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Current and emerging diagnosis tools and therapeutics for giant cell arteritis

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Abstract

Introduction: Giant cell arteritis (GCA) is the most common large-vessel vasculitis in individuals older than 50 years from Western countries. The goal of the treatment is to achieve improvement of symptoms and clinical remission as well as decrease the risk of severe vascular complications.

Areas covered: The review summarizes the main epidemiological and clinical features of GCA and discusses in depth both the classic and the new therapies used in the management of GCA.

Expert commentary: Prednisone/prednisolone of 40-60 mg/day is the mainstay in GCA therapy. It yields improvement of clinical features and reduces the risk of permanent visual loss in patients with GCA. Other drugs are used in patients who experience relapses (flares of the disease) or side effects related to glucocorticoids. Methotrexate is the most common conventional immunosuppressive drug used as a glucocorticoid sparing agent. Among the new biologic agents, the most frequently used is the recombinant humanized anti-IL-6 receptor antibody, which is effective to improve clinical symptoms, decrease the cumulative prednisone dose and reduce the frequency of relapses in these patients. Anti-tumor necrosis factor-α therapy is not useful in GCA. Experience with other biologic agents, such as abatacept or ustekinumab, looks promising but it is still scarce.

Keywords: anti-IL6-receptor tocilizumab, biologic agents, giant cell (temporal) arteritis, methotrexate, prednisone, relapses.

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1. *Introduction*

Giant cell arteritis (GCA), formerly called temporal arteritis, is a large-vessel vasculitis that occurs in people 50 years and older **[1,2**]**. It is the most common vasculitis in elderly people from Europe and North America **[1,2**]**. It is possible that the gradual aging of the population in Western countries may have accounted for the increased incidence of GCA in these countries. In this regard, the peak of incidence of GCA is observed within the 70-80 age group **[3]**. The typical GCA pattern is characterized by the presence of cranial ischemic manifestations, such as headache, jaw claudication or visual loss **[4,5**]**. However, the advent of new imaging techniques has allowed the clinicians to be aware of the presence of large vessel vasculitis (LLV) involvement in the setting of GCA **[6*]**, which may be asymptomatic or typically present as limb claudication, in some cases without the presence of the typical cranial ischemic features **[7]**. Moreover, GCA is often associated with polymyalgia rheumatica (PMR), a disease that affects the shoulders and proximal aspects of the arms in individuals older than 50 years **[8**]**. Also, patients with LVV in the setting of GCA may present a systemic inflammatory response syndrome of unknown origin **[9,10,11]**. This clinical presentation is by far more frequent than limb claudication that is a typical feature of Takayasu arteritis, a vasculitis that is more common in young women of oriental background. Also, GCA patients may present as fever of unknown origin or as unexplained anemia **[12,13]**.

Environmental factors in patients genetically predisposed may be the triggers for the development of GCA **[1,14*]**. As occurred in patients with isolated PMR, GCA is also more common in people of Scandinavian descent **[1,2**,14*]**. In contrast, GCA is rare among Asian or African individuals **[1,14*]**. Furthermore, a strong association of GCA

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with HLA class I and II molecules, particularly with HLA-DRB1*04 alleles, has been described **[15,16]**.

Regarding the pathophysiology of GCA, it has recently been demonstrated that certain proinflammatory cytokines play a key role in the pathogenesis of the disease **[17*]**, what has led to use therapies specifically aimed to block inflammatory pathways.

The last goal of the treatment of patients with GCA is to control the disease, not only to improve the symptoms. It is also very important to avoid relapses of the disease and reduce the long-term therapy-related side effects. Currently, the cornerstone in the treatment of GCA is based on the use of glucocorticoids at the initial dose of 40-60 mg/day of prednisone until the complete remission of the symptoms is reached, followed by a gradual prednisone tapering. However, relapses are frequent when glucocorticoids are reduced and, on the other hand, prolonged glucocorticoid use increases the risk of potentially severe side effects in aging individuals. For this reason, in glucocorticoid refractory patients or in those subjects who are more predisposed to glucocorticoid complications, it is important to keep in mind the use of alternative therapies that may have a glucocorticoid-sparing effect.

In the present review we discuss the classic management and the new biologic therapies used for the management of GCA.

2. *Areas covered*

Since some of the readers of this review may not be familiar with this pathology, a brief summary of the main epidemiological and clinical data of GCA is described. It is also the case for the tests and procedures to make a diagnosis of GCA. With regard to therapy, glucocorticoids represent the mainstay of the treatment of GCA as above mentioned. In refractory patients to glucocorticoids, conventional immunosuppressive

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therapies, such as methotrexate can be added. Nevertheless, their effect is often modest. Due to this, several biologic agents, generally monoclonal antibodies directed against cytokines implicated in the proinflammatory cascade, have recently been used for the management of GCA with variable results, which will be discussed in depth in this review.

2.1. What are the main clinical features of GCA?

The classic form of GCA manifests by cranial ischemic features that are the result of the arteritic involvement of the cranial arteries derived from the carotid artery **[1]**. More specifically, the inflammation of branches of the external carotid artery is responsible for the most common manifestations of GCA, such as headache, scalp tenderness, facial pain or jaw claudication **[8**]**. However, visual loss is generally due to anterior ischemic optic neuropathy that is the result of the inflammation of the posterior ciliary arteries, branches of the ophthalmic artery, which in turn, is a branch derived from the internal carotid artery **[18]**.

In patients with cranial GCA, headache is observed in at least 80% of the cases **[4]**. Patients often complain of other cranial manifestations, such as facial pain and scalp tenderness. Around 40% of these patients describe jaw claudication, which is defined as jaw pain associated with chewing **[4]**. The physical examination in patients with typical GCA often discloses thickened and painful temporal arteries **[4]**. Data from recent reviews and population-based studies indicate that there is a progressive reduction in the frequency of visual ischemic events in GCA patients **[18,19*,20**]**. Nevertheless, these ominous complications are observed in many patients with GCA, being permanent visual loss observed in at least 12.5% of the biopsy-proven GCA patients **[18,19*,20**]**. Transient visual loss can precede the development of irreversible visual loss in some subjects. In this regard, amaurosis fugax is the best predictor of permanent

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visual loss **[18]**. In others, however, blindness is not preceded by any previous ischemic visual manifestations. Cerebrovascular accidents may be observed at the time of disease diagnosis or within the first month after GCA diagnosis in around 3% of patients in whom this vasculitis is confirmed by a temporal artery biopsy **[20**,21]**. Strokes seen shortly after the diagnosis of GCA occur more commonly in vertebrobasilar territory than in the territory of the carotid artery **[21]**. In contrast, as observed in elderly people, strokes seen in the prospective follow-up of these patients are more common in the carotid territory **[22]**. Aortic aneurysmal disease may be a late complication seen over the extended follow-up of patients with GCA **[23,24]**. Some investigators have emphasized the relevant role of the traditional cardiovascular risk factors (CVRF) in the development of aortic aneurysms in these patients **[23]**. In this regard, the presence of traditional CVRFs prior to the onset of GCA, especially hypertension, was found to be a risk factor for the development of further severe ischemic complications in these patients **[25]**. The main clinical features of patients with the typical pattern of cranial GCA are summarized in **Table 1** **[26]**.

