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Current and emerging treatment approaches for acromegaly: A literature review

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ABSTRACT

This article reviews current therapies for managing acromegaly caused by pituitary adenomas. The literature analysis identifies three treatment approaches: Surgical intervention, medical treatment using first- and second-generation somatostatin analogs, growth hormone receptor antagonists, and radiotherapy. We analyzed each line regarding its adaptation to the individual situation of each patient and available prognostic factors for a positive response. The analysis concludes that the most advantageous approach remains to initiate treatment with surgical intervention, followed by subsequent utilization of other treatment lines starting from first-generation somatostatin analogs and, in case of their inefficacy, second-generation somatostatin analogs and growth hormone antagonists. Given the dynamic development of second-generation somatostatin analogs and growth hormone antagonists, which exhibit high therapeutic efficacy, radiotherapy diminishes in significance. It only applies to patients for whom all other treatment modalities have failed.

Keywords: Acromegaly, pituitary adenoma, growth hormone, pasireotide, pegvisomant

1. INTRODUCTION

Acromegaly is an endocrine disorder caused by excessive growth hormone (GH) secretion. This results in the stimulation of insulin-like growth factor 1 (IGF-1) production, which is responsible for the manifestation of symptoms. The most prominent effects include bone growth stimulation, excessive cartilage, and soft tissue growth, ultimately leading to organ enlargement and the characteristic phenotype of the disease, along with numerous serious complications (Chiloiro et al., 2022). If the disease is left untreated or is poorly controlled, it can reduce the quality of a patient's life and shorten life expectancy (Holdaway et al., 2008). The leading cause of excessive GH production as a result of a pituitary tumor is diagnosed in 98% of the cases (Bolanowski et al., 2019; Chiloiro et al., 2022).

Treatment modalities include surgical intervention as the first-line approach or using somatostatin analogs (SSAs) in cases where surgery is contraindicated.

Recently, novel therapies have been developed for acromegaly patients unresponsive to first-generation somatostatin analogs. Among these therapies are pasireotide, a second-generation somatostatin analog, and pegvisomant, a GH receptor antagonist, which have shown promising effects in controlling acromegaly in patients failing first-line treatment (Quiñones-Hinojosa, 2012; Bernabeu et al., 2015). This study aims to provide a comprehensive summary of the current knowledge regarding therapeutic methods in managing acromegaly and their observed effects. Through scrutiny of available clinical data and literature, our objectives are to identify critical features of the effectiveness and safety of the therapies employed and their relevance in managing patients who are unresponsive to standard treatment.

Epidemiology

According to estimates, the prevalence of acromegaly in Poland is approximately 70 cases per 1 million individuals, with an annual incidence rate of 3–4 new cases per 1 million individuals. The disease occurs with similar frequency in both sexes Capatina and Wass, (2015), with the most common age of diagnosis being between the fourth and sixth decades of life. Unfortunately, recent population studies suggest that the prevalence of acromegaly may be considerably higher than initially thought. Acromegaly is associated with increased mortality, shortening the lifespan of affected individuals by an average of 10 years (Bolanowski et al., 2019). However, recent studies indicate that effective disease control, maintaining average GH levels below 2,5 μg/l, and normalization of IGF-1 values to those appropriate for sex and age can lead to achieving a lifespan similar to that of the general population (Holdaway et al., 2008). Maintaining normal GH levels appears to be more crucial than IGF-1.

2. CLINICAL MANIFESTATIONS

The clinical presentation of the disease is initially nonspecific. It can lead to significant delays in diagnosis, averaging from 7 to 10 years from the onset of symptoms (Rajasoorya et al., 1994). Acromegaly affects nearly every organ system, with crucial red flag symptoms including the onset of diabetes or impaired glucose tolerance (affecting 40% to 52% of patients), hypertension (affecting 18% to 60% of patients), and sleep apnoea (affecting 67% to 75% of patients, compared to 13% in the general population) (Capatina and Wass, 2015; Mestron et al., 2004).

Additionally, typical features of the disease phenotype include enlargement of the hands and feet, headaches, hepatomegaly and splenomegaly, macroglossia, carpal tunnel syndrome (affecting 20% to 40% of patients), colonic polyps, and, in cases of large pituitary tumors, visual field disturbances (Capatina and Wass, 2015). Upon presentation of such symptoms, screening for acromegaly through serum IGF-1 level determination is recommended (Bolanowski et al., 2014). It should be noted that patients with elevated GH and IGF-1 levels are predisposed to developing malignancies, as IGF-1 acts as a cell proliferation stimulant. The highest risk is associated with colorectal cancer. Therefore, the Polish Society of Endocrinology recommends a colonoscopy every 2-3 years (Bolanowski et al., 2019).

