoline with further hypercortisolemia progression. The patient experienced one of the expected osilodrostat AE because, after its initiation and dose titration, testosterone levels increased significantly. However, clinically the patient did not present hirsutism or other hyperandrogenic features. Increased testosterone concentration in females during osilodrostat treatment have been reported in 11.7–24.7% during clinical trials [18,21]. It results from the shift of adrenal steroidogenesis towards androgens after the inhibition of cortisol production [22]. In the presented patient, testosterone level then returned to baseline with time on continued osilodrostat after longer follow-up (week 144). That observation is consistent with data from extension phases of LINC studies, where increased

testosterone levels in females resolved during long-term treatment [19,21,23]. Nevertheless, hirsutism in most CD females during osilodrostat treatment improves or remains stable from baseline [18,24].

The second of the presented patients illustrated a spectacular improvement in uncontrolled, refractory hypercortisolemia upon osilodrostat treatment. The osilodrostat allowed for a normalization of mUFC (24× ULN at basline) and mLNSC (8.35× ULN at baseline) after 20 and 26 weeks, respectively, which confirms its effectiveness, even in patients with a more severe course of the disease. As in the previously discussed case, this patient also experienced osilodrostat AE related with 11β-hydroxylase enzyme blockade—a significant adrenal hormone precursor increase (the concentration of DOC exceeded 31× ULN at one point) manifesting as hypertension and mild hypokalemia that occurred from week 108. The patient required further antihypertensive treatment intensification with implementation of spironolactone, which allowed for BP re-control at week 156, and oral potassium supplementation. Mineralocorticoid precursor increase-related AEs have been reported in patients during clinical trials, represented by hypertension (12.4–21.9%), hypokalemia (13.1%), and peripheral edema (15.3–16.4%) [17,18,21].

The third patient we presented, after an initial good response to osilodrostat treatment, developed a significant COP after 72 weeks, requiring a multimodal approach, including osilodrostat up-titration, surgery, and radiosurgery. Tumor size changes have been previously reported with osilodrostat. In the LINC-3 study, tumor volume decreased or increased significantly (by ≥20%) in 32.8% and 37.5% of CD osilodrostat-treated patients, respectively [17]. Fontaine-Sylvestre et al. described a specific LINC-3 trial case of CTP requiring surgical intervention after long-term treatment (over four years) with osilodrostat for persistent CD [25]. Antonini et al. presented a patient with significant CTP after six months of osilodrostat therapy that was eventually treated with radiosurgery [26]. CTP was also reported during treatment with ketoconazole [27,28] and mifepristone [29], which suggests that blocking cortisol production or action by medications may provoke the growth of the corticotroph adenoma. It is suggested that osilodrostat therapy should be stopped if CTP is observed [30]; however, no specific recommendations are available. In the described case, we decided to continue osilodrostat and increased the daily dose to stabilize the hypercortisolemia and the patient's clinical condition, which allowed for safe subsequent treatment procedures (TSS, pituitary radiosurgery) and resulted in CD re-control. Controversy exists about whether CTP during osilodrostat treatment is caused by loss of negative cortisol feedback (due to a decrease in cortisol concentration) or whether it is driven by genetic mechanisms implicated in corticotroph tumor development, implying that it is a part of the natural history of CD. In vitro studies did not show that osilodrostat had an impact on ACTH production or cell growth [31]. However, the case we presented and previously mentioned by Fontaine-Sylvestre et al. [25] and Antonini et al. [26] implies that regular biochemical and radiological monitoring is necessary for patients treated with osilodrostat, even when they are well controlled on a stable osilodrostat dose. In addition, an increase in ACTH concentration was observed in each of the patients participating in the study. Median ACTH concentration significantly increased during the whole study period, and at 156 weeks' follow-up (91.6 pmol/L, 8.25× ULN, range: 11.1–200 pmol/L), it was 9.49-fold higher ($p = 0.031$) compared to baseline (9.65 pmol/L, WRR, range: 2.9–28.60 pmol/L). Detailed analysis of tumor volume was not possible in the presented group; however, in 2/6 patients the tumor remained stable, in 2/6 patients there was a significant (>20%) increase in tumor volume, and in 2/6 patients there was a radiological disappearance of the initially visible tumor. There was no clear correlation between change in tumor volume and osilodrostat dose nor ACTH concentration. These data are consistent with those observed in clinical trials, indicating that the effect of osilodrostat on corticotropic tumor size is ambiguous and requires further study. However, data show that there is no correlation between change in tumor volume and change in ACTH concentration [19]. The evolution of pituitary tumor in every patient is summarized in Table 4.

Table 4. Evolution of pituitary tumor image on MRI during study period. The size of the tumor is presented in millimeters. In case of small pituitary tumors, only two or one (maximal) dimensions are given.

	Baseline	Week 26	Week 48	Week 72	Week 96	Week 144
Patient 1	4 × 3	No visible	No visible	No visible	4 × 3	5 × 3
Patient 2	10 × 13 × 10	10 × 13 × 10	10 × 13 × 10	10 × 13 × 10	14 × 16 × 14	14 × 16 × 14
Patient 3	1.5	3.5 × 5.5	7 × 5 × 8	12 × 8 × 14 *	14.5 × 8.5 × 15.5 **	11.5 × 7 × 13
Patient 4	2.5 × 4	3 × 4	2.5 × 4	2.5 × 4	no visible	no visible
Patient 5	4.5 × 4	4 × 3	3.5 × 2.5	3.5 × 2.5	3.5 × 2.5	3.5 × 2.5
Patient 6	3 × 2.5 × 2	2	2	2	2	no visible

* Performed at week 84. ** Performed at week 120.

The second most common AE reported in the 156 weeks of osilodrostat treatment was AI (5/6 patients). AI/hypocortisolism-related AEs have been reported in 14.6–54.0% of patients, mainly during osilodrostat titration [16–18,21,23]. However, the percentage of patients experiencing AI was increasing in longer follow-up and occurred even in patients on a stable dose of osilodrostat after prolonged treatment [23,32]. AI events in the analyzed group generally occurred during the titration phase and were not associated with a specific osilodrostat dose, which is consistent with previous observations [33]. In two patients, AI occurred after a longer time of observation (as presented earlier); however, in the third of the detailed cases, the late AI occurrence might not have been strictly related to osilodrostat but was the effect of concomitant neuro- and radiosurgery. None of the patients discontinued osilodrostat because of the hypocortisolism—dose adjustment and in some cases transient hydrocortisone implementation was sufficient. Ours and previously reported experience indicates that patients treated with osilodrostat should be thoroughly educated about its potential side effects (especially the risk of AI and related symptoms) and supplied with "in case" hydrocortisone tablets, as hypocortisolemia can occur at any time during osilodrostat treatment [30,34,35]. In the presented patients, it was sufficient to administer hydrocortisone for a few days at a typical replacement dose and reduce the osilodrostat dose. The osilodrostat dose was then readjusted to achieve eucortisolemia. However, given osilodrostat's high effectiveness in hypercortisolemia control and, therefore, the relatively high risk of AI, a "block and replace" approach should be considered in specific cases. However, AI is not specific to osilodrostat AE, and the possibility of its occurrence in patients treated with oral steroidogenesis inhibitors in general (5.3–18.5% with ketoconazole, 3.2–9.5% with levoketoconazole, 12% with metyrapone) should be expected [13,14]. The higher incidence of AI during osilodrostat treatment is probably due to its particular potency and 11-beta-hydroxylase selectivity compared to other steroidogenesis inhibitors. It is worth mentioning that escaping after the initial response may occur in up to 22.7% of patients treated with ketoconazole and 18.7% with metyrapone [13,14]. Furthermore, the safety profile of osilodrostat appears to be favorable. The main limitations of using ketoconazole and levoketoconazole are hepatotoxicity and elevations in liver enzymes, which are reported in 2.6–18.4% and 11.7–44.6% of patients, respectively [13,14]. In the analyzed group, only one patient had a mild, transient increase in liver enzyme activity >ULN during the study. Mean ALT and AST activity even decreased compared to baseline during the study period in the analyzed group. No liver-related AEs of osilodrostat were reported in previous studies. [16–18,21,23]. Adrenal androgens and mineralocorticoid precursor increase-related AEs are the main limitations of metyrapone use; however, they may occur in 42.3–58.4% of patients on osilodrostat, as previously mentioned [14,21]. Nevertheless, Bonnet-Serrano et al. showed a smaller increase in 11-deoxycortisol and androgen concentrations in patients with osilodrostat compared with metyrapone therapy [36]. Additionally, mean levels of adrenal hormone precursors and androgens decreased during long-term osilodrostat treatment [23]. Osilodrostat also has

a longer half-life compared with metyrapone and ketoconazole, which allows for BID administration and may increase patient compliance [12–14]. Moreover, ketoconazole and levoketoconazole are unavailable in Poland at the moment. In specific scenarios (especially of severe hypercortisolemia), osilodrostat in combination with other anticortisolic agents can be considered; however, data on such an approach are limited [37,38].

5. Conclusions

Despite progress in the treatment of CD, it remains a real challenge for endocrinologists and neurosurgeons, especially in the case of recurrent disease and when patients cannot feasibly undergo surgery. In light of the unmet need for the optimal treatment of patients with CD, osilodrostat emerged as a novel steroidogenesis inhibitor. The analyzed group of patients shows the long-term effectiveness and safety of the treatment with osilodrostat in real-life clinical practice, as treatment in all patients was reimbursed by the Health National Fund after completing the clinical trial. Our study reinforced previous reports demonstrating that osilodrostat is an effective and well-tolerated treatment option for patients with CD and provides sustained hypercortisolemia control. Treatment with osilodrostat should be individualized for each patient, and the clinical evidence gathered through this study might assist in optimizing treatment decisions by physicians.

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Abbreviations

ACTH—adrenocorticotropin; AI—adrenal insufficiency; ALT—alanine transaminase; AST—aspartate transaminaze; BID—twice a day; BMI—body mass index; CD—Cushing's disease; CS—Cushing's syndrome; CRH—corticotropin-releasing hormone; CTP—corticotroph tumor progression; DBP—diastolic blood pressure; DOC—11-deoxycorticosterone; ECG—electrocardiogram; FPG—fasting plasma glucose; HbA1c—glycated hemoglobin; IGT—impaired glucose tolerance; IFG—impaired fasting glucose; mLNSC—mean late-night salivary cortisol; mUFC—mean urinary free cortisol; MRI—magnetic resonance imaging; OGTT—oral glucose tolerance test; QTcF—corrected QT interval; SBP—systolic blood pressure; TC—total cholesterol; TG—triglycerides; TSC—total serum cortisol; ULN—upper limit of normal; WRR—within reference range.

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TEACHING CASE PRESENTATIONS

Cushing's syndrome: a combined treatment with etomidate and osilodrostat in severe life-threatening hypercortisolemia

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Abstract
Endogenous Cushing's syndrome (CS) is associated with increased morbidity and mortality. Early diagnosis and initiation of therapy are essential, but effective treatment remains a challenge. In a long-term follow-up, biochemical control of hypercortisolemia, especially when severe, is difficult to achieve. Life-threatening hypercortisolemia is difficult to control due to the limitations of pharmacotherapy, including its side effects, and may require etomidate infusion in the intensive care unit (ICU) to rapidly lower cortisol levels. The effectiveness of hypercortisolemia management can be increased by a dual blockade of cortisol production. We report the efficacy, safety, and tolerability of combined therapy with two steroidogenesis inhibitors, etomidate, and osilodrostat, in a 32-year-old woman diagnosed with severe ACTH-dependent hypercortisolemia, subsequently maintaining a stable level of cortisol with osilodrostat monotherapy. This approach enabled achievement of relatively rapid control of the hypercortisolemia while using an etomidate infusion and concomitant increasing doses of oral osilodrostat applying a "titrations strategy." Our experience shows that it is worth taking advantage of the synergistic anticortisolic action of etomidate with osilodrostat.

Keywords Cortisol · Cushing's syndrome · Etomidate · Osilodrostat · Severe hypercortisolemia

Introduction

Endogenous Cushing's syndrome (CS), which results from excess cortisol production, has an annual incidence of 0.2 to 5 cases per million population [1, 2]. Approximately 80% of all endogenous CS cases are caused by corticotrophin (ACTH) hypersecretion (ACTH-dependent CS), of which 90% are represented by corticotroph pituitary adenomas (Cushing's disease, CD), while ectopic ACTH syndrome (EAS) occurs in about 10% of cases [1, 2]. CS is associated with increased morbidity and mortality; thus, early diagnosis and implementation of therapy are necessary to prevent numerous complications, especially in the case of severe hypercortisolemia (SH) [3–5]. SH is defined as a significantly elevated random serum cortisol level (> 36–41 μg/dL), a 24-h urinary free cortisol (UFC) level greater than four-fold the upper limit, and/or profound hypokalemia (< 3.0 mmol/L) [6, 7].

The treatment of choice for CS, which gives the possibility of complete recovery, is surgical resection of the primary lesion which caused excess cortisol production [2, 8]. Pharmacological therapy is essential, especially in patients with contraindications to surgical procedure, as adjuvant treatment when the surgery was not radical, and in recurrent cases of CS [9]. Prompt pharmacological intervention leading to normalization of cortisol production is crucial in the case of life-threatening SH and while awaiting surgery (bridging therapy) since there might be a significant delay before an unequivocal diagnosis is established [6, 9]. Medical treatment options include steroidogenesis inhibitors, pituitary-targeting agents, and glucocorticoid receptor antagonists [8, 10]. These drugs can be used synergistically, increasing the potency of anticortisolic action and reducing the risk of possible side effects by lowering the dose of the individual agent [2]. The choice

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of a particular medication and therapeutic protocol is highly individualized and depends on the center's experience; however, etomidate — a short-acting intravenous anesthetic agent — is considered the most effective for the rapid inhibition of cortisol overproduction [2, 10–12]. It acts by reversible blockage of the 11-β-hydroxylase enzyme (the final step of cortisol biosynthesis) and, additionally, 17α-hydroxylase/17,20-lyase and cholesterol side-chain cleavage enzyme [13–16]. Alternatively, rapid-acting oral steroidogenesis inhibitors, such as ketoconazole, metyrapone, or osilodrostat, might be considered in SH management. Osilodrostat is a novel adrenostatic agent that inhibits the activity of 11-β-hydroxylase as well as 18-hydroxylase enzyme (suppressing cortisol and also aldosterone synthesis) [17–21]. Recent reports show that osilodrostat can control SH relatively quickly [22–24].

A potential therapeutic option for life-threatening hypercortisolism is the use of combined treatment with etomidate and osilodrostat; however, no such procedure has to date been documented. Herein, we present a patient with ACTH-dependent SH brought under control with the combinative therapy of two steroidogenesis inhibitors, etomidate and osilodrostat.

Case presentation

A 32-year-old female, diagnosed with multiple sclerosis (SM) years ago and treated with dimethyl fumarate for 2.5 years, was admitted to the Department of Internal Medicine, due to deterioration of her general condition, polydipsia, polyuria, qualitative disturbance of consciousness, and profound hypokalemia (1.9 mmol/L) found during SM therapy routine assessment. For about 2 months before the hospital admission, facial hair growth, acne lesions, rounded facial features without accompanying weight gain, and a tendency to bruise had been observed. In addition, at the same time, secondary amenorrhea was noted: the patient had been taking contraceptive drugs for 2 years and had discontinued them a few days after the onset of symptoms.

Physical examination revealed elevated blood pressure, moon face with visible acne lesions, and muscular atrophy of the limbs. BMI was 22.4 kg/m^2. The laboratory tests showed severe hypokalemia (2.2 mmol/L), hyperglycemia meeting the criteria for diabetes mellitus with an HbA1c value of 5.9%, and preserved C-peptide secretion (3.5 ng/mL, *N*: 0.78–5.19). During the hospital stay, oral hypoglycemic drugs (linagliptin and empagliflozin) were administered. Despite compensation of disturbances in the water–mineral balance, it was not possible to stabilize the kalemia.

Due to the clinical features of hypercortisolemia, the hormonal diagnostics was extended: the abnormal circadian rhythm of cortisol secretion was confirmed and impaired glucocorticoid feedback was demonstrated with an overnight 1 mg dexamethasone suppression test. A significant degree of ACTH-dependent hypercortisolemia was diagnosed [UFC: 7155 µg/24 h (*N*: 4.3–176) midnight serum cortisol: 69.64 µg/dL (*N*: < 5.4), ACTH: 167 pg/mL (*N*: 6–48)].

During hospitalization in the Department of Internal Diseases, the psychotic symptoms worsened: the patient was consulted psychiatrically and treated with quetiapine, hydroxyzine, and lorazepam. Due to the exhaustion of diagnostic and therapeutic possibilities in the abovementioned hospital, the patient was referred to our Clinic — the Department of Internal Medicine, Endocrinology and Diabetes, Medical University of Warsaw, Warsaw, Poland — for treatment continuation.

Laboratory tests on admission to the Department of Endocrinology revealed profound hypokalemia (2.1 mmol/L) and elevated levels of serum cortisol (106 µg/dL), ACTH (154 pg/mL) and androgens [DHEA-S 1200 µg/dL (*N*: 95.8–511.7), and total testosterone 4.29 ng/dL (*N*: 0.38–1.97)]. The CRH stimulation test showed a significant (over fivefold) increase in concentration of ACTH and cortisol (by 33%). Treatment with an oral steroidogenesis inhibitor, osilodrostat, was started at increasing doses, which improved the patient's general condition in the first days of therapy. Osilodrostat dose titration is presented in Fig. 1. During treatment, transient increase in alanine aminotransferase activity (122 U/L, *N*: 0–55) and persistent hypokalemia were observed despite intravenous and oral potassium supplementation and high doses of spironolactone.