Patients with GCA and LVV involvement may have stenosis of the primary and secondary branches of the aorta. In some cases, they do not complain of the typical cranial ischemic manifestations. Therefore, clinician should be aware of the potential risk of clinical signs of occlusive manifestations in GCA, mainly claudication of the extremities, due to subclavian, axillary or brachial artery stenosis, which yield clinical signs of occlusive manifestations, such as claudication of the extremities and tissue gangrene **[24]**.

2.2. GCA and PMR, implications in the management

As previously discussed, patients with GCA often present PMR features **[8**]**.

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Besides the typical bilateral shoulder girdle involvement, patients with PMR also have severe bilateral pain and stiffness involving the arms and less commonly the neck, the pelvic girdle and the proximal aspects of the thighs **[1,2**,8**]**. PMR patients complain of morning stiffness generally lasting more than 45-60 minutes. They experience problems to carry out daily life activities, such as combing or dressing, which are more severe in the morning **[2**,8**]**. Although PMR may be an isolated condition, up to 40%-50% of patients with classic cranial features of GCA have PMR manifestations **[2**,27]**.

Some authors consider that patients presenting as an isolated PMR, without any clinical evidence of GCA, in whom imaging signs of LVV involvement is found, are not predisposed to suffer vascular ischemic complications of GCA [**28**]. However, PMR manifestations may be the presenting feature in 20% of patients who later experience the typical cranial ischemic manifestations of GCA **[29]**. A population-based study showed that patients with both isolated PMR and GCA associated to PMR manifestations have in most cases elevation of the erythrocyte sedimentation rate (ESR). However, isolated PMR patients have less commonly anemia and thrombocytosis than those with PMR associated with the classic biopsy-proven GCA **[30]**. Also, the mean ESR is lower in patients with isolated PMR than in those with GCA associated to PMR **[30]**.

Since the initial dose of prednisone used in isolated PMR to improve symptoms is lower than that required to prevent the risk of blindness in GCA **[2**]**, clinicians should be aware of the risk of blindness in some GCA patients presenting as isolated PMR. In this regard, relapses of the disease characterized by the presence of typical features of GCA, such as cranial ischemic manifestations, upper extremity vascular insufficiency due to stenotic involvement of the arteries and visual ischemic complications, have been

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reported in the follow-up of adequately treated patients initially diagnosed as having isolated ("pure") PMR **[31**]**. These observations highlight the need of close follow-up to patients with isolated PMR due to the frequent overlap between these two diseases **[31**]**.

A point of interest is to determine how clinicians can decipher the therapeutic response for the GCA and PMR components in patients who have both conditions. In this regard, PMR symptoms may improve rapidly with a dose of prednisone between 12.5 and 25 mg/day. However, this dose is considered insufficient to prevent the development of visual loss associated with GCA **[32]**. Moreover, the dose of glucocorticoids required to treat GCA patients who present with visual ischemic manifestations is much higher (at least 60 mg/day of prednisone) than that required to yield rapid improvement of PMR symptoms.

2.3. How can we make a diagnosis of GCA?

The classic approach to make a diagnosis of GCA is based on a positive temporal artery biopsy. In general, in subjects with the typical pattern of cranial GCA, a biopsy of the temporal artery on the most symptomatic side of at least 1 cm length is sufficient to make a histological diagnosis of GCA **[33]**. Biopsy-proven GCA patients exhibit histological features in the temporal artery that include disruption of the internal elastic lamina with an inflammatory infiltrate composed mainly of mononuclear cells and giant multinucleated cells in approximately 50% of the cases **[34]**. A positive temporal artery biopsy for GCA was included among the criteria proposed by the American College of Rheumatology (ACR) to classify a patient as having GCA **[35]**. Besides an abnormal temporal artery biopsy, another four criteria (age at disease 50 years or older, new onset of headache, temporal artery abnormality on physical examination of the temporal arteries, and an ESR equal to or greater than 50 mm/1st hour) are included in this set of

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classification criteria **[35]**. For the purpose of classification, a patient was considered to have GCA if he/she fulfilled 3 of these 5 criteria **[35]**. Although the ACR classification criteria are useful to identify patients with the classic cranial pattern of GCA, they are often inadequate to identify GCA patients presenting with LVV [**36***]. A study that assessed differences between 120 GCA patients with LVV involvement and 212 GCA patients with the typical cranial ischemic manifestations of the disease showed that those with LVV involvement were younger and had longer duration of symptoms at the time of disease diagnosis than those with the classic pattern of cranial GCA **[36*].** Several studies have confirmed that Doppler ultrasonography (US) of the temporal artery may be an alternative to the classic approach of performing a temporal artery biopsy to make a diagnosis of GCA, in particular in those patients presenting with the typical cranial pattern of the disease. In these cases, the assessment of the temporal arteries by Doppler US can disclose the typical finding consisting of edema, characterized by a dark, hypoechoic, circumferential wall thickening "halo" around the lumen of the temporal artery that does not disappear upon compression **[37]**. The compression sign should always be performed in the presence of a suspected halo because it has demonstrated to be a robust marker with excellent inter-observer agreement **[37]**. Other findings that can be disclosed by US in patients with arteritic involvement of the temporal artery are the presence of stenosis and occlusion **[37]**. In contrast, the absence of this "halo sign" involving the temporal artery makes the diagnosis of cranial GCA unlikely **[38].**

The use of imaging techniques, such as the positron emission tomography (PET), may allow to disclose the presence of LVV involvement in patients presenting as isolated PMR without cranial ischemic manifestations **[8**]**. Apart from the PET/computed tomography (CT) scan, other imaging techniques, such as the CT and the magnetic

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resonance imaging (MRI) angiography, have contributed to identify the presence of LVV involvement in patients with GCA and PMR **[6,39,40**,41,42]**. These new imaging techniques have been of great help to redefine the actual spectrum of GCA, emphasizing the relevance of the extracranial LVV involvement in these patients **[40**]**. However, CT-angiography is not any more recommended. PET is costly and some experts do not recommend PET as the preferred diagnostic tool. Moreover, in contrast to MR-angiography, PET does not provide sufficient information regarding the vessel wall, and its relevance in the follow-up of patients with LVV requires further investigation. Modern MRA techniques, such as the dark-blood technique of extracranial arteries, constitute promising tools for the diagnosis of GCA. Interestingly, the recent European League Against Rheumatism (EULAR) recommendations for the use of imaging in patients with LVV include the use of an early imaging technique in individuals in whom LVV is suspected **[43**]**.

