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Giant Cell Arteritis: A review of current knowledge and new biological treatment options

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Abstract

Introduction and objective

Giant cell arteritis (GCA) is the most common primary systemic vasculitis in Europe. It mainly affects individuals over the age of fifty, its incidence increases with age. The most common clinical manifestation is bilateral headache accompanied by systemic symptoms. The disease may be associated with serious complications, such as permanent vision loss, stroke or rupture of aortic aneurysm. The aim of this study is to discuss the current knowledge about giant cell arteritis and new possibilities of biological treatment.

Review methods

To prepare this review, PubMed and Google Scholar databases were used, searching the following terms: "giant cell arteritis," "temporal arteritis," "giant cell arteritis biological treatment," "giant cell arteritis biological therapy," "giant cell arteritis treatment," "giant cell arteritis epidemiology." The search results were limited to publications from 2007 to 2024, as well as key studies from earlier years, including original papers and randomized, double-blind, placebo-controlled studies.

Brief description of the state of knowledge

The pathogenesis of GCA remains unclear. Since inflammatory factors appear to play an important role, new therapeutic strategies are aimed in direction to interfere these pathways. Setting a diagnosis of GCA requires imaging studies or a temporal artery biopsy. The results of current treatment with high doses of glucocorticoids are unsatisfying, which has led to ongoing research into new therapeutic options.

Summary

Early diagnosis and initiation of treatment are crucial for preventing occurrence of complications. Although the current treatment regimen is effective, it leads to many side effects and does not prevent relapses. This highlights the need to better understand the pathomechanism of the disease to develop more precise therapeutic strategies, including biological treatment.

Keywords: giant cell arteritis; biological treatment; tocilizumab; upadacitinib

I INTRODUCTION AND PURPOSE OF THIS WORK

Giant cell arteritis (GCA) together with Takayasu disease (TAK Takayasu arteritis) belong to the group of primary large vessel vasculitis (LVV) of an idiopathic cause [1]. The current theory of pathogenesis is related to the action of an external factor that triggers an immune reaction in a genetically predisposed individual. The most common clinical manifestation of GCA are symptoms related to the involvement of extracranial branches of the carotid arteries. The aim of this paper is to review the literature and discuss the current information on giant cell vasculitis, especially new therapeutic options related to the use of biological treatment.

II. REVIEW METHODS

PubMed and Google Scholar databases were used to review the information, searching for the following phrases in English: "giant cell arteritis", "temporal arteritis", "giant cell arteritis biological treatment", "giant cell arteritis biological therapy", "giant cell arteritis treatment", "giant cell arteritis epidemiology". The search results were limited to publication years from 2007 to 2024 and key publications from earlier years, including original papers and randomized, double-blind, placebo-controlled studies. Original articles in Polish or English were included. In the end, 50 articles were included in the review.

III. DESCRIPTION OF THE STATE OF KNOWLEDGE

Introduction

Giant cell arteritis is a chronic inflammatory disease of immunological origin, which mainly affects large and medium-sized vessels. The pathogenesis of the disease has not yet been fully determined. Currently, the prevailing view is that the development of GCA is associated with the action of an external factor (bacteria, viruses, toxins) that triggers an immune response in a predisposed individual. GCA is the most common primary systemic vasculitis in Europe, affecting mainly people over the age of 50, which may be associated with dysregulation of the immune system with age. The incidence of GCA is on the rise [2]. Early diagnosis may be challenging due to the non-specific symptoms, such as headache, fatigue, fever or excessive sweating. Chronic inflammation within the vessel walls can lead to stenoses, occlusions, dissections and aneurysm formation. The most serious complications of the disease include permanent vision loss, stroke, rupture of the aortic aneurysm and ischemic changes of the limbs. Thanks to research conducted in recent years, there has been a gradual shift leading to the change of viewing giant cell arteritis as a localized disease and emphasizing its systemic nature. This has a significant impact on changing the therapeutic approach to patients, which is becoming more holistic and focused on the multiple coexisting aspects of the disease. The core therapy of GCA is still an oral immunosuppressive treatment using high doses of glucocorticoids**,** which is associated with a high risk of adverse effects and relapses. Therefore, many studies are being conducted to identify the factors responsible for the development of the disease, which may lead to discovery of new therapeutic targets for biological treatment.

