

Graves' disease – management of Graves' orbitopathy and thyrotoxicosis, including new therapies

Choroba Gravesa i Basedowa – postępowanie w orbitopatii tarczycowej i tyreotoksykozie z uwzględnieniem nowych terapii

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KEYWORDS:

- Graves' disease
- Graves' orbitopathy
- thyrotoxicosis
- new therapies

ABSTRACT

Graves' disease (GD) is the most common cause of hyperthyroidism in countries with adequate iodine supply. Its main extrathyroid manifestation is thyroid orbitopathy (TO), also known as Graves' orbitopathy (GO) or thyroid eye disease (TED). For many years, thyrotoxicosis has been treated with antithyroid drugs, radioactive iodine therapy, and thyroidectomy. Glucocorticoids have remained the standard treatment of TED. Currently, there is a growing trend of using targeted therapies in the treatment of GO. The significant development of immunobiology, a better understanding of the pathophysiology of the disease, and a multitude of studies on new therapies give hope for better treatment results and an improvement in the quality of life of patients.

The aim of the paper is to discuss the current principles of management of Graves' disease, including GO, with particular emphasis on new therapeutic methods. The potent role of K1-70TM and small molecule thyroid stimulating hormone (TSH) receptor antagonists in the treatment of hyperthyroidism is indicated. Not only do we point out the promising outcomes of combining glucocorticoids with mycophenolates, but also highlight the use of teprotumumab, rituximab, cyclosporin A, azathioprine, methotrexate, tocilizumab, and sirolimus in the therapy of active moderate to severe form of orbitopathy. The protective and supportive effect of statins in the treatment of GO is noted. The limitations of the research results mentioned in the paper are remarked and the need for further randomized studies of long-term safety and efficacy in a larger group of patients is underlined.

SŁOWA KLUCZOWE:

- Choroba Gravesa i Basedowa
- orbitopatia tarczycowa
- tyreotoksykoza
- nowe terapie

STRESZCZENIE

Choroba Gravesa i Basedowa stanowi najczęstszą przyczynę nadczynności tarczycy w krajach o prawidłowej podaży jodu, a jej główną pozatarczycową manifestacją jest orbitopatia tarczycowa, znana także jako orbitopatia Gravesa lub tarczycowa choroba oczu. Od wielu lat w leczeniu tyreotoksykozy stosuje się tyreostatyki, terapię jodem promieniotwórczym oraz tyreoidektomię, a standardem leczenia tarczycowej choroby oczu pozostają glikokortykosteroidy. Obecnie widoczny jest rosnący trend stosowania terapii celowanych w leczeniu orbitopatii tarczycowej. Znaczący rozwój immunobiologii, lepsze zrozumienie patofizjologii choroby i mnogość badań nad nowymi terapiami dają nadzieję na lepsze wyniki leczenia i poprawę jakości życia pacjentów.

Celem pracy jest omówienie aktualnych zasad postępowania w chorobie Gravesa i Basedowa, w tym orbitopatii tarczycowej, ze szczególnym uwzględnieniem nowych metod terapeutycznych. Wskazujemy potencjalną rolę K1-70TM i drobnocząsteczkowych antagonistów receptora TSH w leczeniu hipertyreozы. Przedstawiamy obiecujące efekty połączenia glikokortykosteroidów z mykofenolanami, a także uwzględniamy zastosowanie teprotumumabu,

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rituximabu, cyklosporyny A, azatiopryny, metotreksatu, tocilizumabu i sirolimusu w terapii aktywnej umiarkowanej do ciężkiej postaci orbitopatii. Zauważamy ochronny i wspomagający wpływ statyn w leczeniu tarczycowej choroby oczu. Dostrzegamy ograniczenia przytoczonych wyników badań i podkreślamy potrzebę dalszych, randomizowanych badań nad długoterminowym bezpieczeństwem i skutecznością terapii wśród większej grupy pacjentów.