According to this group of experts, US should be the first choice for the diagnosis of GCA. They consider that CT-scan or PET may be used indistinctly **[43**]**. In a study by Bley et al comparing color-coded duplex US and high-resolution MRI in the diagnosis of GCA, the sensitivity of high-resolution MRI and US compared with the temporal artery biopsy was 83% and 79%, respectively whereas the specificity was 71% and 59% **[44]**.

2.4. Importance of early treatment in patients with GCA

The final goal of GCA therapy is to induce the remission of the disease, not only to improve the symptoms. It is also important to avoid relapses and the development of irreversible complications as well as the occurrence of severe treatment-related side-effects in the long term.

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A higher physician awareness is probably the reason for the progressive reduction in the frequency of visual ischemic complications and permanent visual loss observed over the last two decades in different population-based studies **[3,19*,45*]**. Nevertheless, GCA remains as one the main causes of blindness in elderly people in Western countries **[19,45*]**.

Another important point regarding GCA therapy is the urgency of treatment even before the diagnosis is confirmed, especially when ocular symptomatology appears (diplopia, amaurosis fugax, transient visual loss) because of the risk of acute and permanent visual loss. This is an important challenge in real life which requires urgent decision and therapy. In these cases, it is advisable to start treatment before the diagnosis can be confirmed and other causes have been excluded.

Once the diagnosis has been made, patients must be prospectively followed-up to reduce the risk of cardiovascular complications. Population-based studies from Southern Europe reported in the past decade highlighted the influence of the traditional CVRFs in the risk of severe ischemic complications **[21,25,46]**. Also, socio-economic deprivation was associated with ischemic manifestations in patients with GCA from the UK **[47]**.

A meta-analysis disclosed that the use of antiplatelet or anticoagulant therapies before GCA diagnosis is not associated with a decrease in the incidence of severe ischemic complications when the disease is diagnosed **[48]**. However, the use of antiplatelet or anticoagulant therapies once the diagnosis of GCA has been made seems to reduce the risk of further ischemic events **[48]**. In this regard, a committee of experts supported by EULAR recommended the use of low-dose aspirin in all patients with GCA **[49]**.

Finally, the evolution of the GCA must be seen globally, from a point of view of both symptoms as well as laboratory findings. Often there is some discordance between the

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two fields, which would make it necessary to rule out an intercurrent disease different from GCA. In case of doubt, clinicians should use imaging examinations, such as MRI or PET, which if positive, will confirm that the process continues still active.

2.5. Treatment of GCA: Classic and new therapies

Table 2 summarizes the main therapies used in patients with GCA **[26]**.

2.5.1. Glucocorticoids. The pivotal drugs

Glucocorticoids are the mainstay of therapy in patients with GCA **[50*]**. Whereas the initial dose of prednisone/prednisolone recommended in patients with isolated PMR to achieve a rapid improvement of symptoms ranges between 12.5 and 25 mg/day **[8**,51]**, high-dose glucocorticoid therapy is required to yield remission in patients with GCA **[49]**. With respect to this, the initial prednisone/prednisolone dose in individuals with GCA ranges between 40-60 mg/day for 3-4 weeks **[34,50]**. In most cases, improvement of cranial symptoms, such as headache or scalp tenderness, is seen within the first 24 to 72 hours after the onset of glucocorticoid therapy. It is also applicable for PMR manifestations. Some authors recommend starting with a prednisone dose of 40 mg/day in GCA patients without severe ischemic complications **[14*,15,25]**. However, the experts from the EULAR suggest using an initial dose of prednisolone of 1 mg/kg/day (maximum 60 mg/day) **[49]**. In keeping with this approach, there is general agreement on the use of an initial dose of 60 mg/prednisone or prednisolone/day or the initial administration of intravenous methylprednisolone pulse therapy (1g daily for 3 consecutive days) in patients who present with severe ischemic manifestations, in particular if they have visual impairment **[18,34]**. GCA patients with visual loss lasting more than 24 hours have a poor response to glucocorticoids **[52,53]**. Therefore, intensive glucocorticoid therapy must be started soon when the diagnosis of GCA is suspected to reduce the risk of blindness.

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Regarding the use of intravenous glucocorticoid therapy in patients without visual ischemic manifestations, a study showed that an initial treatment of GCA with intravenous glucocorticoid pulses (methylprednisolone 15 mg/kg of ideal body weight/day) for 3 consecutive days along with oral prednisone (40 mg/day) yielded faster tapering of oral prednisone and higher rate of patients who achieved sustained remission of the disease after discontinuation of treatment **[54]**. Moreover, patients who started with intravenous methylprednisolone along with oral prednisone had a lower median dose of prednisone a fewer relapses than those from the control group who only received oral prednisone **[54]**. Although these results look promising, they were based on a series of only 27 patients **[54]**. In this regard, another study did not support a long-term glucocorticoid -sparing effect of intravenous methylprednisolone in the management of non-complicated patients with GCA **[55]**.

In most cases, the acute phase proteins ESR and C-reactive protein (CRP) become normal within 2 to 4 weeks after the onset of the glucocorticoids **[50,56]**. Afterwards, the glucocorticoid dose should be gradually tapered **[49]**. Based on our experience with a large series of 287 biopsy-proven GCA patients **[21]**, we usually taper 5 mg of prednisone every 2-4 weeks up to 25 mg/day, generally every 2 weeks. Then, we carry out prednisone reduction more slowly by 2.5 mg every 2-4 weeks until the dose reached is 10 mg/day and later by approximately 2.5 mg every 2 months **[57]**. However, we realize that our proposed recommendation to lower prednisone does not correspond with the EULAR recommendations **[49]**. In this regard, EULAR experts recommended decrease the dose of prednisone more rapidly, reaching a dose 10-15 mg/day of prednisone at week 12 if patients had not experienced relapses of the disease **[49].** In this regard, classic studies have emphasized that prolonged use of glucocorticoids in patients with GCA are associated with side effect such as diabetes mellitus, fractures,

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gastrointestinal bleeding, hypertension, cataracts and infections that in some cases may be fatal **[58,59].**

Close monitorization of GCA patients during the follow-up, searching for relapses of the disease and assessing routine laboratory markers of inflammations is mandatory. In general, clinicians gradually taper the glucocorticoids in the follow-up if patients have no symptoms of GCA and the acute phase proteins ESR and CRP are normal **[57,60]**. Also, at the time of tapering prednisone, it is important to keep in mind that alternate day glucocorticoid use should not be performed because it often leads to a relapse of the disease **[34,49]**.