Etiology and epidemiology

The etiology of giant cell arteritis has not been fully elucidated. Some studies have shown the role of polymorphisms in genes encoding tumor necrosis factor (TNF), vascular endothelial growth factor (VEGF), toll-like receptors, ICAM-1 surface glycoprotein, and protein tyrosine phosphatase in the pathogenesis of GCA. Mutations in the HLA II class antigens have also been associated with the disease [3]. As a result of the immune response to the underlying factor, CD4+ T lymphocytes are activated, leading to the subsequent stimulation of macrophages that secrete pro-inflammatory factors such as interleukin-1 and interleukin-6. These cytokines cause inflammation along with proliferation and destruction of the vessel wall. Described process leads to concentric hypertrophy of the intima and fragmentation of the internal elastic membrane of the vessel, which may increase the risk of aneurysmal

dilatation and dissection [4]. The incidence of giant cell vasculitis is 200 cases per million people per year, making it the most common primary vasculitis in Europe and North America[5, 7]. The disease predominantly affects white individuals over the age of 50, with women being affected almost three times more often than men[2, 6, 8]. Epidemiological studies have shown a correlation between the incidence of GCA and increasing latitude in the northern hemisphere[2]. The risk of developing the disease is lower among Black and Asian populations. It may coexist with polymyalgia rheumatica (PMR)[6, 8].

Symptoms

Symptoms of giant cell arteritis typically result from restricted flow through the affected arteries. In the literature, the following types are distinguished based on the location of the lesions: large vessel GCA (LV-GCA), cranial GCA (C-GCA), and mixed type, with large vessel involvement and a cranial component [3]. The most common symptom is an onset of severe headache, which occurs in two thirds of cases, and is typically bitemporal, but can also occur in the frontal or occipital regions, be unilateral or generalized [9, 10]. The suspicion of giant cell arteritis should be raised by the appearance of previously absent headache associated with scalp tenderness, especially in individuals over 50 years of age. One of the most serious symptoms is a permanent vision loss due to ischemia of the optic nerve and retina, most often caused by occlusion of the posterior ciliary artery - a branch of the ophthalmic artery originationg from the internal carotid artery [4, 11-14]. Symptoms may appear suddenly or be preceded by one or more episodes of monocular vision loss (amaurosis fugax), characterized by visual disturbances in the form of a gray "curtain/veil" in the peripheral parts of the visual field. In most cases, permanent vision loss is painless and unilateral. However, in patients who do not receive treatment, the risk of vision loss in the previously unaffected eye is 25-50% within a week [13]. Other symptoms include jaw or tongue claudication, diplopia, dry cough, tongue or scalp necrosis, as well as systemic symptoms such as fatigue, weight loss, fever and general malaise [9, 10, 15]. Physical examination may reveal a tender swelling of the affected temporal artery with weakened or absent pulsation [4, 15]. In 15% of patients, symptoms of upper limb claudication may occur, most often related to stenosis of the subclavian or axillary artery [3, 10]. More than half of patients with GCA show symptoms of polymyalgia rheumatica with morning stiffness and pain of the neck, pain in the shoulder and pelvic girdle [4, 10]. Untreated GCA may lead to ischemia-related visual impairment in 25% of patients and result in permanent vision loss in 10-15% of cases [6, 15]. A retrospective study of 287 patients with giant cell arteritis

demonstrated an increased risk of an ischemic stroke, especially in the vertebrobasilar region, in patients with histopathologically confirmed diagnosis of GCA [16]. The conducted population studies have also shown an increased risk of developing thoracic and abdominal aortic aneurysms in the patient population [17, 19]. In studies using imaging techniques such as positron emission tomography with fluorodeoxyglucose, computed tomography of vessels and Doppler ultrasonography, among patients with histopathologically confirmed diagnosis of giant cell arteritis through temporal artery biopsy, involvement of large vessels beyond the temporal artery was observed in 30-74% of cases [18, 20, 21, 22, 24]. Given these findings, it is important to remember that giant cell arteritis is a systemic condition and the diagnostic vigilance should be kept for the occurrence of ischemic changes, aneurysmal dilatation, and dissection of large and medium-sized arteries in these patients.

