

Giant Cell Arteritis in Ophthalmology – Current Treatment Options. A Review

Diblík Pavel, Heissigerová Jarmila

Department of Ophthalmology, 1st Medical Faculty, Charles University and General Faculty Hospital in Prague, Czech Republic



MUDr. Pavel Diblík, MBA

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Correspondence address:

Oční klinika 1. LF UK a VFN v Praze

U nemocnice 499/2

128 08 Praha 2

Czech Republic

E-mail: pavel.diblik@email.cz

SUMMARY

Giant cell arteritis (GCA) is a systemic granulomatous vasculitis of medium and large-sized arteries, which represents an ophthalmic emergency because of the risk of sudden, severe and often irreversible loss of vision. Its most important ocular manifestation is arteritic anterior ischemic optic neuropathy; less frequent manifestations include central retinal artery occlusion, cilioretinal artery occlusion, posterior ischemic optic neuropathy, choroidal ischemia and ocular motor nerve palsies. Giant cell arteritis should be actively considered in every patient over 50 years of age presenting with new-onset ischemic optic neuropathy, amaurosis fugax, diplopia or another cranial ischemic manifestation. The diagnosis is based on a combination of the clinical findings, inflammatory laboratory markers, ultrasonography of the temporal and axillary arteries, temporal artery biopsy when appropriate, and additional imaging modalities. However, in patients with high clinical suspicion, treatment must not be deferred until definitive diagnostic confirmation. Systemic glucocorticoids remain the cornerstone of acute therapy; in patients with ocular ischemic involvement, intravenous methylprednisolone pulses followed by high-dose oral glucocorticoids are usually recommended. New glucocorticoid-sparing treatment options, particularly interleukin-6 receptor blockade with tocilizumab and JAK1 inhibition with upadacitinib, expand the possibilities for long-term disease control and reduction of cumulative steroid exposure. Early identification of the pathology by the ophthalmologist and close interdisciplinary collaboration with rheumatologists, internists, neurologists, infectious disease and imaging specialists are essential to prevent bilateral visual loss and systemic ischemic complications.

Key words: giant cell arteritis, temporal arteritis, arteritic anterior ischemic optic neuropathy, visual loss, glucocorticoids, tocilizumab, upadacitinib

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INTRODUCTION

Giant Cell Arteritis (GCA) is a systemic granulomatous vasculitis of medium and large-sized arteries, in which ocular affliction may be the cause of severe impairment of visual acuity (VA) of one, or in the case of late treatment, both eyes. We differentiate between cranial (temporal or Horton's arteritis) and extracranial forms. An increase in the incidence of the disease is expected worldwide due to increased awareness of GCA and better diagnosis. On the other hand, therapeutic options are improving thanks to anti IL-6 preparations and Janus kinase (JAK) inhibitors.

Epidemiology

The incidence of GCA is higher in the northern hemisphere, more common among the white race, in Europe 7.3/100 000 of the population, but in Scandinavia 21.6/100 000 of the population. The expected incidence is as high as 51/100 000 in persons over the age of

50 years [1,2]. It is assumed that the disease is linked to a certain genetic predisposition (HLA-DR3, HLA-DR4, HLA-DR5 and HLA-DRB1*04) [3]. The majority of patients are aged over 50 years, and the highest incidence is in the population aged over 70 years. Women are affected 2x as frequently as men.

Pathophysiology

The inflammatory process in the vascular walls is probably initiated by activation of the dendritic cells in the adventitia, with subsequent activation of CD4⁺ T-lymphocytes, macrophages, the formation of a granulomatous infiltrate and remodeling of the vascular wall. Activation of the dendritic cells and the cascade of further processes leads to differentiation of effector lymphocytes into Th17 and Th1 subtypes of CD4⁺ lymphocytes [4]. Th17 cells are dependent upon IL-6, and among other factors produce IL-17. They appear mainly in the early phase of inflammation and respond well to glucocorticoids. Th1 cells indu-

ced by IL-2 and IL-18 producing interferon- γ are resistant to glucocorticoids and appear more in the chronic phase of inflammation [5]. When untreated, the disease results in obstruction of the vascular lumen with destruction of the intima and media layers, and ischemia in the supplied area.