Typical relapses of GCA occur with an important rise of ESR (≥ 40 mm/1st hour) and they are associated with disease-related manifestations such as headache or other cranial manifestations, PMR, fever or constitutional symptoms. However, sometimes relapses of the disease are associated with only mild elevation of ESR. Therefore, relapses are considered to be present when clear and worsening symptoms occurred with an ESR equal to or greater than 20 mm/1st hour **[61]**. A population-based study disclosed that 71 (41%) of 174 biopsy-proven GCA patients experienced relapses of the disease. The total duration of corticosteroid therapy was significantly longer in those patients who had relapses **[61]**. In keeping with these results, 57 (45.6%) of 125 patients from Olmsted County (Minnesota, USA) diagnosed with GCA between 1950 and 1991 had relapses **[59]**. Furthermore, 103 (86%) of them experienced adverse events associated with glucocorticoid use. A higher cumulative dose of glucocorticoids was associated with the development of adverse glucocorticoid side effects **[59]**. The high frequency of relapses and side effects related to glucocorticoids justify the use of glucocorticoid-sparing agents.

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Another situation that may require the use of glucocorticoid-sparing agents is in glucocorticoid resistant PMR patients, in whom a LVV is disclosed by imaging techniques such as PET/CT scan when they are evaluated to rule out a relapse **[62]**.

2.5.2. Conventional immunosuppressive drugs: Role as glucocorticoid sparing agents

Conventional immunosuppressive agents are used in patients with GCA to reduce the duration of the glucocorticoid therapy, in particular in patients who experience relapses of the disease **[49]**. These agents are also used in individuals with severe glucocorticoid-related side effects.

Methotrexate (MTX) is the most commonly conventional immunosuppressive drug used as a glucocorticoid sparing agent **[49]**. Three randomized controlled trials of MTX as adjunctive therapy to glucocorticoids have been reported **[63,64*,65]**.

The first trial included 21 patients with GCA who were treated with high dose glucocorticoids along with MTX (n=12) or placebo (n=9) **[63]**. However, no significant difference in the cumulative glucocorticoid dose, number of weeks to reach discontinuation of glucocorticoids, weeks required to taper prednisone to less than 10 mg/day and bone mineral density in lumbar spine or hip at one year were observed between those treated with MTX or placebo **[63]**. In contrast, in another study that included 50 biopsy-proven GCA patients from a single center with less than 2 weeks of treatment with more than 10 mg/day of prednisone, significant differences between MTX -treated and the placebo group were seen **[64]**. In this second study, a single dose of 10 mg/week of oral MTX or placebo was started and maintained throughout the period of study. Discontinuation of MTX and placebo was allowed after 24 months of follow-up if the patient was in clinical remission. In this study, the initial dose of prednisone was 60 mg/day, which was gradually tapered **[64]**. In this trial, MTX use was associated with a significant decrease in the frequency of relapses of GCA **[64]**.

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The third randomized clinical trial on MTX in GCA enrolled 98 patients from different centers **[65]**. In the study the initial dose of prednisone was 1 mg/kg/day (maximum 60 mg/day) along with 0.15 mg/kg/week MTX (increased to 0.25 mg/kg/week, for a maximum weekly dose of 15 mg) or placebo. The median dose of MTX was 15 mg/week. This study did not show any beneficial effect of the use of MTX along with glucocorticoids in GCA patients **[65]**. The frequency of treatment failure after 12 months was similar in both groups **[65]**. No differences between MTX and placebo groups in the cumulative glucocorticoid dose were observed **[65]**.

A meta-analysis of these three-randomized placebo-controlled trials yielded a modest role of MTX (10-15 mg/week) to reduce the frequency of relapses and decrease the cumulative prednisone dose **[66]**.

With regard to the use of other conventional immunosuppressive agents, azathioprine use led to lower requirement of glucocorticoids in a double blind randomized placebo-controlled study in patients with GCA or PMR **[67]**. However, this study only included 31 patients.

Although a study that included 12 patients with PMR and 11 with GCA suggested a potential efficacy of leflunomide as a glucocorticoid-sparing agent **[68]**, experience with this drug in GCA is scarce. Cyclosporine A, hydroxychloroquine or dapsone did not show beneficial effects as glucocorticoid-sparing agents in patients with GCA **[69]**. In this regard, a meta-analysis that assessed the efficacy of different conventional immunosuppressive drugs showed that prednisone or prednisolone alone is in most cases similar in terms of efficacy and safety to the use of glucocorticoids with adjunctive immunosuppression in patients with GCA **[69]**.

2.5.3. A new era for GCA therapy: Role of the biologic agents

2.5.3.1 *Anti-tumor necrosis factor (TNF) therapy*

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Over the last two decades, biologic therapies, in particular anti-TNF-α agents, have been used in patients with rheumatic diseases refractory to conventional drugs. They were also tested in patients with GCA. The most important trial was performed by Hoffman et al. They carried out a phase II study, randomized, double-blind, placebo-controlled trial to assess whether the chimeric monoclonal antibody-infliximab was a useful in GCA patients with new onset disease **[70]**. Patients included into the study (n= 44) were required to have experienced resolution of symptoms and normalization of ESR following treatment with 40-60 mg/day of prednisone/prednisolone and to have been in remission of the disease for at least 1 week before randomization **[70]**. All of them received an initial dose of 40-60 mg/prednisone/day. Patients were randomized to receive placebo (n=16) or infliximab 5 mg/kg/infusion (n=28) at baseline (week 0) and at weeks 2, 6, 14, 22, 30, 38 and 46. However, after 22 weeks of follow-up, there were no differences between infliximab and placebo-treated patients in terms of patients free of relapses or in the cumulative doses of prednisone **[70]**. The second more important study on anti-TNF agents was done with the human anti-TNF monoclonal antibody adalimumab **[71]**. This biologic agent was administered for 10 weeks to patients with a recent diagnosis of GCA. Adalimumab did not show superiority in the number of patients in remission on less than 0.1 mg/kg of prednisone at 6 months. Furthermore, the use of this biologic agent was associated with an increased risk of infection **[71]**. Likewise, etanercept also failed to demonstrate efficacy in GCA **[72]**. Therefore, anti-TNF therapy is not generally indicated in patients with GCA.