Diagnosis

The diagnosis of giant cell arteritis is a combination of clinical findings and additional tests results and should always be supported by imaging techniques or temporal artery biopsy [23]. According to the 1990 American College of Rheumatology criteria, in order to differentiate GCA from other vasculitides, at least 3 of the following 5 criteria must be met: (1) age ≥50 years (2) an onset of the localized headache (3) tenderness to palpation over the temporal artery or its decreased pulsation (4) ESR ≥50 mm/h (5) positive arterial biopsy.

2022 American College of Rheumatology/EULAR Classification Criteria for Giant Cell Arteritis [50]	Score
-Necessary criterion is age ≥50 years and the exclusion of other causes for the symptom	-
-Positive temporal artery biopsy result or the presence of the "halo" sign on temporal artery ultrasound	5
-ESR 50 ≥mm/h or CRP ≥10mg/L before starting treatment; -Sudden loss of vision	3
-Morning stiffness of the shoulders/neck; -Jaw or tongue claudication; -New onset of temporal pain; -Scalp tenderness; -Temporal artery tenderness on palpation, its stiffness or decreased pulsation; -Bilateral changes in the axillary arteries (stenosis, occlusion, aneurysmal dilatation); -Increased fluorodeoxyglucose uptake in FDG-PET examination in the wall of the thoracic and abdominal aorta	2

Tab. 1: Classification criteria for giant cell vasculitis according to the American College of Rheumatology/EULAR 2022 guidelines [50].

A cohort study conducted with 705 patients with a clinical diagnosis of giant cell arteritis revealed inflammatory tissue changes in 69% of patients who underwent temporal artery biopsy. These changes included the presence of giant cells, fragmentation of the internal elastic membrane, thickening of the intima layer, and a dominant infiltration of lymphocytes [24, 25]. The sensitivity of the biopsy ranges from 39 to 77.3% and may depend on the disease phenotype (with lower sensitivity in patients with involvement of large and medium-sized vessels - LV-GCA), the applied glucocorticoid treatment (which dominates the optimal time for a biopsy procedure ongoing up to 2 weeks after the initiation of treatment) and the number and length of the biopsy samples taken [26, 27]. Due to the modest increase in diagnostic sensitivity associated with bilateral temporal artery biopsy and the potential increase of the risk of infectious and hemorrhagic complications, a unilateral biopsy on the symptomatic side is currently the standard procedure [11, 23, 26]. A negative biopsy result does not exclude the diagnosis of GCA. Imaging tests used in the diagnosis of giant cell vasculitis include ultrasonography with Doppler effect, high-resolution magnetic resonance imaging (MRA magnetic resonance angiography), computed tomography (CT), and positron emission tomography with fluorodeoxyglucose (FDG-PET). Conventional angiography is not used as a first-line diagnostic test in these patients [28, 29, 30]. In order to maintain diagnostic sensitivity and specificity, imaging tests should be performed within 72 hours of initiation of the glucocorticoid therapy [30]. According to the EULAR 2023 guidelines, the preferred early imaging test for patients with GCA is a Doppler ultrasonography (USG Doppler) of the temporal and/or axillary arteries. Moreover, in patients with a high clinical pre test probability, ultrasonography may serve as an enough confirmation of the diagnosis of the disease [30]. A typical presentation of GCA on ultrasound is the presence of the "halo" sign, defined as homogeneous, hypoechoic thickening of the arterial wall without a visible blood flow [4, 11, 26, 30], which may be accompanied by stenosis, dissection or occlusion of the artery. As an alternative to ultrasonography, high-resolution magnetic resonance imaging (MRI) is used in cases primarily affecting the cranial arteries, where it can visualize wall thickening and increased gadolinium uptake in inflamed vessel walls. MRI can also be used to diagnose GCA with large vessel involvement and mixed phenotype [28, 30] as it allows the assessment of large and medium size arteries anatomy, possible aneurysmal dilatation, dissection or occlusion. In the computed tomography (CT) scan, thickening/swelling of the arterial walls is visible, with enhancement after contrast administration. Contrary to previous recommendations, recent scientific studies have proven the usefulness of FDG-PET and CT scans in diagnosing disease changes located in the cranial arteries [20]. Its limitations include

