The studying of giant cell arteritis (GCA) is relevant in connection with the aging of the population and the highest prevalence of this systemic vasculitis among people over 50 and especially aged 70–79. It is projected that between 2014 and 2050, more than 3 million people will have been diagnosed with GCA in Europe, North America, and Oceania [1–2].

In order to characterize the risks, strategies, medicines and outcomes of the treatment of GCA, we have studied specialized literature data published in English, Russian and German, found by electronic and manual search, checked for indexing in the main computer databases of evidence-based medicine (Cochrane Library and Medline) and selected without time limiting. Special attention is paid to prevention of early and severe complications and adverse effects of therapy—eye, cardiovascular, cerebrovascular and infectious diseases, diabetes, osteoporosis, fractures and malignancies. Best practice and the results of the introduction of an accelerated approach to management of a patient with suspected giant cell arteritis in primary healthcare setting are described, as well as current evidence base and prospects for early diagnosis and use of glucocorticoids and adjuvant immunosuppressive and biologic therapy with a focus on methotrexate and tocilizumab. Main principles, recommendations and evidence base of the 2020 British Society for Rheumatology guidelines on diagnosis and treatment of this vasculitis are represented and discussed.

**Keywords:** giant cell arteritis; drug therapy; complications; treatment outcome; standards; review

**Abstract.** Giant cell arteritis is the most common systemic vasculitis in adults and especially in older people. Its development and treatment is often associated with comorbidities, relapses and various complications. The paper represents an analytical review, systematic generalization and discussion of evidence on modern strategies, main risks, medicines and outcomes of the treatment of patients with giant cell arteritis. We studied specialized literature data published in English, Russian and German, found by electronic and manual search, checked for indexing in the main computer databases of evidence-based medicine (Cochrane Library and Medline) and selected without time limiting. Special attention is paid to prevention of early and severe complications and adverse effects of therapy—eye, cardiovascular, cerebrovascular and infectious diseases, diabetes, osteoporosis, fractures and malignancies. Best practice and the results of the introduction of an accelerated approach to management of a patient with suspected giant cell arteritis in primary healthcare setting are described, as well as current evidence base and prospects for early diagnosis and use of glucocorticoids and adjuvant immunosuppressive and biologic therapy with a focus on methotrexate and tocilizumab. Main principles, recommendations and evidence base of the 2020 British Society for Rheumatology guidelines on diagnosis and treatment of this vasculitis are represented and discussed.

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The studying of giant cell arteritis (GCA) is relevant in connection with the aging of the population and the highest prevalence of this systemic vasculitis among people over 50 and especially aged 70–79. It is projected that between 2014 and 2050, more than 3 million people will have been diagnosed with GCA in Europe, North America, and Oceania [1–2].

In order to characterize the risks, strategies, medicines and outcomes of the treatment of GCA, we have studied specialized literature data published in English, Russian and German, found by electronic and manual search, checked for indexing in the main computer databases of evidence-based medicine (i.e. Cochrane Library and Medline) and selected without time limiting.

Talking on the approaches to treatment of patients with CCA, let’s note that this is considered to be a disease of unknown etiology occurs in genetically predisposed persons (i.e. carriers HLA-DRB1*04) and of crucial pathogenic role of immune disorders triggered by an infection (parvovirus B19, varicella zoster virus, etc.) or toxins [3–4]. Mentioned immune disorders concern innate and adaptive immune systems’ interaction, stromal and endothelial cells, and axes «interleukin (IL) 12 – T-helper cell (Th) 1 – interferon γ» and «IL6 — Th17 — IL12 or IL21»; both ischemia and cytokines’ imbalance are of great importance in the development of symptoms of the disease [5–8].

So, etiologic treatment of GCA does not exist. With regard to the correction of modified risk factors, the association between smoking and the development of GCA was proven in the systematic review and meta-analysis by the authors from the Mayo Clinic in 2018. Having searched evidence in both Medline and Embase with the search terms «giant cell arteritis», «temporal arteritis», «cranial arteritis» and «Horton disease», D. Brennan et al. selected 13 studies (eight prospective, five retrospective ones) from 3312 found and shown that, when compared to non-GCA persons, patients with GCA more often smoked in their past (odds ratio (OR) 1.19; 95 % confident interval (CI) 1.01–1.39) or at present (OR 1.18; 95 % CI 1.01–1.38). However, significant heterogeneity of primary sources was noted [9].

In turn, we did not find evidence on effect of quitting smoking on the outcomes with GCA. In the future, this...
association may be proved in regions with a high prevalence of GCA (Northern Europe) and effective mass prevention of smoking — that is, a reduction in the number of smokers observed, for example, in Sweden [10]. According to population-based studies, in Norway there is a leveling the incidence of GCA, as well as a persistent increase in incidence with age, and a predominance of women among patients. For instance, L. K. Brekke et al. (2017) presented the results of their retrospective hospital-based cohort study of the GCA incidence «in an expected high-incidence region during a 41-year period» (1972-2012) — it was Bergen health area. The average annual cumulative incidence of GCA was 16,7 (95 % CI 15,5-18,0) per 100,000 people age 50 or older (as for diagnosis verified with temporal artery biopsy (TAB), it was 11,2; 95 % CI 10,2-12,3). With regard to gender, the incidence rate was a twofold to threefold higher in women, the average annual incidence was 37,7 (95 % CI 35,8-39,6) in women vs 14,3 (95 % CI 13,2-15,5) in men. With regard to age, the average annual incidence of GCA increased in both genders until the 7th decade of life: with 95 % CI, for age under 60 it was 2,8 (2,3-3,3), for age 60-69 — 15,5 (14,4-16,8), for age 70-79 — 34,5 (32,8-36,4), for age over 80 — 26,8 (25,3-28,4). With regard to the study period, the incidence of GCA increased from 1972 through 1992, thereafter it leveled out [11].

**Early diagnosis and treatment** of GCA are especially important with regard to possible prevention of irreversible blindness, life-threatening aortic complications (such as aortic aneurysm dissecans or its rupture) [12], and stroke as well [13].

As for the benefits of early diagnosis of GCA in the elderly, I. F. Baig et al. (2019) in their recent review wrote: «From an ophthalmologic perspective, GCA is an urgent diagnosis because if not recognized and treated early, ischemic complications may result in permanent vision loss (up to 15 % — 25 % of cases) [14]». Referring to S. S. Hayreh et al. (2003) [15], they indicated that «35 % patients had systemic symptoms for an average of 10,8 months before suffering permanent vision loss and 65 % had transient visual symptoms for 8,5 days prior to diagnosis» [16]. This fact should be taken into account by general practitioners. As known, in 2010, the British Society for Rheumatology and British Health Professionals in Rheumatology (BSR/BSHR) determined the predictive features of developing neuroophthalmologic complications (such as jaw claudication, diplopia, and temporal artery abnormalities) and recommended to pay them a «particular attention» [17].

Nevertheless, according to the Research Institute for Primary Care and Health Science, even if cranial symptoms are present, the extent of diagnostic delay for GCA (i.e. a time period from their onset) in Great Britain is 7,7 weeks (95 % CI 2,7-12,8), while in their absence — 17,6 weeks (95 % CI 9,7-25,5), average 9 weeks (95 % CI 6,5-11,4), that was established in the systematic review and meta-analysis by J. A. Prior et al. (2017) and confirmed «the need for improved public awareness and fast-track diagnostic pathways» for this disease[18]. In general, from 6 to 19 % of patients with GCA develop blindness [15, 19-20]. Besides, there is an increased risk with GCA not only for irreversible vision loss as a result of ischemic optic neuropathy, but also for developing glaucoma often related to therapy with glucocorticoids (GCs). An increased risk of its development is associated with their high doses’s use [21].

Speaking of the doctrine of early recognition of GCA, let’s note that the 1990 American College of Rheumatology’s (ACR) classification criteria are used first of all in clinical trials and remain a basis for diagnosis of this vasculitis in clinical practice, however, a number of new diagnostic approaches and tools have been proposed (among them the «classification tree» by the ACR, the concept of «three whales» by D. Lariviére et al., the diagnostic algorithm used in the Mayo Clinic, etc.) [12]. So, the new criteria for early diagnosis of GCA are developed by I. Salehi-Abari (2016) — for using «during the initial presentation of the disease when by clinical/lab- oratory judgement of an expert rheumatologist, early diagnosis of GCA can be established». Table 1 shows these criteria (of entry, domains I and II, and exclusion). Note-worthy is the high diagnostic value of both the symptoms of polymyalgia rheumatica (PMR) and temporal artery’s anormalities [22].

A year before, M. A. El-Dairi et al. proposed a «highly predictive for a positive TAB» clinical algorithm, which «can be valuable in the evaluation process of suspected cases of GCA». They have re-reviewed 213 consecutive cases of pathologic TAB specimens seen at a single academic center over a period from 2000 to 2009 and created a composite clinical score by adding 1 point for each of the following criteria: 1) anterior extracranial ischemia, 2) new onset headache, 3) jaw claudication, 4) abnormal or tender superficial temporal artery, 5) constitutional symptoms, 6) PMR, 7) abnormal laboratory tests (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), or platelet count). If any comorbidity could explain a criterion, one point was subtracted. The results shown the following: 1) it was namely diabetes mellitus (DM) and kidney diseases «often explanation for the symptoms and abnormal clinical findings that led to a negative TAB»; 2) TAB-positive patients were older and often had jaw claudication, thrombocytosis and elevated ESR; 3) all cases of low clinical score (less than 2 points) were associated with negative TAB [23].