Due to the ineffectiveness of the above treatment in lowering the serum cortisol, persistent hypokalemia (Fig. 2), increasing severe edema of the lower limbs found in the physical examination (weight gain by 3.1 kg within 7 days), and the patient's reported significant deterioration in well-being, on the 11th day of treatment with osilodrostat, after obtaining the patient's consent, it was decided to begin therapy with etomidate combined with the current cure with osilodrostat at a gradually increasing dose (Fig. 1). Etomidate therapy was conducted in the conditions of an intensive internist supervision room (non-ICU) at the initial dose 0.015 mg/kg/h and then modified according to the value of cortisolemia, kalemia, and glycemia and blood pressure control. During the treatment with etomidate, the monitoring of potassium and cortisol values was performed several times a day, including every 3 h on the first days of treatment. The patient tolerated the combined therapy (etomidate and osilodrostat) well and during the following days, an improvement in her general condition was

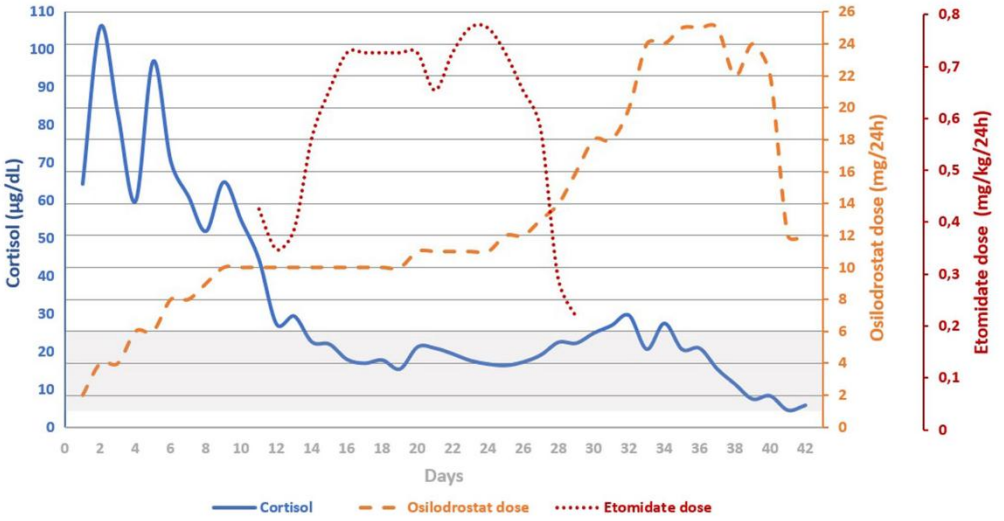

Fig. 1 Evolution of serum cortisol levels during treatment with the osilodrostat and etomidate dosing regimen. Cortisol values are the average of 3–8/day time measurements (depending on the day). The shaded area corresponds to the cortisol reference range

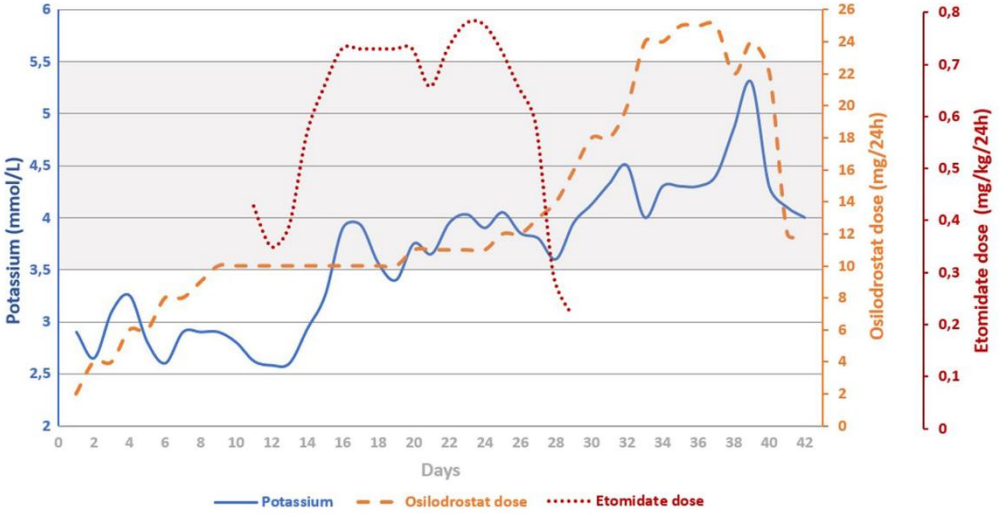

Fig. 2 Evolution of potassium levels during treatment with the osilodrostat and etomidate dosing regimen. Potassium values are the mean of 1–8/day time measurements (depending on the day). The shaded area corresponds to the potassium reference range

observed, including mood balancing and reduction of lower limb swelling. Blood pressure and blood glucose control were correct. Nausea and vomiting were not observed. The patient reported persistent dizziness, which she also experienced after completing the etomidate infusion. During treatment with etomidate, the patient obtained from + 1 to

0 points on the RASS scale. In the first 2 days of combined treatment, due to increased hypokalemia (Fig. 2), the patient required intravenous and oral potassium substitution, and then only oral substitution in combination with spironolactone, which was part of the antihypertensive treatment.

After stabilization of cortisol levels and kalemia, treatment with etomidate was discontinued on the 19th day of the combined therapy (on the 29th day of osilodrostat treatment), and treatment with an oral steroidogenesis inhibitor was continued at doses modified according to the performed hormonal assessments. On the following days, a decrease in the requirement for osilodrostat was observed. In the course of the treatment, the activity of ALT was also normalized, and the levels of testosterone (2.96 nmol/L) and DHEA-S (185 µg/dL) decreased pronouncedly.

Due to the significant drops in blood pressure, the antihypertensives were firstly reduced and then discontinued and the correct values were obtained in the control measurements. During hospitalization at the clinic, the patient was consulted once again psychiatrically: the quetiapine treatment was supplemented with pregabalin, the dose of which was reduced as recommended after the correction of cortisol level.

To further diagnose ACTH-dependent hypercortisolemia, an MRI of the pituitary gland was performed in which the inconclusive image as to the presence of microadenoma was visualized (Fig. 3). In the opinion of the experienced consultant neurosurgeon, an ambiguous change in the pituitary gland is not the source of the patient's autonomous production of ACTH. To search for the ectopic source of ACTH secretion, a chest-abdomen-pelvis CT with contrast was performed in which no abnormalities were visible, while positron emission tomography (PET) with ^{68}Ga-DOTA-conjugated peptides showed no areas of increased tracer accumulation.

The patient was discharged from the clinic in good general condition, with the final cortisol levels as shown in Fig. 1. Continuation of the treatment with osilodrostat at a dose of 6 mg twice a day, quetiapine, pregabalin, and prolonged-release metformin was recommended. A follow-up took place after 14 days. The patient was in good general condition and did not report any complaints. Morning serum cortisol (14.3 µg/dL), UFC (103 µg/24 h), DHEA-S (104.3 µg/dL), and potassium level (4.0 mmol/L) were within normal range. An increased level of testosterone was observed (6.06 nmol/L). The dose of osilodrostat was maintained. The patient is still currently followed up at our clinic.

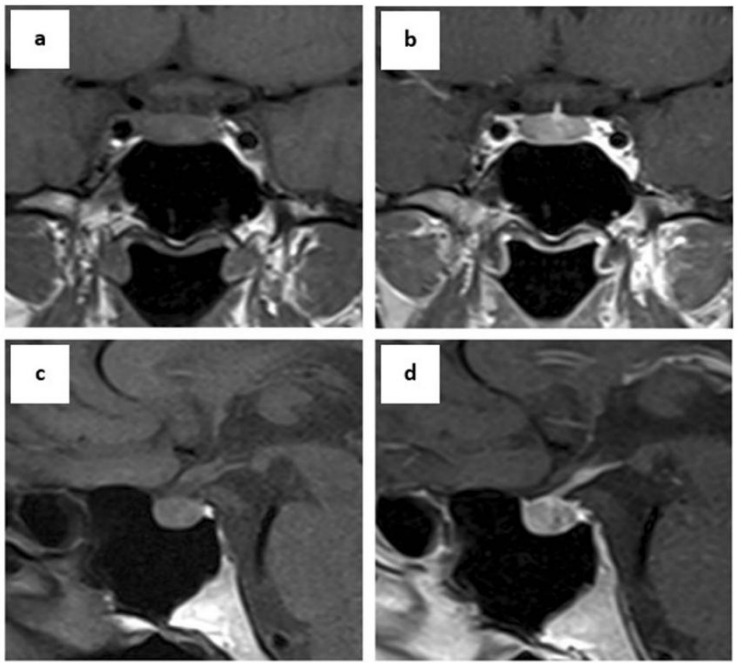

Fig. 3 Frontal and sagittal MRI demonstrating a normal pituitary without signs of microadenoma in the presented patient: **a** Frontal T1-weighted pre-contrast scan. **b** Frontal T1-weighted post-contrast scan. **c** Sagittal T1-weighted pre-contrast scan. **d** Sagittal T1-weighted post-contrast scan

Discussion

The treatment of CS is complex and challenging as no medication has complete and definitive efficacy in hypercortisolemia management. A large, multicenter study showed that biochemical control is not achieved in up to 30% of patients with CD in a long-term follow-up [25]. Conventional pharmacological therapy is often ineffective in controlling life-threatening SH. The use of the drugs individually is also limited by the frequent occurrence of their side effects. A possible therapeutic approach, which minimizes adverse events and increases treatment efficacy, is to use two or more drugs simultaneously with an additive synergistic or/and complementary mechanism of anticortisolic action. The most common is the combined use of high doses of metyrapone and ketoconazole [26–28]. There are also data presenting the option of a triple combination with the additional usage of mitotane [29]. Despite good effectiveness, the latter treatment protocols were, however, associated with numerous serious side effects (mainly liver damage) [27, 29, 30]. In SH, the use of mitotane is limited due to its relatively slow onset of action [29]. Steroidogenesis inhibitors have also been studied in combination with pituitary-directed agents (pasireotide and cabergoline); however, such therapy is used in patients with persistent or recurrent CD rather than for the purpose of controlling SH [31–34]. Lawrence et al. reported a patient with severe EAS, due to a thymic neuroendocrine tumor, who was successfully controlled with a combination regimen of ketoconazole and mifepristone [35]. However, it is difficult to monitor the efficacy and safety of such treatment because measuring serum cortisol and/or UFC is not objective in that case [36].

Osilodrostat is a particularly potent oral and selective inhibitor of 11-beta-hydroxylase compared with other steroidogenesis inhibitors [19]. It also has a prolonged half-life compared with metyrapone, enabling less frequent medication intake, which may improve patient compliance [17, 19]. Typically, in CD, it is initiated at 2 mg orally twice daily and titrated by 1–2 mg every 2 weeks based on cortisol level [8]. In a phase III study (LINC 4) in patients with CD, osilodrostat normalized UFC excretion in 77% of patients after 12 weeks' treatment [20]. Recently, osilodrostat has also been shown to have the potential of controlling SH relatively quickly; however, limited relevant data are available [22, 23]. Haissaguerre et al. reported three patients with SH treated successfully with osilodrostat monotherapy [22]. Starting doses (2–7 mg/day) were titrated every 2–5 days (reaching maximal doses of 7–44 mg/day) and normal plasma cortisol concentration was achieved within 2 weeks [22]. Subsequently, Bessiène et al. reported a case of severe EAS and presented a regimen with an even higher starting dose of osilodrostat (20 mg/day) applying the "block and replace" strategy [23]. This approach allowed for the normalization of cortisol levels in only 6 days [23]. Recently, Amodru et al. also reported successful hypercortisolism control with ketoconazole-osilodrostat combination therapy [24].

In the presented patient, osilodrostat was introduced at 2 mg BID and the dose was gradually increased on subsequent days using a dose-titration strategy. The serum cortisol level was more than halved after 6 days of treatment. On the 10th day, the patient reported worsening well-being, and an increase in peripheral edema was observed. Morning cortisol at that time was 62.9 µg/dL. Due to the deterioration of the patient's condition, insufficient response to current treatment, and no clear protocol for the osilodrostat monotherapy in SH, the patient was started on a continuous etomidate infusion. We decided to continue osilodrostat simultaneously and, therefore, the patient did not receive the initial bolus of etomidate, while the starting dose of medication (0.015 mg/kg/h) was lower than that assumed in most treatment protocols [2, 11, 37, 38]. The premise of that approach was to gradually reduce cortisolemia through combination therapy, with cross-titration of osilodrostat and etomidate so that the etomidate infusion could be stopped with the serum cortisol in the desired range and maintained through osilodrostat monotherapy.

The tolerance of combined osilodrostat and etomidate therapy was surprisingly good: apart from persistent dizziness, the patient did not report any additional side effects. Mild ALT elevation was noted after starting osilodrostat, but it normalized spontaneously within further hospitalization. During etomidate infusion, the patient was assessed with the RASS scale, obtaining + 1 point on the starting day of the combinative treatment and 0 points on each subsequent day until the end of the infusion. However, the patient's condition during the first day of etomidate therapy reflected the effect of hypercortisolemia rather than the side effect of etomidate initiation. This is also evidenced by the fact that despite increasing the dose of etomidate, the patient's assessment on the RASS scale did not change. Moreover, studies suggest that sedative symptoms of etomidate are not experienced at doses smaller than 0.1–0.3 mg/kg/h [39].

The combined therapy lasted 19 days and etomidate infusion was discontinued at the 18 mg daily osilodrostat dose. At that time, serum cortisol and UFC were 17.7 µg/dL and 243 µg/24 h, respectively. Unfortunately, UFC rebounded in 48 h to 3493 µg/24 h and, therefore, the osilodrostat dose was increased to 25 mg/day over the next few days. Unexpectedly, over the following days, a marked decline in cortisol serum level (4.4 µg/dL) and UFC (12 µg/24 h) was noted, and the osilodrostat dose was reduced by half. The patient was discharged home in good general condition on

a stable dose of osilodrostat (12 mg/day). After 14 days, at the follow-up, morning serum cortisol (14.3 µg/dL), UFC (103 µg/24 h) and potassium level (4.0 mmol/L) were correct and osilodrostat dose remained unchanged.

There was also a notable decrease in testosterone and DHEA-S levels during the hospitalization. An increase in testosterone concentration may be expected while using osilodrostat because of compensatory ACTH stimulation and shift from corticosteroid to androgen synthesis [19, 40]. Probably, this concerned the etomidate effect on the activity of other adrenal steroidogenesis enzymes [15, 16]. Some data suggest that higher doses of osilodrostat may affect the 17α-hydroxylase/17,20-lyase activity leading to decreased adrenal androgens synthesis [19, 40]. However, at the follow-up, testosterone level notably increased (6.06 nmol/L), most likely as an osilodrostat side effect in the mechanism described above.

Possibly, the starting dose of osilodrostat in the presented patient could have been higher, with more rapid dose titration: that is, either we should have introduced etomidate earlier or increased its flow more quickly. However, that would have required the "block and replace" strategy, which should be reserved for the most severe and life-threatening cases of hypercortisolemia as in the previously mentioned case reported by Bessiène et al. [2, 23]. In addition, there are no supporting data on the superiority of such a regimen over the "titration strategy" in less severe cases. Furthermore, in the days following the combined treatment, we observed an improvement in the general condition of the patient, which reflected a gradual improvement in hypercortisolemia. Despite the longer time of hypercortisolemia normalization through combination therapy, we were able to balance the level of cortisol with the minimum risk of adrenal insufficiency in non-ICU conditions. Slower hypercortisolemia control also allows the patient to adjust to lower levels of cortisol and to let the receptors regain normal sensitivity [7].

Conclusions

In conclusion, combined therapy with osilodrostat and etomidate was well tolerated and highly effective in controlling ACTH-dependent SH and provides an alternative to the current therapeutic regimens. This strategy enabled us to reduce the risk of medication side effects and control the level of cortisol with minimized risk of adrenal insufficiency in non-ICU conditions, despite the longer time of hypercortisolemia normalization. Complementary observations are needed to confirm the efficacy and safety of the above therapeutic approach in SH management and to establish optimal starting doses and cross-titration strategy of osilodrostat and etomidate.

Author contribution LD: collection analysis and interpretation of data, drafting the article, and final approval of the version to be published.
JS: collection analysis and interpretation of data, drafting the article, and final approval of the version to be published.
WR: drafting the article and revising it critically for important intellectual content, and final approval of the version to be published.
AWL: drafting the article and revising it critically for important intellectual content, and final approval of the version to be published.
PW: drafting the article and revising it critically for important intellectual content, and final approval of the version to be published.
All authors read and approved the final manuscript.

Declarations

Consent to participate Written informed consent for the publication was obtained from the patient.

Conflict of interest The authors declare no competing interests.

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ORIGINAL ARTICLE

Is there still a place for etomidate in the management of Cushing's syndrome? The experience of a single center of low-dose etomidate and combined etomidate-osilodrostat treatment in severe hypercortisolemia

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Abstract

Purpose Severe Cushing's syndrome (SCS) is a life-threatening endocrine condition that requires prompt medical intervention. Intravenous etomidate infusion is considered to be the most effective in rapid cortisol overproduction inhibition. This single-center retrospective study aimed to present the safety and effectiveness of intravenous, low-dose, lipid-formulated etomidate infusion in patients with SCS.

Methods Seven patients with complicated SCS related to ectopic ACTH syndrome (n = 6) or Cushing's disease (n = 1) who received low-dose etomidate infusion as a part of their cortisol-lowering treatment between April 2019 and April 2024 in the Department of Internal Medicine, Endocrinology and Diabetes of Medical University of Warsaw were included in the study. A continuous etomidate infusion was initiated at 0.01–0.02 mg/kg/h.

Results In all patients, rapid control of hypercortisolemia was achieved with a median time of 30 h (range: 12–48 h). Median serum cortisol concentration reduced from 101.9 µg/dL (range: 78.2–119.6 µg/dL) before etomidate to 19.5 µg/dL (range: 18.3–22.5) after 72 h of etomidate treatment. Etomidate infusion was followed by etomidate and osilodrostat combined treatment and then osilodrostat monotherapy in four patients; one patient underwent adrenalectomy, and two patients died during etomidate infusion due to complications of advanced malignancy.

Conclusions This study shows that low-dose and short-term lipid formulation etomidate therapy is highly effective in severe hypercortisolemia management. Combined therapy with etomidate and osilodrostat is well tolerated and could serve as a bridge in long-term SCS treatment.