impaired fluorodeoxyglucose uptake in patients with diabetes and reduced sensitivity after glucocorticoid treatment [28-30]. Hematological and biochemical tests, ESR (erythrocyte sedimentation rate) and CRP (C-reactive protein), are also helpful for diagnosing and monitoring the disease. In patients with GCA, an increase in the erythrocyte sedimentation rate (ESR) above 50 mm/h (even reaching 100 mm/h) is characteristic, however, in some cases it may remain below this value, which does not exclude the diagnosis [10, 26]. It is often accompanied by an elevated CRP level. A complete blood count in patients frequently shows normocytic anemia, which may coexist with thrombocytosis. Additional tests may reveal increased alkaline phosphatase activity and decreased albumin levels. The role of an increased interleukin 6 concentration in pathogenesis and diagnostics has not yet been fully discovered and is the subject of ongoing scientific researches [10, 25, 26]. On physical examination, a swelling of the arteries in the temporal region or scalp may palpable, accompanied by decrease or absence of pulsation. Abnormalities in the physical examination of the temporal artery have been shown to correlate with an increased risk of severe ischemic complications [31]. In patients with peripheral artery involvement, a vascular bruit associated with turbulent flow through the affected vessels may be present.

Treatment

The basic treatment for giant cell arteritis remains high-doses of glucocorticoids (GC) therapy. The optimal goal of treatment is to achieve rapid and sustained remission of the disease, defined by the EULAR criteria as: no clinical symptoms and no elevated values of inflammatory parameters (ESR and CRP) for a period of 6 months, and in patients with the disease with the phenotype involving large vessels (LV-GCA), accompanied by no progression of vascular inflammatory changes [23]. Due to the large number of side effects of glucocorticoids therapy, research is ongoing to develop new treatment using biological preparations. Every patient with suspected diagnosis of giant cell arteritis should be provided with multidisciplinary care, but a specialist connsultation should not lead to a delay in the initiation of treatment. In the case of patients with symptoms typical for GCA and elevated values of ESR/CRP, who suffers visual impairment, treatment should be started immediately, as delaying the start point of the therapy was identified as the strongest risk factor for permanent vision loss in clinical studies [32]. These cases should be treated as an emergency and put on a fast-track diagnostic path.