A classification of GCA’s onset subtype is also called upon to promote both early diagnosis and «timely initiation of treatment that can prevent vascular accidents». According to N. V. Bunchuk (2010), 8 versions are possible:

- classic version of the beginning — with clinically apparent signs of temporal arteritis;
- with clinically latent signs of temporal arteritis (but «always with histological changes»);
- with predominant signs of PMR;
- with predominant signs of damage to extracranial arteries;
- with predominant visual damage;
- with predominant signs of damage to aorta or its main branches;
- with predominant constitutional signs («occult GCA»);
- with the absence of both clinical and morphological features of temporal arteritis («headless GCA») [24, p. 47].

According to the author, 50% cases of GCA begin with apparent signs of temporal arteritis (often with jaw claudication), 30% — with «isolated» PMR. In other cases, of importance are the results of both targeted questioning (about pain in the temples, difficulties in chewing, and transient visual disorders) and focused studying of the state of arterial bed (the identification of the temporal arteries' soreness; asymmetry, reduction or lack of pulse on them and/or the main arteries; bruits as well), while «helping out» the rule according to which, in the presence of fever and/or significantly elevated ERS in the elderly, the probability of latent Horton’s disease should always be kept in mind. Noting the possibility of spontaneous subsidence of complaints caused by damage to temporal arteries, N. V. Bunchuk called the sustained absence of a pulse on them «a visiting card» of GCA [24, p. 48-49]. As for «occult» onset of GCA, the only sign for within 3 months up to 3 years there may be a fever — more often subfebrile, «no more than 39°C...and without any patterns»; both loss of appetite and weight loss (up to 10 kg in 1-2 months) are also possible [24, p. 42-43], as well as declined mood and depression (associated with headache in 1-2 months) are also possible [24, p. 42-43], as well as declined mood and depression (associated with headache and responding to GC-therapy), as confirmed by B. Kumar et al. (2013) [25].

Along with attempts to develop new clinical criteria, scales, algorithms and classifications, the important tools for early diagnosis of GCA today are visualizing methods (i.e. ultrasound of temporal ± axillary arteries as a first-line test in case of clinical suspicion on cranial GCA, while with suggested damage to large vessels — their ultrasound, magnetic resonance imaging (MRI), computed tomography (CT) or positron emission tomography (PET), as recommended in 2018 by the European Anti-rheumatic League (EULAR) and the Mayo Clinic) [26-27], and histological studies of the vessels’ samples — according to the guidelines of BSR/BHPR (2010) [17] and the French group for the study of large vessel systemic vasculitis (GEFA, 2015) [28]. Histological verification of the association of aortitis with GCA should be carried out in accordance with the recommendations of the Society for Cardiovascular Pathology and the Association for European Cardiovascular Pathology (2015) [29].

Talking on evidence based primary health care for patients with suspected GCA, let’s refer to three studies recently conducted in Great Britain [14], Norway [20], and Slovenia [30]. In 2015, P. Patil et al. proved the effectiveness of managing such patient on a fast track pathway: with this, consultation of a rheumatologist during the first working day has been provided in most of the appeals (79 %) than when managing them along a usual route (64,6 %); the rate of developing irreversible blindness has decreased and amounted to 9 % vs 37 %. The authors drew attention to the importance of training general practitioners in early diagnosis and treatment of GCA [14], as was later confirmed by J. A. Prior et al. [18].

In a year, A. P. Diamantopoulos et al. presented the results of implementation of fast track clinic (FTC) in a Norwegian rheumatologic hospital [20]. FTC approach in GCA implied quick evaluation of temporal, axillary and carotid arteries with colour Doppler ultrasound during 24 hours and immediate initiation of treatment if appropriate. Fig. 1 shows the proposed algorithm of fast-track outpatient colour Doppler ultrasound use in suspected GCA.

Their cohort was collected in 2010-2014 and included 75 patients evaluated in FTC (n=43) or conventionally (n=32). It was confirmed a high rate of developing blindness in the conventional care group (21,5 %) and an increased risk of it’s development (by 88 %) when compared with the FTC group; relative risk (RR) of blindness in case of FTC route was 0,12 (95 % CI 0,01-0,97). In

| Table 1. 2016 ACR revised criteria for early diagnosis of giant cell (temporal) arteritis * (according to I. Salehi-Abari, 2016 [22]) |
|---|---|
| **Entry criteria** | Age at onset ≥ 50 years old Absence of exclusion criteria[a] |
| **Domain I criteria** | New onset localized headache[e] Sudden onset of visual disturbances[e] Rheumatic polymyalgia Jaw claudication[e] Abnormal temporal artery[e] |
| | 1 point 1 point 2 points 1 point Up to 2 points |
| **Domain II criteria** | Unexplained fever and/or anemia ESR ≥ 50 mm/hour[a] Compatible pathology[| |
| | 1 point 1 point Up to 2 points |

Notes: ACR — American College of Rheumatology; ESR — erythrocyte sedimentation rate. * In the presence of 3 points or more out of 11 with at least one point belonging to domain I along with all entry criteria, the diagnosis of giant cell arteritis can be established. 
[a] Exclusion criteria are including: ear-nose-throat and eye inflammation, kidney, skin and peripheral nervous system involvement, lung infiltration, lymphadenopathies, stiff neck and digital gangrene or ulceration. * No other etiologies can better explain any one of the criteria. 
[e] Enlarged and/or pulseless temporal artery (1 point) / tender temporal artery (1 point). * It must be ignored in the presence of polymyalgia rheumatica. 
| [Vascular and/or perivascular fibrinoid necrosis along with leucocytes infiltration (1 point) / and granuloma (1 point).]
The FTC group, every fifth patient (20.9%) had transient visual disorders (their rate was as follows: anterior ischemic optic neuropathy — 38%, amaurosis fugax — 22%, blurred vision — 16%, diplopia — 12%, not defined — 12%) and 2.4% — permanent monocular visual loss. The mean number of inpatient days of care was 0.6, while in patients treated conventionally — 3.6 (so, implementation of FTC reduced hospitalization by 3 days). The received evidence of this approach’s clinical effectiveness and cost-effectiveness (for reducing both risk of developing blindness and need for inpatient care) opened the prospect of applying new strategy of managing such patients in primary care [20].

The prospective monocentre study of A. Hocevar et al. (2016) [30], which was conducted in 2011—2014, aimed to evaluate the rate of both permanent visual loss and recurrences of GCA depending on its «early» or «late» diagnosis and treatment with GCs. (Let’s note that their terminology is not generally accepted; for example, E. Liozon et al. (2018) [31] mean by «late GCA» a disease that developed against the background of previous PMR and its treatment with low doses of GC). As for A. Hocevar et al., they took into account presence of GCA’s symptoms before establishing diagnosis and meant «early GCA» in case of their existing for less than 31 days and «late GCA» when they existed longer. In general, 68 patients have been evaluated (share of women 72%, mean age 73.2 years); the «early GCA» patients (n=39) had symptoms for 10-28 days, and the «late GCA» patients (n=29) had them for up to 120 days. The observation lasted from 53 to 126 weeks. As for results, blindness developed in 5.9% of cases — both with «late GCA» (n=3) and in a case of «early GCA»; the recurrence rates were comparable — 43.6 and 48.3% in «early» and «late» diagnosis, respectively. Interestingly, that the average time to first relapse was 14 weeks (from 13 to 34) under «early GCA» and 25 weeks (from 22 to 48) under «late GCA», and recurrence occurred on methylprednisolone dose 6.0 mg/day (from 4 to 12). The authors wrote that «an early GCA diagnosis and prompt GC treatment decreases the permanent visual loss rate…but seem to have no impact on the frequency of relapses which are predicted by...significantly higher levels of inflammatory parameters at baseline» [30].

Literature data confirm predictive value in relation to the development of relapses of GCA of not only features of its onset, but also comorbidity’s profile (i.e. presence of RPM, anemia, DM, hypertension and osteoporosis); an association between GCA or high cumulative doses of GC in this vasculitis and the increased risk of developing a number of conditions has also been proved [12]. So, H. Petri et al. (2015) analyzed data on 4671 patients from the UK Clinical Practice Research Datalink. According to their results (RR with 95% CI), comorbidities strongly

![Fig. 1. The fast-track ultrasound GCA outpatient clinic algorithm (A. P. Diamantopoulos et al., 2016) [20]. GCA – giant cell arteritis; ROM — range of motion; LVV – large vessel vasculitis; MRA – magnetic resonance angiography; CTA – computed tomography angiography; PET – positron emission tomography](image-url)
associated with GCA were PMR (14.9; 11.9-18.7), visual disorders (4.6; 2.7-7.8), facial pain (3.3; 2.1-5.3), osteoporosis (2.9; 2.3-3.7), various infection such as oral and/or esophageal thrush (3.7; 2.2-6.0) and herpes zoster (2.6; 1.6-4.1), hypokalemia (2.5; 1.6-3.9) as well [32]. Identical data on the increased risk of developing osteoporosis with GCA was obtained in a large cohort study conducted in Southern Sweden by A. J. Mohammad et al. (2017). As they shown, compared with the general population (3066 reference persons), patients with biopsy-proven GCA (768 persons, including 571 women) have an increased rate of occurrence of selected comorbidities such as osteoporosis, venous thromboembolism, severe infections (i.e., requiring hospitalization), thyroid diseases, stroke, and DM. The rate ratio for coronary artery disease (CAD) is increased but do not reach statistically significant level (see Table 2). The authors wrote: «Several of these comorbidities may be related to treatment with GCs, emphasizing the unmet need to find alternative treatment for GCA» [33].

