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

SUMMARY

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.