The relationship between atherosclerosis and GCA is not clear. Atherosclerotic changes are accompanied by raised levels of CRP, fibrinogen and pro-inflammatory cytokines (IL-6, IL-18), but it is not clear as to whether this represents a triggering cause or a consequence of aging [6]. The possible influence of endogenous (metabolic products) and exogenous factors (smoking, alcohol, radiation) is also unclear. Although it is possible to consider a potential concurrence and potentiation of pathological processes due to the similarity of changes in the vascular wall, atherosclerotic changes in biopsies of the temporal arteries are rare in patients with GCA, and so it is also possible that GCA has a protective influence on the development of atherosclerosis [7].

Clinical course

We differentiate between cranial and extracranial (arteritis of large vessels, primarily branches of the aorta) forms of GCA. Almost one half of patients with GCA have symptoms of polymyalgia rheumatica and 20% of patients with this diagnosis are diagnosed on the basis of symptoms of GCA [8]. The spectrum of symptoms is broad: fatigue, weight loss, loss of appetite, low-grade fever, nocturnal sweating, headache, loss of performance, apathy, depression, muscle and joint pain, claudication during mastication (chewing).

Of ocular manifestations, the most common is anterior ischemic optic neuropathy (AION), less common is central retinal artery occlusion (CRAO), cilioretinal artery occlusion and palsies of all the oculomotor nerves or other cranial nerves. Rare posterior ischemic optic neuropathy (PION) is most frequently caused by GCA, and other rare manifestations are ischemia of the choroid or of the anterior segment, myotonic pupil or Horner's syndrome. As a rule, arteritic form of AION (AAION) is severe and may end in blindness; partial correction is exceptional and mostly occurs only upon a less deep deterioration of VA. Deterioration of VA is sometimes registered by the patient also during the course of one day, and within a few hours severe impairment of vision occurs. In CRAO the typical image is sudden loss of VA. It is necessary to consider GCA also in the case of amaurosis fugax in the patient's medical history, which is a warning sign of permanent impairment of vision. In GCA the other eye is at risk of the same disorder in the coming hours or few days; the risk is high especially in patients with long-term illnesses in their medical history (general symptoms). Unfortunately, in 10–15% of patients there are no warning signs, and the diagnosis can be determined only on the basis of further examinations.

Diagnosis

Deterioration of VA is generally very severe, mostly to the level of counting fingers, light projection and in the



Figure 1. Arteritic anterior ischemic optic neuropathy (AAION) with pale optic disc edema and small peripapillary splinter hemorrhages at the 6 and 12 o'clock positions. Early age-related macular degeneration (AMD) is present beneath the fovea

following days often progressing to complete blindness. A milder deterioration can sometimes be explained by the applied treatment – weak glucocorticoids, nonsteroid antiphlogistic drugs or immunosuppressants from another indication. In these cases, it is sometimes possible to improve VA by escalating treatment. However, by timely application of adequate therapy it is possible to preserve the functions of the other eye or prevent further damage in other localizations. In the case of high clinical suspicion, treatment must not be deferred due to biopsy or imaging examination.

We usually find pale infiltration of the optic nerve disc on the ocular fundus, while hemorrhages are exceptional, minor peripapillary, cotton wool spots may appear, the venous content is not increased, arteries are generally more constricted. An overall paler fundus due to concurrent impaired filling of the choroidal channel may complete the image (Figure 1).

We conduct a laboratory test to determine high levels of inflammatory markers, although these are not a definitive diagnostic indicator. In patients we find high levels of sedimentation, frequently higher than 100 mm for the first hour, with concurrently high CRP of 50 mg/l or more in 95% of cases. In the remainder of patients there may be dissociation of inflammatory markers with a normal value of one of the observed parameters, in rare cases the finding may be that both values are normal. The finding is completed by anemia and thrombocytosis above 400 000/ μ l [9].