2.5.3.2 *Interleukin (IL)-6 inhibitors*

IL-6 is a pivotal proinflammatory cytokine that is produced in the inflamed arteries of patients with GCA **[73]**. It is also expressed in the monocytes of these patients **[74]**. IL-6 plays a critical role in the induction of acute-phase proteins, and GCA patients have

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increased IL-6 levels in the peripheral circulation **[75,76]**. Persistence of high serum IL-6 levels suggests the presence of disease activity in glucocorticoid-treated patients with GCA **[76]**. Following the use of glucocorticoids there is a rapid decrease of IL-6 levels that generally correlates with a reduction in the activity of the disease **[77,78]**. Because of that, IL-6 blockade was considered as a potential therapeutic option in patients with GCA **[79]**. Interestingly, Seitz et al reported for first time a series of GCA patients successfully treated with the anti-IL-6 receptor (tocilizumab) **[80]**. Additional single cases and small case series indicated that the use of the anti-IL-6 receptor tocilizumab could be effective in both newly diagnosed and relapsing patients with GCA **[81,82]**. Also, retrospective studies supported these promising observations **[82*,83]**. In this regard, an open-label, retrospective, multicenter study on 22 patients classified as having GCA according to the 1990 ACR Classification Criteria, showed that the anti-IL6-receptor tocilizumab was useful in patients with refractory and relapsing GCA **[82*]**. In this series all the patients had been treated with high dose prednisone and 19 of them had also received conventional immunosuppressive drugs and/or biologic agents. The reason for using tocilizumab (8 mg/kg every month) in these patients was absence of efficacy and in some cases severe adverse events related to glucocorticoids or immunosuppressive agents **[82*]**. Tocilizumab yielded a rapid and maintained clinical response in most of them (19 of 22) along with significant reduction of acute phase proteins CRP and ESR **[82*]**. Also, the use of this biologic agent allowed to perform a successful prednisone tapering in 20 out of the 22 patients **[82*].** In keeping with these findings, another retrospective multicenter study showed beneficial effect of tocilizumab in 28 of 34 GCA patients **[83]**. Nevertheless, in this study, six patients experienced side effects that could possibly be related to the treatment with tocilizumab **[83]**.

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Confirmatory data on the efficacy of the anti-IL6 receptor tocilizumab in the management of GCA has recently been reported in two placebo-controlled trials **[84**,85**]**. The first of them, a phase 2 study, was not truly a double-blind study because of the assessor judging clinical response was not blinded to the laboratory findings, being able to make changes in the treatment during the follow-up in function of the appearance of laboratory alterations **[84**]**. This study included 30 patients with GCA (23 of new diagnosis and 7 with relapsing disease) **[84**]**. Patients were randomized to receive intravenous anti-IL-6 receptor tocilizumab at a dose of 8 mg/kg every 4 weeks plus prednisolone (n=20 patients) or placebo infusion every 4 weeks plus prednisolone in the remaining patients (n=10). The primary endpoint was the percentage of patients who reached complete remission at a prednisolone dose of 0.1 mg/kg/day at week 12. Interestingly, 85% of the 20 tocilizumab-treated GCA patients experienced complete remission versus only 40% of the patients from the placebo group at week 12 (p=0.03) **[84**]**. Glucocorticoids were rapidly tapered and discontinued by 36 weeks after the onset of tocilizumab. Due to this, the cumulative prednisolone dose was reduced in the tocilizumab-treated group. In this regard, after 52 weeks the cumulative prednisolone dose was 43 mg/kg in the group treated with tocilizumab and 110 mg/kg in the placebo group (p=0.0005). Moreover, relapse-free survival at 52 weeks was significantly higher in the tocilizumab-treated group than in placebo group (85% versus 20%; risk difference 65%; p=0.001). Also, patients from the placebo group suffered more serious side effects than those treated with tocilizumab (50% versus 35%) **[84**]**. While patients were receiving tocilizumab, only one patient experienced a relapse and no relapses occurred after discontinuation of prednisolone in the subgroup of patients undergoing tocilizumab therapy. Nevertheless, after one-year tocilizumab was discontinued in the investigator-initiated study. This fact led to relapses in more than

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50% of the patients previously treated with tocilizumab. However, the relapses were not associated with irreversible damage **[84**]**. This study showed that tocilizumab was effective to induce remission, prevent relapses, and decrease the cumulative prednisolone dose. By contrast, an important limitation of this study was that CRP and clinical response were considered together as a combined final endpoint, which can overestimate the actual number of remissions, due to the favorable effect of tocilizumab in decreasing CRP **[84**]**.

Much stronger data supporting the benefit and safety of the anit-IL-6 receptor therapy were reported in the tocilizumab in GCA (GiACTA) trial **[85**]**. The central hypothesis of this phase 3 trial was to confirm a powerful glucocorticoid-sparing effect mediated by tocilizumab. For this purpose, the investigators enrolled 251 patients over 22 months from 14 countries and 76 sites (61 from Europe and from 15 North America). Among them, 119 were newly diagnosed and 132 relapsing patients diagnosed with GCA by using the ACR Criteria or by imaging techniques showing LVV. Patients were split into four branches: a weekly dose of tocilizumab (162 mg) given subcutaneously plus a 26-week prednisone taper, another group in which patients received tocilizumab (162 mg) given subcutaneously every other week along with a 26-week prednisone taper, a third group in which patients received weekly placebo along with a 26-week prednisone taper, and a fourth group of weekly placebo plus a 52-week prednisone taper.

Tocilizumab-treated patients reached sustained remission more commonly than those placebo-treated at 52-week. Fifty-six percent of the patients receiving subcutaneous tocilizumab every week and 53% of those treated with subcutaneous tocilizumab every other week achieved remission. In contrast, the placebo plus 26-week prednisone taper and the placebo plus 52-week prednisone taper only obtained sustained remission in 14% and 18% of the patients, respectively **[85**]**. The differences were in both cases

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statistically significant with p-values <0.001. Relapses of the disease were less common in tocilizumab treated patients (23% in those receiving tocilizumab every week and 26% in those treated with tocilizumab every other week) than in those included in the 26 and 52-week placebo arms (68% and 49%, respectively). Tocilizumab therapy also led to a statistically significant glucocorticoid-sparing effect. Patients treated with tocilizumab were longer time free of relapses. This was more evident in the subgroup of GCA who had suffered relapses before randomization. Also, tocilizumab-treated patients had lower serious adverse events than those treated with placebo **[85**]**. Based on those results the weekly use of subcutaneous tocilizumab has been approved by the United States FDA and the European Commission for the treatment of GCA.

Nevertheless, the GiACTA trial has important limitations in the evaluation of its results. Almost half of the patients (47%) had a disease of short time of evolution (diagnosis ≤ 6 weeks before inclusion). Furthermore, remission was defined as the absence of relapse (flare) plus normalization of the CRP, and relapses were defined as the recurrence of signs or symptoms or an elevation of the ESR. Given that tocilizumab is a suppressor of both CRP and ESR, it is unclear if this agent leads to true improvement of vasculitis without histopathology or imaging exams confirmatory of amelioration **[85**]**.

Intriguingly, none of the randomized tocilizumab trials mentioned presented data on the most severe complication of GCA ("vision loss"), which is also an important limitation of these studies. Biologics can also cause serious adverse effects, especially in the elderly or immunosuppressed patients.

Interestingly, open-label studies suggest that tocilizumab may also be effective in cases of isolated aortitis and in Takayasu´s arteritis **[86,87]**. Therefore, tocilizumab appears to be a potentially useful therapy for the management of patients with LVV. Taken

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together these observations, we support its use in LVV patients with relapsing disease **[88]**.

The potential efficacy of a human anti-IL6 monoclonal antibody, different from the previously discussed anti IL6-receptor tocilizumab, is currently under investigation in a phase 3 trial (ClinicalTrials.gov Identifier NCT02531633). Also, sarilumab, another anti-IL-6 receptor agent, is going to be tested for efficacy and safety in GCA.

