DOI: https://doi.org/10.5281/zenodo.14498464

REDUCING RESISTANCE IN DRUG TREATMENT OF ACROMEGALY

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Relevance. *Acromegaly is a severe disabling neuroendocrine disease caused by long-term excessive production of somatotropic hormone and insulin-like growth factor-1 in individuals with complete physiological growth. The problem of drug resistance in patients with acromegaly is quite common in clinical practice and requires a personalized approach taking into account various clinical, morphological, molecular genetic and laboratory predictors of sensitivity to the choice of treatment method. Today, first-generation somatostatin analogues are in most cases first-line drugs in the drug treatment of acromegaly, but up to 50% of patients do not achieve biochemical remission of the disease. The prognosis of sensitivity to somatostatin analogues is of great importance, and the selection of patients for whom this therapy will obviously be unsuccessful allows us to immediately offer alternative treatment. The presented review summarizes potential predictors of sensitivity and resistance to existing drug treatment of acromegaly, discusses possible ways and means of overcoming the resistance to therapy, offers options for a personalized approach to choosing a treatment strategy in the absence of disease control against the background of monotherapy with somatostatin analogues, including an "off-label" combination. Timely addition of the growth hormone receptor antagonist pegvisomant allows avoiding repeated neurosurgery, radiation therapy or the administration of excessively high doses of somatostatin analogues. Optimal use of mono- or combination therapy helps achieve biochemical remission in most treatment-resistant patients.*

KEYWORDS:*acromegaly; biochemical monitoring; drug therapy; resistance; somatostatin analogues; pegvisomant; combination therapy.*

INTRODUCTION

Acromegaly is a severe neuroendocrine disease caused by long-term excessive production of somatotropic hormone (STH) and its-mediated hypersecretion of insulin-like growth factor-1 (IGF-1) in individuals with completed physiological growth [1]. According to various sources, the prevalence of acromegaly is 28–137 cases per 1 million population, the incidence is 2–11 new cases per 1 million per year [2–4]. In the absence of timely and adequate treatment, acromegaly leads to the development of various complications, progressive disability, and significantly reduces life expectancy [2]. The main causes of early mortality are complications caused by long-term hyperproduction of STH: cardiovascular diseases, diabetes mellitus and its complications (micro- and macroangiopathy), respiratory diseases, malignant neoplasms of the gastrointestinal tract (GIT), and some others [5]. Modern approaches to the treatment of acromegaly are aimed at reducing the severity of symptoms, preventing and correcting complications of the disease, reducing the size of the tumor secreting STH, and normalizing biochemical markers of acromegaly activity. Achieving these goals increases survival and improves the quality of life of patients [6]. MODERN METHODS OF TREATMENT OF ACROMEGALIA Currently, three methods of treatment of acromegaly are available - neurosurgical (endoscopic adenomectomy by transnasal transsphenoidal approach), drug therapy (somatostatin analogs, dopamine agonists and STH receptor antagonists), fractional stereotactic radiation therapy or stereotactic radiosurgery [1, 6, 7]. According to international consensus and Russian clinical guidelines, surgery is a priority treatment method, allowing for rapid normalization of STH and IGF-1 levels [6, 7]. The main factor that largely determines the success of surgical treatment is the qualification of the neurosurgeon, while the radicality of the removal of somatotropinomas primarily depends on the size and degree of tumor invasion into the cavernous sinus [8]. However, long-term biochemical control of the disease after tumor resection is achieved in less than 65% of cases [9, 10]. This is mainly due to the predominance of pituitary macroadenomas, which make up 82% according to the unified Russian registry of tumors of the hypothalamic-pituitary region [1], which does not allow for complete resection of the tumor and is initially considered a predictor of an unfavorable postoperative prognosis. Similar data on the incidence of macroadenomas among patients with acromegaly are presented in the combined national registry of acromegaly (19 countries) [11]. Radiation therapy is usually considered as an additional treatment method when neurosurgical treatment is ineffective and the pituitary tumor is resistant to conservative therapy. Today, radiation therapy in our country, as in a number of other countries,ranks last in importance in the treatment of acromegaly [1, 11]. Negative consequences of radiation therapy include delayed clinical effect and high