The image of GCA also includes changes in the branches of the superficial temporal artery. In some places there is absence of a pulse, palpable and painful and/or inflamed nodules appear in places. A positive finding unequivocally supports the diagnosis, a negative finding excludes it. The blood vessel on which the biopsy is performed should be sufficiently long (4 cm), and excision should be performed as soon as possible after commencement of treatment with glucocorticoids [10], even if non-specific

inflammatory changes can be demonstrated as long as one year after the onset of the disease. A typical image incorporates a finding of giant cells, inflammatory reaction throughout the entire thickness of the vessel, necrosis with constriction of the lumen and thrombosis. The diagnostic benefit of perivascular infiltration with affliction of the vasa vasorum is debated [11].

According to current recommendations, ultrasonography of the temporal and axial arteries should be included in the examinations upon suspicion of cranial and extra-cranial (large vessel) GCA. By sonography it is possible to detect changes in the vascular wall (halo sign), manifestations of constriction, compression and occlusion. Data on sensitivity and specificity vary, but there is a consensus on the fact that the examination should be conducted by an experienced examiner [12]. There is a high rate of reliability in the case of GCA of large vessels, the rate is lower in the case of cranial form of the disease.

The use of MRI in diagnosis is debated; a range of protocols are used, of which “black-blood” (in the case of dark imaged blood content the vascular wall is more easily visible) should also be able to identify affliction of the posterior ciliary arteries in AAION.

PET/CT represents a significant contribution in the diagnosis of GCA, especially in the case that large vessels are affected. Nevertheless, the availability of this examination is limited by its use in acute conditions, in the long-term contexts its performance is absolutely crucial for definitive determination of the diagnosis and subsequent indication of therapy with new medications as part of rheumatological care in specialized centers.

Differential diagnosis

Non-arteritic AION is the most important differential diagnosis in ophthalmology, because it decides on the following urgent therapeutic procedure. The local fin-

ding on the optic disc may sometimes be similar also in occlusive diseases of the carotid artery, in other forms of vasculitis, herpetic and other infections.

Migraines, cluster headaches, trigeminal neuralgia pains, tooth complaints or complaints of the temporomandibular joint, and cervicocranial syndrome rank among differential diagnoses of headaches.

In the case of a combination of headache and ocular motor palsies, or upon combination with a disorder of VA, it is necessary to consider changes in the cavernous sinus or pituitary apoplexy.

Therapy

Upon suspicion of ocular ischemic involvement, giant cell arteritis is an urgent condition. The aim of treatment is not primarily to improve already occurred severe loss of sight, which is rare, but above all to prevent affliction of the other eye, prevent further ischemic complications and suppress the systemic activity of vasculitis. Treatment should be commenced immediately in the case of high clinical suspicion and should not be deferred until a biopsy of the temporal artery or other imaging examinations have been performed [13–16].

Systemic glucocorticoids remain the cornerstone of acute therapy. In patients without visual or neurological ischemic symptoms, treatment is usually commenced at a dose of 40–60 mg per day. In the case of acute impairment of vision, amaurosis fugax, diplopia or other cranial ischemic manifestation, intravenous methylprednisolone pulse therapy is recommended, most often 500–1000 mg per day over a period of three days, with subsequent transition to a high dose of prednisone orally and a progressive reduction of the dose according to the clinical response, laboratory parameters and comorbidities [15–17]. In ophthalmological practice it is of crucial importance that the first dose of glucocorticoid is administered