History

Although the first descriptions of patients with symptoms characteristic of Graves' disease (GD) date back about 1000 years, the discovery of the disease is attributed independently to the Irish physician Robert James Graves and the German physician Karl Adolph von Basedow. The patients described by them in the first half of the 19th century manifested exophthalmos, palpitations, goitre, and nervousness (1). Initially, cardiac disorders were suspected as the cause of the disease, followed by neurological disorders. At the end of the 19th century, the positive effect of thyroidectomy on reducing the symptoms of the disease was noticed and the attention of physicians was directed to the thyroid gland. In 1930, thyroid stimulating hormone (TSH) was discovered, and 28 years later the long-acting thyroid stimulator (LATS) was identified, which is now known as thyrotropin receptor antibodies (TSH-R-Ab) (1).

Epidemiology

Graves' disease is the most common cause of hyperthyroidism in countries without iodine deficiency (2). The annual incidence is about 20 cases/100,000, with a peak incidence between 30-60 years of age, 5-10 times more often in women (3). The cause of female predisposition to the disease is not entirely clear. The influence of sex hormones or, due to the more frequent occurrence of the disease also in postmenopausal women [until the age of 65, then the proportions even out (2)], X chromosome inactivation is suggested (4). Genetic predisposition, and environmental conditions such as stress, infections, smoking, high iodine intake, and vitamin D deficiency may contribute to the onset of the disease (3, 5, 6).

New insights into the pathogenesis

In GD, autoantibodies that bind to TSH receptors are produced. These receptors are found mainly in the membrane of thyroid follicular cells and also in the orbital fibroblasts (7). Depending on the type of action, either inhibitory, neutral, or stimulatory TSH-R-Ab can be distinguished, with most of them having stimulatory functionality. As a consequence, in the thyroid tissue there is an excessive, uncontrolled secretion of thyroid hormones, a proliferation of thyrocytes and as a result thyrotoxicosis and goiter develop. In the orbits, the antibodies have pro-inflammatory effects, leading to adipogenesis, accumulation of hyaluronic acid, and tissue oedema. Available bioassays are able to distinguish between different types of TSH-R-Ab, which allows for the determination of the concentration of stimulatory antibodies only (8).

In recent years, the role of the insulin-like growth factor 1 (IGF-1) receptor as another autoantigen in the pathogenesis of thyroid eye disease has been discovered. This receptor forms a physical and signaling complex with the TSH receptor (7, 9, 10). Overexpressed on orbital fibroblasts, B and T lymphocytes, it contributes to the production of interleukins

or extracellular matrix molecules, causing the expansion of adipose and muscle tissue (11).

The production of pro-inflammatory cytokines, such as interleukin 6 (IL-6) and interleukin-17 (IL-17), is increased in patients with GD. It is suspected that cytokines may stimulate the TSH receptor on orbital fibroblasts (12), and IL-17 may additionally promote fibrosis.

There are reports that antibodies against carbonic anhydrase 1 and alcohol dehydrogenase 1B were found more often in the connective tissue of orbits in patients with thyroid orbitopathy compared to controls (13), and the expression of 11betahydroxysteroid dehydrogenase 1 might promote the development of orbitopathy by inducing adipogenesis (14).

Researchers are looking for a link between the gut microbiome and Graves' disease. It has been noted that the classes *Deltaproteobacteria* and *Mollicutes*, as well as the genera *Ruminococcus torques* group, *Oxalobacter*, and *Ruminococcaceae* UCG 011 were identified as risk factors for GD, while the family *Peptococcaceae* and the genus *Anaerostipes* seemed to have a protective effect (15).

Clinical presentation

According to current observations, the symptoms of the disease at the time of diagnosis are now slightly milder than in the past (16, 17). Earlier diagnosis, lower frequency of smoking, and proper iodine intake are the probable causes.

In addition to the commonly known symptoms of thyrotoxicosis, in GD there are specific extrathyroidal symptoms resulting also from the autoimmune process. The most common extrathyroid manifestation of the disease, leading to serious consequences, is thyroid orbitopathy (TO), also known as Graves' orbitopathy (GO) or thyroid eye disease (TED). Meta-analyses have shown that the prevalence of GO is even 30-40% in patients with GD (18). The disorder may vary in severity, from redness and swelling of the conjunctiva and eyelids, pain in the eyeballs, through proptosis, double vision (diplopia), and even compression neuropathy of the optic nerve or serious damage to the cornea, which may lead to the loss of vision (19). For many patients it is also a cosmetic defect.