2.5.3.3 Other biologic agents. Abatacept and Ustekinumab

Abatacept, a fusion protein composed of the Fc region of the immunoglobulin IgG1 fused to the extracellular domain of CTLA-4, blocks the co-stimulatory signal required for T cell activation. A recent study has evaluated the safety and efficacy of intravenous abatacept in patients GCA **[89**]**. For this purpose, patients with newly-diagnosed or relapsing GCA were treated with abatacept (10 mg/kg intravenously) on days 1, 15, 29, and week 8, together with prednisone. At week 12, 41 patients who had achieved remission underwent blindly randomization to receive either monthly placebo intravenous infusions (n=21) or monthly intravenous abatacept (n=20). Patients included in both study arms received a standardized prednisone taper with discontinuation of prednisone at week 28. Relapse-free survival at 12 months was higher in those treated with abatacept (48% in abatacept-treated versus 31% in the placebo group, p=0.049). Also, the median duration of remission was longer in the group treated with abatacept (9.9 months in abatacept-treated versus 3.9 months in those undergoing intravenous placebo; p=0.023). The primary outcome of the study, relapse-free survival at 12 months, was reached by 48% patients who received abatacept and 31% of those with placebo (p=0.049) **[89**]**. Moreover, the duration of remission was longer in those treated with abatacept (on average 6 months). No differences in the presence of side effects were found **[89**]**. Although data looks promising, we feel that

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additional studies should be conducted to confirm these results. For this reason, we do not use intravenous abatacept in relapsing GCA patients treated in our Division. On the other hand, to our knowledge, the abatacept multicenter trial was discontinued.

Ustekinumab, a monoclonal antibody directed against IL-12/ 23p40 complex, may block the inflammatory Th1 (IL-12) and Th17 (IL-23) pathways. Patients with refractory GCA treated with ustekinumab obtained an effect of modulating the Th1/Th17/Treg imbalance **[90*]**. After three injections of 45 mg of ustekinumab given at week 0, week 4 and week 16, a marked reduction of Th1 and Th17 cells and cytotoxic T lymphocytes was observed compared to baseline. Also, after three injections of this biologic agent, a significant increase of Tregs was observed **[90*]**. Moreover, an open label study that included 14 patients with refractory GCA has shown promising results following ustekinumab therapy **[91*]**. In this study, the patients were classified as having GCA according to the ACR Criteria and had long disease duration (median 30 months). This relapsing series of patients were treated with ustekinumab 90 mg at weeks 0, 4, and then every 12 weeks (median 8 months) **[91*]**. Ustekinumab use was associated with a reduction of the glucocorticoid dose **[91*]**. Glucocorticoids were successfully discontinued in 3 patients and in 8 patients ustekinumab allowed the discontinuation of the baseline immunosuppressive agents. Although there were not relapses while the patients were undergoing ustekinumab therapy, they were common once that ustekinumab was discontinued. To further support these data on ustekinumab therapy in GCA there is an ongoing phase 2 trial (ClinicalTrials.gov Identifier NCT02955147).

Recent data on an experimental model in mice have shown that a disruption of the PD1/PD-L1 checkpoint system releases vasculitic immunity and regulates the

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pathogenic remodeling of the inflamed arterial wall, which opens a new avenue in the pathogenesis and therapy of GCA **[92].**

2.5.3.4 Small molecules: JAK/STAT inhibitors

The Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway plays an important role in the cellular regulation in humans. A great number of cytokines, such as IL-2, IL-4, IL-6, IL-7, IL-9, IL-12, IL-15, IL-21, IL-23, IL-27, type 1 interferon and interferon-gamma (IFN-γ), which are immune relevant mediators involved in the pathogenesis of autoimmune diseases, use this pathway to transduce intracellular signals **[93**]**. Ligand binding of these immune mediators to their cell surface receptors leads to activation of associated JAKs. In turn, the activated JAKs increase their kinase activity, recruit, bind and activate STAT. The STAT molecules constitute hetero- or homo-dimers which translocate to the nucleus, inducing transcription and expression of target genes. Polymorphisms of JAK and STAT genes have been associated with autoimmune diseases **[93**]**. IFN-γ is strongly implicated in the pathogenesis of GCA and in the process leading to vascular luminal occlusion **[94]**. High concentrations of IFN-γ messenger RNA are observed in the temporal arteries of patients with GCA who present severe ischemic complications **[94]**.

STAT-1 signaling regulates the activity of vascular dendritic cells, controlling T cell trafficking and retention of inflammatory T cells in the vascular lesions **[95, 96**]**.

Interestingly, IFN-γ is the major inducer of STAT-1. In a mouse model of experimental GCA, dexamethasone suppressed the innate immunity with inhibition of dendritic cell activation, IL-6 and IL-1β expression in the vascular lesions. However, this glucocorticoid maintained IFN-γ-producing Th1 unaffected **[95]**. In contrast, the JAK/STAT-inhibitor tofacitinib, a kinase inhibitor for JAK3 and JAK1, prevented T cell accumulation in the vessel wall and suppressed IFN-γ production and signaling in a

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model of vascular inflammation in human arteries engrafted into immunodeficient mice that were reconstituted with T cells and monocytes from patients with GCA **[95, 96**]**. Tofacitinib also yielded a marked reduction of the blood levels of IFN-γ in this vasculitis-induced model **[95, 96**]**.

Currently there is a phase 2 trial evaluating the effect of baricitinib (inhibitor of JAK1 and JAK2 inhibitor) in patients with relapsing GCA (ClinicalTrials.gov Identifier NCT03026504).

2.5.4. Prevention of osteoporosis

Since glucocorticoids are the classic treatment in GCA, osteoporosis prophylaxis has to be kept in mind in the management of GCA **[97,98]**. Glucocorticoids induce lower activity and higher death rate of osteoblasts and prolonged lifespan of osteoclasts. This yields a reduction in bone formation and increases bone resorption **[99,100]**. The effect of glucocorticoids on the gut, kidney, parathyroid glands and gonads also leads to alteration in the calcium/phosphate metabolism.

Calcium and vitamin D along with a potent oral bisphosphonate, such as alendronate (70 mg/wk) or risedronate sodium (35 mg/week), should be considered in the management of GCA patients undergoing glucocorticoid therapy **[101]**. Intravenous bisphosphonates may be used in people intolerant of oral bisphosphonates.

Administration of intermittent parathormone (PTH) may induce formation of new bone and counteract the bone loss induced by the glucocorticoids **[102]**. In long-term glucocorticoid-treated patients, switching from bisphosphonates to denosumab, a potent antiresorptive agent, yielded gain of the spinal bone density and suppression of bone turnover markers after 12 months of therapy **[103]**.