percentage of hypopituitarism development (up to 50% of cases), and the frequency of achieving remission of the disease after stereotactic radiosurgery is from 25 to 60% over the next 10-15 years and requires the appointment of drug treatment for a long period [12, 13]. In recent decades, new pharmacological drugs with multidirectional action have entered clinical practice, which have proven their effectiveness in controlling secretory and, in some cases, proliferative tumor activity. In connection with the improvement and spread of neurosurgical treatment, drug therapy is mainly used as a second line, prescribed in case of ineffectiveness of previous transsphenoidal adenomectomy [6]. Today, first-generation somatostatin analogues (octreotide and lanreotide) are considered first-line drugs in the drug treatment of acromegaly in most cases, while dopamine agonists and STH receptor antagonists are usually prescribed when somatostatin analogues are ineffective [7, 14]. When monotherapy is ineffective, combination drug therapy is practiced (Fig. 1). FIRST-GENERATION SOMATOSTATIN ANALOGS USED IN CLINICAL PRACTICE Octreotide is the first somatostatin analogue used in clinical practice since the mid-1980s. Short-acting octreotide drugs are currently not used for the long-term treatment of acromegaly due to the need for frequent injections. They can be prescribed as an adjunct to prolonged-release octreotide in case of severe cephalgic syndrome [6]. Another actively used first-generation synthetic somatostatin analogue is lanreotide, a synthetic peptide containing the amino acids D-alanine and D-tryptophan, which increase the stability of the molecule and enhance the selectivity of binding to somatostatin receptors (SSR) [15]. Indications for therapy with somatostatin analogues are the expectation of the effect of radiation therapy, non-radical nature of transsphenoidal adenomectomy, contraindications to surgical treatment due to the patient's somatic status or tumor growth characteristics, as well as the patient's refusal of surgical intervention [16]. There are reports on the possible use of this group of drugs to relieve cephalgic syndrome in the preoperative period [17]. According to a meta-analysis published in 2005, first-generation somatostatin analogues are effective in normalizing STH and IGF-1 levels in approximately 55% of patients [18].In later studies, the frequency of achieving a safe level of STH and normalization of IGF-1 decreased to 20–30% with octreotide and to 30–50% with lanreotide [19–21]. Such discrepancies in the results of studies are due to the preliminary selection of obviously sensitive patients, which led to a possible overestimation of the effectiveness of long-term treatment with somatostatin analogues in acromegaly. In addition, the use of only one hormonal indicator (STH or IGF-1) as an endpoint may also lead to higher efficacy rates [22]. In addition to the antisecretory effect, somatostatin analogues have a pronounced antiproliferative effect due to the inhibition of proliferation of both normal and tumor cells. It has been shown that activation of CSR subtypes 1, 2, 4 and 5 leads to cell cycle

arrest, while the effect on CSR subtypes 2 and 3 is accompanied by induction of apoptosis [23]. The action of somatostatin analogues is also possible indirectly, due to a decrease in the production of vascular endothelial growth factor and suppression of angiogenesis [24]. According to the literature, a decrease in tumor size is observed in 53–85% of cases, which is an undeniable advantage of somatostatin analogues over other drugs for the treatment of acromegaly [25, 26]. The prognosis of sensitivity to somatostatin analogues is of great importance, and the selection of patients in whom this therapy will be successful provides invaluable assistance in choosing the optimal treatment method. PREDICTORS OF RESISTANCE TO FIRST-GENERATION SOMATOSTATIN ANALOGUES Existing clinical guidelines define the criteria for the effectiveness of acromegaly treatment and disease remission as achieving the IGF-1 level corresponding to the gender and age norm and a decrease in STH by 1.0 ng/ml [6]. There are several approaches to defining the concept of "resistance" in the literature. According to the clinical point of view, resistance to drug treatment is interpreted, on the one hand, as the absence of normalization of biochemical parameters (STH and IGF-1), and on the other hand, as an increase in tumor size or its decrease by less than 20% compared to the initial volume, assessed no earlier than after 12 months of continuous treatment. In the case of a decrease in the IGF-1 level by more than 50% of the initial, but without achieving normalization of this indicator even against the background of maximum doses of somatostatin analogs, resistance can be considered partial [27]. Although most investigators report a close association between biochemical control of acromegaly activity and tumor size reduction [28], in some patients such a relationship is not observed [29]. In recent years, many in vitro and in vivo studies have focused on identifying a number of potential clinical, immunohistochemical, and molecular markers of sensitivity and resistance to somatostatin analog therapy (Table 1) [30, 31].Some of the predictors of the effectiveness of this group of drugs are the features of the receptor phenotype of various STH-secreting pituitary tumors, the study of which is the subject of the largest amount of literature data. Somatostatin receptors are a family of G-protein-coupled receptors, through which somatostatin realizes its biological effects in the body. To date, 5 subtypes of SSR (SSR 1–5) have been identified, which are expressed by different types of cells in neuroendocrine tumors, the gastrointestinal tract, pancreas, lungs, and other localizations, as well as pituitary adenomas, paragangliomas, meningiomas, and some other types of tumors [32]. In vitro studies have demonstrated preferential binding of first-generation somatostatin analogues to subtype 2 SSRs and, to a lesser extent, to subtype 5 SSRs, while the second-generation somatostatin analogue (pasireotide), on the contrary, is highly tropic to subtypes 4 and 5 SSRs [33]. In STH-secreting pituitary tumors, subtype 2 SSRs are also predominantly detected in more