Keywords Cushing's syndrome · Ectopic ACTH syndrome · Etomidate · Osilodrostat · Severe hypercortisolaemia

Introduction

Endogenous Cushing's syndrome (CS) is an endocrine condition caused by cortisol overproduction, with an incidence of 2–8 cases per million people per year [1]. Most cases (approximately 80%) are caused by adrenocorticotropin (ACTH) hypersecretion—either by pituitary (Cushing's disease [CD], 85–90%) or neuroendocrine non-pituitary tumors (ectopic ACTH syndrome [EAS], 10–15%) [2–4]. Severe CS (SCS) is a life-threatening endocrine emergency with numerous complications and high mortality, especially if it is not diagnosed promptly enough and appropriate treatment is not implemented [5]. Although SCS seems to constitute less than 5% of CS cases, it remains a great therapeutic challenge for endocrinologists and appears to be an important interdisciplinary clinical issue [6]. SCS is defined as dramatically elevated random serum cortisol concentration (>41 µg/dL; 1100 nmol/L), a 24-h urinary free cortisol greater than five-fold the upper limit of normal, and/or profound hypokalemia (<3.0 mmol/L) with the co-occurrence of at least one of the following hypercortisolemia complications: sepsis,

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Table 1 Summary of baseline patients characteristics

Patient	Sex and age	Diagnosis	Hypercortisolemia complications	Baseline serum cortisol, μg/dL	Baseline ACTH, pg/mL	Baseline potassium, mmol/L
1	F/31	EAS (thymic LCNEC)	DM, HK, HT, P, PM	78.2	936.7	2.2
2	F/34	CD	DM, HK, HT, P, PM	106.0	167.0	1.9
3	F/61	EAS (SCLC)	DM, HF, HK, HT, PM	101.9	603.9	1.9
4	M/74	EAS (pulmonary LCNEC)	HF, HK, HT, PM, S	115.3	1088.0	2.4
5	M/75	EAS (SCLC)	DM, HF, HK, HT, PM, S	83.2	932.1	2.1
6	M/84	EAS (urinary bladder SCNEC)	DM, HF, HK, HT, PM, S	119.6	149.7	2.2
7	F/74	EAS (SCLC)	DM, HK, HT, PM, S	93.0	284.5	2.0

ACTH adrenocorticotropin, *CD* Cushing's disease, *DM* diabetes mellitus, *F* female, *HF* heart failure, *HK* hypokalaemia, *HT* hypertension, *LCNEC* large-cell neuroendocrine carcinoma, *M* male, *P* psychosis, *PM* proximal myopathy, *S* sepsis, *SCLC* small cell lung cancer, *SCNEC* small cell neuroendocrine carcinoma

opportunistic infection, refractory hypokalemia, uncontrolled hypertension, heart failure, gastrointestinal hemorrhage, acute psychosis, progressive debilitating myopathy, thromboembolism or uncontrolled hyperglycemia and ketoacidosis [5].

SCS requires rapid medical intervention, including symptomatic treatment of cortisol-induced complications and hypercortisolemia control with adrenal steroidogenesis inhibitors and simultaneously complex diagnostic workup determining the primary source of the disease [5, 7]. Choosing a particular steroidogenesis inhibitor is highly individualized and depends on the center's experience, as there are no strict recommendations and therapeutic protocol for SCS.

The most effective in rapid cortisol overproduction inhibition is considered to be etomidate—a short-acting intravenous anesthetic agent [8, 9]. It reversibly inhibits 11-β-hydroxylase enzyme (CYP11B1)—the last step of cortisol biosynthesis, 17α-hydroxylase/17,20-lyase (CYP17A1) and cholesterol side-chain cleavage enzyme (CYP11A1) [9, 10]. Etomidate can be used to control hypercortisolemia quickly and as a bridging therapy to other medical or surgical interventions when the patient's condition improves. However, despite its high therapeutic potential in SCS, it is rarely utilized in endocrinological practice.

In this article, we present the effectiveness and safety of etomidate treatment in patients with SCS hospitalized in the Department of Internal Medicine, Endocrinology and Diabetes of the Medical University of Warsaw, a tertiary center in Poland, between April 2019 and April 2024.

Material and methods

This descriptive, retrospective study was conducted on seven patients with SCS hospitalized in the Department of Internal Medicine, Endocrinology, and Diabetes, Medical University of Warsaw, Poland between April 2019 and April 2024. The patients were included in the study if they met the criteria for SCS and received etomidate infusion as a part of their cortisol-lowering treatment.

Etomidate therapy was conducted in the conditions of an intensive internist supervision room (non-intensive care unit, ICU) with metabolic, hemodynamic, respiratory, and neurologic monitoring. Level of sedation was assessed by using the Richmond Agitation-Sedation Scale (RASS) score. The target RASS score was 0, which correlates with alert and calm patient. We used etomidate compounded in a lipid emulsion formulation (*Etomidate lipuro*) in a 2 mg/mL concentration. A continuous etomidate infusion was initiated at a rate of 0.01 to 0.02 mg/kg/h and administered intravenously through a drug pump. No initial intravenous bolus of etomidate was administered prior to infusion.

During the etomidate infusion serum cortisol concentration and potassium were assessed initially every 6 h and then every 12 h after hypercortisolemia stabilization. Blood samples were collected via an arterial cannulation. All measurements of cortisol were performed with the Abbott Alinity immunoassay (normal range: 3.7–19.7 μg/dL). Plasma ACTH was measured by using the LIAISON XL chemiluminescent immunoassay (normal range: 4,7–48,8 pg/mL).

Vital signs (heart rate, blood pressure, respiratory rate, blood oxygen saturation) assessment was conducted every 3 h. The etomidate infusion was titrated in increments of 0.005 to 0.01 mg/kg/h based of the absolute values and the rate of change in serum cortisol concentration. The infusion rate was not up titrated more frequently than every 6 h. The initial therapeutic serum cortisol concentration target was 15–25 μg/dL. This was higher than the average physiological cortisol level, but it was necessary to ensure appropriate cortisol concentration in patients with severe general condition. For patients with a milder general condition or for those whose initial severe condition improved, a

Table 2 Summary of etomidate treatment in presented patients

Patient	Starting etomidate dose, mg/kg/h	Max etomidate dose, mg/kg/h	Target cortisol, µg/dL	Time totarget cortisol, hours	Time to potassium normalization, hours	Duration of etomidate infusion, days	Reason to stop etomidate therapy
1	0.02	0.06	10–20	36	24	11	Adrenalectomy
2	0.015	0.03	10–20	48	72	19	Osilodrostat implementation
3	0.02	0.08	10–20	12	6	19	Osilodrostat implementation
4	0.01	0.015	15–25	30	12	5	Death
5	0.015	0.025	15–25	30	36	17	Osilodrostat implementation
6	0.015	0.06	15–25	18	12	11	Death
7	0.01	0.025	15–25	24	18	14	Osilodrostat implementation

therapeutic cortisol target of 10–20 µg/dL was considered appropriate. A change in the patient's general condition (deterioration or improvement) was followed by an adequate change in the target serum cortisol. Once the target cortisol concentration was achieved, the etomidate infusion was continued to maintain serum cortisol in the desired range until implementation of long-term oral medical or surgical treatment could be initiated. The study was approved by the Ethics Committee of Medical University of Warsaw (permission number: AKBE/170/2024).

Results

We identified 7 patients (four women) with median age 74 years (range: 31–84) treated with etomidate for SCS between April 2019 and April 2024. In six patients CS was secondary to EAS, and one patient presented with CD. Median baseline serum cortisol was 101.9 µg/dL (range: 78.2–119.6 µg/dL) and median ACTH was 603.9 pg/mL (range: 149.7–1088.0 pg/mL). Mean baseline serum potassium concentration was 2.10 ± 0.17 mmol/mL. Hypercortisolemia complications from the most common included: hypertension, hypokalemia, proximal myopathy (all patients), diabetes (six patients), sepsis (four patients), heart failure (three patients) and psychosis (two patients). All patients with EAS had distant metastases at the time of SCS diagnosis. Details of each patient are summarized in Table 1.

Dosing and effectiveness

A continuous etomidate infusion was initiated at rate of 0.01–0.02 mg/kg/h. In six patients etomidate was a first-line therapy, and in one patient (with CD) it was introduced as an additional form of treatment due to the ineffectiveness of oral steroidogenesis inhibitor. The initial goal serum cortisol was 10–20 µg/dL in four and 15–25 µg/dL in three patients. Target serum cortisol concentration was achieved in all patients with median time of 30 h (range: 12–48 h). Median serum cortisol concentration reduced from 101.9 µg/dL (range: 78.2–119.6 µg/dL) before etomidate to 27.2 µg/dL (range: 11.3–33.4), 21.3 µg/dL (range: 18.6–24.4), and 19.5 µg/dL (range: 18.3–22.5) after 24, 48, and 72 h of etomidate treatment, respectively. The median maximum achieved etomidate infusion rate to maintain cortisol in the targeted level was 0.03 mg/kg/h (range 0.02–0.08 mg/kg/h). The infusion was continued for a median duration of 14 days (range: 5–19 days). Normokalaemia was achieved with median time of 18 h (range: 6–72 h). Hypokalemia was corrected in all patients through combined intravenous and oral administration of potassium along with spironolactone 50–200 mg/day per os in five and potassium canrenoate 200-400 mg/day intravenously in two patients. Mean serum

potassium concentration rise from 2.10 ± 0.17 mmol/mL before etomidate to 3.40 ± 0.86 mmol/L, 4.10 ± 0.67 mmol/L, and 4.20 ± 0.48 mmol/L after 24, 48, and 72 h of etomidate treatment, respectively. Glucose control improved from the beginning and in three out of six patients with cortisol-induced diabetes it was possible to withdrawn insulin therapy during etomidate infusion. Similarly, improvement in hypertension control was observed in all patients, which allowed for reduction (in four patients) or discontinuation (in two patients) antihypertensive therapy during etomidate infusion. Data regarding the treatment with etomidate are summarized in Table 2 and Table 3.

In four patients, the etomidate infusion was continued until the oral steroidogenesis inhibitor (osilodrostat) was successfully implemented, and in one, until the adrenalectomy. Before switching to osilodrostat monotherapy, patients were receiving combination therapy (etomidate and osilodrostat). The median duration of combined etomidate and osilodrostat therapy was 7 days (range: 5–19 days). Two patients continued osilodrostat in „block and replace" approach and in two patients osilodrostat was titrated by gradual dose increase. Data regarding the treatment with osilodrostat are summarized in Table 4 and. Figure 1 presents evolution of serum cortisol concentration during combined treatment with etomidate and osilodrostat.

Safety

All patients tolerated their etomidate infusion well. At baseline, five of them had a RASS score of 0. Two patients initially presented with hypercortisolemia-induced psychosis, one with a RASS score of +1 and second with +2, that improved to 0 during etomidate treatment. One patient with an initial 0 RASS score experienced slight somnolence with a RASS score of -1. In the rest of the patients the initial RASS score remained unchanged throughout the etomidate infusion. Two patients died during the etomidate infusion: one due to antibiotic resistant *Acinetobacter baumannii* sepsis and the other from respiratory failure secondary to unresectable large cell neuroendocrine carcinoma of the lung. One patient experienced adrenal insufficiency episode with hypotension requiring transient hydrocortisone implementation and etomidate dose reduction. No substantial changes in renal function during the etomidate infusion were observed. Mild hyperkaliemia occurred in one patient, but reducing potassium supplementation was sufficient to correct it.

Discussion

In this study, we report the effectiveness and safety of continuous intravenous low-dose, lipid-formulated etomidate infusion treatment outside the ICU in seven patients

Table 3 Serum cortisol response to etomidate therapy during first 72 h of treatment

Time of etomidate treatment, hours	0	12	24	36	48	60	72
Serum cortisol, μg/dL	101.9 (78.2–119.6)	41.0 (20.4–55.8)	27.2 (11.3–33.4)	24.4 (16.7–36.5)	21.3 (18.6–24.4)	21.2 (12.4–24.5)	19.5 (18.3–22.5)
Etomidate dose, mg/kg/h	0.015 (0.01–0.02)	0.02 (0.01–0.02)	0.02 (0.01–0.03)	0.02 (0.01–0.03)	0.02 (0.02–0.03)	0.02 (0.02–0.04)	0.025 (0.02–0.04)

Values are shown as medians and ranges

Table 4 Summary of osilodrostat treatment in presented patients

Patient	Time of combined therapy, days	Osilodrostat treatment strategy	Max osilodrostat dose, mg/d	Maintenance osilodrostat dose, mg/d
2	19	Titration	25	12
3	8	Titration	40	32
5	4	Block and replace	50	50
7	7	Block and replace	60	50

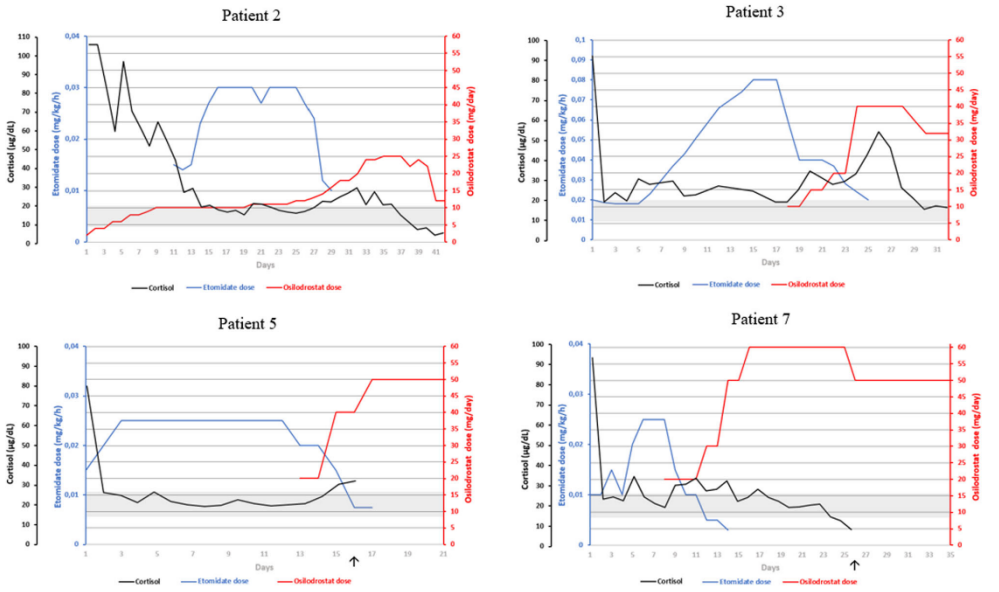

Fig. 1 The evolution of serum cortisol levels during treatment with etomidate and osilodrostat is depicted. Cortisol values represent the average of 2 to 4 measurements taken during the day. The shaded area indicates the target cortisol level. An arrow marks the beginning of hydrocortisone administration for patients who initiated the "block and replace" treatment regimen with osilodrostat

with SCS in our center's experience. All analyzed patients achieved a target cortisol level and normalized serum potassium concentration within a median of 30 and 18 h, respectively. The etomidate infusion served as bridging therapy for osilodrostat monotherapy in four patients and for adrenalectomy in one patient.

SCS is a challenging and life-threatening condition accompanied by acute cardiovascular, infectious and metabolic complications, leading to high mortality. Rapid control of cortisol levels is essential with simultaneous preventive and curative treatments of cortisol-induced comorbidities. In most cases, SCS is associated with EAS —neuroendocrine tumors found in different locations, with varying degrees of histological differentiation and aggressiveness, may secrete ACTH and lead to SCS [7, 11]. Nevertheless, SCS may also occur in patients with CD and ACTH-independent hypercortisolemia.

Etomidate is an imidazole derivative, intravenous anesthetic agent, and one of its side effects includes suppression of adrenocortical function [12, 13]. It reversibly inhibits CYP11B1, CYP17A1 and (at higher doses) CYP11A1, ultimately inhibiting cortisol biosynthesis [13]. Inhibition of adrenal steroid synthesis significantly limits the use of etomidate in anesthetic practice but gives the possibility of its off-label use in patients with SCS. Etomidate allows for highly effective and rapid control of hypercortisolemia, and normalization of cortisol concentration could be achieved within a dozen or so hours [8, 9]. In addition, it is the only steroidogenesis inhibitor which may be administered parenterally, therefore, it can also be used as a first-line treatment in severely ill patients or when oral cortisol-lowering agents cannot be used [5, 9, 10].

Since the first report of etomidate-induced steroidogenesis inhibition [13], several studies of its effectiveness in

hypercortisolemia control have been published, and various therapeutic protocols have been proposed [8, 14–17]. A standard etomidate infusion protocol requires patient hospitalization in the ICU. Initially, the patient receives a bolus etomidate dose of 2.5–5 mg over 2–3 min, followed by a continuous infusion (0.1–1.0 mg/kg/h), titrated according to the therapeutic response. However, such a procedure results in a complete blockade of adrenal steroid biosynthesis and necessitates implementing hydrocortisone substitution [8, 9, 14]. It also increases the risk of adrenal crisis and propylene glycol toxicity if etomidate in propylene glycol formulation is used. Therefore, the possibility of using low-dose etomidate treatment to control SCS was suggested, which does not require hospitalization of the patient in the ICU [16]. Constantinescu et al. studied the outcome of two series of SCS patients treated either with a standard etomidate dose in ICU or a low dose in non-ICU settings. The low-dose group achieved target cortisol levels slower, but without inducing adrenal insufficiency or other side effects, and without the need for intensive care resources [14]. In addition to this data, Carroll et al. proposed a standardized intravenous low-dose etomidate infusion protocol [15].

In our cohort of patients, we used an even lower starting dose of etomidate (0.01–0.02 mg/kg/h) and omitted its initial loading dose. In all patients, etomidate effectively reduced cortisol concentration to the target range in a median time of 30 h. That further confirms the use of a very low dose of etomidate in SCS management. Interestingly, the median time to reach the target cortisol concentration in our group was shorter, despite using lower doses of etomidate compared to the studies mentioned [14, 15]. This could be attributed to the higher target cortisol concentration in some of the septic patients we analyzed and the older age of the group we studied; elderly patients require decreased etomidate doses due to reduced protein binding and clearance [18]. Indeed, the longest time to achieve the target cortisol concentration was observed in the youngest patients in our group. Therefore, doses of etomidate need to be individualized in each clinical situation and rely on patient's clinical careful assessment. The standard treatment protocol should be rather considered only in the most severe, critical cases requiring hospitalization in the ICU. It is also important to note that the effect of etomidate on adrenal blockage may continue even after treatment discontinuation due to accumulation in the subcutaneous tissue [9].