Diagnosis

The easiest way to obtain a diagnosis is to measure levels of IGF-1 and GH in serum; if they are above reference levels, they indicate disease. In cases where GH elevation is absent, which may be due to its pulsatile secretion, but IGF-1 levels are high, additional testing is required. The first line test is GH measurement after an oral glucose tolerance test (OGTT), which remains the gold standard for diagnosing acromegaly. If there is no decrease in GH levels below <0,4 μg/l when using highly sensitivity tests and <1 μg/l when using older tests during hyperglycemia, it confirms the disease (Akirov et al., 2021). Definitive disease exclusion is achieved by obtaining GH levels <0,4 μg/l with IGF-1 within the reference range.

Additionally, obtaining a random GH measurement <1 μg/l rules out the disease (Capatina and Wass, 2015). Following the diagnosis of acromegaly, the imaging modality of choice for confirming or ruling out a pituitary tumor is contrast-enhanced magnetic resonance imaging (MRI), with computed tomography being an alternative in cases of contraindications or unavailability of MRI. Visual field testing is recommended in the presence of a pituitary macroadenoma near the optic chiasm (Katznelson et al., 2014). Failure to visualize a pituitary tumor raises suspicion of ectopic GH secretion and requires further investigation.

3. THERAPEUTIC METHODS

In the case of pituitary adenoma-induced acromegaly, the first-line treatment, as long as the tumor remains resectable, is surgical intervention (Melmed et al., 2002; Katznelson et al., 2011; Katznelson et al., 2014; Buchfelder and Schlaffer, 2016b). Approximately 95% of procedures are performed transsphenoidally using either endoscopic techniques or microsurgery, which remains the gold standard of surgical treatment (Dorward, 2010; Buchfelder and Schlaffer, 2016b). The effectiveness of surgery depends on the size, location, and histological characteristics of the lesion. The specialization of the center where the surgery is performed and the surgeon's experience also play a significant role (Bates et al., 2008). The more specialized the center is, the better results are observed. The measurement of this so-called good result is the change in GH and IGF-1 levels, which should be significantly lower than before the intervention.

Centers are highly specialized, where a single neurosurgeon performs at least 50 transsphenoidal resections yearly (Melmed et al., 2009). In highly experienced clinical centers, the rate of satisfactory disease remission after surgical intervention ranges from 75 to 90% for microadenomas and from 45 to 70% for macroadenomas (Buchfelder and Schlaffer, 2016b). Surgical intervention offers two significant benefits over alternative treatments. Firstly, it can eliminate the need to use somatostatin analogs by patients chronically because it is a radical intervention, which means an improvement in their quality of life. Efforts are also made to preserve part of the unchanged pituitary to avoid the need for supplementation with other hormones due to its insufficiency (Buchfelder and Schlaffer, 2009). Second, the cost of surgical treatment compared to other methods is significantly lower (Caulley et al., 2022).

Surgical treatment in the first-line therapy of acromegaly also demonstrates observed benefits for patients, even in cases of incomplete tumor resection requiring using somatostatin analogs in the form of lower drug doses and better response to treatment (Wass, 2005). Studies indicate that GH level reduction correlates with the degree of pituitary tumor resection, which later translates into better therapeutic outcomes (Colao et al., 2006). In the case of incomplete resection, classical reoperation is not considered a second-line treatment but may be considered in specific cases (Buchfelder and Schlaffer, 2016b). The use of preoperative therapy with somatostatin analogs remains controversial. Especially in terms of long-term effects, different authors are obtaining different results. Some advocate for its inclusion in therapy Biermasz et al., (1999), Buchfelder and Schlaffer, (2016a), while others argue that it does not provide therapeutic benefits (Colao et al., 1997; Mao et al., 2010).

However, short-term outcomes were consistently better for patients undergoing such treatment (Carlsen et al., 2008; Shen et al., 2010). However, such an approach is not a standard that may be considered for some patients. Second-line therapy in cases where normalization of GH and IGF-1 levels is not achieved after a surgical intervention or in patients disqualified from surgical treatment involves using somatostatin analogs (Bolanowski et al., 2019). It should be noted that skipping surgical intervention is associated with a lower percentage of achieved remissions, at 45% without surgical intervention and using somatostatin analogs, versus 67% after surgical intervention without using somatostatin analogs (Abu-Dabrh et al., 2014). First-generation somatostatin analogs provide satisfactory disease control in 35%-76% of patients (Chiloiro et al., 2022). These include octreotide and lanreotide (Majos et al., 2015).

