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Giant cell arteritis and innovative treatments

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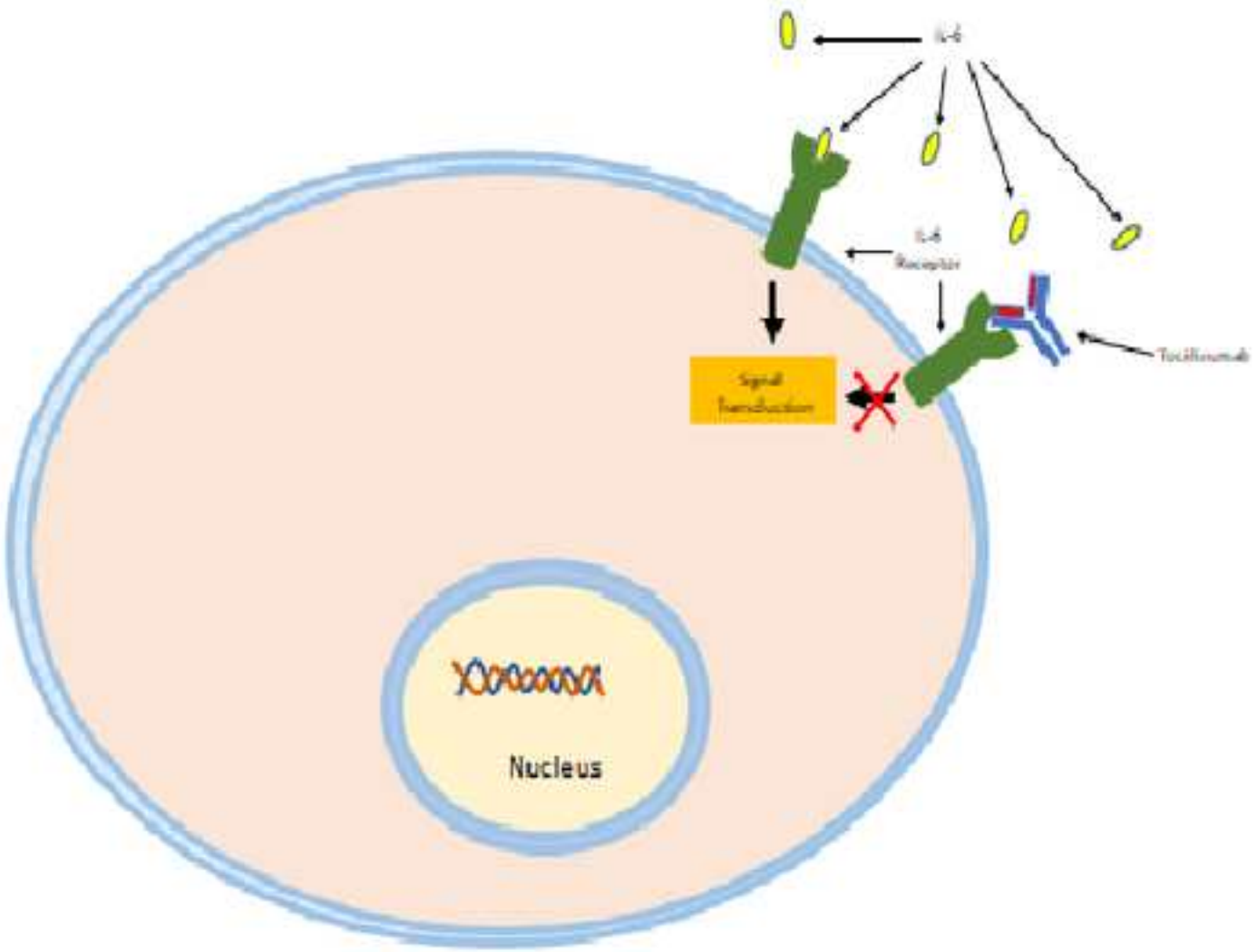