How to qualify patients with SCS for treatment in or outside the ICU remains to be determined. It was previously recommended that etomidate treatment in patients with SCS only occur in the ICU setting [8]. However, this was mainly related to using a classic therapeutic protocol and high doses of etomidate. In previous years, collected data indicate that low-dose etomidate infusions can be administered outside of the ICU and do not necessarily have to be conducted under anesthesiologic control. In our opinion, the decision regarding the place of treatment should be made primarily based on the patient's clinical condition and the given center's experience in managing patients in severe state. In the analyzed group, endocrinologists carried out the treatment within the intensive internist supervision room, a coherent part of our department intended to treat patients in general severe condition. This room has a system of continuous patient monitoring, so its concept is similar to the ICU. Most internal medicine departments in Poland have at least one bed adapted for intensive supervision. In case of any doubts regarding etomidate pharmacotherapy, we could consult the ICU team. Similarly, in case of a sudden deterioration of the general condition, the patient could be qualified for further treatment in the ICU. However, we are aware that in different countries and healthcare systems, the organization of given units varies and the treatment conditions of specific groups of patients may differ significantly. Not all endocrinology centers have the expertize and appropriate facilities to allow treatment to be carried out in a general ward. On the other hand, intensive care specialists might not be familiar with the complexity of SCS and the specifics of therapy for such patients. In such cases, etomidate therapy should be conducted in close cooperation between the endocrinologist, the intensive care specialist, and the anesthesiologist. Some authors suggest that etomidate treatment could be initiated in the ICU and continued in the general ward after the patient has clinically stabilized [19]. However, given the rarity and potentially lethal complications of SCS, we strongly recommend that these patients be managed in tertiary centers with experience in fully managing this condition.

It is considered that formulations of etomidate in a lipid emulsion should be preferred due to possible propylene glycol toxicity [9, 15], which may result in plasma hyperosmolarity, lactic acidosis, thrombosis, and acute kidney injury [10, 15, 20]. However, published data on its use in patients with SCS are lacking, as in the most reports, etomidate in propyl glycol formulation was used [14, 15, 17]. To our knowledge, this report summarizes the largest cohort of patients treated with lipid formulation of etomidate, confirming its equal effectiveness to the propylene glycol formulation. Considering the known and potential complications of propylene glycol toxicity, the lipid formulation of etomidate should be regarded as superior in the case of etomidate use consideration in SCS.

Regardless of the formulation, etomidate treatment appears to have a high safety profile as an cortisol-lowering agent, and its use in SCS has been reported in adolescents [21, 22], children [23], and even infants [24]. Sedation is typically observed at higher doses than those that suppress cortisol production [9, 10]. However, the level of sedation should be assessed through the etomidate treatment, for example, using

the RASS score [15]. In our cohort, only one patient experienced slight somnolence with a RASS score of −1 during etomidate infusion. The same patient presented with a brief episode of adrenal insufficiency, requiring temporary hydrocortisone implementation and etomidate dose reduction. However, it occurred during the infusion of a relatively low dose of etomidate (0.015 mg/kg/h) during the second day of the treatment. This patient had significantly increased liver enzyme activity, most likely secondary to numerous liver metastases and cortisol-induced hepatotoxicity. Because hepatic enzymes metabolize etomidate, liver damage presumably led to increased etomidate half-life. Very rarely does etomidate cause significant hepatotoxicity, which, nevertheless, must be considered [18]. However, the increased activity of liver enzymes in our patient was not likely the result of etomidate therapy itself, as it was already observed at baseline before the introduction of etomidate. Although the activity of liver enzymes initially increased during treatment, it significantly improved during subsequent days of therapy. Two of the presented patients died during the etomidate infusion; however, their death was a result of their end-stage malignancy disease and initial hypercortisolemia complications, and was not etomidate-related.

We have previously published our initial experience with etomidate and osilodrostat combination therapy in a 32-year-old female with SCS due to CD [25]. At that time, evidence for the osilodrostat monotherapy in SCS and dose titration strategy was limited. We initiated the patient's treatment with osilodrostat at a gradually increased dose. After one week, due to an insufficient response, we decided to start treatment with etomidate. However, we continued osilodrostat simultaneously. This approach aimed to control hypercortisolemia quickly and then cross-titrate the doses of osilodrostat and etomidate to eventually discontinue the etomidate infusion and maintain hypercortisolemia control with osilodrostat monotherapy. This patient is also included in the current study. Since then, real-world evidence of osilodrostat use in SCS and EAS has emerged [26, 27], and an algorithm for the practical use of osilodrostat in SCS has been proposed [27]. That raises the question of whether there is still a place for etomidate in managing SCS in the era of new oral steroidogenesis inhibitors.

Despite increasing evidence of the effectiveness of osilodrostat as a first-line therapy in SCS, its global availability, especially considering the treatment price, is limited. For example, in Poland, innovative medications are financed through a specific emergency access procedure. The process of obtaining osilodrostat for a patient takes at least several days. It may not significantly affect the prognosis in cases of milder forms of CS, but in patients with SCS, even a delay of several days in the hypercortisolemia treatment may have disastrous consequences. On the other hand, another oral steroidogenesis inhibitor, ketoconazole, is not registered for the treatment of CS in Poland and currently is unavailable in our country. Moreover, metyrapone is not reimbursed in Poland, and the hospital must cover the eventual treatment fee. Mitotane is an additional therapeutic option, but it is mainly intended for patients with adrenocortical cancer and its use in SCS is limited due to the relatively slow onset of action. Taking this into account, etomidate therapy remains the only salvation for patients with SCS, serving as bridging therapy until the possibility of treatment with osilodrostat is available. Ultimately, the etomidate infusion was followed by combined etomidate and osilodrostat treatment and, eventually, osilodrostat monotherapy in four of the presented patients. Continuous etomidate infusion was maintained while initiating osilodrostat treatment to prevent rebound hypercortisolemia. The combination treatment aimed to provide stable control of hypercortisolemia while increasing the osilodrostat dose and reducing the etomidate dose until its discontinuation. In two patients, the osilodrostat dose was gradually increased, while in the other two patients, osilodrostat was implemented at a high dose with rapid escalation and continued in the „block and replace" regimen. However, no specific protocol was followed, and therapeutic decisions were made based on the patient's clinical condition and laboratory tests results. This significantly limits the possibility of proposing a specific scheme for transitioning from etomidate to osilodrostat. However, on Fig. 1 we present graphs showing the evolution of the mean serum cortisol concentration to illustrate the combined treatment process with etomidate and osilodrostat.

Our study has several limitations. The most important one is relatively small number of participants; however, it is still significant when taking into account how extremely rare SCS is and how infrequently etomidate is utilized in this indication. Our study also lacks patients with ACTH-independent CS. The study has a retrospective nature, therefore presents the results of real clinical practice, as no strict treatment protocol was followed.

Conclusions

Low-dose and short-term etomidate therapy is effective in SCS control and safe to conduct in non-ICU settings. Our experience also suggests that initiating treatment with an etomidate bolus may not always be necessary, but this requires further investigation. Lipid formulation of etomidate appears to have similar effectiveness to propylene glycol-formulated one; however, given the potential propylene glycol-induced toxicity, etomidate in lipid formulation should be preferred in SCS management. In cases where quick access to a potent oral steroidogenesis inhibitor is not available, etomidate may be the only viable treatment

option for SCS patients. Furthermore, combined therapy with etomidate and osilodrostat was well tolerated and could serve as a bridge in long-term SCS treatment. However, this requires further reports on the use of other oral steroidogenesis inhibitors in combination with etomidate.

Data availability

No datasets were generated or analysed during the current study.

Author contributions L.D.: conceptualization, investigation, data acquisition, draft writing and editing; J.S.: investigation, data acquisition, draft writing and editing; W.R.: investigation, data acquisition, draft editing, supervision; A.W.-L.:, draft editing and supervision; P.K.: draft editing and supervision; P.W.: conceptualization, draft editing and supervision. All authors have read and agreed to the published version of the manuscript.

Compliance with ethical standards

Conflict of interest Authors L.D. and P.W. reports receiving speaker fees and consulting fees from Recordati Rare Diseases. Author J.S., W.R., A.W-L., and P.K. declare no conflict of interest.

Ethical approval The study was approved by the Ethics Committee of Medical University of Warsaw (permission number: AKBE/170/2024) and was performed in accordance with the Declaration of Helsinki.

Consent to participate As this was a retrospective study on medical files and all the procedures being performed were part of the routine care, patient's informed consent in the opinion of the local bioethics committee was not required. However, before etomidate infusion and after obtaining comprehensive information (including off-label use of etomidate), each patient signed informed consent for etomidate treatment and for the use of data obtained during treatment for scientific purposes, which is included in the patient's medical history.

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Real-World Experience with Pasireotide-LAR in Cushing's Disease: Single-Center 12-Month Observational Study

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Abstract: Background/Objectives: Pasireotide-LAR represents a novel therapeutic option for patients with Cushing's disease (CD). Its efficacy and safety were assessed in clinical trials; however, the real-world evidence is still scarce. **Methods**: The study aimed to evaluate the impact of 12-month pasireotide-LAR therapy on disease control, glucose metabolism, lipid profiles, and adverse effects in a real-life setting. We retrospectively studied prospectively collected data of patients with persistent or recurrent CD administered with pasireotide-LAR in a single pituitary center. **Results:** Mean urinary free cortisol (mUFC) showed a sustained decrease from baseline, with the most pronounced decrease in the first 3 months of therapy ($p = 0.007$). The analysis of mean late-night salivary cortisol showed fluctuations over time, with the largest mean reduction in mLNSC at 3 months. During the therapy, an improvement in blood pressure control was observed, with a significant decrease in systolic blood pressure during the first 6 months of treatment ($p = 0.005$). Hyperglycemia was the most common adverse effect. Fasting plasma glucose and glycated hemoglobin (HbA1c) showed a gradual increase during pasireotide-LAR treatment, with the HbA1c significantly increasing at the last follow-up ($p = 0.04$). **Conclusions**: Pasireotide-LAR is an effective alternative treatment in selected patients with CD. Pasireotide-LAR is overall safe and well tolerated, with hyperglycemia being the most common but manageable adverse event.

Keywords: cortisol; Cushing's disease; hyperglycemia; pasireotide; pituitary tumor

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1. Introduction

Adrenocorticotrophin (ACTH)-secreting pituitary tumors are the leading cause of endogenous Cushing's syndrome (CS) and traditionally are defined as Cushing's disease (CD) [1,2]. Both in the active phase of the disease and after achieving remission, CD is associated with the presence of various comorbidities and a significantly reduced quality of life [3,4]. Optimization of the long-term outcomes in CD requires an early accurate diagnosis, careful selection of treatment, and management of the disease and its comorbidities by experienced clinicians [1,4].

Transsphenoidal selective surgery (TSS) is considered a first-line treatment, with a remission rate of approximately 80% in patients with micro- and 60% with macroadenomas, if the procedure is performed by an experienced neurosurgeon [1]. For patients with non-radical surgery or recurrent disease and when surgery is contraindicated, not feasible, or not accepted, in recent years, the possibility of pharmacotherapy has emerged as a second-line treatment due to the availability of new drugs. The medical agents utilized in

CD treatment target adrenal steroidogenesis, somatostatin and dopamine receptors in the pituitary gland, and glucocorticoid receptors [5,6].

Pasireotide is a second-generation somatostatin receptor ligand (SRL) with the highest affinity for somatostatin receptor subtype 5 (SSTR5), the most abundantly expressed SSTR in corticotropinomas [7–9]. Pasireotide long-acting release (LAR) is a modified, long-acting version of pasireotide which is administered intramuscularly once monthly, with a similar efficacy and safety profile as the short-acting form [5,8]. In a phase 3 clinical trial (NCT01374906), at month seven, mean urinary free cortisol (mUFC) normalization was achieved in 41% of CD patients [8].

The data from clinical practice on patients with CD treated with pasireotide are limited, and most of them concern the subcutaneous formulation of pasireotide [10–13], with isolated data on pasireotide LAR [14]. Hence, in this study, we aim to present the impact of 12 months of pasireotide LAR treatment on the disease control, cardiovascular parameters, and glucose and lipid profiles in patients with persistent or recurrent CD at a single center in Poland in a real-world setting.

2. Materials and Methods

2.1. Study Population

We identified 8 patients with active CD treated with pasireotide LAR under the National Health Fund drug program in the Department of Internal Medicine, Endocrinology, and Diabetes of the Medical University of Warsaw. The patients were evaluated between January 2022 and June 2024 during routine outpatient visits by the drug program schedule. Six patients received pasireotide LAR for at least 12 months and were considered suitable for the analysis. The patients' detailed characteristics before and during the pasireotide LAR treatment are summarized in Table 1.

Table 1. Patient characteristics.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Sex	F	F	F	M	F	F
Diagnosis	Recurrent CD	Recurrent CD	Persistent CD	Persistent CD	Recurrent CD	Persistent CD
Number of neurosurgeries	1	1	1	2	2	2
Other therapies prior to pasireotide	-	-	Osilodrostat RTH	Ketoconazole Temozolomide RTH	-	Ketoconazole RTH
Comorbidities	Hypertension IGT Dyslipidemia	Hypertension IGT Dyslipidemia	Hypertension DM2 Dyslipidemia Osteoporosis	Hypertension DM2 Dyslipidemia Osteoporosis	Hypertension IGT Dyslipidemia	Hypertension Dyslipidemia
Pituitary MRI Prior to pasireotide At LFU	U m, 3 mm m, 3 mm	 Undetectable Undetectable	 Undetectable Undetectable	 M, 54 × 45 × 47 mm M, 55 × 40 × 47 mm	 m, 8 × 7 × 5 mm m, 7 × 7 × 4 mm	 Undetectable Undetectable
mUFC (μg/24 h) Prior to pasireotide At LFU	U 132.0 92.2	 144.0 113.0	 217.7 55.8	 192.4 36.4	 245.6 192.2	 182.4 59.0
mLNSC (ng/mL) Prior to pasireotide At LFU	U 12.8 10.8	 7.0 7.4	 6.9 2.4	 Not available 0.1	 12.9 13.6	 Not available 6.8
Max pasireotide LAR dose (mg/28 days)	20	40	20	20	40	10
Pasireotide LAR side effects	Hyperglycemia Hyporcortisolism Elevated ALT and AST Hair loss	Hyperglycemia Hypocortisolism	Hyperglycemia Detectable biliary sludge	Hyperglycemia Elevated ALT, AST, and GGT Abdominal pain and diarrhea	Hyperglycemia	Hyperglycemia Abdominal pain and diarrhea

2.4. Statistical Analysis

Statistical analysis was carried out using the Prism 9.0 software package (GraphPad Software, Inc., Bonstron, MA, USA). The differences between the timing points were analyzed with a one-way ANOVA, followed by a Dunnett's post hoc test. The level of statistical significance was set at a p-value < 0.05. The results were expressed as means and SDs.

3. Results

3.1. Characteristics of Study Population

Six patients (five women) received pasireotide LAR for at least 12 months (the mean [SD] pasireotide LAR exposure was 16.6 [6.40] months) and were considered suitable for the analysis. The study cohort's mean (SD) age was 45.8 (9.6) years. All patients but one harbored a pituitary microadenoma (in three patients, the pituitary tumor was not detectable on MRI). At diagnosis, all patients underwent TSS as a first-line treatment; three patients had persistent and three patients had recurrent disease. Two patients underwent repeated TSS, and three received previous pituitary radiotherapy. Three patients were previously treated pharmacologically (including osilodrostat, ketoconazole, and temozolomide). The mean (SD) mUFC and mLNSC at study entry were 185.68 ug/24 h (41.11) and 9.90 nmol/L (4.10), respectively. The detailed patient characteristics are summarized in Table 1.

3.2. Effectiveness and Hormonal Parameter Analysis

The analysis of mean (SD) mUFC showed a significant decrease from a baseline of 185.68 ug/24 h (43.11) to the subsequent time points, with the last observed value (LOV) showing a mean (SD) mUFC of 91.93 µg/24 h (56.54). The post hoc Dunn's test revealed statistically significant reductions in the mUFC levels at all analyzed time points. The analysis of mean mLNSC levels showed fluctuations over time, with a baseline mean (SD) of 9.90 nmol/L (4.10) and an LFU of 6.85 nmol/L (5.04); the analysis of differences relative to the baseline revealed the largest mean reduction in mLNSC at 3 months.

The analysis of morning serum cortisol showed stable mean (SD) values over time, ranging from a baseline of 14.62 µg/dL (4.24) to 13.13 µg/dL (4.67) at the LFU. The analysis of mean (SD) midnight serum cortisol showed a decrease from a baseline of 16.22 µg/dL (4.64) to 9.75 µg/dL (3.77) at the LFU. The analysis of morning ACTH levels showed relatively stable mean (SD) values over time, ranging from a baseline of 48.38 pg/mL (11.17) to 53.51 pg/mL (30.68) at the LFU. The post hoc Dunn's test comparing the baseline levels of mLNSC, morning and midnight serum cortisol, and ACTH to the subsequent time points revealed no statistically significant differences.

A complete hormonal evaluation at each time point during pasireotide LAR treatment is detailed in Table 2 and Figure 1.

Table 2. Hormonal parameter changes during pasireotide LAR treatment in analyzed group.