Other, less common symptoms characteristic of GD, occurring only in patients with orbitopathy, include thyroid dermopathy, otherwise known as pretibial oedema, and acropachy, manifesting as finger clubbing. They occur in approximately 4% and 1.5% of patients, respectively (20).

Treatment of hyperthyroidism

So far, there has been no causal treatment, and therapies aimed mainly at reducing symptoms. Over the last few decades, the proposed methods of treatment have not undergone major changes. In patients, depending on the clinical presentation and age, antithyroid drugs, radioactive iodine therapy or thyroidectomy have been used.

Antithyroid drugs

Most patients begin treatment for hyperthyroidism with antithyroid drugs (ATD) for 12-18 months. Not only do thionamides decrease thyroid hormone synthesis by inhibiting thyroid peroxidase, but also have a weak immunosuppressive effect. The drug of choice is oral thiamazole in the initial dose of 20 or 30 mg daily, depending on the severity of symptoms and the concentration of free thyroid hormones (21). Propylthiouracil is the drug of choice in the first trimester of pregnancy. In patients with persistent TSH-R-Ab or hyperthyroidism after completing a course of treatment, which concerns up to 50% of patients (22), three options may be offered: continuation of the treatment with low doses of thiamazole with the antibody titer test repeated after the next 12 months, or radioiodine treatment, or else strumectomy (21, 23). Many patients prefer pharmacotherapy, being afraid of more invasive methods of treatment, but one cannot forget about the limitations associated with the use of ATD. Treatment is related to relatively frequent recurrences and the risk of side effects, the most serious of which is agranulocytosis, occurring in up to 0.5% of patients (24), and liver damage. Most of the side effects occur within the first 3 months of treatment (21, 24).

Radioactive iodine

Radioactive iodine (RAI) treatment is recommended when ATD are ineffective or contraindicated, for instance after the occurrence of serious side effects or treatment intolerance, in the case of relapse of thyrotoxicosis, or if the patient prefers such therapy (2, 21, 23). Contraindications to RAI therapy include pregnancy, breastfeeding, thyroid nodules suspected of malignancy, and active moderate to severe GO (21). Radioiodine may worsen the course of orbitopathy, especially in smokers, since it increases the titer of TSH-R-Ab (21, 25). Therefore, such treatment should be avoided especially with other coexisting risk factors for exacerbation of orbitopathy, including high titer of TSH-R-Ab, severe hyperthyroidism, and smoking. Radioiodine can be used in a mild and clinically active form of orbitopathy, with stabilized orbitopathy risk factors, with the use of glucocorticosteroid prophylaxis (21, 25). It is generally considered safe for both sexes to conceive at least 6 months after treatment (26), although some sources, due to the duration of spermatogenesis, allow a shorter, 4-month interval between treatment and planned conception in men (27). It is recommended that in women conception should be preferably delayed for 12 months. It is estimated that 70-90% of patients recover from hyperthyroidism within 12 months after receiving a single dose of RAI therapy (27). Long-term increased risk of malignant neoplasms in patients treated with radioiodine has not been proven (28), but there is a lifelong risk of hypothyroidism which arises in up to 90-100% of subjects.

Thyroidectomy

An alternative method of treatment is thyroidectomy, which is recommended in patients with a large goitre (>80 ml) and symptoms of compression (2) [according to the guidelines of the European Thyroid Association with a thyroid size of more than 50 ml (23)], with coexisting primary hyperparathyroidism, and suspected thyroid cancer. Thyroid surgery

might be undertaken in pregnant hyperthyroid women on rare occasions in the second trimester (2, 21, 23, 26). Possible complications, such as hypocalcemia or laryngeal nerve palsy should be kept in mind, but when the operation is performed by an experienced surgeon, these complications are very rare (<10% and <1%, respectively) (21). Surgery is associated with the need for levothyroxine supplementation.