Let’s note that presence of GCA can be considered a risk factor for developing the diseases mentioned in Table 2, since calculation of an incidence coefficient such as rate ratio in analytical epidemiological studies is carried out to establish a casual relationship. But, the data received by A. J. Mohammad et al. with regard to CAD and DM are not quite consistent with those by the Mayo Clinic’s experts (P. Ungprasert et al., 2014-2015) given earlier [12].

Other investigators also note a heterogeneity of evidence on association between GCA and cardiovascular diseases (CVDs), DM, and malignancies [34-40]. E.g., M. Pujades-Rodriguez et al. (2016) evaluated the association of GCA and PMR with 12 CVDs, having analyzed the British registers of both trials and patients of primary care settings and hospitals for the period of 1997-2010. The study included men and women without CVDs at baseline, among them all patients with PMR only (n=9776), GCA only (n=1164), PMR/GCA (n=627) and 105504 persons without these rheumatic diseases. It was shown that during three years of observation, CVDs developed in 24.1 and 20.4 % persons with and without PMR/GCA, respectively. Both fatal and non-fatal coronary outcomes given in Table 3 were less likely to develop under PMR and/or GCA than in the absence of them.

There was neither association between PMR/GCA and other CVDs and cerebrovascular diseases revealed, nor dependence on sex and age. The authors wrote: «In this large contemporary population-based cohort the presence of PMR and/or GCA was not associated with an increased risk of CVDs or cerebrovascular diseases regardless of PMR/GCA duration» [34]. In the same time, J. C. Wilson et al. (2017) published two papers on the incidence of outcomes and serious adverse effects (AEs) potentially associated with GC-therapy under GCA [41-42]. They quantified the epidemiological parameters of osteoporosis, bone fractures, diabetes, glaucoma, serious infections and death in retrospective study of the UK Clinical Practice Research Datalink. The data of 5011 patients with GCA diagnosed at age 50 or older (a share of women 74 %, mean age of diagnosis 72.9 years) with receipt of at least one prescription for prednisolone were compared to 5011 GCA-free subjects of the control group «of equal size, sex, general practice, and calendar time». For the mentioned outcomes, both incidence rates (including those for hospitalizations) and incidence rate ratios were compared between the groups. The results given in the Table 4 confirm an increased risk for developing these potential AEs of GC-therapy with GCA. The authors also concluded that GCA patients were «at a marginally increased risk for death», when compared to age- and sex-matched patients without GCA [41].

To evaluate the associations between doses of prednisolone used and the development of above-mentioned AEs, the ORs were calculated. As a result, J. C. Wilson et al. observed «a trend of increasing risk of diabetes and osteoporosis with increasing cumulative dose of oral prednisolone». As Table 5 shows, the GCA patients in the highest average daily dose category (30 mg/day) compared to those with lower average daily prednisolone doses (5 mg/ day) were at increased risk for developing diabetes, osteoporosis, fractures, glaucoma, serious infections, and death [42].

As Tables 4 and 5 show, in order of decreasing risk of their development, the clinical outcomes with CGA potentially related to GC-therapy are as follows: osteoporosis, glaucoma, serious infections, diabetes, fractures. Treatment with higher average daily doses of prednisolone (30 mg/day orally) is associated with such a range of

<table>
<thead>
<tr>
<th>Disease</th>
<th>Rate ratio (95 % CI) under GCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoporosis</td>
<td>2.81 (2.33–3.37)</td>
</tr>
<tr>
<td>Venous thromboembolic diseases</td>
<td>2.36 (1.61–3.40)</td>
</tr>
<tr>
<td>Severe infections</td>
<td>1.85 (1.57–2.18)</td>
</tr>
<tr>
<td>Thyroid diseases</td>
<td>1.55 (1.25–1.91)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.40 (1.12–1.74)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.29 (1.05–1.56)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1.20 (1.00–1.44)</td>
</tr>
</tbody>
</table>

Notes: GCA — giant cell arteritis; CI – confidence interval.
outcomes’ risks (in order of decreasing): diabetes, glaucoma, serious infections, fractures, and death, which is even more likely than the development of osteoporosis.

Thus, consistent evidence confirmed the association between an increased risk of developing serious AEs in GCA and use of higher average daily doses of prednisolone when compared to lower doses [42]. Nevertheless, it should be noted inconsistency of evidence on the association between the development of severe infections and using GC under GCA, which has been recently received in Canada (M. Durand et al., 2012) [43], the USA (P. D. Udayakumar et al., 2014) [44], and France (J. Schmidt et al., 2016; T. Chazal et al., 2018) [35, 45].

So, M. Durand et al. estimated the increased «infectious risk associated with GCA and its treatment» especially in first 6 months following diagnosis of this vasculitis and in patients age under 75, with no regard to sex [43]. They conducted a matched historical cohort study using data from the Health Improvement Research Network and obtained results on incidence rates and rate ratios for lower respiratory tract infections, urinary tract infections, sepsis and their subsets. A total of 1664 patients with GCA were matched to 8078 non-GCA ones; respectively, 48 % and 37 % of them had at least one episode of systemic infection during follow-up. Table 6 shows the adjusted incidence rate ratios for these conditions. According to the results, all of the increased risks with GCA (except of the risk for developing sepsis) were of statistical significance. The authors wrote: «This is the first study to show that patients with GCA are at increased risk of systemic infections, particularly in the first few months following diagnosis. New GCA medications that allow steroid sparing are needed to treat this condition» [43].

Two years later, P. D. Udayakumar and other Mayo Clinic researchers retrospectively studied 245 patients with GCA diagnosed between 1950 and 2009 and compared the morbidity in this cohort to 245 non-GCA persons matched for age and sex. Having obtained similar data on infection episodes requiring and acquired during

<table>
<thead>
<tr>
<th>Coronary event</th>
<th>Incidence (per 1000 person-years)</th>
<th>Adjusted incidence ratio (with 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden coronary death</td>
<td>3.18</td>
<td>3.61</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>5.11</td>
<td>5.61</td>
</tr>
<tr>
<td>Composite end-point</td>
<td>24.17</td>
<td>25.80</td>
</tr>
</tbody>
</table>

Notes: GCA — giant cell arteritis; PMR — polymyalgia rheumatica; CI – confidence interval.

Table 4. Giant cell arteritis’ outcomes potentially associated with glucocorticoid therapy
(according to J. C. Wilson et al., 2017 [41])

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Incidence rate ratio (with 95% CI) under GCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoporosis</td>
<td>2.4 (2.1–2.8)</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>2.0 (1.6–2.5)</td>
</tr>
<tr>
<td>Serious infections</td>
<td>1.5 (1.3–1.7)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.4 (1.2–1.7)</td>
</tr>
<tr>
<td>Fractures</td>
<td>1.4 (1.2–1.6)</td>
</tr>
<tr>
<td>Death</td>
<td>1.2 (1.0–1.3)</td>
</tr>
</tbody>
</table>

Notes: GCA — giant cell arteritis; CI – confidence interval.

Table 5. Giant cell arteritis’ outcomes when using higher daily doses of prednisolone compared to lower doses
(according to J. C. Wilson et al., 2017 [42])

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Adjusted odds ratio (with 95% CI) under GCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>4.7 (2.8–7.8)</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>3.5 (2.0–6.1)</td>
</tr>
<tr>
<td>Serious infections</td>
<td>3.3 (2.2–5.2)</td>
</tr>
<tr>
<td>Fractures</td>
<td>2.6 (1.6–4.3)</td>
</tr>
<tr>
<td>Death</td>
<td>2.1 (1.3–3.5)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>1.9 (1.2–2.9)</td>
</tr>
</tbody>
</table>

Notes: GCA — giant cell arteritis; CI – confidence interval.
hospitalization (rate ratio 0.94; 95 % CI 0.74–1.18), as well as on infection episodes required secondary hospitalization (rate ratio 1.04; 95 % CI 0.80–1.36), the authors noted that it was «lower respiratory tract infections, urinary tract infections, skin and soft tissue infections...accounted for the majority of infections required hospitalization in the first 6 months after the GCA incidence (rate ratio 3.93; 95 % CI 0.85–56.52)... No difference between the cohorts was noted in overall infections acquired during hospitalization (rate ratio 0.68; 95 % CI 0.41–1.08)». They concluded that there was no overall increased risk of infections requiring or acquired during hospitalization in patients with GCA who were taking GC, and that it «may be an increased risk of infections requiring hospitalization, especially in the urinary tract, in the first 6 months after GCA incidence, although this did not achieve statistical significance» in their study [44].