Currently, no robust data shows one preparation's superiority over the other. Octreotide provides slightly better disease control regarding GH and IGF-1 levels Murray and Melmed, (2008) and more significant tumor mass reduction (Freda et al., 2005). The concept of resistance to first-generation somatostatin analogs still needs to be defined. Partial resistance to first-generation somatostatin analogs occurs when there is at least a 50% decrease in GH and IGF-1 secretion without achieving complete remission and at least a 20% reduction in tumor size. Full resistance to first-generation somatostatin analogs is attempted to be defined as a decrease in GH and IGF-1 levels below 50% of baseline values with unchanged tumor size or an increase in tumor size in any case (Colao et al., 2011; Chiloiro et al., 2022).

The reasons for resistance to first-generation somatostatin analogs may lie in either biochemical mechanisms resulting from tumor histological malignancy, which is significant in 30% of patients, or from its large size (Chiloiro et al., 2022). Several tumor characteristics are important prognostic factors for treatment response within the biochemical mechanisms. Two histological types of GH-producing tumors are distinguished based on the distribution of cytokeratin in cells: densely granulated (DG) and sparsely granulated (SG). Tumors with a scattered cytokeratin structure (SG) respond worse to treatment with first-generation somatostatin analogs. They are usually more extensive and invasive and occur in younger patients (Gomes-Porras et al., 2020). Somatostatin receptors on tumor cells are essential to make the tumor more susceptible to pharmacotherapy (Gola et al., 2006).

SSTR2 receptors are present in 95% of cases, and SSTR5 receptors are present in 85% of cases, a favorable prognostic factor. The cell proliferation index (Ki67) also plays a role in the therapeutic response assessment, with a high-level correlating with a poorer response

to treatment with first-generation somatostatin analogs (Gomes-Porras et al., 2020). Moreover, electron microscopy assessment of tumor preparations is functional in prognostic evaluation, as sparse granulation of the adenoma correlates with a poorer response to pharmacological treatment (Mayr et al., 2013; Kiseljak-Vassiliades et al., 2015). The tumor's hormonal activity level is also significant, with those with high GH secretion and, consequently, high IGF-1 levels responding poorly to treatment (Berton et al., 2022).

The second hypothesis regarding tumor size is supported by research indicating a correlation between the degree of radicality of tumor resection, GH, and IGF-1 levels and subsequent response to pharmacological treatment (Buchfelder and Schlaffer, 2016b). Recent studies have highlighted the significance of tumor imaging in MRI scans, suggesting that tumors with high signal intensity in the T2 sequence of pituitary MRI correlate with a poorer response to first-generation somatostatin analogs (Berton et al., 2022). This association is attributed to imaging patterns corresponding to sparsely granulated (SG) tumor types. Other factors contributing to the ineffectiveness of first-generation somatostatin analog therapy include incorrect drug dosing or patient non-adherence to treatment recommendations, accounting for the highest percentage of unsatisfactory disease control, reaching up to 40% of cases in Germany (Chiloir, 2022).

In patients where disease control is not achieved, consideration should be given to second-generation somatostatin analogs, such as pasireotide and growth hormone receptor antagonists, such as pegvisomant. Due to these drugs' molecular mechanisms of action, individual selection for each patient is imperative (Chiloir, 2022). Pasireotide, a synthetic somatostatin analog, binds to somatostatin receptors, inhibiting growth hormone. It is more effective than octreotide in reducing GH levels and achieving remission (Colao et al., 2014). A significant adverse effect of pasireotide is the induction of hyperglycemia, which affects 31% to 57% of patients (Colao et al., 2014; Gadelha et al., 2014). The second therapeutic option is the use of pegvisomant. It is a growth hormone receptor antagonist and acts by blocking GH activation. It has the highest affinity for SSTR5 but can also bind to SSTR 5, 2, 1, and 3 receptors.

Due to its different way of acting, other parameters, besides GH levels, are required to monitor disease activity during pegvisomant therapy. Although pegvisomant effectively lowers IGF-1 levels, it may paradoxically increase GH levels due to its mechanism of action. However, it has no clinical significance and does not mean deterioration in disease control (Van-der-Lely et al., 2001). That way of acting has its disadvantages because, during the therapy with pegvisomant, there may be a slightly higher risk of primary tumor growth, estimated at 2.2% (Freda et al., 2015). This is because pegvisomant does not exhibit as potent anti-proliferative effects on cells as somatostatin analogs. Pegvisomant has a significant advantage over somatostatin analogs because it does not induce hyperglycemia. It even improves glycaemic control and insulin sensitivity, which makes it a viable therapeutic option for patients with acromegaly and concomitant diabetes (Colao et al., 2006; Schreiber et al., 2007).