Fig. 1 Mechanism of action of Tocilizumab

Figure

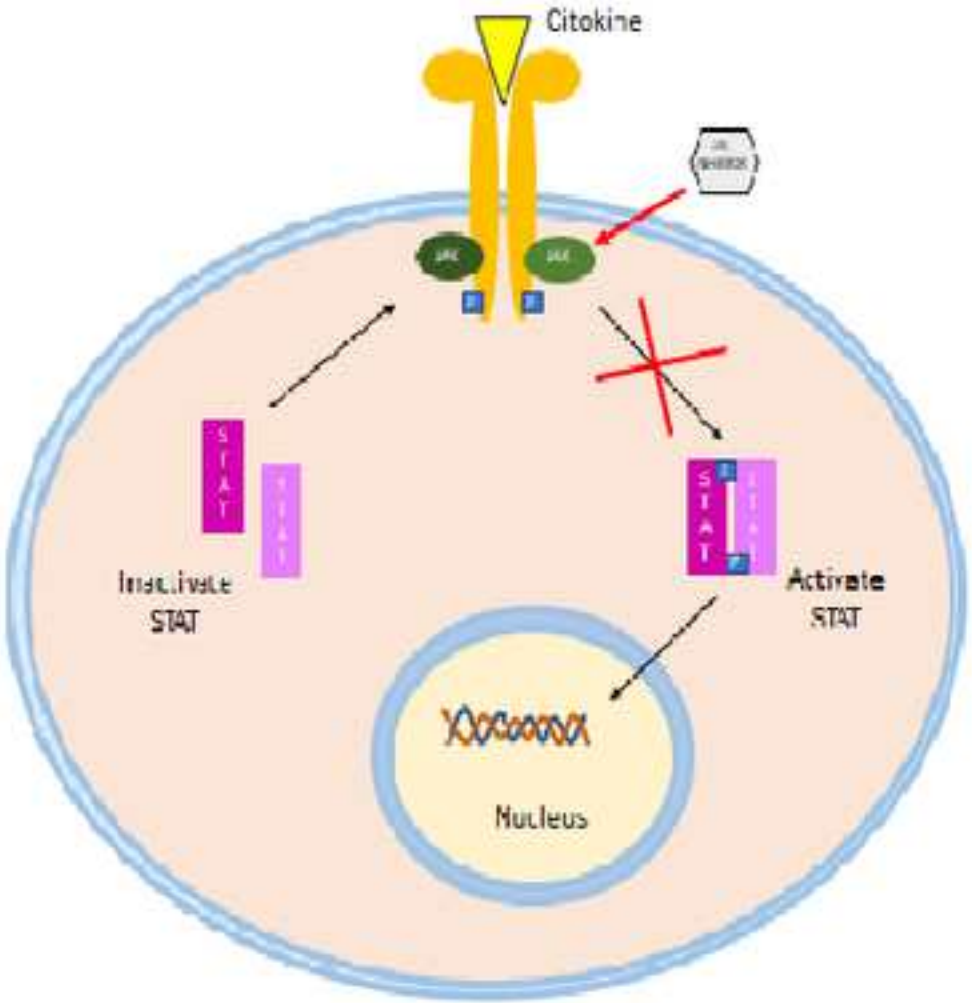

Fig.2 Mechanism of action of Jak Inhibitors

Giant cell arteritis and innovative treatments

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Abstract

Purpose of review: Giant cell arteritis (GCA) is an idiopathic and persistent condition characterized by granulomatous vasculitis of the medium and large vessels with overlapping phenotypes, including conventional cranial arteritis and extra-cranial GCA, also known as large-vessel GCA. Vascular problems linked with large vessel involvement may partly be caused by delayed diagnosis, emphasizing the necessity of early detection and the fast beginning of appropriate therapy. Glucocorticoids are the cornerstone of treatment for GCA, but using them for an extended period has numerous, often severe, side effects.