	Baseline	3 Months		6 Months		9 Months		12 Months		LOV	
	Mean (SD)	Mean (SD)	p-Value [a]	Mean (SD)	p-Value [a]	Mean (SD)	p-Value [a]	Mean (SD)	p-Value [a]	Mean (SD)	p-Value [a]
ACTH, pg/mL	48.38 (11.17)	46.43 (17.57)	0.94	50.1 (17.42)	0.98	48.9 (29.39)	0.99	47.03 (21.99)	0.99	53.51 (30.68)	0.95
Morning serum cortisol, µg/dL	14.62 (4.24)	13.08 (3.49)	0.64	13.13 (3.11)	0.73	13.7 (4.86)	0.99	14.27 (3.57)	0.99	13.13 (4.67)	0.95
Midnight serum cortisol, µg/dL	16.22 (4.64)	12.73 (3.76)	0.66	11.13 (3.6)	0.38	11.68 (2.19)	0.15	11.48 (3.07)	0.11	9.75 (3.77)	0.05

Table 2. *Cont.*

	Baseline	3 Months		6 Months		9 Months		12 Months		LOV	
	Mean (SD)	Mean (SD)	*p*-Value [a]	Mean (SD)	*p*-Value [a]	Mean (SD)	*p*-Value [a]	Mean (SD)	*p*-Value [a]	Mean (SD)	*p*-Value [a]
mUFC, µg/24 h	185.68 (43.11)	86.72 (43.54)	0.007	106.53 (47.33)	0.02	87.99 (31.83)	0.01	95.85 (53.9)	0.03	91.93 (56.54)	0.04
mLNSC, ng/mL	9.9 (4.1)	7.17 (3.36)	0.16	12.46 (2.67)	0.88	8.32 (3.2)	0.79	9.07 (3.67)	0.82	6.85 (5.04)	0.60

[a] Dunnett's post hoc test, comparison to baseline. Abbreviations: ACTH, adrenocorticotropin; LAR, long-acting release; LOV, last observed value; mLNSC, mean late-night salivary cortisol; mUFC, mean urinary free cortisol.

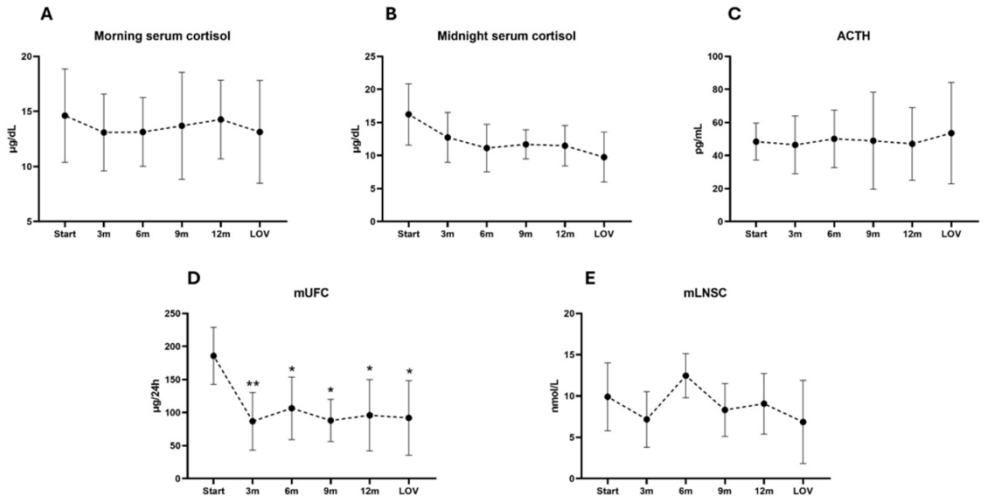

Figure 1. Mean and SD changes in morning serum cortisol (**A**), midnight serum cortisol (**B**), ACTH (**C**), mUFC (**D**), and mLNSC (**E**) throughout study. * is provided when significant difference ($p < 0.05$) compared to baseline was found, and ** when $p < 0.01$. Abbreviations: ACTH, adrenocorticotropin; LOV, last observed value; mLNSC, mean late-night salivary cortisol; m, months; mean late-night salivary cortisol; mUFC, mean urinary free cortisol.

3.3. Effects on Metabolic and Cardiovascular Parameters

The analysis of body weight and BMI revealed a gradual decrease in the mean [SD] values from the baseline (81.70 kg [13.08] and 29.33 kg/m^2 [5.80], respectively) to the LFU (77.30 kg [8.83] and 27.91 kg/m^2 [4.00], respectively). However, the post hoc Dunn's test comparing the baseline to the subsequent time points indicated no statistically significant differences. The analysis of SBP and DBP showed a reduction in the mean [SD] values from the baseline (146.00 mmHg [13.04] and 95.83 mmHg [13.06], respectively) to the LFU (126.67 mmHg [9.00], 89.67 mmHg [9.16], respectively). The post hoc analysis revealed statistically significant differences for the SBP at 6 months, 9 months, and LFU, but no significance was observed for the DBP. A complete evaluation of the metabolic and cardiovascular parameters at each time point during pasireotide LAR treatment is detailed in Table 3 and Figure 2.

Table 3. Metabolic, cardiovascular, and liver parameter changes during pasireotide LAR treatment in analyzed group.

.	Baseline	3 Months		6 Months		9 Months		12 Months		LOV	
	Mean (SD)	Mean (SD)	*p*-Value [a]	Mean (SD)	*p*-Value [a]	Mean (SD)	*p*-Value [a]	Mean (SD)	*p*-Value [a]	Mean (SD)	*p*-Value [a]
Body weight, kg	81.7 (13.08)	79.63 (12.39)	0.15	78.58 10.86)	0.19	77.4 (9.90)	0.2027	77.67 (8.72)	0.35	77.3 (8.83)	0.45
BMI, kg/m^2	29.33 (5.80)	28.59 (5.60)	0.10	28.44 (5.40)	0.34	28.04 (5.08)	0.3213	28.11 (4.69)	0.47	27.91 (4.00)	0.49
SBP, mmHg	146 (13.04)	131.17 (11.79)	0.07	126.17 (5.95)	0.005	129 (7.85)	0.02	131 (4.94)	0.11	126.67 (9.00)	0.03
DBP, mmHg	95.83 (13.06)	90.33 (9.71)	0.75	86.5 (12.82)	0.45	92.33 (6.86)	0.86	92.83 (5.71)	0.94	89.67 (9.16)	0.50
FPG, mg/dL	93.9 (10.65)	98.17 (16.07)	0.53	105 (31.52)	0.63	96.33 (14.07)	0.97	109 (25.3)	0.27	113.67 (27.33)	0.12
HbA1c, %	5.59 (0.33)	5.95 (0.44)	0.14	5.88 (0.55)	0.46	6.14 (0.69)	0.25	6.17 (0.80)	0.27	6.57 (0.89)	0.04
ALT, IU/mL	29.42 (13.26)	52.83 (64.57)	0.82	35.83 (14.11)	0.30	29.63 (9.90)	0.99	25.67 (9.09)	0.88	39.67 (29.15)	0.88
AST, IU/mL	20.88 (10.23)	24.67 (18.20)	0.98	21.67 (5.79)	0.99	22.4 (4.76)	0.99	19.83 (3.13)	0.99	34.17 (32.98)	0.56
GGT, IU/mL	34.33 (24.86)	37.17 (22.69)	0.93	35.67 (21.49)	0.99	26.33 (23.69)	0.56	30.33 (13.63)	0.97	41.67 (34.76)	0.54
Bilirubin, mg/dL	0.51 (0.09)	0.53 (0.13)	0.99	0.56 (0.17)	0.90	0.48 (0.18)	0.99	0.43 (0.14)	0.64	0.41 (0.13)	0.64
TC, mg/dL	222.5 (61.48)	180 (33.89)	0.35	157 (21.06)	0.20	183.42 (74.92)	0.12	166.83 (36.75)	0.11	156.83 (38.35)	0.01
HDL-C, mg/dL	50.47 (9.67)	45 (11.45)	0.05	41.33 (15.29)	0.21	42.33 (8.07)	0.01	41.5 (9.22)	0.01	42.67 (12.71)	0.16
LDL-C, mg/dL	134.6 (53.74)	104.33 (34.93)	0.52	87 (24.02)	0.30	108.25 (62.9)	0.20	96.17 (30.20)	0.21	87.5 (33.41)	0.06
TGs, mg/dL	185.82 (62.44)	153 (65.67)	0.14	146.17 (80.13)	0.22	161.58 (88.72)	0.79	145.33 (73.57)	0.37	128.5 (45.76)	0.06

[a] Dunnett's post hoc test, comparison to baseline. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GGT, gamma-glutamyltransferase; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LAR, long-acting release; LDL-C, low-density lipoprotein cholesterol; LOV, last observed value; SBP, systolic blood pressure; TC, total cholesterol; TGs, triglycerides.

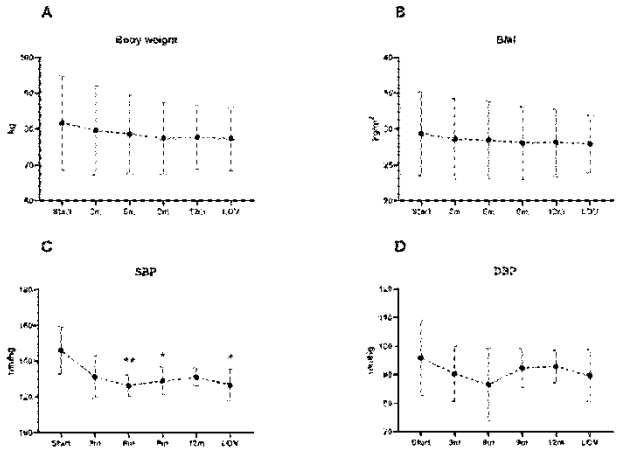

Figure 2. Mean and SD changes in weight (**A**), BMI (**B**), SBP (**C**), and DBP (**D**) throughout study. * is provided when significant difference ($p < 0.05$) compared to baseline was found, and ** when $p < 0.01$. Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; LOV, last observed value; SBP, systolic blood pressure.

3.4. Effect on Lipid Profiles

The analysis of TC levels showed a general decrease in the mean [SD] values from the baseline (222.50 mg/dL [61.48]) to the LFU (156.83 mg/dL [38.35]), with some fluctuations observed at intermediate time points. A statistically significant decrease was observed at the LFU. The analysis of LDL-C and HDL-C levels showed a decrease in the mean [SD] values from the baseline (134.6 mg/dL [53.74] and 50.47 mg/dL [9.67], respectively) to the LFU (87.50 mg/dL [33.41] and 42.67 mg/dL [12.71], respectively), with some fluctuations observed at intermediate time points. A statistically significant decrease was observed for the HDL-C at 9 and 12 months. The analysis of TG levels showed a gradual decrease in the mean [SD] values from the baseline (185.82 mg/dL [62.44]) to the LFU (128.50 mg/dL [45.76]); however, there was no statistical significance at subsequent time points. A complete evaluation of the lipid profiles at each time point during pasireotide LAR treatment is detailed in Table 3.

3.5. Effect on Glucose Metabolism

The baseline mean (SD) FPG level was 93.90 mg/dL [10.65], and the mean (SD) HbA1c was 5.59% [0.33]. In the analyzed group, initially, five patients presented with glucose metabolism impairment (two patients had diabetes, and three had prediabetes) and were receiving hypoglycemic medications (three patients were taking metformin, and two patients were taking semaglutide). The analysis of FPG and HbA1c showed a gradual increase in the mean [SD] values from the baseline to the LFU (113.67 mg/dL [27.33] and 6.57% [0.89], respectively). The most considerable FPG level and HbA1c increases from the baseline was observed at the LFU. A statistically significant increase in HbA1c was observed at LFU; however, the changes in the FPG level did not reach statistical significance. These results indicate a general upward trend in the FPG level and the HbA1c, with more pronounced increases at later time points. A complete evaluation of the glucose metabolism parameters at each time point during pasireotide LAR treatment is detailed in Table 3 and Figure 3.

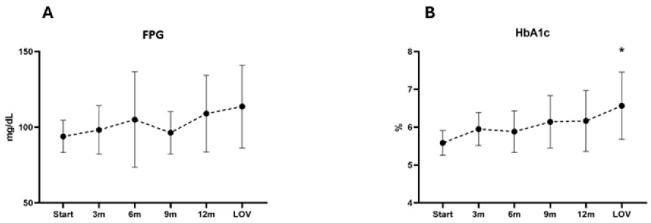

Figure 3. Mean and SD changes in FPG (**A**) and HbA1c (**B**) throughout study. * is provided when significant difference ($p < 0.05$) compared to baseline was found. Abbreviations: FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; LOV, last observed value.

In all patients, hyperglycemia-related adverse events (AEs) occurred; one initially prediabetic patient was diagnosed with diabetes. The remaining patient who had a normal glucose metabolism at study entry developed impaired fasting glucose during pasireotide-LAR treatment, which was managed with diet therapy. None of the patients in the current study dropped out due to hyperglycemia-related AEs. All cases were managed safely and successfully: the deterioration of the glucose metabolism required an increase in the dose (in two patients) or the addition of new hypoglycemic drugs (in three patients) to achieve the optimal glycemic control. The preferred drugs were metformin and semaglutide. There was no need to introduce insulin in any of the patients. Detailed data on the adjustments to antidiabetic drugs are provided in Table 4.

Table 4. Glycemic status and antidiabetic treatment during pasireotide LAR treatment in analyzed group.

		Baseline	6 Months	12 Months	LFU
Patient 1	Status	Prediabetes	Prediabetes	Prediabetes	Prediabetes
	HbA1c, %	5.3	5.0	5.7	5.7
	Treatment	S [a], 0.25 mg/week	S [a], 0.25 mg/week	S [a], 0.5 mg/week	S [a], 0.5 mg/week
Patient 2	Status	Prediabetes	Prediabetes	Prediabetes	Prediabetes
	HbA1c, %	5.7	5.7	5.9	5.9
	Treatment	M, 1.5 g/day	M, 1.5 g/day S [a], 0.25 mg/week	M, 1.5 g/day S [a], 0.5 mg/week	M, 1.5 g/day S [a], 0.5 mg/week
Patient 3	Status	Diabetes	Diabetes	Diabetes	Diabetes
	HbA1c, %	5.6	6.5	7.1	7.3
	Treatment	S [b], 7 mg/day	S [b], 7 mg/day M-XR, 1 g/day	S [b], 7 mg/day M-XR, 1 g/day	S [b], 14 mg/day M-XR, 2 g/day D, 10 mg/day
Patient 4	Status	Diabetes	Diabetes	Diabetes	Diabetes
	HbA1c, %	6.0	6.0	5.9	7.6
	Treatment	M, 1.5 g/day	M, 1.5 g/day	M, 1.5 g/day	M, 2.550 g/day
Patient 5	Status	Prediabetes	Diabetes	Diabetes	Diabetes
	HbA1c, %	5.8	6.4	7.2	7.2
	Treatment, dose	M-XR, 1 g/day	M-XR, 2 g/day	S [a], 0.5 mg/week M-XR, 2 g/day	S [a], 0.5 mg/week M-XR, 2 g/day
Patient 6	Status	Normal glycemic status	Prediabetes	Prediabetes	Prediabetes
	HbA1c, %	5.1	5.7	5.2	5.7
	Treatment	-	Diet	Diet	Diet

[a] Subcutaneous formulation of semaglutide. [b] Oral formulation of semaglutide.

3.6. Safety

Pasireotide was generally well tolerated, with the AEs mainly mild and manageable. The most common side effect was pasireotide-related hyperglycemia, which occurred in all patients analyzed, as described above. Two patients reported moderate hypocortisolism-related AEs. The symptoms of low cortisol were usually observed for several days after pasireotide injection, which required the transient use of a single morning dose of hydrocortisone. Transient gastrointestinal symptoms (abdominal pain and diarrhea) occurred in two patients. No increase in the bilirubin concentration was observed. The analysis of bilirubin levels showed relatively stable mean [SD] values over time, with a slight decrease from the baseline (0.51 mg/dL [0.09]) to the LFU (0.41 mg/dL [0.13]). However, the changes in the bilirubin levels were minimal and not statistically significant over time. Two patients experienced a rise in ALT and AST activity (exceeding 3x the ULN in one, which required the temporary discontinuation of pasireotide LAR treatment). One patient also experienced a transient mild increase in GGT activity. The analysis of ALT, AST and GGT levels showed fluctuations over time, with the mean [SD] values ranging from the baseline (29.42 IU/mL [13.26], 20.88 IU/mL [10.23], and 34.33 IU/mL [24.86], respectively) to the LFU (39.67 IU/mL [29.15], 34.17 IU/mL [32.98], and 41.67 IU/mL [34.67], respectively). The post hoc Dunn's test comparing the baseline to the subsequent time points revealed no statistically significant differences. A complete evaluation of the liver parameters at each time point during pasireotide LAR treatment is detailed in Table 3. One patient, who had a normal gallbladder upon ultrasonographic examination at baseline, displayed detectable biliary sludge during treatment. Hair loss was reported in one patient. No significant QT prolongation was observed in any of the patients.

4. Discussion

This analysis reports the efficacy and safety of treatment with pasireotide LAR in patients with CD in a real-life setting based on the experience of a single center in Poland. To our knowledge, this is the first report of pasireotide LAR treatment efficacy in Poland in patients with CD.

The results of our observational study are mostly consistent with those obtained from clinical trials. In our cohort, the mean mUFC showed a significant and sustained decrease from the baseline to the LFU with statistical significance at all analyzed time points, with the most pronounced decrease in the first 3 months of therapy. mUFC normalization upon pasireotide-LAR treatment was achieved in all four patients with an elevated mUFC at baseline; however, during the entire analyzed observation period in one patient, there was an escape from pasireotide-LAR's initial efficacy, and no further normalization of the mUFC, despite the escalation of therapy, was achieved.

Pasireotide LAR therapy was discontinued in half of the analyzed patients due to its long-term ineffectiveness, including two patients with initially normal mUFC, where the decision to stop treatment was based on persistently elevated mLNSC. Initial disease control with mUFC normalization was achieved in another patient, but an escape from pasireotide LAR efficacy was observed during further follow-ups. The analysis of mean late-night salivary cortisol showed fluctuations over time, with the largest mean reduction in mLNSC at 3 months. mUFC and mLNSC are considered to be complementary measurements for monitoring pharmacological treatment responses in CD. However, the best clinical improvement is seen in patients with the normalization of both parameters [15]. Identifying patients who could benefit from pasireotide LAR treatment is essential for efficient patient management. Research indicates that lower baseline mUFC levels are associated with higher rates of UFC normalization in response to pasireotide treatment [8,16]. However, studies evaluating the efficacy of pasireotide LAR therapy did not include patients with CD and normal mUFC. It would seem that these patients should respond very well to pasireotide LAR therapy. However, our observations show that pasireotide LAR was not able to restore this group of CD patients' normal circadian rhythms of cortisol secretion; the clinical effects in these patients were unsatisfactory due to the persistently disturbed circadian cortisol secretion with elevated LNSC. The patients who completed pasireotide LAR therapy were switched to osilodrostat and are now well controlled. It should be noted, however, that the group of patients we analyzed who are continuing treatment with pasyreotide LAR are the patients who have a history of pituitary radiotherapy. Thus, the potential influence of baseline radiotherapy treatment on the subsequent improved response to pasireotide LAR therapy cannot be entirely excluded.

