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EDITORIAL

New drugs in pituitary diseases

Nuevos fármacos para las enfermedades hipofisarias

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In recent years, the field of endocrinology has experienced significant advancements in the treatment of pituitary diseases, driven by research and the development of new therapies. These advancements include the introduction of innovative medications and the re-evaluation of classic drugs for new indications. The most recent advances in the pharmacological treatment of pituitary diseases are presented below, with innovative therapies that seek to improve treatment efficacy and optimize patient outcomes through more personalized approaches.

With the aim of improving treatment adherence and reducing the burden associated with daily growth hormone (GH) injections, different formulations of long-acting GH (LAGH) have been developed, such as somapacitan (a reversible albumin-binding GH derivative), somatrogon (a fusion protein containing GH and three copies of the C-terminal peptide of human chorionic gonadotropin, hCG) and lonapegsomatropin (transcon GH).[1,2] Some of these formulations are now approved in several countries for use in children and adults. Effectiveness, safety, and tolerability of these LAGH formulations appear similar to daily GH injections in both age groups. Transitioning from daily to long-acting weekly formulations requires periodic serum IGF-1 monitoring. In adult patients with GH deficiency (AGHD), somapacitan administered once weekly demonstrated superiority over placebo, and the overall treatment effects and safety of somapacitan were in accordance with known effects and safety of GH replacement for up to 86 weeks of treatment. This suggests that somapacitan may offer an effective alternative to daily GH in AGHD.[3]

Medical treatment of acromegaly is currently performed through a trial-error approach using first generation somatostatin receptor ligands (fgSRLs) as first-line drugs, with an effectiveness of about 50%, and subsequent drugs are indicated through clinical judgment.[4] Some clinical, radiological, pathological and biomarkers can predict fgSRLs response. A different and more personalized approach for the treatment of acromegaly is possible employing classic drugs but modifying its use according with a different protocol. In the ACROFAST study, a clinical trial in which a protocol based on predictive biomarkers of fgSRLs was evaluated. Patients from a personalized treatment group were controlled in a shorter period of time.[5]

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Oral octreotide capsules (OOCs) have been employed in patients with acromegaly who previously demonstrated biochemical control while receiving injectable SRLs. OOCs may be an effective therapy for patients with acromegaly who previously were treated with injectable SRLs.[6] Patients with acromegaly maintained long-term biochemical response while receiving OOC, with no new adverse events observed with prolonged OOC exposure.[7] OOC have been associated with improved patient-reported quality of life measures compared with those reported for lanreotide and octreotide.[8]

Acromegaly treatment has advanced significantly in recent decades, and the perspective is that new options will be available in a short time, helping to improve disease control and to increase treatment convenience and, therefore, improving patient quality of life. Both paltusotine (a once daily oral nonpeptide selective agonist of somatostatin receptor type 2, SST2) and CAM2029 (an octreotide subcutaneous depot formulation) are somatotropinoma-directed drugs, that are in more advanced stages of development (phase 3 trials) than the drugs that block the GH receptor such as site 1-binding helix (S1H) and AZP-3813 (currently only phase 1 trials), having a higher probability of being available in the near future in clinical practice. Paltusotine will represent a novel alternative of oral treatment with a more convenient posology, and CAM2029 will allow more convenient administration of octreotide, with the possibility of self-injection.[9] In a recent phase 3 trial, replacement of injected SRLs by once-daily paltusotine was effective in maintaining both biochemical and symptom control in patients with acromegaly and was well tolerated.[10]

When surgical therapies have failed or are not feasible, medical therapy has been increasingly used for all types of endogenous Cushing syndrome (CS) as symptomatic treatment to control hypercortisolism. Medical therapy for Cushing's disease (CD) can be categorized into three groups: pituitary-targeting drugs, steroid synthesis inhibitors, and glucocorticoid receptor (GR) antagonists. Among the available medical therapies, pasireotide and osilodrostat are approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for use in patients with CD and CS, who have failed surgery or are poor surgical candidates. Mifepristone and levoketoconazole are FDA-approved medications for endogenous hypercortisolemia secondary to CS. Ketoconazole and metyrapone are officially approved for use by the EMA but are used *off label* in the United States. Cabergoline is used *off label*. The role for medical therapy for CD was limited for years, but in the last decade, important new developments in all three drug categories expanded the possibilities for (chronic) medical therapy. Perhaps the most interesting new drug is the steroid synthesis inhibitor osilodrostat. A complete normalization of urinary free cortisol has been reached in 77% of patients treated with osilodrostat.[11] Within this steroidogenesis inhibitor class of drugs, osilodrostat is the most potent in decreasing cortisol, but symptoms consistent with possible adrenal insufficiency may occur in almost half of the patients. Doses should be increased slowly and close observation is needed.[12]