Recent findings: clinical practice and novel discoveries on the pathogenic pathways suggest that steroid-free biologic treatments may be efficient and safe for GCA patients.

Summary: since now, only Tocilizumab is approved for GCA treatment, but several drugs are currently used, and ongoing trials could give both researchers and patients novel therapeutic strategies for induction, maintenance, and prevention of relapse of GCA. The aims of this work is to synthesize evidence from current studies present in scientific literature about innovative treatment of Giant cell artheritis

Keywords

Vasculitis, Giant cell arteritis, inflammation, anti interleukin 6, biological drugs.

Introduction

Giant-cell arteritis is the most common form of primary systemic vasculitis, usually affecting people over the age of 50 and rarely affecting those under 50 or over 80. The risk of developing the disease is 1% in women and 0.5% in men, with a higher frequency in the Scandinavian population than in the Mediterranean, African or Asian populations. The disease has been linked to a genetic predisposition and is associated with the HLA-DRB1*04 allele. GCA is a vasculitis characterized by granulomatous inflammation of large and medium-caliber vessels. Initially, it was thought it could mainly involve the branches of the carotid and vertebral arteries. Still, subsequent bioptic studies during autopsy revealed the involvement of large vessels in 80% of cases. Many imaging studies in patients affected by GCA revealed widespread X-ray involvement of large vessels (e.g., aorta and its main branches) in up to 83% of patients(1,2,3). Histopathologically, GCA is characterized by inflammation of arterial walls with the fragmentation of the inner lamina and with thickening of the intima. In about one-third of temporary artery

biopsies, giant multinucleate cells are generally associated with a granulomatous inflammatory infiltrate composed of CD4+ T cells located in the conjunction between the intimate and the median. The thickening of the intima with partial or complete occlusion of the lumen can lead to ischemic complications such as ischemic anterior optic neuropathy.

Pathogenesis relates to inappropriate activation, maturation, and retention of adventitious antigen-presenting dendritic cells. These cells provide a favorable environment for viral and bacterial pathogens through the action of toll-like receptors (TLRs). Particular profiles of TLR are specific for vessels. Mouse models show activation of wall-embedded dendritic cells that release chemokines that recruit CD4+ T cells and macrophages. The pattern of arterial inflammation corresponds to TLR4 stimulation that induces panarteritis and TLR5 that stimulates perivasculitis. The onset of GCA tends to be insidious: new-onset headache, scalp tightness, jaw claudication, fever, fatigue, malaise, anorexia, weight loss, polymyalgia, painless and irreversible vision loss (bilateral or unilateral) are red flags that should immediately make us think of a start of GCA. The onset of GCA can last for weeks or months before manifesting with a symptom spectrum attributable to the localized effects of vascular or systemic inflammation. The headache is usually constant, sudden onset, and typically located in the temporal region where it is severe enough to prevent nighttime sleep. It may also present alternately or worsen without treatment. Scalp tension, increased prominence, and decreased temporal artery pulsation increase suspicion of GCA, although one-third of patients have negative biopsies of temporal artery specimens. Polymyalgia rheumatica that generally occurs alone could be found in 40-50 % of patients affected by giant cell arteritis. Moreover, among patients who complained only symptoms of isolated polymyalgia rheumatica (shoulder, hips, and thighs muscle stiffness), 10 -20 % of those later developed giant cell arteritis. This substantial clinical relationship, along with findings from pathophysiologic research, has increasingly supported the idea that giant cell arteritis and polymyalgia rheumatica constitute different clinical spectrums of the same disease process. The classification of GCA is based on the presence of 3 or more criteria among age greater than 50 years, newly localized headache, decreased temporal artery tension or pulse, erythrocyte sedimentation rate (ESR) greater than 55mm/h, and abnormal biopsy. The definitive diagnosis is obtained with the biopsy. From a laboratory point of view, the acute phase markers are often significantly elevated; there is normocytic normochromic anemia associated with thrombocytosis, and transaminases may be elevated with reduced albumin. In particular, the combination of increased C reactive Protein and positive biopsy has very high sensitivity and specificity for GCA. A useful, non-invasive, and inexpensive test is ultrasonography of the temporal arteries, which renders the inflammation picture of the inflamed temporal arteries characterized by oedematous wall swelling. With the advent of glucocorticoids, survival is similar to age reference.