Ubiquitin-specific protease 8 (*USP-8*) gene mutational status could be a potential marker of the pasireotide response, as mutant *USP8* forms may upregulate SSTR5 transcription [1,17,18]. Indeed, recent in vitro studies report a significantly better response to pasireotide treatment in human corticotroph tumors carrying *USP8* mutations [17,19]. Studies report that *USP8*-mutant tumors are smaller, but have worse long-term postoperative outcomes compared to wild-type tumors, with a tendency toward shorter recurrence-free survival in *USP8*-mutant patients [17,20].

The analysis of ACTH levels showed relatively stable mean values over time. A detailed analysis of tumor volume was not possible in the presented group because, in three patients, the pituitary tumors were not detectable on MRI at either baseline or LFU. In the other three, the sizes of the pituitary tumors remained stable, including a patient with a large (54 × 45 × 47 mm) solid-cystic tumor after repeated TSS, Gamma Knife radiosurgery, and temozolomide treatment. One factor that should be considered in the selection of pharmacological therapy for patients with CD should also be the size of the pituitary tumor.

In patients with corticotroph macroadenomas, pasireotide may decrease the size of the tumor, or at least limit its potential for further growth [21]. Pasireotide LAR therapy may also be considered in such cases as an add-on therapy to steroidogenesis inhibitors [22], especially considering the growing number of reports of corticotroph tumor progression during osilodrostat treatment [23,24].

Considering all this, pasireotide LAR therapy seems effective in a particular group of patients with CD. The most significant benefit from the treatment may be obtained by patients with a milder form of the disease (mUFC < 2x the ULN), but at the same time with a specific secretion profile (where the increased LNSC is not the dominant abnormality). Additionally, patients with macroadenomas may benefit from the stabilization/reduction in tumor size. The *USP8* mutation status may be helpful in selecting treatment.

A decrease in the mean SBP values from the baseline to the LFU was observed in the analyzed group, with the most pronounced effect after 6 months of pasireotide LAR therapy. The analysis of DBP showed a slight decrease in the mean values from baseline during the observation period. In two patients, reducing the doses of antihypertensive drugs was possible. Interestingly, a reduction in BP values was also observed in the patients in whom hypercortisolemia control was not achieved. However, according to clinical trial data, pasireotide treatment improves hypertension control independently from cortisol reduction [25]. The body weight and BMI in the analyzed group gradually decreased during the observation, but no statistical significance was found. The lipid profile assessment revealed a gradual decrease in the TC, LDL-C, HDL-C, and TGs upon analysis. Interestingly, statistical significance was found only for the HDL-C decrease at months 9 and 12.

Hyperglycemia is a known side effect of pasireotide treatment. The stimulation of pancreatic SSTR-5 suppresses insulin secretion, which, combined with negative effects on incretin hormone secretion, leads to pasireotide-induced hyperglycemia. [26,27]. Previous data also indicate that if hyperglycemia occurs, it is most likely during the first three months of treatment with pasireotide, with stabilization over time [28–30].

Pasireotide-related hyperglycemia occurred in all analyzed patients. Consistent with previous studies on pasireotide, the hyperglycemia-related AEs were mainly mild and manageable. However, in the analyzed group, gradually increasing FPG and HbA1c levels were observed, with the greatest differences in relation to the initial value and LOV. That difference in the time of the most significant deterioration in the glucose metabolism compared to earlier reports may be due to several factors. Firstly, the risk of hyperglycemia was closely monitored in the analyzed group, as nearly all patients, except for one, exhibited signs of impaired glucose metabolism upon entering the study. Most patients were taking glucose-lowering drugs before starting treatment with pasireotide-LAR. The initial deterioration in the glucose metabolism control in the first months of treatment led to the intensification of hypoglycemic treatment, which may not reflect the actual effects of pasireotide-LAR therapy in the first analyzed time points. Additionally, at the LFU, in half of the patients, the CD was not controlled biochemically, which was associated with an escape from pasireotide-LAR initial efficacy, and the active hypercortisolism likely worsened the glucose metabolism control. None of the patients discontinued pasireotide treatment because of hyperglycemia.

At our center, we recommend closely monitoring blood glucose in patients treated with pasireotide and management with antidiabetic medications, focusing on metformin and/or incretin-based therapy. Experts indeed recommend that after lifestyle changes and pharmacotherapy with metformin, combination therapy with agents targeting the incretin pathway is recommended [31–34]. Some experts go even further and propose that when, in pasireotide-induced hyperglycemia, pharmacotherapy is necessary, incretin-based medications should be considered as first-line treatment as an alternative to metformin [33,35].

It is also worth mentioning that the glucose metabolism status returned to the initial in the three patients in whom pasireotide was discontinued due to lack of effectiveness; that supports previous observations that pasireotide-related hyperglycemia is reversible upon treatment discontinuation [36]. To conclude, the hyperglycemia observed during pasireotide treatment is manageable in most patients without the need for treatment discontinuation. The risk factors may be used to identify patients who require more careful and proactive monitoring to optimize their outcomes during pasireotide treatment, thereby ensuring continuous treatment and improved results.

In two patients, symptoms of adrenal insufficiency were observed during pasireotide LAR therapy. Low morning serum cortisol levels were usually observed for several days after pasireotide LAR injection, which required the transient implementation of a morning dose of a hydrocortisone substitution. Interestingly, these were the two patients who had a normal mUFC at baseline. That may indicate that treatment with pasireotide LAR in patients with such a secretory profile of the pituitary tumor is not able to normalize mLNSC, on the one hand, and on the other hand, leads to low morning cortisol levels and the need for temporary hydrocortisone substitution during the day. Both patients are currently well controlled with a single evening dose of osilodrostat. Less commonly reported AEs, in line with the previous evidence, included gastrointestinal disturbances and transient elevations of liver enzyme activity. In one patient, the ALT activity exceeded 3x the ULN, but this occurred while the patient was using alternative therapies (unspecified herbs); therefore, the actual effect of pasireotide LAR cannot be fully assessed. Cholelithiasis is a recognized AE associated with long-term treatment with SRLs [26]. In our cohort, three patients were post-cholecystectomy at baseline. One patient who had a normal gallbladder upon ultrasonographic examination at baseline developed detectable biliary sludge during pasireotide LAR treatment managed with ursodeoxycholic acid. Two patients presented with gallbladder polyps at baseline, whose size did not change during observation. One patient experienced significant hair loss that occurred after more than 6 months of therapy and resolved when pasireotide LAR was discontinued.

The study's main limitations are its small number and retrospective nature. However, considering the rarity of CD, the limited number of patients treated with pasireotide LAR in Poland, and the lack of previously published data in this area from our country, it remains representative. Another limitation is the lack of complete data on the mLNSC in two patients, which did not allow for a detailed analysis of this parameter.

5. Conclusions

In conclusion, the current study, based on real-world evidence and performed on a limited cohort of patients, demonstrated that treatment with pasireotide LAR is an effective therapeutic option for selected patients with CD. However, even in the patients whose complete biochemical control of the disease was not achieved, pasireotide LAR improved BP control, improved anthropometric parameters including the weight and BMI, and ameliorated the lipid profile. Glucose metabolism impairment was the most common adverse effect, and it can usually be successfully controlled. Patient-tailored, effective medical therapies are needed to optimize the long-term outcomes for patients with persistent CD.

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Informed Consent Statement: Written informed consent was obtained from all patients for the use of the clinical data in the study after being provided all information regarding the purpose of the study.

Data Availability Statement: The data analyzed or generated during the study are available from the corresponding author on reasonable request.

Conflicts of Interest: L.D. and P.W. report receiving speaker fees and consulting fees from Recordati Rare Diseases. W.R. declares no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript] ACTH—adrenocorticotropin; AE—adverse event; ALT—alanine transaminase; AST—aspartate transaminaze; BMI—body mass index; CD—Cushing's disease; CS—Cushing's syndrome; DBP—diastolic blood pressure; ECG—electrocardiogram; FPG—fasting plasma glucose; GGT—gamma-glutamyltransferase; HbA1c—glycated hemoglobin; IGT—impaired glucose tolerance; IFG—impaired fasting glucose; mLNSC—mean late-night salivary cortisol; mUFC—mean urinary free cortisol; LFU—last follow-up; LOV—last observed value; MRI—magnetic resonance imaging; QTc—corrected QT interval; SBP—systolic blood pressure; TC—total cholesterol; TG—triglycerides; TSS—transsphenoidal selective surgery; ULN—upper limit of normal; USP8—ubiquitin-specific protease 8.

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7. PODSUMOWANIE

Zespół Cushinga, stanowi ciężkie zaburzenie endokrynologiczne o zróżnicowanym obrazie klinicznym oraz istotnie zwiększonej chorobowości i śmiertelności, zwłaszcza w przypadku braku adekwatnego leczenia. Standardem postępowania pozostaje leczenie operacyjne. U stosunkowo dużej grupy chorych, pomimo zastosowania leczenia chirurgicznego, dochodzi jednak do nawrotu lub utrzymywania się hiperkortyzolemii, co wymaga wdrożenia innych form leczenia, w tym farmakoterapii. W ostatnich latach nastąpił istotny postęp w opracowywaniu nowych cząsteczek farmakologicznych oddziałujących na różnych poziomach osi podwzgórze–przysadka–nadnercza. Pomimo rosnącej liczby danych pochodzących z badań klinicznych, konieczna jest dalsza ocena ich skuteczności i bezpieczeństwa w warunkach rzeczywistej praktyki klinicznej. Niniejsza rozprawa doktorska odpowiada na tę potrzebę, przedstawiając doświadczenia terapeutyczne związane ze stosowaniem osilodrostatatu, pasyreotydu LAR oraz etomidatu – zarówno w monoterapii, jak i w schematach leczenia skojarzonego – u pacjentów z ACTH-zależną hiperkortyzolemią.

W pierwszej pracy *Cushing's Disease: Long-Term Effectiveness and Safety of Osilodrostat in a Polish Group of Patients with Persistent Hypercortisolemia in the Experience of a Single Center* omówiono długoterminowe efekty stosowania osilodrostatatu w grupie pacjentów z przetrwałą lub nawrotową chorobą Cushinga. Jest to pierwsze takie opracowanie dotyczące pacjentów w Polsce. Uzyskane wyniki jednoznacznie wskazują wysoką skuteczność i bezpieczeństwo stosowania osilodrostatu w warunkach rzeczywistej praktyki klinicznej. Osilodrostat umożliwił osiągnięcie pełnej kontroli biochemicznej i ustąpienie klinicznych objawów hiperkortyzolemii oraz poprawę jakości życia wszystkich leczonych pacjentów. Mediana czasu potrzebnego do osiągnięcia normalizacji mUFC wynosiła 5 tygodni, przy medianie stosowanej dawki osilodrostatu wynoszącej 10 mg na dobę. Pod koniec okresu obserwacji prawidłowe mUFC utrzymywało się u wszystkich pacjentów przy medianie dawki osilodrostatu wynoszącej 3 mg na dobę. Z kolei mediana czasu potrzebnego do normalizacji mLNSC wyniosła 9,5 tygodnia, a mediana dawki osilodrostatu wynosiła 10 mg na dobę. Nie stwierdzono wyraźnego związku między wyjściowym stopniem nasilenia hiperkortyzolemii a dawką osilodrostatu potrzebną do normalizacji mUFC lub mLNSC. Zakres dawek stosowanych w celu utrzymania długoterminowej kontroli choroby u poszczególnych pacjentów był szeroki (od 1 mg co trzy dni do 60 mg na dobę), co odzwierciedlało indywidualną zmienność odpowiedzi na leczenie i podkreśla konieczność dostosowywania dawki leku do potrzeb każdego pacjenta. Wszystkich sześciu pacjentów osiągnęło i utrzymało pełną

odpowiedź na leczenie, przy czym żaden nie przerwał terapii z powodu jej nieskuteczności w ciągu 156 tygodni obserwacji.

U wszystkich pacjentów obserwowano istotną poprawę parametrów kardiometabolicznych w trakcie terapii osilodrostatem. Najwyraźniejsza poprawa wystąpiła w ciągu pierwszych 36. tygodni leczenia i utrzymywała się przez cały okres obserwacji. U części pacjentów możliwe było zmniejszenie dawki lub całkowite odstawienie leków hipoglikemizujących, hipotensyjnych i/lub hipolipemizujących.

Działania niepożądane, które wystąpiły podczas terapii osilodrostatem miały charakter przejściowy i były skutecznie kontrolowane. W żadnym przypadku nie zaistniała konieczność trwałego przerwania leczenia. U większości pacjentów wystąpił przynajmniej jeden epizod hipokortyzolemii indukowany osilodrostatem, głównie w okresie dostosowywania dawki – nie wymagało to jednak odstawienia leku, a jedynie redukcję dawki oraz czasowe wprowadzenie hydrokortyzonu w dawkach substytucyjnych. Ze względu na ryzyko działań niepożądanych związanych z hipokortyzolemią, niezbędna jest kompleksowa edukacja pacjentów, w ramach której na początku terapii należy omówić objawy wskazujące na niedoczynność kory nadnerczy oraz przeszkolić pacjentów w zakresie stosowania glikokortykosteroidów.

Szczegółowa analiza troje pacjentów ujawniła różnorodne sytuacje kliniczne oraz potencjalne specyficzne działania niepożądane związane z terapią osilodrostatem, takie jak akumulacja androgenów i prekursorów steroidogenezy nadnerczowej o działaniu mineralokortykoidowym oraz ryzyko progresji wielkości guza przysadki.

W publikacji *Cushing's syndrome: a combined treatment with etomidate and osilodrostat in severe life-threatening hypercortisolemia*, po raz pierwszy w literaturze przedstawiono przypadek pacjentki z ciężkim zespołem Cushinga u której celem kontroli hiperkortyzolemii wykorzystano leczenie skojarzone osilodrostatem i etomidatem. U prezentowanej pacjentki osilodrostat początkowo zastosowano w monoterapii z szybką eskalacją dawki, uzyskując wstępnie zadowalający efekt kliniczny. Ze względu na pogorszenie stanu pacjentki w kolejnych dniach leczenia, obserwowaną niewystarczającą odpowiedź na terapię oraz brak jednoznacznego protokołu dotyczącego monoterapii osilodrostatem w ciężkiej hiperkortyzolemii, do leczenia wdrożono etomidat. Terapia była kontynuowana w formie skojarzonej, a dawki osilodrostatu i etomidatu były tak dobierane, aby możliwe było przerwanie wlewu etomidatu przy utrzymaniu stężenia kortyzolu w pożądanym zakresie i dalsze prowadzenie leczenia osilodrostatem w monoterapii. Terapia skojarzona trwała 19 dni, a infuzję etomidatu zakończono po skutecznej stabilizacji stężeń kortyzolu i potasu przy dawce osilodrostatu wynoszącej 18 mg na dobę. Połączenie osilodrostatu i etomidatu okazało się

wysoce skuteczne w kontroli hiperkortyzolemii – pozwoliło na szybkie obniżenie stężenia kortyzolu, co umożliwiło stabilizację stanu klinicznego pacjentki. W kolejnych dniach hospitalizacji dawka osilodrostatu była dostosowywana, a ostatecznie pacjentka w dobrym stanie ogólnym, przy stabilnej dawce 12 mg na dobę, mogła zostać wypisana ze szpitala.

Przypadek ten wskazuje, że kombinacja leczenia osilodrostatu i etomidatu stanowi wartościową alternatywę terapeutyczną w leczeniu ciężkich, zagrażających życiu postaci hiperkortyzolemii, szczególnie w sytuacjach, gdy monoterapia jest niewystarczająca lub istnieją ograniczenia w stosowaniu innych leków. Krótkoterminowa terapia skojarzona była dobrze tolerowana i nie wiązała się ze zwiększonym ryzykiem działań niepożądanych.

W publikacji *Is there still a place for etomidate in the management of Cushing's syndrome? The experience of a single center of low-dose etomidate and combined etomidate-osilodrostat treatment in severe hypercortisolemia* oceniano skuteczność i bezpieczeństwo niskodawkowej terapii etomidatem u pacjentów z zagrażającą życiu hiperkortyzolemią. Dodatkowo w wybranych przypadkach przeprowadzono analizę schematu terapeutycznego opartego na terapii skojarzonej etomidatem i osilodrostatem.

U pacjentów terapię etomidatem rozpoczęto w dawce 0,01–0,02 mg/kg/h. Osiągnięcie docelowego stężenia kortyzolu w surowicy odnotowano u wszystkich pacjentów w medianie czasu wynoszącej 30 godzin, przy czym mediana maksymalnej szybkości infuzji koniecznej do utrzymania kortyzolu w pożądanym zakresie wynosiła 0,03 mg/kg/h. Mediana czasu potrzebnego do normalizacji stężenia potasu w surowicy wynosiła 18 godzin, natomiast mediana całkowitego czasu prowadzenia wlewu etomidatu wynosiła 14 dni.

Wszyscy pacjenci dobrze tolerowali wlew etomidatu, bez wystąpienia działań niepożądanych wymagających przerwania terapii. U jednego pacjenta wystąpił epizod niedoczynności kory nadnerczy, który wymagał czasowego wprowadzenia hydrokortyzonu oraz redukcji dawki etomidatu. Dwóch pacjentów zmarło w trakcie leczenia, jednak zgony te nie były bezpośrednio związane z samym leczeniem etomidatem, lecz wynikały ze stopnia zaawansowania choroby nowotworowej oraz powikłań hiperkortyzolemii. Obserwacje te wskazują, że terapia etomidatem w ciężkich przypadkach zespołu Cushinga jest bezpieczna, a ryzyko poważnych działań niepożądanych jest ograniczone przy odpowiednim monitorowaniu pacjentów i zapewnieniu właściwego wsparcia klinicznego.