than 95% of adenomas, with subtype 5 SSRs being present somewhat less frequently (85% of cases). Subtypes 1 and 3 SSRs are found in approximately 40% of somatotropinomas, while subtype 4 SSRs are virtually nonexistent [30, 34]. It is assumed that activation of CCP subtypes 2 and 5 is the main mechanism underlying the suppression of STH secretion, blocking the proliferative activity of tumor cells and preventing further development of pathological changes [35]. To date, highly specific rabbit monoclonal antibodies to CCP subtype 2A (clone UMB-1) have been developed, as well as a clear system for assessing their expression, which reliably demonstrates that a high level of CCP 2A expression correlates with the response to treatment with somatostatin analogs [36, 37]. Indeed, tumors with high expression of CCP subtype 2 are more sensitive to therapy with somatostatin analogs, which has been proven in a large number of studies. The response rate to treatment is approximately 50–53%, whereas with low expression of CCP subtype 2, treatment is effective only in 15–20% of cases [37, 38]. However, even with high expression of the 2nd subtype of SSR, up to 50% of patients receiving treatment with first-generation somatostatin analogues are resistant to this drug therapy [39]. One of the reasons may be point gene mutations of SSR, which are capable of changing the species structure of the receptor apparatus of cells and, accordingly, their sensitivity to somatostatin [40]. In addition, in the study of Taboada G. et al. [41], it was suggested that the detection of a low SSR 2/SSR 5 ratio during immunohistochemical examination predicts resistance to therapy with first-generation somatostatin analogues. In addition to SSR, the histological characteristics of somatotropinomas also determines sensitivity to somatostatin analogues. Tumors consisting of densely granulated chromophilic (acidophilic) cells,predominantly express subtype 2 SSR and are characterized by the highest sensitivity to first-generation somatostatin analogues, whereas in sparsely granulated and mixed pituitary tumors, subtype 5 SSR is expressed to a greater extent, which, due to the peculiarity of the receptor phenotype, explains the low sensitivity to treatment [37]. When comparing the frequency of achieving biochemical control of acromegaly in the postoperative period depending on the histological characteristics of the tumor, it was shown that patients with densely granulated tumors responded to treatment with somatostatin analogues in 70–90% of cases and demonstrated a more pronounced decrease in IGF-1 compared to patients with a sparsely granulated tumor type according to immunohistochemical studies [37, 42]. To date, there are conflicting data regarding the prognostic value of the Ki-67 proliferative activity index and the response to therapy with somatostatin analogues. Several studies have shown that high proliferative activity of somatotropin is associated with low sensitivity to first-generation somatostatin analogues [43, 44], but this issue remains a subject of debate and does not allow for an unambiguous recommendation for the use of the Ki-67 index as a

predictive marker. In most studies, the efficacy of somatostatin analogues was assessed in the postoperative period, but there are reports of patients who underwent neurosurgical treatment after long-term therapy with somatostatin analogues. In such studies, the histological type of the resected tumor correlated with the preoperative response to therapy with somatostatin analogues [42, 45]. It is assumed that invasive tumor growth, which prevents the possibility of its complete resection, reduces the frequency of achieving remission both after neurosurgical treatment and in response to therapy with somatostatin analogues. However, previous radiation therapy increases the likelihood of IGF-1 normalization in the late period while taking somatostatin analogs, while the effect on the level of STH is insignificant [46]. Finally, dysfunctions of proteins such as AIP (aryl hydrocarbon receptor-interacting protein), Zac1 (zinc finger protein), RKIP (phosphorylated Raf-kinase inhibitory protein), E-cadherin, β-arrestin, involved in the transmission of intracellular signals after the interaction of somatostatin analogs with CCP, somatic mutations in somatotrophs can also be the causes of variability in response to therapy with somatostatin analogs [47]. WAYS TO OVERCOME RESISTANCE TO SOMATOSTATIN ANALOGUESWhen comparing the frequency of achieving biochemical control of acromegaly in the postoperative period depending on the histological characteristics of the tumor, it was shown that patients with densely granulated tumors responded to treatment with somatostatin analogs in 70–90% of cases and demonstrated a more pronounced decrease in IGF-1 compared to patients with a sparsely granulated tumor type according to immunohistochemical studies [37, 42]. To date, there are conflicting data regarding the prognostic value of the Ki-67 proliferative activity index and the response to somatostatin analog therapy. Several studies have shown that high proliferative activity of somatotropin is associated with low sensitivity to first-generation somatostatin analogs [43, 44], but this issue remains a subject of discussion and does not allow us to unambiguously recommend the use of the Ki-67 index as a predictive marker. Most studies have evaluated the efficacy of somatostatin analogs in the postoperative period, but there are reports of patients who underwent neurosurgical treatment after long-term therapy with somatostatin analogs. In such studies, the histological type of the resected tumor correlated with the preoperative response to somatostatin analog therapy [42, 45]. It is assumed that invasive tumor growth, which prevents the possibility of its complete resection, reduces the frequency of achieving remission both after neurosurgical treatment and in response to somatostatin analog therapy. However, previous radiation therapy increases the likelihood of normalization of IGF-1 in the late period against the background of taking somatostatin analogs, while the effect on the level of STH is insignificant [46]. Finally, dysfunctions of proteins such as AIP (aryl hydrocarbon receptor-interacting protein), Zac1 (zinc finger protein),