Table 1. Proposed Clinical Practice Recommendations

Clinical Situation	Recommended Approach
Age > 50 years with new-onset AION, severe vision loss, pale optic disc edema, amaurosis fugax, CRAO, diplopia or choroidal ischemia	Immediate high-dose intravenous pulse glucocorticoid therapy (500–1000 mg/day); do not delay treatment while awaiting temporal artery biopsy or imaging studies
Suspected GCA without ocular ischemic manifestations	Prednisone 40–60 mg/day; urgent laboratory evaluation and confirmatory imaging and/or temporal artery biopsy
Relapse during glucocorticoid tapering	Consider escalation of glucocorticoid therapy and initiation of glucocorticoid-sparing treatment
High risk of glucocorticoid toxicity	Consider early initiation of tocilizumab or upadacitinib in collaboration with a rheumatologist
Treatment with tocilizumab	Do not rely solely on CRP levels; monitor clinical status, ophthalmic findings, and, when appropriate, imaging studies
Treatment with upadacitinib	Assess infectious, cardiovascular, thromboembolic, and malignancy risks before treatment initiation

AION – anterior ischemic optic neuropathy, CRAO – central retinal artery occlusion, GCA – giant cell arteritis, CRP – C-reactive protein

before the definitive confirmation of the diagnosis in the case of high clinical suspicion. Immunological glucocorticoids rapidly suppress the expression of pro-inflammatory cytokines, migration and activation of T-lymphocytes and macrophages, and relatively effectively suppress the IL-6/Th17 axis, which is significant especially in the earlier phase of the pathology. However, they have a lesser influence on chronic Th1 response with the production of interferon- γ and processes leading to the remodeling of the vascular wall. This may explain frequent relapses upon reduction of the dose and the need for long-term treatment or glucocorticoid-sparing therapy [18,19]. Long-term administration of glucocorticoids is associated with serious morbidity, especially in older patients.

Clinically significant adverse effects include hypertension, diabetes mellitus or decompensation thereof, osteoporosis and fractures, cataract, glaucoma, retention of fluids, myopathy, mood swings and disrupted sleep, increased risk of infections and gastrointestinal complications. As a consequence, already when commencing treatment it is advisable to plan prevention of steroid toxicity: control of blood pressure and glycemia, protection of the skeleton, assessment of gastrointestinal risk, vaccination history and regular ophthalmological and internal monitoring.

The targeted glucocorticoid-sparing treatment with the best proven effect is **tocilizumab**.

Tocilizumab is a humanized monoclonal antibody acting to inhibit the interleukin 6 receptor.

By blockade of IL-6 signaling it reduces the differentiation and activity of Th17 response, production of acute phase proteins in the liver and systemic manifestations of inflammation. In the randomized GRACTA trial, treatment with tocilizumab in combination with 26-week reduction of prednisone demonstrated a higher proportion of sustained remission in the 52nd week than regimens with prednisone alone [20]. Tocilizumab is administered mainly subcutaneously (although intravenous form of administration is also available); in clinical practice it is suitable above all for patients with relapsing or refractory GCA, for patients with a high risk of glucocorticoid toxicity and for patients for whom a more rapid, safe reduction of the cumulative dose of glucocorticoids is desirable [14,20,21]. Upon treatment with tocilizumab it is necessary to take into account the specifics of monitoring. IL-6 blockade leads to suppression of CRP and often also of systemic symptoms, therefore normal CRP may not reliably exclude activity of vasculitis. Evaluation of remission and relapse must be based primarily on the clinical picture, ophthalmological finding and according to necessity on imaging methods. Important adverse effects of tocilizumab include infection, neutropenia, thrombocytopenia, elevation of liver enzymes, hyperlipidemia, hypersensitive reaction and in rare cases gastrointestinal perforation, especially in patients with diverticulitis or a risk gastrointestinal anamnesis [21,22]. Before commencing treatment it is appropriate to perform screening for latent tuberculosis and viral hepatitis, to check the blood count, conduct liver tests and lipid profile, and to continue to monitor these parameters.