W zastosowanym schemacie terapeutycznym pominięto typowo stosowaną wstępną dawkę inicjującą etomidatu w postaci dożylnego bolusa, a do terapii wykorzystano etomidat w emulsji lipidowej. W większości opublikowanych doniesień dotyczących terapii etomidatem oceniano jednak skuteczność preparatu w formulacji z glikolem propylenowym. Niniejsza praca

obejmuje największą dotychczas kohortę pacjentów leczonych etomidatem w emulsji lipidowej, potwierdzając jego porównywalną skuteczność w stosunku do formulacji z glikolem propylenowym. W świetle tych obserwacji oraz znanego ryzyka toksyczności glikolu propylenowego, wyniki te sugerują, że w leczeniu SCS etomidat w emulsji lipidowej powinien być preferowany.

U czterech pacjentów wlew etomidatu prowadzono aż do skutecznego wprowadzenia doustnego inhibitora steroidogenezy – osilodrostatu. Przed przejściem na monoterapię osilodrostatem pacjenci otrzymywali terapię w schemacie skojarzonym, co pozwoliło na stopniowe ustabilizowanie stężenia kortyzolu i przygotowanie pacjentów do kontynuacji leczenia doustnego. Mediana czasu trwania terapii skojarzonej wynosiła 7 dni. Dane pochodzące z niniejszej pracy potwierdzają obserwacje wcześniejszego opisanego przypadku i wskazują na wysoką skuteczność terapii skojarzonej etomidatem i osilodrostatem w szybkiej kontroli hiperkortyzolemii. Obserwacje te podkreślają również, że terapia skojarzona, przy właściwym monitorowaniu i kontroli działań niepożądanych, może być bezpiecznie stosowana w praktyce klinicznej.

W ostatniej pracy *Real-World Experience with Pasireotide-LAR in Cushing's Disease: Single-Center 12-Month Observational Study* oceniono skuteczność i bezpieczeństwo pasyreotydu LAR w leczeniu choroby Cushinga w warunkach rzeczywistej praktyki. Jest to pierwsze takie opracowanie dotyczące polskich pacjentów.

U wszystkich pacjentów stwierdzono istotne obniżenie mUFC, szczególnie w pierwszych miesiącach terapii, a u czterech chorych z podwyższonym mUFC na początku leczenia uzyskano jego normalizację. Analiza mLNSC wykazała zmienność w czasie, przy czym największy średni spadek obserwowano w ciągu pierwszych trzech miesięcy terapii. Uwagę zwraca jednak ograniczona skuteczność pasyreotydu LAR w zakresie przywracania prawidłowego rytmu dobowego wydzielania kortyzolu – utrzymujące się podwyższone wartości LNSC korelowały z niezadowalającą poprawą kliniczną u części pacjentów.Terapia pasyrotydem LAR została przerwana u połowy analizowanych pacjentów z powodu długoterminowej nieskuteczności leczenia. Wśród nich było dwoje pacjentów, którzy początkowo mieli prawidłowe wartości mUFC, jednak decyzja o zakończeniu terapii została podjęta ze względu na utrzymujące się podwyższone wartości mLNSC. U kolejnego pacjenta początkowo uzyskano kontrolę choroby i normalizację mUFC, jednak w trakcie dalszej obserwacji stwierdzono utratę skuteczności terapii. Mając na uwadze komplementarność mUFC i mLNSC w monitorowaniu leczenia oraz fakt, że najlepsze efekty kliniczne obserwuje

się przy normalizacji obu parametrów, podczas kwalifikacji do terapii pasyreotydem LAR warto dodatkowo uwzględniać profil wydzielniczy guzów kortykotropowych.

W analizowanej grupie obserwowano spadek średnich wartości skurczowego ciśnienia tętniczego w porównaniu z wartościami wyjściowymi, przy czym efekt ten był najbardziej wyraźny w ciągu pierwszych sześciu miesięcy terapii pasyrotydem LAR. Analiza rozkurczowego ciśnienia tętniczego wykazała niewielki spadek średnich wartości w trakcie okresu obserwacji. Co istotne, obniżenie wartości ciśnienia tętniczego zaobserwowano także u pacjentów, u których nie uzyskano pełnej kontroli biochemicznej hiperkortyzolemii.

Hiperglikemia związana z leczeniem pasyrotydem LAR wystąpiła u wszystkich analizowanych pacjentów. W badanej grupie obserwowano stopniowy wzrost stężenia glukozy na czczo oraz odsetka hemoglobiny glikowanej, przy czym najbardziej nasilone zmiany odnotowano w późniejszych punktach obserwacji. W żadnym przypadku hiperglikemia nie stanowiła jednak przyczyny przerwania leczenia pasyrotydem LAR. Warto również podkreślić, że u trzech pacjentów, u których terapię pasyrotydem LAR zakończono z powodu jej nieskuteczności, parametry gospodarki węglowodanowej powróciły do wartości wyjściowych.

Farmakologiczne leczenie hiperkortyzolemii odgrywa coraz istotniejszą rolę w postępowaniu z pacjentami z zespołem Cushinga, zarówno jako terapia pomostowa jak i też leczenie długoterminowe w przypadkach nieskuteczności lub niemożności zastosowania metod radykalnych. Dobór odpowiedniej strategii terapeutycznej powinien mieć charakter zindywidualizowany i uwzględniać stopień nasilenia hiperkortyzolemii, profil chorób współistniejących, ryzyko działań niepożądanych, a także dostępność poszczególnych leków, ich rejestrację oraz koszty leczenia. Dostępne obecnie leki różnią się mechanizmem działania, skutecznością oraz profilem bezpieczeństwa, co stwarza możliwość elastycznego dopasowania terapii do potrzeb klinicznych pacjenta, ale jednocześnie wymaga doświadczenia oraz ścisłego monitorowania leczenia. Niezbędne są dalsze badania oceniające skuteczność i bezpieczeństwo farmakoterapii hiperkortyzolemii w warunkach rzeczywistej praktyki klinicznej. Pozwolą one na pełniejszą ocenę długoterminowej efektywności leczenia, lepsze zrozumienie profilu działań niepożądanych oraz identyfikację rzadkich i nietypowych powikłań, które mogą nie ujawniać się w badaniach klinicznych. Takie dane są kluczowe dla dalszej optymalizacji strategii terapeutycznych i poprawy rokowania pacjentów z zespołem Cushinga.

8. WNIOSKI

- Nowoczesne terapie farmakologiczne (osilodrostat, pasyreotyd LAR, skojarzona terapia osilodrostatem i etomidatem) stanowią istotne uzupełnienie leczenia zespołu Cushinga, szczególnie u pacjentów z nawrotem choroby, przetrwałą hiperkortyzolemią oraz w ciężkich przypadkach wymagających pilnej interwencji klinicznej.

- Osilodrostat jest skutecznym i dobrze tolerowanym doustnym inhibitorem steroidogenezy nadnerczowej, umożliwiającym zarówno szybką kontrolę hiperkortyzolemii, jak i poprawę parametrów metabolicznych oraz sercowo-naczyniowych, nie tylko w krótkoterminowej obserwacji, lecz także w ramach leczenia przewlekłego.

- Etomidat stosowany w niskich dawkach pozostaje wartościową opcją terapeutyczną w ciężkich postaciach ACTH-zależnej hiperkortyzolemii, zapewniając szybkie działanie i korzystny profil bezpieczeństwa. Terapia skojarzona etomidatem i osilodrostatem może stanowić skuteczną strategię terapeutyczną w sytuacjach krytycznych, wymagających bardzo szybkiej normalizacji stężenia kortyzolu.

- Pasyreotyd LAR jest efektywną opcją terapeutyczną u wybranych pacjentów z przetrwałą lub nawrotową chorobą Cushinga, szczególnie w przypadkach łagodnego nasilenia hiperkortyzolemii.

- W każdym przypadku zespołu Cushinga konieczna jest indywidualizacja i personalizacja leczenia farmakologicznego z uwzględnieniem stanu klinicznego pacjenta, chorób współistniejących oraz występujących powikłań hiperkortyzolemii.

- Prace wchodzące w skład niniejszej rozprawy mają zarówno charakter oryginalny, jak i poznawczy oraz stanowią źródło praktycznych wskazówek dla endokrynologów zmagających się z tą bardzo rzadką, ale obciążającą endokrynopatią, jaką jest zespół Cushinga.

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10. OPINIA KOMISJI BIOETYCZNEJ

Komisja Bioetyczna
przy Warszawskim Uniwersytecie Medycznym

Tel.: 022/ 57 - 20 -303
Fax: 022/ 57 - 20 -165

ul. Żwirki i Wigury nr 61
02-091 Warszawa

e-mail: komisja.bioetyczna@wum.edu.pl
www.komisja-bioetyczna.wum.edu.pl

Warszawa, dnia 09.10 2023

AKBE/ 271 / 2023

Lek. Łukasz Działach
Katedra i Klinika Chorób Wewnętrznych,
Endokrynologii i Diabetologii
ul .Kondratowicza 8
03-242 Warszawa

OŚWIADCZENIE

Niniejszym oświadczam, że Komisja Bioetyczna przy Warszawskim Uniwersytecie Medycznym w dniu 09 października 2023 r. przyjęła do wiadomości informację na temat badania pt ."Skuteczność osilodrostatu w długoterminowej kontroli hiperkortyzolemii u pacjentów z chorobą Cushinga" Przedstawione badanie nie stanowi eksperymentu medycznego w rozumieniu art. 21ust.1 ustawy z dnia 5 grudnia 1996 r. o zawodach lekarza i lekarza dentysty (Dz.U. z 2018 r poz. 617) i nie wymaga uzyskania opinii Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym, o której mowa w art. 29 ust.1 ww. ustawy.

Przewodnicząca Komisji Bioetycznej

Prof. dr hab. n. med. Magdalena Kuźma –Kozakiewicz

Komisja Bioetyczna
przy Warszawskim Uniwersytecie Medycznym

Tel.: 022/ 57 - 20 -303
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ul. Żwirki i Wigury nr 61
02-091 Warszawa

e-mail: komisja.bioetyczna@wum.edu.pl
www.komisja-bioetyczna.wum.edu.pl

Warszawa, dnia 10.06.2024

AKBE/ 170 / 2024

Lek. Łukasz Działach
Katedra i Klinika Chorób Wewnętrznych,
Endokrynologii i Diabetologii
ul .Kondratowicza 8
03-242 Warszawa

OŚWIADCZENIE

Niniejszym oświadczam, że Komisja Bioetyczna przy Warszawskim Uniwersytecie Medycznym w dniu 10 czerwca 2024 r. przyjęła do wiadomości informację na temat badania pt ."Czy w leczeniu zespołu Cushinga wciąż jest miejsce na etomidat? Przedstawione badanie nie stanowi eksperymentu medycznego w rozumieniu art. 21ust.1 ustawy z dnia 5 grudnia 1996 r. o zawodach lekarza i lekarza dentysty (Dz.Uz 2018 r poz. 617) i nie wymaga uzyskania opinii Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym, o której mowa w art. 29 ust.1 ww. ustawy.

Przewodnicząca Komisji Bioetycznej

Prof. dr hab. n. med. Magdalena Kuźma –Kozakiewicz

Komisja Bioetyczna
przy Warszawskim Uniwersytecie Medycznym

Tel.: 022/ 57 - 20 -303
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ul. Żwirki i Wigury nr 61
02-091 Warszawa

e-mail: komisja.bioetyczna@wum.edu.pl
www.komisja-bioetyczna.wum.edu.pl

Warszawa, dnia 16.12.2024

AKBE/ 335 / 2024

Lek. Łukasz Działach
Katedra i Klinika Chorób Wewnętrznych
Endokrynologii i Diabetologii WUM,
ul. Kondratowicza 8
03 – 242 Warszawa

OŚWIADCZENIE

Niniejszym oświadczam, że Komisja Bioetyczna przy Warszawskim Uniwersytecie Medycznym w dniu 16 grudnia 2024 r. przyjęła do wiadomości informację na temat badania pt. „ Skuteczność terapii pasyreotydem-LAR w chorobie Cushinga:analiza retrospektywna w oparciu o praktykę kliniczną w doświadczeniu pojedynczego ośrodka ." Przedstawione badanie nie stanowi eksperymentu medycznego w rozumieniu art. 21ust.1 ustawy z dnia 5 grudnia 1996 r. o zawodach lekarza i lekarza dentysty (Dz.U. z 2018r poz.617) i nie wymaga uzyskania opinii Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym, o której mowa w art. 29 ust.1 ww. ustawy.

Przewodnicząca Komisji Bioetycznej

Prof. dr hab. n. med. Magdalena Kuźma –Kozakiewicz

11. OŚWIADCZENIA WSPÓŁAUTORÓW PUBLIKACJI

Warszawa, 08.01.2026 r.

Lek. Joanna Sobolewska

OŚWIADCZENIE

Jako współautor pracy pt. ***Cushing's Disease: Long-Term Effectiveness and Safety of Osilodrostat in a Polish Group of Patients with Persistent Hypercortisolemia in the Experience of a Single Center***, Biomedicines 2023, 11(12), 3227; https://doi.org/10.3390/biomedicines11123227, oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: gromadzenie i opracowanie danych do analizy, interpretację wyników oraz przygotowanie manuskryptu.

Mój udział procentowy w przygotowaniu publikacji określam jako 35%.

Wkład Łukasza Działacha w powstanie publikacji oceniam na 55%, obejmował on konceptualizację pracy, gromadzenie i opracowanie danych do analizy, interpretację wyników, przygotowanie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie ww. pracy jako część rozprawy doktorskiej lek. Łukasza Działacha.

Sobolewska Joanna

.....

(podpis oświadczającego)

Warszawa, 08.01.2026 r.

Lek. Joanna Sobolewska

OŚWIADCZENIE

Jako współautor pracy pt. ***Cushing's syndrome: a combined treatment with etomidate and osilodrostat in severe life-threatening hypercortisolemia,*** Hormones-International Journal of Endocrinology and Metabolism, 2022, DOI: 10.1007/s42000-022-00397-4, oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: konceptualizacja pracy, gromadzenie i opracowanie danych, przygotowanie manuskryptu.

Mój udział procentowy w przygotowaniu publikacji określam jako 40%.

Wkład Łukasza Działacha w powstanie publikacji oceniam na 50%, obejmował on konceptualizację pracy, gromadzenie i opracowanie danych, przygotowanie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie ww. pracy jako część rozprawy doktorskiej lek. Łukasza Działacha.

Sobolewska Joanna

.....

(podpis oświadczającego)

Warszawa, 08.01.2026 r.

Warszawa, 08.01.2026 r.

Lek. Joanna Sobolewska

OŚWIADCZENIE

Jako współautor pracy pt. ***Is there still a place for etomidate in the management of Cushing's syndrome? The experience of a single center of low-dose etomidate and combined etomidate-osilodrostat treatment in severe hypercortisolemia,*** Endocrine 87, 1305–1313 (2025), https://doi.org/10.1007/s12020-024-04135-1, oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: gromadzenie i opracowanie danych do analizy, przygotowanie manuskryptu.

Mój udział procentowy w przygotowaniu publikacji określam jako 7.5%.

Wkład Łukasza Działacha w powstanie publikacji oceniam na 80%, obejmował on konceptualizację pracy, gromadzenie i opracowanie danych do analizy, interpretację wyników, przygotowanie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie ww. pracy jako część rozprawy doktorskiej lek. Łukasza Działacha.

Sobolewska Joanna

.....
(podpis oświadczającego)

Warszawa, 08.01.2026 r.

Dr n. med. Wioleta Respondek

OŚWIADCZENIE

Jako współautor pracy pt. ***Cushing's Disease: Long-Term Effectiveness and Safety of Osilodrostat in a Polish Group of Patients with Persistent Hypercortisolemia in the Experience of a Single Center***, Biomedicines 2023, 11(12), 3227; https://doi.org/10.3390/biomedicines11123227, oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: gromadzenie i opracowanie danych do analizy, krytyczna rewizja artykułu oraz ostateczna akceptacja pracy.

Mój udział procentowy w przygotowaniu publikacji określam jako 5%.

Wkład Łukasza Działacha w powstanie publikacji oceniam na 55%, obejmował on konceptualizację pracy, gromadzenie i opracowanie danych do analizy, interpretację wyników, przygotowanie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie ww. pracy jako część rozprawy doktorskiej lek. Łukasza Działacha.

Wioleta Respondek
.....
(podpis oświadczającego)

Warszawa, 08.01.2026 r.

Dr n. med. Wioleta Respondek

OŚWIADCZENIE

Jako współautor pracy pt. ***Cushing's syndrome: a combined treatment with etomidate and osilodrostat in severe life-threatening hypercortisolemia,*** Hormones-International Journal of Endocrinology and Metabolism, 2022, DOI: 10.1007/s42000-022-00397-4, oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: gromadzenie i opracowanie danych, krytyczna rewizja artykułu oraz ostateczna akceptacja pracy.

Mój udział procentowy w przygotowaniu publikacji określam jako 5%.

Wkład Łukasza Działacha w powstanie publikacji oceniam na 50%, obejmował on konceptualizację pracy, gromadzenie i opracowanie danych, przygotowanie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie ww. pracy jako część rozprawy doktorskiej lek. Łukasza Działacha.

Wioleta Respondek
.....
(podpis oświadczającego)

Warszawa, 08.01.2026 r.

Dr n. med. Wioleta Respondek

OŚWIADCZENIE

Jako współautor pracy pt. ***Is there still a place for etomidate in the management of Cushing's syndrome? The experience of a single center of low-dose etomidate and combined etomidate-osilodrostat treatment in severe hypercortisolemia,*** Endocrine 87, 1305–1313 (2025), https://doi.org/10.1007/s12020-024-04135-1, oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: gromadzenie danych do analizy, krytyczna rewizja artykułu oraz ostateczna akceptacja pracy.

Mój udział procentowy w przygotowaniu publikacji określam jako 5%.

Wkład Łukasza Działacha w powstanie publikacji oceniam na 80%, obejmował on konceptualizację pracy, gromadzenie i opracowanie danych do analizy, interpretację wyników, przygotowanie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie ww. pracy jako część rozprawy doktorskiej lek. Łukasza Działacha.

Wioleta Respondek
(podpis oświadczającego)

Warszawa, 08.01.2026 r.

Dr n. med. Wioleta Respondek

OŚWIADCZENIE

Jako współautor pracy pt. ***Real-World Experience with Pasireotide-LAR in Cushing's Disease: Single-Center 12-Month Observational Study*** Journal of Clinical Medicine, 2025, DOI: 10.3390/jcm14082794, oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: gromadzenie danych do analizy krytyczna rewizja artykułu oraz ostateczna akceptacja pracy.