1. Glucocorticoids

Glucocorticoids (GC) are the gold standard in the GCA treatment. The initial dose is 40-60 mg/d of prednisone taken orally and is usually administrated for 3-4 weeks until remission is achieved [26, 28, 30], which is accomplished in the majority of patients treated using this protocol [29]. Lower doses should not be used in the initiation of therapy due to the lack of the expected therapeutic effect [32, 33, 34]. In patients with sudden vision loss or amaurosis fugax, guidelines allow the treatment to be initiated with intravenous boluses of 0.25-1 g/day of methylprednisolone administered for 3 days [23, 35]. This approach is consistent with the findings of a study in which patients receiving this therapy model were shown to be able to reduce a total dosage of glucocorticoids administered during treatment [35], although it should be considered with caution due to the low quality of evidence. Once inflammatory parameters (ESR, CRP) have normalized, which in most patients occurs within 2-4 weeks [10, 26], the GCs doses should be tapered to 15-20 mg/day in the 2-3rd month of treatment and ≤5 mg/day after a year of therapy [29]. Despite their indispensable role, glucocorticoids in case of prolonged oral use in most patients [11] cause a number of side effects, including impaired glucose tolerance or the development of diabetes, weight gain, hypertension, cardiovascualr side effects, decreased muscle strength, increased susceptibility to infections, osteoporosis, and gastritis. GCS therapy also does not prevent disease relapse, which occurred in 34-75% of cases in population based studies [11, 28, 29] and required an increase in the dosage of medications. The statistical discrepancy in the presented data could be largely due to the the lack of a standardized definition of relapse characteristics [29]. According to present EULAR recommendations, a major disease relapse is defined as the occurrence of clinical features of ischemia (such as jaw claudication, visual disturbances or loss of vision, scalp necrosis, stroke or limb claudication) or the occurrence of inflammatory complications (aneurysmal dilatation, stenosis or dissection) in the aorta or large vessels that occurs in a patient with clinical, imaging, histopathological or biochemical features of the disease activity. A minor relapse is defined as the occurrence of clinical, imaging, histopathological or biochemical features of disease activity that do not meet the criteria for a major relapse [23].

2. Classical immunosuppressants

Due to the multiple side effects of a long-term therapy and frequent disease relapses, ongoing efforts are focused on identifying agents that can reduce the cumulative dose of administered GCs, while simultaneously reducing the risk of relapse. Randomized, double-blind studies

conducted with the use of methotrexate (MTX), a folic acid antagonist, have proven its modest role in achieving this goal [36]. EULAR guidelines recommend its use as an alternative to tocilizumab (TCZ) therapy in patients who are refractory to standard treatment (not achieving remission with glucocorticoid therapy), with relapsing disease or in those at increased risk of adverse effects and complications as a result of GCs therapy [23]. It is emphasized that the choice of treatment should always be based on an assessment of the individual risk of therapy for the patient. There is evidence supporting the effectiveness of leflunomide, azathioprine and cyclophosphamide, which have not been included in the current standard treatment protocol, and their use should be considered on an individualized basis [23, 37, 38]. Studies using other classic immunosuppressive drugs, such as dapsone and hydroxychloroquine, have not shown the superiority of combination therapy with these agents over GCs monotherapy [39].

3. Biological treatment

TNF-alpha antagonists

Due to the significant concentration of tumor necrosis factor alpha (TNF-alpha) observed in histopathological tests of temporal artery biopsies, attempts were made to use targeted therapy using drugs, such as infliximab (a chimeric human-mouse IgG1 monoclonal antibody against TNF-alpha) and adalimumab (a recombinant human monoclonal antibody against TNF alpha). Unfortunately these therapies did not show the superiority over monotherapy with glucocorticoids [39, 40]. A study involving etanercept (a soluble fusion protein of the human tumor necrosis factor Fc receptor) demonstrated a promising reduction in the total prednisone dose required to administer in patients with GCA, however, due to the small sample size (the study included 17 patients), these results have a low statistical value.

Modulators of T-cell activity

Abatacept is a fusion protein that shows the ability to bind to and alter the function of CD80 and CD86 molecules on the surface of antigen-presenting cells, thereby influencing the modulation of the T lymphocyte co-stimulation signal involving CD28 molecules. Its theoretical effect on modulating the immune response involving Th1 and Th17 lymphocytes was studied, showing a potential positive effect on the duration of remission in patients undergoing treatment. However, the value of these data is questionable due to the small statistical sample and the complex design of the study [41, 42].