1. FIRST LINE THERAPY

1.1 Systemic glucocorticoids

The first line of therapy for GCA has been systemic glucocorticoids (CSs) since their development in the 1950s. Although there are no randomized trials, most experts recommend starting immediately with high doses of corticosteroids (40mg to 60mg of prednisone per day) until clinical and laboratory values regress (4). Treatment every other day, even if combined with drugs such as methotrexate, does not seem to have greater efficacy. The response to CSs is so rapid that it is a diagnostic criterion of GCA: most symptoms improve already after 2 or 3 days of therapy, while symptoms related to blood flow, such as jaw claudication and visual impairment, can take longer to resolve. Visual loss may not be reversible, but CS therapy minimizes the

risk of further deterioration. CSs can be gradually tapered as early as the first month after the resolution of symptoms considered reversible and the reduction of CRP or ESR values by at least 50%. The treatment should then be continued for at least two years, with some patients requiring 4-5 years of therapy (4).Unfortunately, as known, the use of OCS is linked to important side effects, so between 50% and 100% of patients experience at least one adverse event from OCS. Furthermore, in case of discontinuation or tapering of OCS, the risk of exacerbation is 43-79%.(5). For these reasons, the need arises to find other drugs that can replace or integrate SCs in the treatment of GCA.

2. Non-glucocorticoid immunomodulatory medications: Monoclonal antibodies

2.1 Tocilizumab

So far, only tocilizumab, an interleukin 6 inhibitor, has shown safety and efficacy in reducing exacerbations and decreasing the daily dose of CS, and is the only drug to be cleared by the FDA and EDC for the treatment of GCA and this reason it was immediately incorporated into clinical practice (5)(Fig1). Some authors of the Cochrane Collaboration concludes that tocilizumab has an essential role in increasing the percentage of patients who undergo sustained remission and the number of patients who do not require escape therapy. Tocilizumab also reduces the mean cumulative CS dose by lengthening the mean time to the first exacerbation after remission induction. Tocilizumab also improves the quality of life from a mental and general health perspective. The frequency of AEs in standardized studies appears to be similar between tocilizumab and placebo; most AEs for tocilizumab are infections (4). Although tocilizumab has dramatically improved the treatment of this pathology, patients treated with tocilizumab have an exacerbation rate of 15-26%. According to clinical trials and observational data, 30-47% of patients do not achieve a remission sustained clinic at 12 months. The length of treatment with tocilizumab also remains unknown at present. Therefore, further treatments are urgently needed, especially for patients who do not achieve remission or who, for various reasons, are not eligible for tocilizumab (5).

2.2 Ustekinumab

Ustekinumab is a fully human IgG1κ monoclonal antibody binding the interleukin IL-12/23 p40 used in Chron's disease and ulcerative colitis. The results in the literature are mixed. A prospective, single-center, open-label study evaluated the efficacy of ustekinumab in combination with prednisone in 13 patients with active GCA without demonstrating a significant rate of prednisone-free remission. Another prospective study in patients with refractory GCA who previously had difficulty tapering prednisone despite combination with another immunosuppressant showed that at 52 weeks, the daily prednisolone dose was reduced from 20mg to 5mg with 24% of patients were able to discontinue OCS, and no patient experienced GCA relapse (6)