Patients with very high body mass index and those receiving high doses of glucocorticoids are at increased risk of having lower levels of 25(OH) vitamin D. In

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these patients, oral calcidiol supplementation was found to be more effective than cholecalciferol to reach adequate 25(OH) vitamin D levels **[104]**.

2.6. Conclusions

GCA is the most common vasculitis in elderly people from Western countries. Glucocorticoids are the mainstay of treatment GCA. They generally lead to improvement of symptoms of GCA. However, they are frequently associated with side effects. Alternative therapies are used in patients with refractory or relapsing disease. They are also used in an attempt to "spare" glucocorticoids. MTX, the most commonly used conventional immunosuppressive drug for the management of refractory GCA, has mild beneficial effect. Whereas anti-TNF-α agents yielded poor results, the use of anti-IL-6 receptor tocilizumab has proved to be effective in the management of GCA. This result is of potential relevance in patients with refractory disease. Abatacept and ustekinumab have shown potential beneficial effect in patients with GCA. The use of JAK/STAT inhibitors in the management of GCA is still under investigation.

3. ***Expert commentary***

Figure 1 summarizes our point of view on the treatment of GCA.

Based on our own experience, we strongly support the use of prednisone (initial dose of 40-60 mg/day) in patients with GCA. We and others have observed that glucocorticoids are associated with a rapid improvement of most clinical features and have proved to prevent the risk of blindness. However, we previously reported that glucocorticoids do not yield visual recovery in most cases if therapy is not started soon when the visual loss occurred **[52]**. Few GCA patients experience visual improvement when glucocorticoid therapy is started 24 hours after the episode of visual loss **[52]**.

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Therefore, we believe that early diagnosis is essential to improving patients' outcomes and to prevent irreversible damage, such as blindness, in patients with GCA.

We also support the classic approach for the diagnosis of cranial GCA by performing a temporal artery biopsy **[34]**. However, experts consider that the temporal artery biopsy should be replaced by the temporal artery sonography **[43**]**. Nevertheless, we also support the use of the imaging techniques for the diagnosis and monitoring of patients with LVV. We use PET/CT scan when an extracranial GCA is suspected, in particular in patients with persistent PMR despite glucocorticoid therapy **[62**]**.

One of our major concerns in the management GCA comes from the high frequency of relapses when the prednisone dose is tapered **[61]**. The frequency in our series (41%) **[61]** was similar to that found in Reggio-Emilia (Italy) (57 [37%] of 157 biopsy-proven patients) **[105]**. In our experience, relapses occur mainly when prednisone dose is lower than 10-15 mg/day **[61]**. Relapsing patients require longer duration of glucocorticoid therapy. In these patients, we use MTX as the first glucocorticoid-sparing agent. However, as previously described, the effect of MTX is often modest **[66*]**. We have obtained good results by the use of the anti-IL-6 receptor tocilizumab in GCA patients refractory to glucocorticoids and MTX **[82*]**. Our clinical experience is in line with data from placebo-controlled studies that have supported the use of this biologic agent in GCA **[84**,85**]**. However, relapses are not uncommon when tocilizumab is discontinued. Moreover, autopsy results have shown have active vascular inflammation in patients who were apparently in clinical remission following tocilizumab therapy **[106]**.

Although the GiACTA study on the use of the anti-IL-6 receptor tocilizumab constituted a major step forward in the management of GCA **[85**]**, we are concerned about some results from this study **[85**]**. In this regard, around 50% of patients had

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relapses under ongoing tocilizumab use. Therefore, we wonder if there was a true glucocorticoid-sparing effect. Another criticism on this trial was that in this study the increase of CRP levels was proposed as a marker of relapse under tocilizumab, while we know that CRP and other acute phase proteins of inflammation are rarely increased under this treatment even though there was persistence of the inflammatory process. In our opinion, the fact that CRP and clinical response were considered together as a combined final endpoint may constitute an important limitation of the GiACTA trial because it may have overestimated the actual number of remissions due to the favorable effect of tocilizumab in decreasing CRP **[85**]**.

We feel that a research question that needs to be addressed in daily clinical practice is to confirm if biologic agents, in particular tocilizumab, may allow to perform glucocorticoid discontinuation in a shorter period of time than conventional immunosuppressive agents such as MTX. Also, we feel that although the use of tocilizumab appears to decrease the risk of side effects related to glucocorticoid therapy, additional studies are required to confirm that early use of this biologic agent may truly reduce the risk of severe ischemic complications, such as blindness, in patients with GCA.

Another issue that requires further investigation is to determine if patients with isolated PMR undergoing anti-IL-6 receptor tocilizumab therapy, without any vascular manifestation, in whom subclinical large vessel involvement is disclosed by imaging techniques such as PET/CT scan, are truly protected against the development of sudden vascular complications by the use of this biologic agent. On the other hand, we have to keep in mind the potential risks, mainly infections, related to the use of biologic therapy. Because of that, due to the frequent adverse events of these agents, sometimes potentially fatal, we believe that the current use of biologics in general and of

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tocilizumab in particular should only be reserved for some profiles of patients such as those with inefficacy to conventional therapy, patients with a history of relapses despite a good adherence to treatment, impossibility of tapering off glucocorticoids, patients suffering severe adverse effects related to glucocorticoids, in patients with LVV refractory to conventional therapy, imminent risk of fatal complications such as stroke or at the onset of the treatment in the elderly fragile patients with high burden of comorbidities.

Finally, we think that it is very important to emphasize that the ultimate goal in the management of GCA is always to reach sustained remission. This constitutes a challenge not yet fully achieved. Because of that, it is possible that new drugs, such as the JAK inhibitors that have a broader effect on inflammatory pathways, may be more useful for the management of refractory GCA. Nevertheless, further investigation needs to be done.

4. ***Five-year view***

In the near future, it is possible that affordable imaging techniques will allow us to make an early diagnosis of the disease. Also, genetic or serological biomarkers will help us to identify specific patterns of the disease, in particular to disclose GCA patients at risk of severe ischemic complications such as blindness. Although we feel that glucocorticoids will still remain as the pivotal therapy for the management of GCA, new biologic therapies will be used soon after the diagnosis of the disease in an attempt to induce early disease remission and reduce glucocorticoid side effects. In this regard, the use of new therapies such as JAK inhibitors or perhaps interferon gamma antagonists may lead to a more efficient management of patients with GCA.

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5. ***Key Issues***

1. GCA is the most common large-vessel vasculitis in individuals older than 50 years from Western countries.

2. Proinflammatory cytokines, such as IL-6, play a key role in the pathogenesis of GCA

3. In at least 20% of the patients, GCA features are preceded by PMR symptoms.

4. The main complication of GCA is the development of anterior ischemic optic neuropathy that can lead to blindness if early diagnosis and treatment are not performed.

5. Imaging techniques constitute a major breakthrough in the diagnosis of the disease, especially for the assessment of extracranial LVV involvement.