In 2016, J. Schmidt et al. assessed an incidence of severe infections, an infections-related mortality, as well as their risk factors with GCA in a prospective 5-year observational study [45]. At the time of GCA diagnosis, 486 patients were enrolled (75 % of them women); the control group consisted of age- and sex-matched persons randomly selected from the general population. Like in the Canadian study cited above [43], it was shown that compared to the control, serious infections were more frequent among GCA patients in the first 6 months following the diagnosis: the incidence rate ratio was 2.1 (95 % CI 1.2–3.4). Incidence rates (per 100 patient-year) were as follows: with GCA — 11 (95 % CI 8.3–14), without GCA — 5.9 (95 % CI 4.0–8.4). The authors wrote that «septic shock and infectious colitis were more frequent among patients with GCA. Mortality caused by infections was higher in patients with GCA compared to controls» (Table 7). The results of the study allowed to establish risk factors of infection-related death in GCA: with no regard to age, it was both using GC in doses greater than 10 mg/day after 12 months of treatment (hazard ratio (HR) 4.61; 95 % CI 1.38–15.36) and presence of DM (HR 3.3; 95 % CI 1.4–7.7). After increasing incidence of death in the first year of the study, it’s leveling out was observed. J. Schmidt et al. concluded that «the risk of infections increases in GCA patients with older age or in presence of DM, or is greater when the dosage of GC has been increased to >10 mg/day after 12 months of treatment» [45].

The next recently presented studies concern mortality with GCA. Having analyzed 4628 French death certificates for the period 2005–2014 mentioning GCA, T. Chazal et al. (2018) calculated age-adjusted mortality rates for this vasculitis. The authors established a stable standardized mortality rate in GCA patients (7.2 per million people), the mean age of death (86 ± 6.8 years) and its significant increasing throughout the study period in both genders, as well as the most frequent GCA’s associations — CVDs and infections. They were listed respectively in 79 and 39 % of certificates indicating GCA as an underlying cause of death, but when other was indicated as such a cause, that was CVD (40 % of cases), cancer (13 %), neurodegenerative disease (11 %) and infection (10 %). Compared to general population, the patients with GCA more often had the age-adjusted observed/expected ratios greater than 1 for tuberculosis, pneumonia and CVD [35].

In 2019, having retrospectively analyzed the medical records and death causes in a hospital-based cohort of Norwegian patients with GCA diagnosed during 1972–2012, L.K. Brekke et al. reported no difference in its overall survival compared to general population. The researchers compared the data of those 792 fulfilling the ACR criteria (including 528 patients with biopsy-verified GCA) with 2577 matched population controls without GCA. The most frequent underlying death cause in both groups were CVDs followed by different forms of cancer.

<table>
<thead>
<tr>
<th>Table 6. Risk for developing infections in giant cell arteritis (according to M. Durand et al., 2012 [43])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious disease</td>
</tr>
<tr>
<td>Lower respiratory tract infections</td>
</tr>
<tr>
<td>Urinary tract infections</td>
</tr>
<tr>
<td>Serious infections</td>
</tr>
<tr>
<td>Sepsis</td>
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</tbody>
</table>

Notes: GCA — giant cell arteritis; CI – confidence interval.

<table>
<thead>
<tr>
<th>Table 7. The most common type of infection during the first year after the diagnosis of giant cell arteritis (according to J. Schmidt et al., 2016 [45])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
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<tr>
<td>Pyelonephritis</td>
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<tr>
<td>Colitis</td>
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<tr>
<td>Septic shock</td>
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</tbody>
</table>

Note: GCA — giant cell arteritis.
Interesting that having increased risk of dying of CVDs (HR 1.31; 95 % CI 1.13-1.51), the GCA patients had lower risk of dying of cancer (HR 0.56; 95 % CI 0.42-0.73) compared to matched population controls [36].

So, evidence based treatment of patients with GCA implies organizing an accelerated route of out-patient with suspected GCA (or «fast-track clinic» including both evaluation by rheumatologist and colour Doppler ultrasound of temporal, axillary and carotid arteries, that is consistent with the 2018 EULAR recommendations) [26] as well as an immediate use of high doses of GCs — to reduce a risk of irreversible loss of vision, as noted in the British, French, and Finnish guidelines in 2010, 2015, and 2017, respectively [17, 28, 46], and in the new recommendations of the BSR (2020) [2].

It should be noted a heterogeneity of epidemiological evidence on the association between GCA and both DM and malignancies, which risk under GCA is being reviewed in Northern Europe and America (G. Myklebust et al., 2002; P. Ungrprasert et al., 2014), in Italia as well (M. Bellan et al., 2017).

In 2002, G. Myklebust et al. published the results of the prospective study conducted in 1987-1997 on 398 patients with GCA or PMR and 1592 control persons of the same age and sex, checking their data with the Cancer Registry of Norway. Prior to inclusion, cancer was diagnosed in 8 % patients with GCA/PMR, whereas after inclusion — in 9.3 %, compared with 10.8 % in the controls (RR 0.86; 95 % CI 0.59-1.26). Thus, there was no difference from the controls regardless prevalence or incidence of neoplasms, their types and time of diagnosis [37].

In 2014, P. Ungrprasert et al. published the systematic review and meta-analysis of 6 cohort studies, in which the association between GCA/PMR with malignancies was evaluated by calculation RR, HR, and standardized incidence rates — comparing with persons free of GCA/PMR. Pooled risk ratio (PRR) for developing cancer under GCA/PMR was 1.14 (95 % CI 1.05-1.22), indicating an increased risk, especially in the first 6-12 months after establishing diagnosis (PRR 2.16; 95 % CI 1.85-2.53). However, as a result of the sensitivity analysis performed with excluding one study with potential selection bias, the PRR decreased below the statistically significant level [38]. In this regard, it is appropriate to quote N.V. Bunchuk (2010): «We can confidently say that the frequency of malignant tumors in PMR is not increased and corresponds to the population level for elderly people. A cause for extended examination of the patients with PMR, including oncological issue, is a very atypical clinical picture, inadequate response to corticosteroids» [24, c. 115-116].

At last, M. Bellan et al. (2017) compared a rheumatological clinic’s cohort of in total 1750 patients (among them 100 with PMR) who were observed during 2005-2012 to a control group of 702 patients with osteoarthritis. As a result, the independent predictors of paraneoplastic PMR were established, such as older age, male sex, and polyarticular type of articular syndrome (i.e., involvement of no less than 6 joints). Rheumatic disease was considered paraneoplastic if tumor was diagnosed during 2 years before or after occurring symptoms of this disease. With PMR, the probability of association with tumor turned out to be strong (OR 5.1; 95 % CI 2.9-8.9), losing only to dermatomyositis/polymyositis (OR 12.09; 95 % CI 2.6-55.8); less common was the paraneoplastic nature of vasculitis (OR 3.7; 95 % CI 1.81-7.52) and Sjögren syndrome (OR 3.6; 95 % CI 1.7-7.5) [39].

With regard to the safety of GC-therapy, it is also important to re-evaluate risk for developing fractures with GCA. In 2018, Z. Paskins presented the results of retrospective data cohort study of the patients of primary care settings of Great Britain (aged over 40, with diagnosis either PMR (n=12136) or GCA (n=2673) established in 1990-2004 and observed up to 2015) who were included in the UK based Clinical Practice Research Datalink. Matched controls (i.e. 4 people for each patient of the main group) were comparable for sex, age and practice. Calculated for 10000 patient-years, the incidence rate of fractures in GCA was 147.15 (95 % CI 132.91-162.91), in PMR — 148.05 (95 % CI 141.16-155.28); when compared to the control, the risk of fracture was increased by 67 % in GCA (HR 1.67; 95 % CI 1.49-1.88) and by 63 % in PMR (HR 1.63; 95 % CI 1.54-1.73). Along with the equally high risks of developing fractures in GCA and PMR, a low adherence to the recommendation on the bisphosphonates’ use in GC-therapy was established — they were prescribed in fewer than 13 % cases. According to the authors, a prospect of further researches is to identify effect of «lower GC starting doses and/or aggressive dose reduction» on the risk of fracture [47].

In the same year, analysis of the register data from the National Database of the German Collaborative Arthritis Center was conducted by K. Albrecht et al. This allowed to evaluate the effects of long-term GC-therapy in PMR (n=1420), GCA (177), and their combination (n=261) in regard to development of osteoporosis, diabetes and CVDs. 3-year data was available for 256 persons. It was established that 76 % patients took GCs, while methotrexate (MTX) was taken by 19 % patients with PMR and 40 % patients with GCA. In the first 6 months of the disease, average daily doses of GC were as follows: 12.5 mg in PMR, 11.3 mg in GCA, 20.0 mg in GCA/PMR. Patients with PMR reached an average GC dose of ≤5 mg in 13-18 months, while those with GCA or GCA/PMR — in 19-24 months. A quarter of patients took GCs more than 3 years. Herewith, according to the multivariate analysis’ results, the following initial data were predictively valuable (RR with 95 % CI): use of MTX (2.03; 1.27-3.24), GC dose >10 mg/day (1.65; 1.07-2.55), high disease activity (1.12; 1.02-1.23), and female sex (1.63; 1.09-2.43). It was uncontrolled activity in the first year of the disease that was called «a good predictor» of the need for long-term GC-therapy. With regard to the comorbidities, in three years only the rate of osteoporosis has increased [40].