2.3 Guselkumab

Guselkumab is a monoclonal antibody (mAb) that binds to the p19 sub-unit of human interleukin (IL)-23 with high affinity and blocks binding of extracellular IL-23 to cell surface IL-23 receptor, inhibiting IL 23 specific intracellular signaling and subsequent activation and cytokine production. It is used to treat psoriatic arthritis, generalized pustular psoriasis, and erythrodermic psoriasis. it is an ongoing clinical trial, NCT04633447, that aims to evaluate, as its primary purpose, the efficacy of guselkumab

compared to placebo, in combination with a 26-week glucocorticoid (GC) taper regimen, in adult participants with new-onset or relapsing giant cell arteritis (GCA) (7)

2.4 Secukinumab

Secukinumab, a fully human monoclonal antibody that selectively inhibits IL-17A, was studied in phase two randomized controlled trial of 52 patients with new-onset or exacerbation GCA who were biologic-naïve. Patients were randomized into two arms, one treated with secukinumab 300 mg, the other with a placebo administered weekly for 5 doses and then every 4 weeks until week 48, combined with a taper of prednisolone at 26 weeks. The rate of patients in sustained remission at 28 weeks was 70.1% in patients with SEC compared to those on placebo. In addition, a higher sustained remission rate was associated with a longer time to first exacerbation in secukinumab patients (6) .

2.5 Mavrilimumab

Mavrilimumab is a monoclonal antibody, specifically an immunoglobulin G4, with demonstrated efficacy in phase 2 studies of rheumatoid arthritis, which blocks Granulocyte-macrophage colony-stimulating factor (GM-CSF) signaling by binding to the alpha chain of the receptor. GM-CSF is a multifunctional cytokine expressed by immune and endothelial cells in the temporal arteries that modulate dendritic cells, CD4+ T cells, and macrophage biology. Preclinical data have suggested a role of GM-CSF in GCA: Blockade of GM-CSF receptors has been associated with a downregulation of the Th1 and Th17 response. In mouse models, inhibition of GM-CSF is associated with reduced arterial remodeling and inflammation. In phase 2 randomized, double-blind, placebo-controlled trial, the safety and efficacy of this drug in GCA were evaluated. The primary efficacy endpoint was the time to first flare (defined as an increase in ESR greater than or equal to 30mm/h or in CRP more significant than 1mg/dL together with the presence of unequivocal cranial or extracranial signs or symptoms or the appearance on imaging of a new finding or sign of worsening abnormality suggestive of active vasculitis. The secondary efficacy endpoint was sustained remission rate, defined as the absence of flare from randomization to week 26. Of 70 randomized patients, 42 were randomly assigned mavrilimumab, and 28 were randomly assigned placebo. 21 patients had a flare within 26 weeks, 8 received mavrilimumab, and 13 received placebo. The median time to exacerbation was 25.1 weeks in the placebo; mavrilimumab was over 26 weeks. Mavrilimumab significantly reduced exacerbations versus placebo; durable remission occurred in 83.2% of patients taking mavrilimumab while only 49.9% of patients taking placebo. (p=0.0038). The cumulative prednisone dose at 26 weeks was also higher in the placebo patients than in the mavrilimumab patients. Regarding safety, adverse events were reported in 78.6% of patients on mavrilimumab compared to 89.3% of patients on placebo (severe adverse events 4.8% vs 10.7%). This trial shows that mavrilimumab with a prednisone taper at 26 weeks is superior to a placebo with a prednisone taper in reducing flares and maintaining sustained remission. Mavrilimumab is well tolerated and presents itself as a promising treatment option (8).

2.6 Ixekizumab

IL-17 blockade with ixekizumab can be a promising steroid-sparing agent in giant cell arteritis. Ixekizumab is a monoclonal antibody targeting IL-17A with efficacy and safety profiles similar to secukinumab in treating skin psoriasis and psoriatic arthritis. IL-17 is thought to exert a significant role in GCA pathogenesis. It is produced by Th-17 cells infiltrating GCA lesions and is responsible for pleiotropic effects on various cells, promoting vascular and systemic inflammation.