Il-6 Tocilizumab

A breakthrough in the treatment of giant cell arteritis occurred when the Food and Drug Administration (FDA) approved for treatment tocilizumab, a monoclonal antibody and an inhibitor of the interleukin-6 receptor. The role of interleukin-6 in the pathogenesis of GCA is supported by the increased concentration of this molecule in temporal artery tissue samples of the patients in the active phase of the disease. A correlation has also been shown between a decrease in serum IL-6 levels and a decreased disease activity together with increased remission rate during treatment [41]. The first strong evidence for the clinical efficacy of tocilizumab in patients with GCA was provided in 2016 by a double-blind, randomized, placebo-controlled study, which showed a statistically significant effect of the drug on shortening the time to achieve remission and reducing the risk of disease relapse compared to standard monotherapy with glucocorticoids [43]. These results led to the inclusion of tocilizumab in the EULAR guidelines as an adjunctive therapy in patients who failed to achieve remission during standard treatment with prednisone, as well as in patients who experienced disease relapse [23]. It is recommended to consider its inclusion in order to reduce the total cumulative dose of glucocorticoids administered during treatment, in patients at high risk of, or already developed, adverse effects and complications associated with long-term oral GCs therapy, including patients with osteoporosis, diabetes, cardiovascular disease or glaucoma [23, 33]. The results of the large, double-blind, randomized "GiACTA" study from 2017 confirmed the effectiveness of TCZ in increasing the remission rate in a shorter time than in patients receiving glucocorticoid monotherapy [44]. The durability of disease remission achieved with tocilizumab and the occurrence of possible complications require further research [45, 46].

Other Interleukin Inhibitors

Ustekinumab, a human monoclonal antibody that is designed to block signaling involving interleukin 12 and 23, is currently undergoing a phase II randomized clinical trial (NCT03711448). Previous studies involving this drug have shown conflicting data regarding its efficacy. Secukinumab, an interleukin 17A inhibitor, is also undergoing the phase III of clinical trial. Its use in patients with psoriasis and giant cell arteritis may have shown the effect of prolonging the time of sustained remission (NCT04930094). In a double-blind, randomized study of a human IL-1 receptor antagonist, which was completed in March 2024, no statistically significant prolongation of the remission time was achieved in patients in the treatment group [47]. Due to the observed dysregulation of the granulocyte-macrophage

colony-stimulating factor (GM-CSF) pathway described in biopsies of patients 'temporal arteries, a clinical trial was conducted using mavrilimumab, a monoclonal antibody targeted against the GM-CSF receptor. This study showed promising results of prolonging the remission time in the group of patients receiving the drug, which, according to the authors, should be the basis for further researche [48].

JAK-STAT signaling pathway inhibitors

The effects of the above-mentioned targeted therapy related to the signaling pathway involving interleukin-6 (tocilizumab), interleukin-12, and interleukin-23 (ustekinumab), have led to research on JAK1 and JAK2 kinase inhibitors. According to the current knowledge of cytokine signaling, inhibition of JAK kinases should contribute to a reduction of the biological effects of IL-6, IL-12, and IL-23. The recently completed SELECT-GCA trial (NCT03725202) using upadacitinib demonstrated a significant reduction in the risk of relapse and disease flare compared with the control group in preliminary efficacy data [49]. The final results of the trial have not yet been published as of the date of this review.

4. Surgical treatment

Surgical interventions in patients with giant cell arteritis should be undertaken during remission of the inflammatory process (excluding emergency conditions), due to the increased risk of complications [23]. The remaining criteria for surgical treatment in these patients do not significantly differ from those in unaffected individuals, but patients should always be provided with care by a multidisciplinary specialist team.

IV SUMMARY

The treatment of giant cell arteritis is still associated with a significant number of adverse effects, the occurrence of which reduces the quality of life of patients. The time necessary to achieve remission is often unsatisfactory. Therefore, further research aimed at a more thorough understanding of the giant cell arteritis's patomechanism seems essential, as it would allow the future development of new therapies, including targeted treatments and biological therapies.

V DATA

Author's contribution: Due to the fact that this review is a section of one author, all the actions essential to create it, such as: conceptualization, methodology, software, check, formal analysis,, investigation, resources, data curation, writing - rough preparation, writing - review and editing, visualization, supervision and project administration was performed by the author alone.

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