The above allows us to conclude that comorbidity is inherent in patients with GCA (for a number of reasons) and probably associated with the risk of developing relapses of
vasculitis (regardless of the timing of its diagnosis) and the risk of developing AEs of GC-therapy.

Let’s move on to consideration of international clinical recommendations as a foundation of evidence-based management of patients with GCA in clinical practice.

In the BSR/BHPR guideline (2010), 5 out of 9 points concerned treatment. According to № 4, «high-dose GC-therapy should be initiated immediately, when clinical suspicion of GCA is raised; GC reduction should be considered only in the absence of clinical symptoms, signs and laboratory abnormalities suggestive of active disease». This was supplemented with a description of starting dosages: 40-60 mg prednisolone daily – in uncomplicated GCA (i.e. «no jaw claudication or visual disturbances»); 0.5-1 g of i.v. methylprednisolone for 3 days before oral GCs – in GCA with evolving visual loss or amaurosis fugax; 60 mg prednisolone daily – in «established visual loss...to protect the contralateral eye» [17]. Note that today, great attention is paid to identifying jaw claudication in the elderly and its diagnostic and prognostic value with GCA [20, 24, 48-49].

The following positions on treatment were: «Low-dose aspirin should be considered in patients with GCA if no contraindications exist. Monitoring of therapy should be clinical and supported by the measurement of inflammatory markers. The early introduction of MTX or alternative immunosuppressants should be considered as adjuvant therapy». A separate point recommended patient education. The guideline pointed to inherent GCA rapid response of symptoms to high-dose GC treatment, «followed by resolution of the inflammatory response. Failure to do so should raise the question of an alternative diagnosis... This should be balanced against the need to use the lowest effective dose, patient wished and GCs' side effects. Steroid reduction may also be appropriate if the acute-phase response is deemed to be due to another cause» [17]. It is noteworthy that a good effect of GCs is also observed in case GCA debuts with depression combined with a headache [25].

Tapering regimen suggested in the British guideline was: «40-60 mg prednisolone continued until symptoms and laboratory abnormalities resolve (at least 3-4 weeks), then dose is reduced by 10 mg every 2 weeks to 20 mg; then by 2.5 mg every 2-4 weeks to 10 mg; and then by 1 mg every 1-2 months provided there is no relapse» [17]. A similar scheme is included in the clinical protocol approved by the order of the Ministry of Health of Ukraine in 2017 [46]. BSR/BHPR noted a possible need for GC dose «adjustment for disease severity, comorbid factors, fracture risk, patient wishes and AEs», as well as a requirement long-term low-dose GC therapy «in some patients», and recommended to provide both bone protection and gastrointestinal protection (using proton pump inhibitors) [17].

Among 15 topics of the French recommendations (GEFA, 2015), 7 tackle issues of treatment of GCA. Their main statements are presented in Table 8; consensus level of 80 % is being reached for all such statements [28, 50-51].

Both accumulation of evidence of frequent involvement of aorta and its main branches (in up to 83 % of cases) and revision of the classification of GCA with the allocation of its large-vessel subtype [12] was followed by the development and publication of the 2018 EULAR recommendations for the use of imaging in large vessels vasculitis in clinical practice [26]. The 2010 BSR/BHPR guideline [17] has been revised in the recently published 2020 BSR guideline on diagnosis and treatment of GCA [2], in particular, «to include diagnostic imaging». The document contains 8 general principles and 11 recommendations, for which a high level of developer agreement is achieved: all principles have a consensus score >7 (from 9.17 to 9.81) that reflects their «crucial importance for decision-making». Let’s consider these principles.

1) How should suspected GCA be treated? Patients in whom GCA is strongly suspected should be treated with high-dose GCs. Consensus score 9.61.

This implies that according to clinical judgement, GCA is a more likely explanation for the present symptoms (fever, weight loss, acute phase markers, etc.) than any other condition.

2) How quickly should patients with suspected GCA be referred for evaluation? It is highlighted that GCA is an emergency. Each local healthcare setting «should have information available to frontline clinicians» (such as general practitioners and those working in acute care) on «how to refer patients with suspected GCA urgently for local specialist evaluation. Patients should be evaluated... on the same working day if possible and in all cases within 3 working days». Consensus score 9.17.

It is noted that rapid specialist evaluation is a key principle of managing GCA. In support of this principle, references are made to the retrospective reports by P. Patil et al. (2015) and A.P. Diamantopoulos et al. (2016) described above [14, 20], as well as to the prospective multicenter TABUL study of effects of clinical evaluation, vascular ultrasound and TAB given within 1st week of high-dose GC-therapy in suspected GCA (R. Luqmani et al., 2016) [52].

3) To whom should patients with suspected GCA be referred? Patients with suspected GCA should be evaluated by a clinician with appropriate specialist expertise, usually rheumatologist. Patients presenting with a history of new visual loss (transient or permanent) or double vision should be evaluated as soon as possible on the same calendar day by ophthalmologist. Consensus score 9.61.

The comments indicate danger of raising diagnostic difficulties in case of «undiscerning use» of high-dose GCs, as well as possible value of the opinions from specialists from multiple disciplines, «where the diagnosis is difficult».

4) What evaluations should be performed when starting treatment? When starting GCs for suspected GCA, diagnostically relevant symptoms and signs should be documented; blood should be taken for full blood count CRP and ESR before or immediately after commencing high-dose GC. If GCA is strongly suspected, the first
dose of GC can be given without waiting for laboratory results. Consensus score 9.61.

Diagnostically relevant symptoms and signs of GCA are as follows: headache; scalp tenderness; jaw or tongue claudication; temporal artery tenderness, nodularity or reduced pulsation; visual disorders including diplopia or damage to colour vision; limb claudication; PMR (i.e. pain and stiffness of the shoulders and hip girdles); fever, sweats, or weight loss. Less common are carotidynia, audiovestibular symptoms, dry cough or signs of crucial ischemia (necrosis) of tongue or scalp. Referring to G. Smetana et al. (2002) [53], they note that none of the symptoms *is* entirely specific (pathognomonic) for GCA, and many are very non-specific, each is of limited use if taken in isolation. It is also indicated that GCA causes an elevation in platelet, CRP and ESR, and plasma viscosity can be evaluated if ESR is unavailable. Taking into account a decrease of these markers under the influence of GCs, all tests must be performed prior to starting treatment «unless there is evidence of critical ischemia such as visual loss or diplopia and no immediate access to phlebotomy» [2].

Table 8. GEFA guideline’s (2015) statements on giant cell arteritis treatment [28]

<table>
<thead>
<tr>
<th>№</th>
<th>Положение</th>
</tr>
</thead>
<tbody>
<tr>
<td>9A</td>
<td>Recommended dose of prednisolone in uncomplicated GCA is 0.7 mg/kg/day with a gradual dose reduction to 15-20 mg/day for 3 months, then to 7.5-10 mg/day by the 6th month, to 5 mg/day by the 12th month and cancellation of GC after 18-24 months of treatment</td>
</tr>
<tr>
<td>9B</td>
<td>Regular use of intravenous methylprednisolone pulse-therapy is not recommended</td>
</tr>
<tr>
<td>10A</td>
<td>Patients with GCA with transient or permanent visual damage need immediate using either oral prednisolone in dose 1 mg/kg/day or intravenous methylprednisolone 500-1000 mg for 1-3 days (with a following use of prednisolone in dose 1 mg/kg/day)</td>
</tr>
<tr>
<td>10B</td>
<td>The rate of dose reduction and the duration of treatment for GCA with ophthalmic complications do not differ from the scheme recommended for uncomplicated GCA</td>
</tr>
<tr>
<td>10C</td>
<td>Aspirin (75-300 mg/day) should be recommended in GCA with visual damage</td>
</tr>
<tr>
<td>11A</td>
<td>Patients with GCA with uncomplicated and asymptomatic involvement of aorta or its branches can be treated according to the scheme recommended for uncomplicated GCA</td>
</tr>
<tr>
<td>11B</td>
<td>If there are complications in the onset of GCA (such as aortic dilation, aneurysm or dissection) or symptoms of aortoarteritis (limb claudication or ischemia), prednisolone in initial dose 1 mg/kg/day can be recommended</td>
</tr>
<tr>
<td>11C</td>
<td>With the exception of emergency, reconstructive interventions in case of aortic damage should be planned after inflammation has decreased</td>
</tr>
<tr>
<td>12A</td>
<td>With recently diagnosed GCA, use of genetic engineering biological agents is not recommended</td>
</tr>
<tr>
<td>12B</td>
<td>Adjunctive use of MTX can be considered in individual cases of recently diagnosed GCA, when GC-therapy is a serious problem</td>
</tr>
<tr>
<td>13A</td>
<td>With recently diagnosed GCA, use of genetic engineering biological agents is not recommended</td>
</tr>
<tr>
<td>14A</td>
<td>Low doses of aspirin (75-300 mg/day) should be considered in each case of recently diagnosed GCA taking into account the ratio of benefit and risks; in the presence of visual damage, low dose of aspirin should be recommended</td>
</tr>
<tr>
<td>14B</td>
<td>Systematic administration of anticoagulants or statins is not recommended</td>
</tr>
<tr>
<td>15A</td>
<td>At the first exacerbation or relapse, the dose of GC depends on the severity of the manifestations of GCA and should not be lower than previously effective dose</td>
</tr>
<tr>
<td>15B</td>
<td>With repeated exacerbations or relapses of GCA in GC-dependent patients (those who take prednisolone in dose 10-15 mg/day), additional administration of MTX can be recommended; with inefficiency of MTX, the use of tocilizumab can be considered</td>
</tr>
<tr>
<td>15C</td>
<td>A purely biological «exacerbation» or «relapse» (i.e. isolated increase in levels of inflammatory biomarkers) dose not necessarily require an increase in dose of GC or adjunction of alternative therapy, but requires more careful monitoring of patients</td>
</tr>
</tbody>
</table>

Notes: GCA — giant cell arteritis; GC — glucocorticoid; MTX — methotrexate.
sual loss, aortic aneurysm and prolonged treatment course.