At Vita-Salute San Raffaele University, in October 2019 a new diagnosis of GCA was made to a 64-year-old man with known skin psoriasis for 5 years in treatment with Methotrexate 7.5 mg per week. Other comorbidities present were hypertension and type 2 diabetes mellitus. In combination with MTX, high-dose glucocorticoid therapy (prednisone 50 mg/day) was immediately initiated, with rapid resolution of symptoms and normalization of inflammatory markers. Two months later, due to increased inflammatory markers, MTX was increased to 15 mg/week in combination with 20 mg/day prednisone. Despite this, 7 months after, for an episode of polymyalgia associated with inflammatory markers always above the normal limits, Tocilizumab 162 mg/week was introduced, with the benefit and the withdrawal of glucocorticoids. In January 2021, a course of steroid therapy was necessary for a new exacerbation of skin psoriasis on the scalp, elbows, and hands, all without benefit. Following the treating dermatologist, it was decided to switch from tocilizumab to ixekizumab (160 mg followed by 80 mg every 4 weeks). The therapeutic effects on psoriasis were immediate; it completely disappeared after just 2 months. Despite discontinuing tocilizumab, in the following 12 months, the inflammatory markers remained within normal limits, and the patient did not experience any recurrence of GCA symptoms. To confirm the maintenance of remission, an FDG-PET scan was repeated in March 2022, one year after the initiation of ixekizumab therapy, showing no evidence of residual vasculitis of large vessels. (9)

3 . Non-glucocorticoid immunomodulatory medications: Janus kinase inhibitors

3.1 Baracitinib

Baricitinib is a small Janus kinase inhibitor (Fig.2) approved for treating certain autoimmune diseases and autoinflammatory disorders. Initially licensed for the treatment of moderately to severe TNF-antagonist-resistant rheumatoid arthritis, its remarkable potential for blocking proinflammatory signaling and its selective effect on immune cells makes it a good candidate for resolving an exaggerated immune response in a large number of inflammatory disturbs. The Koster 2022 study aimed to evaluate the safety and efficacy of this drug in exacerbating GCA. The study showed that the drug is effective and safe in treating forms characterized by exacerbations. The 4mg/day dose appears to have sufficient control over both GC tapering and discontinuation (only 1 out of 14 patients had a flare) with the ability to discontinue cortisone 22 weeks after initiation of therapy, with 13 out of 14 patients achieved and maintained clinical remission at 52 weeks. Treatment should be carefully monitored in patients with renal dysfunction. (10)

3.2 Upadacitinib

Upadacitinib is a second-generation Janus kinase inhibitor. The literature describes the clinical case of a 72-year-old patient with symptoms of fever, anorexia, headache, arthralgia, and jaw claudication who was diagnosed with GCA following a biopsy of the temporal artery. The patient also had pustular psoriasis and type II diabetes mellitus. This patient was administered Upadacitinib 15mg/day associated with prednisolone (0.6mg/kg) which induced a prompt remission of the disease. Following

tapering of OCS for 6 months, Upadacitinib alone therapy maintained remission for 7.5 months without predicting disease progression. This case report suggests that upadacitinib could be another weapon against the GCA. (11)

4. Other drugs

4.1 Anakinra

Anakinra is an IL-1 receptor antagonist (IL-1Ra) that blocks both IL-1α and IL-1β activity and has previously been licensed in the USA, Canada, Europe, and Australia for use in rheumatoid arthritis and different forms of cryopyrin-associated periodic syndromes. A series of three clinical cases show its possible use in GCA. In an initial case report, an 80-year-old male patient with a fever of unknown origin, night sweats, weight loss, and arthralgias were treated with anakinra after the failure of other drugs such as methotrexate, azathioprine, and etanercept. The 100 mg/day dosage allowed remission of symptoms and laboratory abnormalities after one month, allowing a tapering of the OCS from 60mg/day of prednisone up to 7.5mg/day with the maintenance of disease control. A second case is a female patient diagnosed with GCA resistant to methylprednisolone therapy, administered off-label anakinra, with prior informed consent, at a domg/day dosage with a resolution of symptoms and normalization of laboratory values (CRP). Within 3 weeks, allowing a tapering of both the OCS up to 5mg/day of prednisone and of the same anakinra up to 100mg 3 times a week and with the maintenance of remission confirmed by the disappearance on PET/CT of the signs of mural arterial inflammation present at a first test performed before administration of anakinra.