Both pasireotide and pegvisomant represent promising therapeutic options for patients with acromegaly who do not respond to traditional treatment with somatostatin analogs. Simultaneous pegvisomant and pasireotide therapy should be considered a last-line pharmacological treatment option, although it has yet to be routinely used in clinical practice. Studies have demonstrated its high efficacy, achieving IGF-1 normalization in 95% of patients undergoing this therapy (Neggers et al., 2009). Another treatment modality that some patients may consider is the addition of dopamine receptor agonists (DAs), such as cabergoline. While monotherapy with DAs is relatively ineffective and of diminishing clinical significance, it can enhance the efficacy of both somatostatin analogs and pegvisomant when administered concurrently (Sandret et al., 2011; Bernabeu et al., 2013).

If all therapies mentioned above fail, conventional fractionated radiotherapy remains the therapy of last resort (Capatina and Wass, 2015). Administered at moderate doses of 45-50 Gy, it is highly effective in controlling tumor size in 95% of patients Minniti et al., (2005a) and disease activity in 70-77% (Biermasz et al., 2000; Minniti et al., 2005b; Jenkins et al., 2006). However, it is associated with severe adverse effects, such as pituitary insufficiency, brain tumors (2.4% of cases) Minniti et al., (2005a), increased incidence of cerebrovascular events Brada et al., (1999), and optic nerve neuropathy (1-2% of cases). Radiotherapy's therapeutic effects take time to develop, and its side effects can appear gradually, making it essential to weigh its benefits against its drawbacks thoughtfully. Stereotactic radiosurgery (SRS) shows potential for minimizing side effects and providing more precise treatment, but it is still under development (Minniti et al., 2012).

4. EVALUATION OF TREATMENT EFFECTIVENESS

The method of assessing treatment efficacy depends on its type. The initial assessment can be conducted for surgical treatment by measuring the growth hormone (GH) level within a week post-surgery. This is the preferred method for evaluating disease activity in

the first three months post-operation. If the GH level is below two μg/l on the first day after surgery, it is a good prognostic factor for achieving complete remission (Krieger et al., 2003). After three months, assessment of the IGF-1 level is recommended (Feelders et al., 2005). The criteria for cure include maintaining IGF-1 values within the reference range for gender and age and a GH level below 0,4 μg/l during the oral glucose tolerance test (OGTT). This test can also be performed shortly after surgical intervention (Karavitaki et al., 2009; Capatina and Wass, 2015).

If acromegaly remission is confirmed by laboratory tests and the patient does not exhibit clinical symptoms of visual impairment or pituitary dysfunction, there is no need for magnetic resonance imaging (MRI). For somatostatin analog treatment, random GH measurements, the mean GH day curve (GHDC), and IGF-1 levels should be considered parameters for disease control (Giustina et al., 2010; Katznelson et al., 2011). OGTT should not be utilized in disease activity monitoring in patients treated with somatostatin analogs, as these drugs induce hyperglycemia and reduce insulin sensitivity (Carmichael et al., 2009). During pegvisomant treatment, only IGF-1 should be considered as a parameter for disease control (Giustina et al., 2010). GH levels do not correlate with disease control in this case because pegvisomant use increases GH secretion via feedback.

Also, some diagnostic tests may elevate GH levels due to their similarity to pegvisomant (Muller et al., 2004). The disease is considered well-controlled if the IGF-1 level is within the reference range for gender and age, the randomly sampled GH level is below one μg/l, and GH drops below 0.4 μg/l during OGTT (Giustina et al., 2010; Katznelson et al., 2011). Otherwise, the disease should be considered active, requiring treatment intensification or the initiation of further lines.

5. CONCLUSIONS

Numerous therapeutic options are available for treating acromegaly caused by GH-secreting pituitary adenomas. Due to the diverse therapeutic actions and adverse effect profiles of individual drugs, the choice of appropriate therapy for patients should be carefully considered each time. Introducing new drugs, such as second-generation somatostatin analogs and GH receptor antagonists, has significantly improved pharmacological treatment possibilities while pushing radiotherapy treatment into subsequent lines. This currently allows for disease control using a combination of surgical and pharmacological therapies with a favorable benefit-risk profile.

Author's Contributions

Conceptualization- PM and PS; Literature review- PM, UK, and PS; Writing – Abstract, PS, and CK; Writing – Introduction: PM; Writing – Epidemiology: CK; Writing - Clinical Manifestations: CK; Writing – Diagnosis: PS and UK. Writing - Therapeutic Methods: PM, PS and UK; Writing - Evaluation of Treatment Efficacy: PM and CK; Writing – Conclusions: PM; Editing and reviewing: PS, PM and UK. All authors have read and agreed with the published version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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