With regard to evidence received in 1998-2017, «independent predictors» of permanent visual loss are older age, history of transient visual loss and jaw claudication [54], while «potential risk factors» are transient diplopia [55], hypertension and CAD [56-57], as well as peripheral artery disease [58] revealed at baseline [2]. In 2010, the BSR/BHPR considered such risk factors only jaw claudication, diplopia and temporal arteries' abnormalities [17].

Having indicated the risk factors of developing aortic aneurysm such as aortitis [59] and dilatation of subclavian artery [60], and such «possible risk factors» as smoking, male sex, hypertension, atherosclerosis and inflammation of proximal aortic branches [59, 61-64], the guideline’s authors note both lack of evidence «to define high-risk subgroups to select GCA patients for aortic imaging» and uncertainties of routine screenings (primary and repeated); they recommend clinicians «to use their own discretion regarding selection of patients for aortic imaging» [2].

Risk factors of developing GCA’s recurrences and unfavorable prognosis were described earlier [12]. In 2020, the BSR indicates the association between greater rate of relapses and long-term treatment with «severe inflammation» (i.e. presence of three out of four signs such as fever, weight loss, ESR ≥ 85 mm/h, and hemoglobin <110 g/L) [65-67], as well as prolonged treatment of large vessel GCA (proven with imaging) when compared to classical cranial subtype [59, 68].

They referred to the «best practice rule» to evaluate the patient’s blood pressure and level of glycemia (and/or HbA1c) within the first 2 weeks of high-dose GC-therapy. Consistent with the EULAR [69], namely DM, osteoporosis and fractures are called comorbidities related to GC-toxicity, while dose and duration of taking GCs are the risk factors of this toxicity. It is noted that «symptoms and/or exposure to serious infections should be assessed in all patients starting GCs, considering the local prevalence of these infections» and national guidelines [2]. The BSR highlights probability of an increase in intraocular pressure or worsening primary open-angle glaucoma, when taking GC orally. According to the EULAR’s guideline [70], a screening for this complication should be performed by «a suitably trained eye professional» if there is glaucoma or ocular hypertension (in the history as well) or risk factors such as connective tissue disease, type I DM or 1st degree of relationship with the patient with primary open-angle glaucoma or high myopia [2].

During the first 6 months of the disease patients with GCA should see «a clinician with appropriate expertise» at least every 2-8 weeks, then every 12 weeks during the second 6 months, every 12-24 weeks during the 2nd year and additionally in case of relapse or as GC is tapered or discontinued. This schedule is determined by the risk of development of GCs’ AEs and «should be adapted for the individual patient». Each follow-up visit should include careful taking history, physical examination, evaluation of full blood count, ESR and/or CRP, «any abnormalities relevant to the individual patient as well as drug-specific screening for toxicity» [2].

Earlier, the BSR/BHPR recommended measuring glucose, urea and electrolytes in blood at each visit, chest X-ray to monitor for aortic aneurysm — every 2 years (echocardiography, PET and MRI were also assumed), and noted that «bone mineral density might be required» [17].

6) How should ongoing management of GCA be individualized? Full assessment of the disease and comorbidities and consideration on the patient’s personal priorities should inform decision about GC tapering and initiation of additional treatments such as GC-sparing therapies. Consensus score 9.67.

Table 10 presents a schedule of GC tapering in GCA suggested by the BSR (2020). This is based on both a development of BSR/BHPR (2010) described above [17] and a clinical trial of tocilizumab published in 2017 [71]. Table 11 outlines an impact of new symptoms in patients with GCA «in the absence of other risk factors or significant comorbidities» on clinical decision making process [2].

With regard to prevention of osteoporosis and vaccinations in patients with GCA, clinicians are encouraged to refer to the developments of the ACR (2010) [72] and EULAR (2011) [73]. The BSR reminds of a decrease in the efficacy of vaccinations in persons taking GCs and that the use of live vaccines is contraindicated in patients receiving GC is dose >20 mg/day for ≥2 weeks. An optional use of proton pump inhibitors «when taking GC in doses lower than high» is also noted. The GCA patients without a history of chicken pox should be advised to avoid close contact with people who have this disease or shingles [2].

7) What education should patients be offered? All patients with GCA should be provided with information about GCA and its treatment. They should receive advice on diet, physical activity and stopping smoking. Consensus score 9.47.

The BSR notes that it should be done in multiple and written format, and that there is no clinical study of special programs in GCA [2]. The information analysis we conducted earlier showed lack of evidence-based developments on nutrition for patients with systemic vasculitis [74]. The guideline discussed says that diet «should mitigate the potential effects of GC-therapy on body weight, post-prandial glycemia and bone fracture risk», while physical rehabilitation is important given a stimulating effect of exercises on collateral formation, improving general mobility, balance and psycho-emotional status [2]. In the absence of evidence base, the BSR allows the application in GCA of the EULAR’s recommendations for physical activity in people with arthritis (2018) [75] and highlights the GSs’ AEs such as myopathy (which typically develops after weeks or months of starting therapy, particularly at high doses), insulin resistance, osteoporosis and central obesity. Clinicians are advised to encourage relevant patient support groups, as well as to
explain to patients the need to alter their GC doses and ways of administration in case of occurring intercurrent illness (e.g., vomiting, etc.), to describe symptoms of GC withdrawal, and so on [2].

8) What plans should be made for possible future GCA relapses? During GC taper and after GC cessation, patients should be informed what symptoms may suggest GCA relapse and what action the patient should take in these circumstances, including the «first point of contact» for medical advice and how to contact the team providing specialist care. Consensus score 9.81.

Let’s move on to the recommendations for diagnostic tests in suspected GCA. Ten years ago in Great Britain, TAB was considered desirable in each such case [17]. Later, the algorithm of evaluation for patients with suspected GCA depending on the predominance of either cranial or extracranial symptoms, was in the Mayo Clinic developed; this involved a baseline CT- or MRI-angiography even with a confirmed diagnosis of GCA [12, 27]. A proposed by the BSR approach to urgent vascular ultrasound in case of suspected GCA is presented in Fig. 2 [2].

Assessment of the probability of GCA bases on all information available (i.e. symptoms, signs, laboratory tests and alternative diagnoses explaining clinical picture) and can be revised based on new data (i.e. clinical course, results of ultrasound of temporal and axillary arteries and/
or TAB). Its basis is a clinical judgement, ideally individual expertise, and «for a medium...estimated probability of GCA, it may be useful to perform an ultrasound prior to biopsy, in case the biopsy is negative». If clinical probability of GCA is high, a positive ultrasound alone may be sufficient to confirm the diagnosis, but an additional performing TAB «further increase diagnostic certainty». In the absence of signs of cranial GCA, biopsy can still be positive, but «imaging of the extracranial large vessels may be considered instead of, or in addition to, TAB».

Pointing out a great number of clinical tools developed locally for assessing the probability of GCA in clinical practice, the BSR highlights the need to check their validity. If rapid-access vascular ultrasound (see Fig. 2) is not available, patients treated for suspected GCA should all have a TAB. In unison with experts of the EULAR guideline [26], it is emphasized that «none of these tests should delay the prescribing high-dose GC-therapy for patients with strongly suspected GCA» [2].

Actually, two BSR’s recommendations are devoted to the diagnostic tests, and the high levels of agreement achieved reflect their crucial importance.

1) Patients with suspected GCA should have a confirmatory diagnostic test. This could be either a TAB at least 1 cm length or an ultrasound of the temporal and axillary arteries, or both. Strong recommendation. Moderate quality evidence (B), consensus score 9,33.

2) 18F-FDG-PET, MRI- or CT-angiography or axillary artery ultrasound may be used to evaluate involvement of the aorta and its proximal branches. Conditional recommendation. Very low quality evidence (D), consensus score 9,36.

Discussing the imaging tests’ role in the diagnostics of damage to aorta and its proximal branches, the authors note additional advantages of FDG-PET/CT such as a potential value to exclude alternative diagnosis like malignancy and infection. It is possible to use ultrasound for confirming involvement of carotid, axillary and vertebral arteries. But, there is indirect evidence to estimate accuracy of visualizing tests in GCA as well as currently insufficient evidence from prospective studies.

Other 9 recommendations of BSR (2020) relate to the treatment of patients with GCA.