Mój udział procentowy w przygotowaniu publikacji określam jako 2.5%.

Wkład Łukasza Działacha w powstanie publikacji oceniam na 95%, obejmował on konceptualizację pracy, gromadzenie i opracowanie danych do analizy, interpretację wyników, przygotowanie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie ww. pracy jako część rozprawy doktorskiej lek. Łukasza Działacha.

Wioleta Respondek
.....
(podpis oświadczającego)

Warszawa, 08.01.2026 r.

Dr hab. n. o zdr. i n. med. Katarzyna Szamotulska

OŚWIADCZENIE

Jako współautor pracy pt. ***Cushing's Disease: Long-Term Effectiveness and Safety of Osilodrostat in a Polish Group of Patients with Persistent Hypercortisolemia in the Experience of a Single Center,*** Biomedicines 2023, 11(12), 3227; doi.org/10.3390/biomedicines11123227, oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: opracowanie danych do analizy.

Mój udział procentowy w przygotowaniu publikacji określam jako 2.5%.

Wkład Łukasza Działacha w powstanie publikacji oceniam na 55%, obejmował on konceptualizację pracy, gromadzenie i opracowanie danych do analizy, interpretację wyników, przygotowanie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie ww. pracy jako część rozprawy doktorskiej lek. Łukasza Działacha.

Katarzyna Szamotulska
.....
(podpis oświadczającego)

Warszawa, 08.01.2026 r.

Lek. Agnieszka Wojciechowska-Luźniak

OŚWIADCZENIE

Jako współautor pracy pt. ***Cushing's syndrome: a combined treatment with etomidate and osilodrostat in severe life-threatening hypercortisolemia,*** Hormones-International Journal of Endocrinology and Metabolism, 2022, DOI: 10.1007/s42000-022-00397-4, oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: krytyczna rewizja artykułu oraz ostateczna akceptacja pracy.

Mój udział procentowy w przygotowaniu publikacji określam jako 2.5%.

Wkład Łukasza Działacha w powstanie publikacji oceniam na 50%, obejmował on konceptualizację pracy, gromadzenie i opracowanie danych, przygotowanie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie ww. pracy jako część rozprawy doktorskiej lek. Łukasza Działacha.

Agnieszka Wojciechowska-Luźniak

.....

(podpis oświadczającego)

Warszawa, 08.01.2026 r.

Lek. Agnieszka Wojciechowska-Luźniak

OŚWIADCZENIE

Jako współautor pracy pt. ***Is there still a place for etomidate in the management of Cushing's syndrome? The experience of a single center of low-dose etomidate and combined etomidate-osilodrostat treatment in severe hypercortisolemia,*** Endocrine 87, 1305–1313 (2025), https://doi.org/10.1007/s12020-024-04135-1, oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: krytyczna rewizja artykułu oraz ostateczna akceptacja pracy.

Mój udział procentowy w przygotowaniu publikacji określam jako 2.5%.

Wkład Łukasza Działacha w powstanie publikacji oceniam na 80%, obejmował on konceptualizację pracy, gromadzenie i opracowanie danych do analizy, interpretację wyników, przygotowanie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie ww. pracy jako część rozprawy doktorskiej lek. Łukasza Działacha.

Agnieszka Wojciechowska-Luźniak
.....
(podpis oświadczającego)

Warszawa, 08.01.2026 r.

Dr n. med. Paweł Kuca

OŚWIADCZENIE

Jako współautor pracy pt. ***Is there still a place for etomidate in the management of Cushing's syndrome? The experience of a single center of low-dose etomidate and combined etomidate-osilodrostat treatment in severe hypercortisolemia,*** Endocrine 87, 1305–1313 (2025), https://doi.org/10.1007/s12020-024-04135-1, oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: krytyczna rewizja artykułu oraz ostateczna akceptacja pracy.

Mój udział procentowy w przygotowaniu publikacji określam jako 2.5%.

Wkład Łukasza Działacha w powstanie publikacji oceniam na 80%, obejmował on konceptualizację pracy, gromadzenie i opracowanie danych do analizy, interpretację wyników, przygotowanie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie ww. pracy jako część rozprawy doktorskiej lek. Łukasza Działacha.

Paweł Kuca
.....
(podpis oświadczającego)

Warszawa, 08.01.2026 r.

Prof. dr hab. n. med. Przemysław Witek

OŚWIADCZENIE

Jako współautor pracy pt. ***Cushing's Disease: Long-Term Effectiveness and Safety of Osilodrostat in a Polish Group of Patients with Persistent Hypercortisolemia in the Experience of a Single Center***, Biomedicines 2023, 11(12), 3227; https://doi.org/10.3390/biomedicines11123227, oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: konceptualizacja pracy, krytyczna rewizja artykułu oraz ostateczna akceptacja pracy.

Mój udział procentowy w przygotowaniu publikacji określam jako 2.5%.

Wkład Łukasza Działach w powstanie publikacji oceniam na 55%, obejmował on konceptualizację pracy, gromadzenie i opracowanie danych do analizy, interpretację wyników, przygotowanie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie ww. pracy jako część rozprawy doktorskiej lek. Łukasza Działacha.

.....
(podpis oświadczającego)

Warszawa, 08.01.2026 r.

Prof. dr hab. n. med. Przemysław Witek

OŚWIADCZENIE

Jako współautor pracy pt. ***Cushing's syndrome: a combined treatment with etomidate and osilodrostat in severe life-threatening hypercortisolemia,*** Hormones-International Journal of Endocrinology and Metabolism, 2022, DOI: 10.1007/s42000-022-00397-4, oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: krytyczna rewizja artykułu oraz ostateczna akceptacja pracy.

Mój udział procentowy w przygotowaniu publikacji określam jako 2.5%.

Wkład Łukasza Działacha w powstanie publikacji oceniam na 50%, obejmował on konceptualizację pracy, gromadzenie i opracowanie danych, przygotowanie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie ww. pracy jako część rozprawy doktorskiej lek. Łukasza Działacha.

.....
(podpis oświadczającego)

Warszawa, 08.01.2026 r.

Prof. dr hab. n. med. Przemysław Witek

OŚWIADCZENIE

Jako współautor pracy pt. ***Is there still a place for etomidate in the management of Cushing's syndrome? The experience of a single center of low-dose etomidate and combined etomidate-osilodrostat treatment in severe hypercortisolemia,*** Endocrine 87, 1305–1313 (2025), https://doi.org/10.1007/s12020-024-04135-1, oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: konceptualizacja pracy, krytyczna rewizja artykułu oraz ostateczna akceptacja pracy.

Mój udział procentowy w przygotowaniu publikacji określam jako 2.5%.

Wkład Łukasza Działach w powstanie publikacji oceniam na 80%, obejmował on konceptualizację pracy, gromadzenie i opracowanie danych do analizy, interpretację wyników, przygotowanie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie ww. pracy jako część rozprawy doktorskiej lek. Łukasza Działacha.

.....
(podpis oświadczającego)

Warszawa, 08.01.2026 r.

Prof. dr hab. n. med. Przemysław Witek

OŚWIADCZENIE

Jako współautor pracy pt. ***Real-World Experience with Pasireotide-LAR in Cushing's Disease: Single-Center 12-Month Observational Study*** Journal of Clinical Medicine, 2025, DOI: 10.3390/jcm14082794, oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: konceptualizacja pracy, krytyczna rewizja artykułu oraz ostateczna akceptacja pracy.

Mój udział procentowy w przygotowaniu publikacji określam jako 2.5%.

Wkład Łukasza Działacha w powstanie publikacji oceniam na 95%, obejmował on konceptualizację pracy, gromadzenie i opracowanie danych do analizy, interpretację wyników, przygotowanie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie ww. pracy jako część rozprawy doktorskiej lek. Łukasza Działacha.

.....
(podpis oświadczającego)

12. ANALIZA BIBLIOMETRYCZNA DOROBKU PUBLIKACYJNEGO

WARSZAWSKI
UNIWERSYTET
MEDYCZNY

BIBLIOTEKA UCZELNIANA

Nr referencyjny
BIBG/Punktacja/ 655 /2025/AM

Warszawa, 22.12.2025

Sz. Pan
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Endokrynologii i Diabetologii WUM

ANALIZA BIBLIOMETRYCZNA PUBLIKACJI
PANA ŁUKASZA DZIAŁACHA
WCHODZĄCYCH W SKŁAD CYKLU PUBLIKACJI STANOWIĄCYCH ROZPRAWĘ DOKTORSKĄ

Lp.	Opis bibliograficzny	Impact Factor	MNiSW	Najwyższy kwartyl*
Artykuły				
1.	**Działach Ł [korespondencyjny],** Respondek W, Witek P. Real-World Experience with Pasireotide-LAR in Cushing's Disease: Single-Center 12-Month Observational Study. Journal of clinical medicine. 2025;14(8):2794. *Rodzaj publikacji: praca oryginalna*	2,9	140	Q1
2.	**Działach Ł [korespondencyjny],** Sobolewska J, Respondek W, Wojciechowska-Luzniak A, Kuca P, Witek P. Is there still a place for etomidate in the management of Cushing's syndrome? The experience of a single center of low-dose etomidate and combined etomidate-osilodrostat treatment in severe hypercortisolemia. Endocrine. 2025;87(3):1305-1313. *Rodzaj publikacji: praca oryginalna*	2,9	100	Q2
3.	**Działach Ł [korespondencyjny],** Sobolewska J, Respondek W, Szamotulska K, Witek P. Cushing's Disease: Long-Term Effectiveness and Safety of Osilodrostat in a Polish Group of Patients with Persistent Hypercortisolemia in the Experience of a Single Center. Biomedicines. 2023;11(12):3227. *Rodzaj publikacji: praca oryginalna*	3,9	100	Q2

* Kwartyl z roku publikacji, według Impact Factor.

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4.	**Działach L**, Sobolewska J, Respondek W, Wojciechowska-Luzniak A, Witek P. Cushing's syndrome: a combined treatment with etomidate and osilodrostat in severe life-threatening hypercortisolemia. Hormones (Athens). 2022;21(4):735-742. *Rodzaj publikacji: opis przypadku*	3,2	70	Q3
	Łącznie:	**12,9**	**410**	-
Książki				
	-			
Rozdziały w książkach				
	-			

DYREKTOR
Biblioteki Uczelnianej
Warszawskiego Uniwersytetu Medycznego
mgr Agnieszka Czarnocka

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Nr referencyjny
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Warszawa, 22.12.2025

Sz. Pan
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ANALIZA BIBLIOMETRYCZNA CAŁOKSZTAŁTU DOROBKU PUBLIKACYJNEGO
PANA ŁUKASZA DZIAŁACHA,
W POSTĘPOWANIU O NADANIE STOPNIA NAUKOWEGO DOKTORA

Lp.	Opis bibliograficzny	Impact Factor	MNiSW	Najwyższy kwartyl[1]
I. Artykuły opublikowane w czasopismach naukowych lub w recenzowanych materiałach z konferencji międzynarodowych ujętych w aktualnym wykazie MNiSW[2]				
1.	**Działach L, [korespondencyjny],** Respondek W, Siejka A, Witek P. Prolonged adrenal suppression after osilodrostat discontinuation in a patient with Cushing's disease with eventual hypercortisolism relapse: Case Report and literature review. Frontiers in medicine. 2025;(12):1629387. *Rodzaj publikacji: opis przypadku, praca poglądowa*	3,0	70	Q1
2.	Laskowski G, **Działach L**, Maksymiuk-Kłos A, Witek P. Successful non-surgical treatment of bilateral macronodular adrenocortical disease with osilodrostat. Endokrynologia Polska. 2025;76(6):674-675. *Rodzaj publikacji: opis przypadku*	2,1	70	Q3
3.	**Działach L [korespondencyjny]**, Respondek W, Witek P. Real-World Experience with Pasireotide-LAR in Cushing's Disease: Single-Center 12-Month Observational Study. Journal of clinical medicine. 2025;14(8):2794. *Rodzaj publikacji: praca oryginalna*	2,9	140	Q1
4.	**Działach L [korespondencyjny],** Sobolewska J, Respondek W, Wojciechowska-Luzniak A, Kuca P, Witek P. Is there still a place for etomidate in the management of Cushing's syndrome? The experience of a single center of low-dose etomidate and combined etomidate-osilodrostat treatment in severe hypercortisolemia. Endocrine. 2025;87(3):1305-1313. *Rodzaj publikacji: praca oryginalna*	2,9	100	Q2

1 Kwartyl z roku publikacji, według Impact Factor.
[2] Wykaz sporządzony zgodnie z przepisami wydanymi na podstawie art. 267 ust. 2 pkt 2 lit. b Ustawy z dnia 20 lipca 2018 r. - Prawo o szkolnictwie wyższym i nauce (Dz. U. z 2022 r., poz. 574 z późn. zm.). Wykaz stanowi załącznik do komunikatu MNiSW z 5 stycznia 2024 r. w sprawie wykazu czasopism naukowych i recenzowanych materiałów z konferencji międzynarodowych.

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5.	**Działach Ł [korespondencyjny],** Sobolewska J, Zak Z, Respondek W, Witek P. Prolactin-secreting pituitary adenomas: male-specific differences in pathogenesis, clinical presentation and treatment. Frontiers in Endocrinology. 2024;(15):1338345. *Rodzaj publikacji: praca poglądowa*	4,6	100	Q1
6.	Sobolewska J, **Działach Ł,** Respondek W, Wojciechowska-Luźniak A, Witek P. Ectopic ACTH syndrome in the course of ACTH-secreting pancreatic neuroendocrine tumour in a patient with a pituitary lesion - diagnostic challenges and individual approach. Endokrynologia Polska. 2024;75(1):113-114. *Rodzaj publikacji: opis przypadku*	2,1	70	Q3
7.	Sobolewska J, **Działach Ł,** Kuca P, Witek P. Critical illness-related corticosteroid insufficiency (CIRCI) - an overview of pathogenesis, clinical presentation and management. Frontiers in Endocrinology. 2024;(15):1473151. *Rodzaj publikacji: praca poglądowa*	4,6	100	Q1
8.	**Działach Ł [korespondencyjny],** Sobolewska J, Respondek W, Wojciechowska-Luzniak A, Witek P. Pituitary apoplexy as the first manifestation of non-functioning pituitary neuroendocrine tumour. Endokrynologia Polska. 2024;75(1):111-112. *Rodzaj publikacji: opis przypadku*	2,1	70	Q3
9.	Dyrka K, **Działach Ł,** Niedziela M, Jonczyk-Potoczna K, Derwich K, Obara-Moszynska M. Central Diabetes Insipidus in Children as a Diagnostic Challenge. Clinical pediatrics. 2024;63(8):1044-1055. *Rodzaj publikacji: praca oryginalna, opis przypadku*	0,7	70	Q4
10.	**Działach Ł [korespondencyjny],** Wojciechowska-Luzniak A, Maksymowicz M, Witek P. Case report: A challenging case of severe Cushing's syndrome in the course of metastatic thymic neuroendocrine carcinoma with a synchronous adrenal tumor. Frontiers in Endocrinology. 2024;(15):1399930. *Rodzaj publikacji: opis przypadku*	4,6	100	Q1
11.	**Działach Ł [korespondencyjny],** Sobolewska J, Respondek W, Szamotulska K, Witek P. Cushing's Disease: Long-Term Effectiveness and Safety of Osilodrostat in a Polish Group of Patients with Persistent Hypercortisolemia in the Experience of a Single Center. Biomedicines. 2023;11(12):3227. *Rodzaj publikacji: praca oryginalna*	3,9	100	Q2
12.	Kober P, Rusetska N, Mossakowska BJ, Maksymowicz M, Pękul M, Zieliński G, Styk A, Kunicki J, **Działach Ł,** Witek P, Bujko M. The expression of glucocorticoid and mineralocorticoid receptors in pituitary tumors causing Cushing's disease and silent corticotroph tumors. Frontiers in endocrinology. 2023;(14):1124646. *Rodzaj publikacji: praca oryginalna*	3,9	100	Q2
13.	Sobolewska J, Żak Z, **Działach Ł,** Witek P: Autoimmune disorders associated with type 1 diabetes: clinical overview and principles of management. Paediatrics and Family Medicine. 2023; 19 (4): 295–304. *Rodzaj publikacji: praca poglądowa*	0,1	140	Q4

14.	**Dzialach I.**, Sobolewska J, Respondek W, Wojciechowska-Luzniak A, Witek P. Cushing's syndrome: a combined treatment with etomidate and osilodrostat in severe life-threatening hypercortisolemia. Hormones (Athens). 2022;21(4):735-742. *Rodzaj publikacji: opis przypadku*	3,2	70	Q3
15.	Obara-Moszynska M, **Dzialach I.,** Rabska-Pietrzak B, Niedziela M, Kapczuk K. Uterine Development During Induced Puberty in Girls with Turner Syndrome. Frontiers in endocrinology. 2021;(12):707031. *Rodzaj publikacji: praca oryginalna*	6,055	100	Q1
	Łącznie:	**46,755**	**1400**	-
II. Artykuły opublikowane przed 1.01.2019 r. w czasopismach ujętych w wykazie czasopism MNiSW z dnia 25.01.2017 r., o ile czasopismo uzyskało co najmniej 10 pkt.				
	-	-	-	-
	Łącznie:	-	-	-
III. Pozostałe artykuły				
	-	-	-	-
	Łącznie:	-	-	-
	Łącznie (cz. I- III):	**46,755**	**1400**	-
IV. Monografie naukowe/rozdziały w monografiach wydane przez wydawnictwa ujęte w wykazie MNiSW[3] lub jednostki organizacyjne podmiotów, których wydawnictwa są ujęte w tym wykazie				
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V. Pozostałe monografie lub rozdziały w monografiach				
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VI. Patenty				
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[3] Wykaz sporządzony zgodnie z przepisami wydanymi na podstawie art. 267 ust. 2 pkt 2 lit. a Ustawy z dnia 20 lipca 2018 r. - Prawo o szkolnictwie wyższym i nauce (Dz. U. z 2022 r., poz. 574 z późn. zm.). Wykaz ogłoszony komunikatem MEiN z dnia 22 lipca 2021 r. w sprawie wykazu wydawnictw publikujących recenzowane monografie naukowe.

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