A newer option for targeted treatment is **upadacitinib**, an oral selective Janus kinase 1 inhibitor. JAK1 mediates signaling of a series of cytokines that are significant in the pathogenesis of GCA, including IL-6, interferons and other mediators of congenital and adaptive immunity. Upadacitinib therefore intervenes more broadly in cytokine signaling than isolated IL-6 receptor blockade. In the randomized phase 3 trial SELECT-GCA, upadacitinib 15 mg once per day in combination with 26-week reduction of glucocorticoids demonstrated a higher proportion of sustained remission in the 52nd week than a placebo with 52-week reduction of glucocorticoids; a dose of 7.5 mg was not equally effective [23]. The European registration documents of EMA and the Czech regulator SÚKL state a dose of upadacitinib at 15 mg once per day for adult patients, in combination with a progressively reducing dose of corticosteroids. With reference to the chronic character of the disease, after discontinuing glucocorticoid treatment it is possible to continue in monotherapy with upadacitinib based on the activity of the disease, the decision of the doctor and the patient's preference; however, monotherapy is not determined for the treatment of acute relapse [24]. This indication is approved in the SPC (package leaflet) of the pharmaceutical specifically for vasculitis that comes under code M31.5 (giant cell arteritis with polymyalgia rheumatica) and M31.6 (other giant cell arteritis), which encompasses classic temporal form with predicted affliction of the cranial vessels. The safety profile of upadacitinib requires careful selection of the patient. Important adverse effects include herpes zoster infection, laboratory abnormalities of blood count, elevated liver enzymes, increase of lipids, acne and potential risk of serious infections, malignancies, serious cardiovascular events and venous thromboembolism, especially in risk patients. Before commencing treatment it is advisable to examine the blood count, conduct liver tests, lipid profile, screening for latent tuberculosis and hepatitis, and evaluate the cardiovascular and thromboembolic risk [24,25]. In older patients, smokers, patients with a medical history of malignancy, thromboembolic illness or significant cardiovascular risk, it is necessary to consider the indication very carefully.

Conventional disease-modifying antirheumatic drugs (DMARDs), in particular methotrexate, have been tested as glucocorticoid-sparing therapy in the treatment of GCA, though their effect is less convincing in comparison with tocilizumab. They may be considered in individual situations, for example in the case of unavailability or contraindication of biological or targeted synthetic treatment, but should not defer the commencement of adequate acute glucocorticoid therapy [26,27].

From the ophthalmologist's perspective it is of fundamental importance to differentiate between two clinical situations. The first is acute suspicion of GCA with ocular ischemic manifestation, in which the priority is immediate administration of high doses of ideally intravenous corticoids, and urgent interdisciplinary collaboration. The second is long-term monitoring of the systemic illness, in which decisions are taken on the speed of reducing gluco-

corticoids and the addition of tocilizumab or upadacitinib. This long-term treatment should take place in collaboration between an ophthalmologist, rheumatologist, and according to the scope of affliction also an internal medicine specialist, neurologist, angiologist, or specialists in imaging large blood vessels.

CONCLUSION

Although GCA is rare, it is a potentially severely disabling disease, and timely diagnosis and correct treatment may save the sight and health of a large number of patients. In patients over 50 years of age presenting with new-onset ischemic optic neuropathy, central retinal artery occlusion, amaurosis fugax, diplopia or other cranial ischemic manifestation, treatment must be commenced immediately upon clinical suspicion. The current diagnosis is based upon a combination of the clinical findings, laboratory markers, ultrasonogra-

phy of the temporal and axillary arteries, biopsy and other imaging methods. In addition to glucocorticoids, options for treatment also include glucocorticoid-sparing treatment procedures, particularly IL-6 receptor blockade and JAK1 inhibition. With reference to the potential overlap of symptoms of cranial GCA, extracranial forms and polymyalgia rheumatica, the ophthalmologist should be aware of other manifestations of this vasculitis and treat them in a timely manner or refer the patient to a more specialist center that is capable of providing adequate treatment. The ideal solution is to refer the patient directly to a specialized center providing care (rheumatological centers for biological treatment [28]). It is precisely here that the aforementioned modern therapy with unconventional pharmaceuticals may be indicated within essential long-term care, which represents a fundamental step towards the safe discontinuation of glucocorticoid therapy and sustaining the long-term remission of the disease.

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