6. Glucocorticoids are the cornerstone of the therapy in GCA.

7. In elderly patients, with high burden of comorbidity, conventional immunosuppressive agents, such as methotrexate, should be considered in an attempt to reduce the cumulative dose of glucocorticoids.

8. In patients who are refractory to both glucocorticoids and conventional immunosuppressive drugs, biologic agents, in particular tocilizumab, must be considered for the management of the disease.

9. Tocilizumab is the only biologic agent approved for the management of GCA.

10. Adverse effects, especially infections, are not uncommon in patients with GCA undergoing biologic therapy.

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FIGURE LEGENDS

Figure 1. Schematic view of the treatment of giant cell arteritis (GCA).

Figure 1A. Current management of GCA.

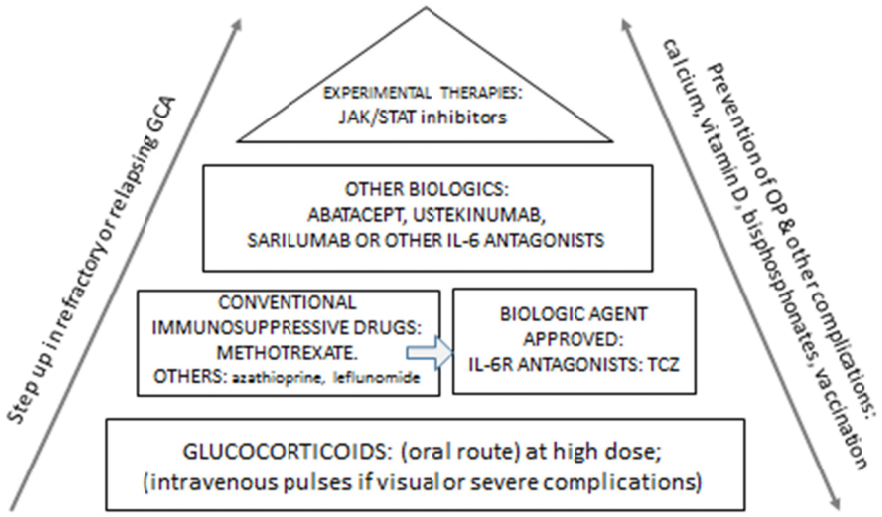

Figure 1A

Figure 1B. Possible scenario for the future management of GCA based on the current knowledge.

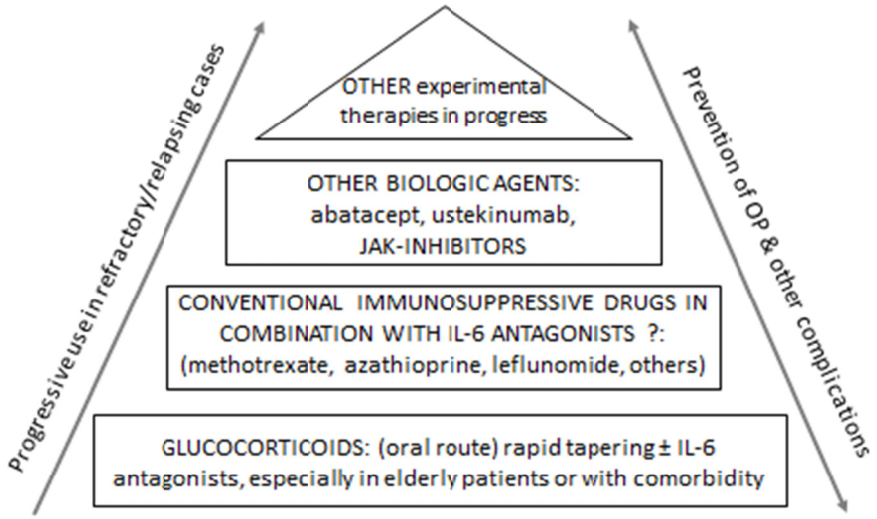

Figure 1B

Abbreviations: GCA: Giant Cell Arteritis; IL-6R: interleukin 6 (receptor); iv: intravenous; JAK/STAT: Janus kinase/Signal Transducer and Activator of Transcription signaling pathway; OP: osteoporosis; TCZ: tocilizumab.

Table 1. Main clinical and laboratory features of patients with biopsy-proven GCA who had the typical pattern of cranial GCA in decreasing order of frequency*. Adapted from [26].

*Frequencies were recalculated using data from studies on the epidemiology of biopsy-proven GCA in Lugo (NW Spain).

Table 2. Main therapies used in patients with giant cell arteritis. Adapted from [26].

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Table 1. Main clinical and laboratory features of patients with biopsy-proven GCA who had the typical pattern of cranial GCA in decreasing order of frequency*. Adapted from [26].

Clinical features	
Headache	85%
Abnormal temporal artery on physical examination	73%
Asthenia, anorexia and weight loss	60%
Jaw claudication on chewing	41%
Polymyalgia rheumatica	40%
Scalp tenderness	33%
Fever (temperature ≥ 38ºC)	10%
Visual ischemic manifestations	23%
Permanent visual loss	13%
Dysphagia	5%
Cerebrovascular accidents	3%
Peripheral arteriopathy of recent onset	2%
Laboratory features	
Erythrocyte sedimentation rate > 40 mm/1st hour	99%
Anemia (hemoglobin < 12 g/dl)	55%
Thrombocytosis (platelet count > 400.000/mm^3)	50%
Elevation of alkaline phosphatase	25%

GCA: Giant cell arteritis.

*Frequencies were recalculated using data from studies on the epidemiology of biopsy-proven GCA in Lugo (NW Spain).

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Table 2. Main therapies used in patients with giant cell arteritis. Adapted from [26].

- Classic treatment: Corticosteroids

  Prednisone: Initial dose 40-60 mg/day

  Methylprednisolone IV pulse therapy: 1g daily for 3 consecutive days in patients with visual ischemic manifestations or other severe ischemic complications

- Alternative-corticosteroid sparing therapies:

  1) Conventional immunosuppressive drugs:

     Methotrexate (first choice)

     Others *such as azathioprine or leflunomide* (not commonly used)

  2) Biologic Agents

     a. *Anti-IL-6- tocilizumab* (useful in GCA refractory to conventional therapy. Also, as glucocorticoid-aspiring agent (approved for GCA)

     b. TNF-alpha blockers such as the *anti-TNF-alpha monoclonal antibody-infliximab* (poor results). Not considered for the management of GCA

     c. Others: Abatacept, Ustekinumab, JAnus Kinases inhibitors (insufficient information. Further studies are needed)

- Therapies to aimed to decrease the risk of ischemic complications in patients with GCA: Antiagregation therapy (*low-dose aspirin*: 80-100 mg/day)

- Drugs for prevention and treatment of glucocorticoid-induced osteoporosis:

  Calcium and vitamin D along with a potent *oral bisphosphonate*

  Denosumab or teriparatide (PTH[1-34]) in selected cases

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