K1-70™

Human monoclonal antibody K1-70™ binds to the TSH receptor, and inhibits its stimulation by other ligands. In 2022, the results of the first phase of the clinical trial were published (29), and they showed a reduction in the symptoms of GD with a tendency to decrease the concentration of free thyroid hormones, and an increase in TSH, and diminishing the symptoms of orbitopathy. Treatment was well tolerated and safe. Only 18 patients participated in the study, and then further research is needed.

Small molecule TSH receptor antagonists

Small molecule agonists and antagonists which bind to the transmembrane domain of the TSH receptor have the potential to directly stimulate, or inhibit receptor signaling that could lead to highly potent therapies for thyroid dysfunction (25, 30). Recently, SYD5115, a novel small molecule TSH receptor antagonist has been discovered. It blocks TSH-R-Ab-induced synthesis of the thyroxine (T₄) *in vivo*, after a single oral dose (31). However, low metabolic stability and potential mutagenicity have been noted and further studies are needed.

Assessment of thyroid orbitopathy

Since the management of GO depends on its activity and severity, these factors should be evaluated before starting the treatment.

The disease is assessed as active or inactive by using Clinical Activity Score (CAS) (32). There are 7 areas subjectively assessed and they relate to pain, swelling, and redness of eye structures. The active character is considered to be the number of points of at least 3. Additionally, it is worth using imaging tests, mainly magnetic resonance imaging of the orbits, which allows for the assessment of oedema and fibrosis of the eyeball muscles, by distinguishing inflamed tissue from connective/fat tissue based on the signal intensity (33). Diagnostic imaging plays a significant role in the diagnosis of GO, allowing for differential diagnosis and detection of other pathologies that may cause exophthalmos, for instance neoplastic tumors of the orbit.

To evaluate the severity of orbitopathy, the 3-point European Group on Graves' Orbitopathy (EUGOGO) score is recommended. It assesses the severity of proptosis, visual disturbances associated with eye muscle involvement, the degree of soft tissue involvement, and the occurrence of optic neuropathy and corneal damage. On this basis, the form of the disease is classified as mild, moderate to severe, or sight-threatening (25). According to a study by Tanda ML et al. conducted on 346 patients, the prevalence of these forms of orbitopathy at the diagnosis of GD was 20% for the mild inactive form, 5.8% for the moderate

to severe and active form, and 0.3% for the most severe form (5, 34). Another method for estimating the severity of orbitopathy is the 7-point NOSPECS scale, being an acronym for the assessed features, ranging from no signs or symptoms, through soft tissue involvement, proptosis, extraocular muscle, and corneal involvement, to sight loss (6, 35).

Treatment of Graves' orbitopathy

It is established that the concentration of TSH-R-Ab correlates with the activity and severity of orbitopathy (36). Maintaining euthyroidism is the foundation of treatment for any form of GO. Hypothyroidism may also intensify orbitopathy through the influence of TSH on its receptors located in the orbital tissues. Antithyroid drugs and thyroidectomy do not worsen the course of GO.

All patients with GO, regardless of the activity of the disease, should avoid smoking. Researchers agree that smoking worsens orbitopathy, although the pathogenesis is not fully clear. The influence of free oxygen radicals or interleukin-1 (IL-1), which may promote adipogenesis and accumulation of glycosaminoglycans, is suspected (33, 37, 38).

Active mild form of orbitopathy

Administration of selenium, which has antioxidant and immunomodulatory properties, at a dose of 200 µg a day for 6 months, and eye lubricants are recommended (25). In randomized studies, it was shown that selenium slowed down the progression of the disease, reduced ocular symptoms, and improved the quality of life of patients with a mild form of orbitopathy (25, 39).

Active moderate to severe form of orbitopathy First-line treatment

Glucocorticoids

Glucocorticoids have been used in treatment for about 70 years. Using intravenous glucocorticoids in weekly pulses is safer and more effective than using them daily (40), or in oral regimen (2). The supply of methylprednisolone at a dose of 0.5 g weekly for 6 weeks and 0.25 g weekly for the next 6 weeks, which gives a cumulative dose of 4.5 g of methylprednisolone, remains a standard treatment. In severe cases classified as moderate/severe disease, doses may be increased by 0.25 g per week, giving a total cumulative dose of 7.5 g.