Recently, there have been new developments in the use of classic medications with different indications or management methods. For example, in addition to its classic use for prolactinoma treatment, cabergoline could be an option for some patients with acromegaly, non-functioning pituitary adenomas and Cushing's disease.[13–15]

Craniopharyngiomas (CPs) are rare and clinically aggressive tumors. There are two types: the papillary CP (PCP), which is associated with BRAF-V600E mutations and the adamantinomatous CP (ACP), characterized by mutations in CTNNB1 (encoding beta-catenin). Treatment is not specific and mostly noncurative, and frequently includes surgery, which may achieve gross total or partial resection, followed by radiotherapy. More recently targeted therapies have been used, particularly in PCP, but also now in ACP and clinical trials are underway or in development.[16] In a phase 2 study in patients with newly diagnosed BRAF-mutated PCP, the BRAF-MEK inhibitor combination vemurafenib–cobimetinib showed a median tumor volume reduction of 91% and progression-free survival of 87% at 12 months in 15 of the 16 patients.[17] These results suggest that this targeted therapy may be an effective option for patients with previously untreated PCP.[18] New targeted therapies are underway also for ACP, like ERK inhibitor therapy and others, changing the landscape of CP management.[19]

Aggressive pituitary adenomas or pituitary neuroendocrine tumors (AgPitNETs) are defined by the presence of radiological invasion, a high rate of cell proliferation, resistance to conventional treatments, and/or a high propensity for recurrence. Lastly, there are the rare pituitary carcinomas, also known as metastatic PitNETs (MetPitNETs), which account for only 0.2% of cases and are defined by the presence of metastases. Surgery is considered the first-line treatment for AgPitNETs and MetPitNETs. Radiation therapy can be effective in controlling tumor growth and regulating hormone hypersecretion. Currently, there are no approved non-endocrine medical therapies for the management of AgPitNETs/MetPitNETs, mainly due to the lack of randomized controlled clinical trials. As a result, many of the medical therapies used are *off-label* drugs, and several are under investigation. Temozolomide (TMZ) with response rates of about 40%, is now recognized as the primary medical treatment following the failure of standard therapy (medical treatment, surgery, and radiotherapy) in AgPitNETs/MetPitNETs due to its ability to improve overall and progression-free survival rates in responding patients. Other therapeutic options include pituitary-targeted therapies (dopamine agonists and somatostatin analogs), hormonal antisecretory drugs, nonhormonal targeted therapies, radionuclide treatments, and immunotherapy.[20] Although no alternative therapies have been formally recommended after TMZ failure, growing evidence regarding potential second- or third-line therapeutic strategies has emerged. The most relevant therapies employed so far, namely immune checkpoint inhibitors, bevacizumab, peptide radionuclide receptor therapy, tyrosine kinase inhibitors and mTOR inhibitors.[21] Overall, immune checkpoint inhibitors have emerged as second-line treatment in MetPitNETs, with currently no evidence for a superior effect of dual therapy compared to monotherapy with PD-1 blockers. Bevacizumab has resulted in partial response in few patients; tyrosine kinase inhibitors and everolimus have generally not been useful. Considering that, AgPitNETs/MetPitNETs are rare, new therapies should preferably be evaluated in shared standardized protocols.

Prognostic and predictive markers to guide treatment decisions are needed and are the scope of ongoing research.[22]

In conclusion, recent advances in the pharmacological treatment of pituitary diseases, including new formulations of GH, octreotide, SRLs, new inhibitors of steroidogenesis, new targeted therapies, immunotherapy, and expanded use of classic drugs such as cabergoline, offer promising opportunities to improve the care of patients with pituitary diseases. Future directions should focus on continued research into new therapies, optimizing treatment regimens to increase adherence, and tailoring therapeutic strategies to individual patient needs. In addition, it is essential to identify new, more precise predictive markers to facilitate early detection and personalized management of the various pituitary disorders.

Conflicts of interest

The authors declare no conflict of interest.

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