Table 11. Examples of symptoms that may signify relapse of giant cell arteritis during glucocorticoid taper and require escalation of glucocorticoid therapy (according to BSR, 2020 [2])

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Possible significance in a patient with GCA</th>
<th>Action to consider if symptom is judged to be due to GCA relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Return of headache</td>
<td>Possible GCA relapse without ischemic manifestations</td>
<td>Return to previous higher dose of prednisolone</td>
</tr>
<tr>
<td>Jaw or tongue claudication</td>
<td>Possible GCA relapse with ischemic manifestations</td>
<td>Consider high-dose oral prednisolone (40-60 mg) with or without GC-sparing agent</td>
</tr>
<tr>
<td>Weight loss, fever, night sweats, anemia, persistent acute phase markers, new or recurrent PMR symptoms, limb claudication, back pain or abdominal pain</td>
<td>Possible GCA-related inflammation of aorta and/or its proximal branches</td>
<td>Investigate with vascular imaging (MRI, CT or FDG-PET/CT); consider increasing dose of oral prednisolone and/or adding GC-sparing agent</td>
</tr>
</tbody>
</table>

Notes: GCA — giant cell arteritis; CT — computed tomography; MRI — magnetic resonance imaging; FDG-PET/CT — 18F-fluorodeoxyglucose positron emission tomography combined with computed tomography. New visual loss or diplopia should be urgently evaluated by an ophthalmologist. Identifying elevated acute phase markers may increase the clinical suspicion of GCA relapse. At present, the only methotrexate and tocolizumab are evidence-based steroid-sparing agents in GCA.

3) The standard initial dose for GCA is 40–60 mg oral prednis(ol)one per day. Conditional recommendation. Very low quality evidence (D), consensus score 9,44.

Discussing this statement, the BSR indicates not only lack of clinical trials comparing different initial oral GC doses for GCA, but also presence of experience confirming symptomatic response in the majority of patients within 1–7 days to a 40–60 mg daily dose (apart from irreversible manifestations such as visual loss, stroke or tissue necrosis). «Failure to respond to this dose should prompt re-evaluation of the diagnosis». When deciding on an initial GC dose, namely body weight remains a factor taken into account, but the risk for developing dose-dependent comorbidities should also be given. Clinicians are advised by the BSR to consider a higher dose within the 40–60 mg/day range for patients who have ischemic visual disorders or jaw/tongue claudication, «acknowledging that the evidence base for this is limited». Speaking of i.v. methylprednisolone pulse therapy for one to three days in comparison with the use of high dose oral prednisolone, BSR refers to the results of four randomized clinical trials (RCTs) [76-79], which did not reveal any difference in the AEs such as infection, cushingoid, psychiatric, cardiovascular and ocular complications, diabetes, gastrointestinal bleedings and disorders, phlebitis/thrombosis, myopathies, osteoporosis, fracture and death. However, the quality of evidence is rated by the BSR as low or very low. «There may possibly be a small benefit in terms of a reduced cumulative GC dose in patients receiving pulse therapy... but the value of intravenous GC in patients without acute or intermittent visual loss in GCA remains uncertain» [2].

4) GCA patients with acute or intermittent visual loss may initially be given 500 mg-1 g i.v. methylprednisolone for up to three consecutive days before commencing oral prednis(ol)one therapy. Conditional recommendation. Very low quality evidence (D), consensus score 9,00.

It is noted both lack of clinical trials in patients with acute ocular ischemia and presence of experience confirmed an occuring the vast majority of visual loss before initiation GC-therapy. In 2010, the BSR recommended a 3-day i.v. methylprednisolone pulse therapy for com-
plicated GCA [17], and in 2014 — for the treatment of organ-threatening other systemic vasculitis [80]. The discussed guideline indicates an alternative to methylprednisolone pulse therapy (if it is not possible) such as 60-100 mg/day oral prednisolone given up to 3 consecutive days [2].

5) GC dose should be tapered to zero over 12-18 months, providing there is no return of GCA symptoms, signs or laboratory markers of inflammation. A more rapid dose reduction is appropriate for patients at high risk of GC-toxicity and/or those receiving concomitant GC-sparing therapy. Conditional recommendation. Very low quality evidence (D), consensus score 8,81.

The evidence base of this statement consists of two RCTs conducted in patients with new GCA; they revealed no difference in the outcomes between different regimens of tapering GCs. One of them was an open single-centre study published in 1989 [81] and provided evidence of low and very low quality; the second modern trial of very high quality [71] was not designed for assessing AEs of GCs.

6) Patients should be prescribed a single daily dose of GC rather than alternate day dosing or divided daily dosing. Conditional recommendation. Very low quality evidence (D), consensus score 9,53. This recommendation is based on the results of an open single-centre RCT «with unclear length of follow-up» published by G.G. Hunder et al. in 1975 [82].

7) No recommendation can be made for use of modified-release prednisone in the treatment of GCA. Insufficient evidence, consensus score 9,72. There is neither clinical trials nor clinical experience on this issue.

8) MTX might be considered for GCA, in combination with a GC taper, in patients at high risk of GC-toxicity or who relapse. There is insufficient evidence to recommend any other oral immunosuppressive agent in GCA, including azathioprine, leflunomide or mycophenolate mofetil. Conditional recommendation. Low quality evidence (C), consensus score 8,82. Evidence base C means that «further research is very likely to have an important impact on our confidence in the estimate the effect and is likely to change the estimate» [2].

With GCA, MTX was studied in three double-blind placebo-controlled RCTs conducted in 2001-2002 (J.A. Jover et al. [83], R. F. Spiera et al. [84]; G. S. Hoffman et al. [77]), then in the meta-analysis by A. D. Mahr et al. (2007) [85]. A single-centre, 24-month study by J.A. Jover et al. (2001) included 42 participants with recent-onset GCA and initial dose of prednisone 60 mg/day; the patients in the main group additionally took MTX 10 mg/week [83]. A multicentre, 12-month study by G. S. Hoffman et al. (2002) included 98 participants with recent-onset GCA and initial dose of prednisone 1 mg/kg/day; the dose of MTX in the main group was 15 mg/week [77]. A smaller (n=21) single-centre study by R. F. Spiera et al. (2001) MTX at a dose 7,5 mg/week was added to GCs after reducing their dose to 30 mg/day, and the patients with visual symptoms initially received intravenous GC pulse-therapy [84]. The BSR notes that pooling of the two larger RCTs’ data allowed to receive moderate quality evidence (B) that adjuvant therapy with MTX reduces a proportion of patients with relapses of GCA at 12-24 months when compared to placebo (RR 3,2; 95 % CI 1,49-6,87). The outcome such as «treatment
failure» (defined as having either ≥2 relapses or relapse that was not controlled by an increment of prednisone dose) was evaluated in the largest trial [77] and revealed no difference between MTX and placebo (low quality evidence — C).

It is noted in the BSR guideline that in none of the RCTs was an influence of MTX on cumulative GC dose observed (evidence of low and very low quality). According to the data of all three RCTs, effect of MTX did not differ from placebo regarding GC-related AEs, mortality, visual loss, malignancies, infections, psychiatric complications, fractures, cataracts, diabetes, cushingoid habitus, gaining weight, skin atrophy (all evidence of low and very low quality) and hypertension (evidence of moderate quality). The BSR indicates lack of strong evidence on the association between taking MTX with either developing its serious AEs or an increase in rate of nausea, vomiting, elevation of transaminases, thrombocytopenia, oral ulcers, diarrhoea or gastric pain (all evidence of low and very low quality), noting that none of the trials was not powered to detect difference in AEs between MTX and placebo [2].

As stated above, the BSR refers to the meta-analysis by A. D. Mahr et al. (2007) of individual data of the participants of all three RCTs (n=161) [85], which proved the following effects of adding MTX to prednisolone: a moderate decrease in risks of developing first and second relapses (HR 0.65 and 0.49, respectively); a higher rate of GC-free remissions lasting more than 24 weeks (HR 2.8); and lower cumulative GC dose at 96th weeks (an average of 1.1 g). In general, «three small RCTs indicated that there might be a modest benefit of MTX in GCA in reducing relapse and cumulative GC dose and….regarding reducing the risk of second relapse as well as first relapse; however…the evidence remain equivocal». There is no evidence on effects of higher doses of MTX (up to 25 mg/week) used in clinical practice [2].

Let’s note that the BSR guideline does not include the less quoted [86] meta-analysis of the same three RCTs, which was performed by M. Yates et al. (2014) [87] and revealed only a tendency to reducing the risk of relapse of GCA when adding MTX (RR 0.85; 95 % CI 0.66-1.11), as well as a tendency to an increase in risk of infection (RR 1.58; 95 % CI 0.90-2.78).

Characterizing the effects of azathioprine, the BSR refers to M. da Silva et al. (1986) [88] who presented the results of a single-centre, 52-week double-blind placebo-controlled RCT of the patients with PMR with or without GCA (n=31) treated with prednisolone at a dose of ≥5 mg/day. Noting the association between taking this drug and a lower dose of GC at the end of the follow-up period (an average of 3 mg) as well as similar rates of AEs, the BSR indicates both the very low quality of evidence received and the impossibility of making recommendation on the use of azathioprine with GCA.