Mycophenolate

According to the 2021 EUGOGO guidelines (25), glucocorticoids are still the first-line of treatment, but a new method of first-line treatment, recommended in most patients with moderate to severe orbitopathy, is a combination of glucocorticoid with mycophenolate sodium, an immunosuppressive drug, registered so far for kidney transplant patients. Mycophenolate works by inhibiting the proliferation of fibroblasts, B, and T lymphocytes (41), and reducing the production of antibodies by B lymphocytes (42). The combination of treatment with glucocorticoids and sodium mycophenolate

at a dose of 720 mg orally per day for 24 weeks is not only more effective (43) but also safe (44). It is also recommended to add the drug when, after 6 weeks of methylprednisolone monotherapy, the disease progresses, but its activity is still assessed as moderate/severe (25).

Active moderate to severe form of orbitopathy Second-line treatment

If the first-line treatment is ineffective, the above-mentioned higher doses of methylprednisolone (25), radiotherapy of the orbits, which can be especially effective in patients with eye muscle involvement and diplopia (10, 25), and newly introduced immunosuppressive and biological drugs can be used. There is a growing trend of targeted treatment in GO.

Teprotumumab

Teprotumumab is a human monoclonal antibody against the IGF-1 receptor which, by binding to the receptor, inactivates it (5, 25). It has been proven that teprotumumab reduces the TSH-induced release of pro-inflammatory cytokines by fibroblasts (45), and reduces the expression of the TSH receptor and IGF-1 receptor on the fibroblasts in patients with Graves' disease. The drug underwent phase II and III trials, showing significant effectiveness, especially in the reduction of proptosis and diplopia (5), and acceptable tolerance. The most commonly reported side effects of the treatment were mild to moderate in severity. These included muscle cramps, nausea, alopecia, diarrhoea, hearing impairment, or hyperglycemia (5, 25). The drug is contraindicated in pregnancy and inflammatory bowel disease (25). In January 2020, teprotumumab was approved by the Food and Drug Administration (FDA) for the treatment of active thyroid orbitopathy. It is administered intravenously every 3 weeks, with a total of 8 doses of the drug. According to the 2021 EUGOGO guidelines, the use of the drug may be considered for the second-line treatment of moderate/severe active form of GO (25). Its implementation is limited by its high price, poor availability, lack of registration by the European Medicines Agency (EMA), and lack of long-term studies on efficacy and safety.

Rituximab

The antibody against CD20 antigen located on the surface of B lymphocytes inhibits their activation and differentiation. Available data suggest that rituximab used in the early phase of the disease may shorten its active phase (46). However, studies on the drug effectiveness and safety in GO are still ongoing and the results are ambiguous.

Cyclosporin A

It inhibits the proliferation of T lymphocytes and the production of interleukin-2 (IL-2) (33). Although 90% efficacy in the treatment of orbitopathy has been demonstrated in combination with oral glucocorticoids (47), few new studies on the use of cyclosporin in the treatment of orbitopathy have been published in recent years.

Azathioprine

Anti-proliferative drug, acting similarly to mycophenolate. Its effectiveness in combination with glucocorticoids has been proven (10). Due to more frequent side effects, such as bone marrow suppression, leukopenia, or infections, its usage is less often.

Methotrexate

Anti-proliferative drug, folic acid antagonist, which inhibits the synthesis of purine nucleotides. It is effectively used in monotherapy at a weekly dose of 7.5-10 mg, depending on body weight, in patients with contraindications to glucocorticoids (13). An interesting study was conducted by Liun Shen et al., who studied the effectiveness and safety of the combination of methotrexate with methylprednisolone at a cumulative dose of 4.5 g, compared to methotrexate with methylprednisolone at a cumulative dose reduced to 3 g and monotherapy with methylprednisolone at a cumulative dose of 4.5 g. The combination of methotrexate with methylprednisolone in a reduced dose appeared effective and safer than the use of methylprednisolone alone (48).

Tocilizumab

Anti-interleukin-6 (anti-IL-6) receptor antibody. Tocilizumab is effective in reducing ocular symptoms in patients with glucocorticoid-resistant active orbitopathy as demonstrated in several studies (49, 50), including a randomized trial (51). The therapy was well tolerated, and the baseline serum IL-6 concentration did not correlate with the response to treatment (49).