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To date, there are several therapeutic options for increasing the effectiveness of therapy with somatostatin analogues (see Fig. 1). The standard starting dose of prolonged-release octreotide preparations is 20 mg once every 28 days, lanreotide - 90 mg monthly with the possibility of reducing the dose to 60 mg or increasing it to 120 mg. If therapy is ineffective after 3-6 months, the octreotide dose can be increased to 3 or 40 mg. In the study by Colao A. et al. [57], an increase in the octreotide dose to 40 mg/28 days contributed to the normalization of IGF-1 levels and the achievement of biochemical control of the disease in 35% of patients with partial resistance to somatostatin analogues. The efficacy and safety of reducing the interval between injections to 21 days or increasing the prolonged-release octreotide dose to 60 mg/28 days was studied in a multicenter, open-label, randomized study. The use of octreotide LAR® in high doses (60 mg/28 days) contributed to a significant decrease in the level of IGF-1 in 90% of cases compared with the group of patients receiving treatment at a dose of 30 mg/21 days. Thus, a reduction in the interval between drug administrations is less effective in achieving biochemical control of the disease compared with an increase in the dose of the drug. A recent study by Giustina A. et al. [59] showed that an increase in the dose of lanreotide Autogel® (180 mg/28 days) and more frequent administration of the drug (120 mg/21 days) normalize IGF-1 levels in approximately 30% of patients with acromegaly whose disease cannot be controlled with standard doses. However, the regimen of increasing the dose was most effective compared with a reduction in the interval between injections. Thus, increasing the dose of extended-release octreotide or decreasing the intervals between injections when treating with extended-release lanreotide may help to achieve biochemical control of the disease. In case of severe resistance, intra-group replacement of octreotide with lanreotide or pasireotide "off-label" is possible [60]. SECOND-GENERATION SOMATOSTATIN ANALOGUES Pasireotide is a long-acting, multiligand analogue of natural somatostatin that affects CSR 1–3 and CSR 5 subtypes. In vitro studies have shown that pasireotide has 40-, 30-, and 5-fold higher binding affinity for CSR 5, CSR 1, and CSR 3 subtypes, respectively, compared to octreotide [61]. Due to this, the use of pasireotide may be effective in patients resistant to first-generation somatostatin analogues, while sensitivity to the drug correlates with the expression of the 5th subtype of SSR in tumor cells, which was demonstrated in the work of Iacovazzo D. et al. [37] (see Table 1).In a prospective, randomized, double-blind study, pasireotide 40 mg/28 days in patients with acromegaly demonstrated significantly greater efficacy than extended-release octreotide (20 mg/28 days) in achieving biochemical disease control (31.3% vs. 19.2%, p=0.007), but both drugs were equally effective in achieving safe GH levels (48.3% in the pasireotide group and 51.6% with octreotide, p=0.002) [62].

CONCLUSION.

The problem of resistance to therapy in patients with acromegaly is quite common in clinical practice and requires a personalized approach taking into account various clinical, morphological, molecular genetic and laboratory predictors of sensitivity to the choice of treatment method. Today, first-generation somatostatin analogues are in most cases first-line drugs in the drug treatment of acromegaly, but up to 50% of patients do not achieve biochemical remission during therapy. One of the possible ways to overcome resistance is to increase the octreotide dose or reduce the inter-injection intervals during treatment with lanreotide, as well as intra-group replacement of octreotide with lanreotide. Thanks to the creation and introduction into clinical practice of new drugs, primarily the growth hormone receptor antagonist pegvisomant, the possibilities and effectiveness of treating patients with acromegaly resistant to somatostatin analogues have significantly expanded. In cases of severe resistance or poor tolerance to somatostatin analogues, the addition of pegvisomant is indicated to achieve normalization of IGF-1 levels. Further study of the possibility of using pegvisomant as first-line therapy and additional prospective studies are needed.

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