The effects of adjunctive use of dapsone at a dose of 50-100 mg/day were studied by F. Liozon et al. (1993) in 47 participants of an open multicentre placebo-controlled RCT [89]. The quality of the evidence obtained on reducing the risk of developing relapses of GCA (RR 0.37; 95 % CI 0.16-0.84) was rated by the BSR as very low; the evidence of more common anemia (RR 8.89; 95 % CI 1.27-61.99) in the dapsone group was of low quality. A very low quality of evidence was established on no difference between the groups on such AEs as skin rash, diabetes, bone and cardiovascular complications, infections and blindness [2].

Speaking of cyclosporin, the BSR guideline’s authors refer to two open trials conducted by C. Schaufelberger et al. (1998, 2006) in 82 patients [2, 90]. The drug was used at a dose of 2,0-3,5 mg/kg/day during 6 or 12 months, and showed no effect on cumulative dose of GCs, active phase markers and patient’s and physician’s global assessments (evidence of very low quality); however, there was an increased risk of treatment discontinuation due to cyclosporin-related AEs (RR 13,00; 95 % CI 1,78-95,10; low quality of evidence). The BSR concludes that «the potential toxicity of dapsone or cyclosporin is likely to overweight any possible benefit and their use is not recommended» in GCA [2].

The absence of RCTs of leflunomide is highlighted: the evidence of its benefit with GCA were obtained in 2012-2019 in open non-randomized trials and case series. Both cyclophosphamide and mycophenolate mofetil «have been occasionally used in clinical practice…for severe GCA by analogy with their use in other systemic vasculitis, but they have not been formally investigated in GCA» [2].

9) Tocilizumab can be considered for GCA, in combination with a GC taper, especially in patients at high risk of GC toxicity or who relapse. Strong recommendation. Moderate quality evidence (B), consensus score 9,61.

Tocilizumab (TCZ) is recombinant humanized monoclonal antibody against the II-6 receptor. Selectively binds soluble as well as membrane IL-6 receptors, TCZ inhibits both classical and trans-signal receptor ways. In 2017, TCZ was approved for GCA in the USA and Europe based on the results of two placebo-controlled RCTs [71, 79]. In the larger of these trials conducted by J. H. Stone et al. (2017) [71], both patients with onset and patients with relapse of vasculitis participated; TCZ was combined with a standardized prednisolone taper according to which GC cessation occurred at 6 months. Two alternative schedules of tapering GC were used in the placebo group, by which prednisolone cessation was achieved at either 6 or 12 months. As a result, in a year, a proportion of patients in sustained remission were larger in the main group (56 % of those received TCZ weekly, and 53 % of those treated every other week), when compared to control (14 and 18 % of those tapering GC over 6 and 12 months, respectively). The probability of achieving sustained remission with weekly administration of TCZ was much higher than with placebo on a background of 6-month tapering GC: RR 4,0 (95 % CI 1,97-8,12), which was regarded by BSR as high quality evidence (A). Moderate quality evidence (B) confirmed greater probability of achieving «a sustained remission that did not
require CRP normalization». In this RCT and in the trial by P.M. Villiger et al. (2016) [79], such effects of TCZ as an increase in relapse-free survival at 1 year (RR 3.57; 95 % CI 2.29-5.5) and a reduction in the cumulative GC dose were seen; the quality of evidence was recognized by BSR as high. Pooling the data from both RCTs (moderate quality evidence) shown a lower risk for developing serious AEs in patients treated with TCZ than those treated with placebo: RR 0.64 (95 % CI 0.41-1.00). Discussing the achievement of steroid-sparing effects with the use of TCZ, the BSR notes a number of practical limitations, including economic [2].

Speaking of TCZ for GCA with severe comorbidities, let’s cite the conclusion by T. V. Beketova et al. (2018) about «the potential effectiveness of short courses and small doses…, with which, probably, it is preferable to begin treatment in elderly patients with risk factors for adverse reactions» [91]. Adjuvant TCZ-therapy in the elderly patients with GCA may also have an advantage like influence upon depressive disorders [8]. For the treatment of GCA, the use abatacept (a recombinant soluble protein consisting of extracellular domain of cytotoxic T-lymphocytes antigen 4 combined with modified Fc-fragment of human immunoglobulin G1) and ustekinumab (an inhibitor of IL-12 and IL-23) also look promising [27, 92].

It is noted in the BSR guideline that the effects of abatacept vs placebo have been recently studied in a small RCT in patients with GCA in remission. Such outcome as time to relapse «significantly favoured abatacept», but the proportions of patients in remission at 12 months were comparable [92]. BSR considers quality of evidence low and highlights that abatacept is not approved for treatment of GCA at present. It is also noted that TNF inhibitors cannot be recommended for GCA — given the results of two RCTs [93-94] proven both ineffectiveness of infliximab and adalimumab and an increase incidence of infectious complications with their use. A small RCT of etanercept [95] «did not fulfill the inclusion criteria for the literature review and…failed to show a significant result for its primary outcome» [2].

10) The routine use of antiplatelet and anticoagulant agents for GCA is not recommended. Insufficent evidence, consensus score 9.61. BSR notes that the Cochrane review by S.P. Mollan et al. (2014) shown no evidence from RCTs to determine the efficacy and safety of low-dose aspirin for an adjuvant therapy in FKA, and recommends clinicians to follow national guidelines [96] on secondary prevention of atherosclerosis.

11) The routine use of cholesterol-lowering agents such as statins for GCA is not recommended. Insufficent evidence, consensus score 9.53. BSR notes lack of relevant RCTs and recommends clinicians to follow national guidelines on secondary prevention of atherosclerosis [2].

So, the goal of treatment of patients with GCA is recovery or persistent remission. Taking into account the guidelines of both GEFA (2015) and BSR (2020), oral administration of prednisolone remains a mainstay of GCA therapy; an early use of its high dose plays a key role (like ultrahigh doses of i.v. methylprednisolone, with or without aspirin, if there are signs of cranial ischemia) and their tapering under the control of clinical symptoms during 12-24 months until withdrawal. Patients with GCA have inherent comorbidity, which is associated with increased risks of relapses (regardless of the timing of diagnosis) and GCs’ AEs and determines the appropriateness of the systematic administration of statins, antiplatelet agents and anticoagulants as well. Adjuvant therapy should first of all provide GC-sparing effect (especially given an increased risk of developing their AEs in the elderly). It is with either a high risk of GC-toxicity or presence of GCA’s relapses that the use of MTX should be considered, as well as of TCZ — according to the BSR guideline. Prospects for early use of biologic disease-modifying anti-rheumatic drugs with GCA are important in light of increased risk of developing infectious complications during first 6 months of GC-therapy, and namely TCZ has the strongest evidence base among them.

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Гігантоклітинний артеріїт: доведені й дискусійні аспекти лікування

Резюме. Гігантоклітинний артеріїт — найпоширеніший системний васкулит у дорослих та особливо осіб похилого віку. Його розвиток і лікування нерідко пов’язані з супутніми захворюваннями, рецидивами та різними ускладненнями. У статті наведено аналітичний огляд, систематичне узагальнення й обговорення доказів щодо сучасних стратегій, основних ризиків, засобів та результатів лікування хворих на гігантоклітинний артеріїт. Досліджено дані спеціальної літератури, опубліковані англійською, російською та німецькою мовами, знайдені за допомогою електронного та ручного пошуків, перевірені на предмет індексації в основних комп’ютерних базах даних доказової медицини (Cochrane Library та Medline) та відібрани без обмежень у часі. Особливу увагу приділено профілактиці ранніх і тяжких ускладнень і побічних ефектів терапії — офтальмологічних, серцево-сосудистих, нервових ускладнень, залозистих пухлин тощо. Описано перспективи активного пошуку та лікування цього васкуліту.

Ключові слова: гігантоклітинний артеріїт; фармакотерапія; осложнения; исходы лечения; стандарты; огляд

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Гигантоклеточный артериит: доказанные и дискуссионные аспекты лечения

Резюме. Гигантоклеточный артериит — самый распространенный системный васкулит у взрослых и особо пожилых людей. Его развитие и лечение нередко связаны с сопутствующими заболеваниями, рецидивами и различными осложнениями. В статье представлены аналитический обзор, систематическое обобщение и обсуждение доказательств, касающихся основных рисков, современных стратегий, средств и исходов лечения больных гигантоклеточным артериитом. Изучены данные специальной литературы, опубликованные на английском, русском и немецком языках, найденные с помощью электронного и ручного поиска, проверенные на предмет индексации в основных компьютерных базах данных доказательной медицины (Cochrane Library и Medline) и отобраны без ограничений во времени. Особое внимание уделено профилактике ранних и тяжелых осложнений и побочных эффектов терапии — глазных, сердечно-сосудистых, нервных ускладнений, диабета, остеопороза, переломов и злокачественных опухолей. Описаны передовой опыт и результаты внедрения ускоренного подхода к ведению пациента с подозрением на гигантоклеточный артериит в первичном звене здравоохранения, доказательная база и перспективы ранней диагностики и применения глокококортикоидов, а также дополнительной иммуносупрессивной и биологической терапии с акцентом на метотрексат и тоцилизумаб. Представлены и обсуждены основные принципы, рекомендации и доказательная база руководства Британского общества ревматологов 2020 года по диагностике и лечению этого васкулита.

Ключевые слова: гигантоклеточный артериит; фармакотерапия; укладения; результаты лечения; стандарты; обзор