Sirolimus

Anti-proliferative drug that inhibits the activation of T lymphocytes and is characterized by a good safety profile when used in low doses. G. Lanzolla et al. studied the effectiveness and safety of sirolimus compared to methylprednisolone in the second-line treatment of moderate/severe orbitopathy in a group of 30 patients, obtaining a better response to treatment with sirolimus, without serious adverse effects of treatment in both study groups (52). The use of the drug in clinical practice requires further randomized trials on a larger group of patients.

Statins

Statins are commonly used drugs that lower the level of low-density lipoprotein (LDL) and reduce cardiovascular risk. Due to their pleiotropic effect, they may support the treatment of autoimmune diseases, including GD (53). It is suggested that statins may change the pro-inflammatory response of T lymphocytes into anti-inflammatory effects by increasing the expression of Th2 lymphocytes and regulatory lymphocytes, contributing to clinical remission (54). A study has proven that patients with recently diagnosed GD taking statins were less likely to develop orbitopathy (55). A similar effect has not been demonstrated with cholesterol-lowering drugs other than statins, nor with COX-2 inhibitors (56).

Therefore, the beneficial effect of statins does not seem to be related to the reduction of blood cholesterol levels, but may result from a mechanism of action other than an anti-inflammatory one (55). In another study, the addition of atorvastatin to the treatment of active moderate to severe orbitopathy with intravenous glucocorticoids in patients with hypercholesterolaemia improved the outcome of orbitopathy treatment (57). The protective effect of statins against the development of orbitopathy should be further investigated.

Sight-threatening orbitopathy

The risk of sight loss, the most severe form of GO, may occur as a result of compression of the optic nerve leading to neuropathy, as well as corneal ulceration or subluxation of the eyeball (2). Patients may complain, among others, about the deterioration of visual acuity, color vision disorder, and rapidly increasing exophthalmos. Such patients should be under constant ophthalmological supervision. The first line treatment for optic neuropathy in this case is a high dose of methylprednisolone – 500-1000 mg daily for three days (25). In case of improvement, it is recommended to repeat the treatment cycle in the next week, and in the absence of a satisfactory response, urgent decompression surgery is indicated. Orbital decompression is aimed to reduce the pressure in the orbit by removing some of the bone fragments in the event of an excessive volume of soft tissues. Recently, open surgeries have been increasingly replaced by less invasive endoscopic procedures (25). In the case of corneal ulceration, similarly to optic nerve neuropathy, intravenous glucocorticoids or orbital decompression may be used. Other therapeutic options include amniotic membrane graft, tarsorrhaphy, blepharorrhaphy, punctal plug, antibiotics, eyelid surgery, and extraocular muscle recession (25, 58). Subluxation of the eyeball is treated with orbital decompression (25).

Summary

A relatively small number of patients with Graves' disease and thyroid orbitopathy, the high costs of introduced drugs, and the need for cooperation between physicians of various specialties make it difficult to search for and test new therapeutic methods. Nevertheless, the significant development of immunobiology, a better understanding of the pathophysiology of Graves' disease and thyroid orbitopathy, and the multitude of studies conducted on new therapies using immunosuppressive and biological drugs give hope for better treatment results and an improvement in the quality of life of patients.

In particular, many new treatment options are proposed in active, moderate to severe GO. The combination of methylprednisolone with sodium mycophenolate in the first line of treatment is more effective than glucocorticoids, which have been used for many years in monotherapy and is not associated with serious side effects. As a second line of treatment, teprotumumab, already registered in the United States, can be considered, since it significantly reduces the symptoms of proptosis and diplopia, or in the case of resistance to glucocorticoids, tocilizumab, which reduces the disease activity assessed on the CAS scale, can be considered. Also, monotherapy with methotrexate, sirolimus, and a combination of glucocorticoids with cyclosporine A or with azathioprine performed favorably in some studies. The use of statins in selected patients may further improve treatment outcomes.

The limitations of the research results mentioned above include small groups of patients, short observation time, and often a lack of control groups. Further randomized studies of long-term safety and efficacy in a larger group of patients are indicated.

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