The third case is that of an 80-year-old female patient suffering from symptoms of polymyalgia and ischemic pain in the upper and lower limbs with the abolition of the radial and cubital pulse due to peripheral arterial occlusive disease with thrombosis of the right humeral artery resistant to OCS therapy. The patient underwent therapy with anakinra 100 mg every other day, associated with 20mg/day of prednisone, with the achievement to taper the OCS up to 5mg/day with the maintenance of remission. These cases suggest a possible use of anakinra in forms of GCA refractory to other treatments. (12) Another case series published in 2021 concerns 6 patients, 5 with corticosteroid dependence; one patient had corticosteroid resistance prior to administering anakinra, while the other five individuals had a dependence on corticosteroids. Four individuals displayed signs of aortitis and major vascular involvement (LVI). After an average disease duration of 13 months, anakinra was given subcutaneously to these individuals at an initial 100mg/dl dose. Patients had PET/CIT and CT angiography of the aorta performed when they were diagnosed. The four patients with LVI were reevaluated using the same imaging techniques an average of 25 weeks after starting anakinra. All five patients demonstrated total clinical and biochemical remission of both GCA after a median duration of therapy of 19 months. Moreover, one patient's aortitis vanished on anakinra, while three other patients with LVI who did not respond to corticosteroids had decreased vascular uptake. This case series suggests that anakinra has good tolerance, even over the long term, and a steroid-sparing effect. Moreover, it may be effective for LVI, an essential issue in the management of GCA (13)

4.2 Abatacept

Abatacept, a biologic used in rheumatoid arthritis, is a recombinant fusion protein composed of the extracellular domain of

human CTLA-4 and the modified Fc region of human IgG1 that inhibits T cell activation by explicitly binding to CD80 and CD86. Abatacept also modulates the activation of naïve T cells. The critical concept beyond the idea to use abatacept as a treatment for GCA is that the pathogenesis is driven by antigen and the crosstalk between T, B lymphocytes, and dendritic cells. Abatacept blocks the signaling cascade mediated by CTLA-4, so T cell activation is supposed to be one of the mechanisms behind the pathogenesis of GCA. Examined in a randomized trial of 49 patients with newly diagnosed or exacerbating GCA. Participants received abatacept every 14 days for 8 weeks until they were divided into two arms, one continuing the drug, the other switching to placebo associated with a progressive prednisone taper with total discontinuation at 28 weeks. The authors found that one-year survival in the absence of relapse was 48% in patients who continued abatacept vs 31% in those who switched to placebo (p=0.0049) (6).

Conclusion

Management of GCA should be based on a shared decision between patient and physician recognizing the need for urgent treatment of GCA to avoid ischaemic complications. It should aim at maximizing health-related quality of life. The treatment targets are achieving and maintaining remission and preventing tissue ischemia and vascular damage. Comorbidities must be considered when assessing disease activity and selecting treatment (14)

The therapeutic approach in giant cell arteritis has profoundly changed thanks to the latest discoveries on pathogenetic pathways. The widespread use of oral corticosteroids as induction and maintenance therapy has stimulated scientists to develop cutting-edge drugs that prevent organ damage accumulated due to chronic oral corticoid use. Tocilizumab has been used primarily as an anchoring drug with a known steroid-saving effect. Mavrilimumab also seems to be an excellent alternative to starting and continuing GCA therapy; its efficacy underscores translational research's importance in highlighting novel pathogenic pathways and promising potential therapeutic targets. JAK inhibitors are among the most promising drugs in treatments for GCA, also thanks to their pharmaceutical formulation in pills, which is associated with greater compliance. Eventually, the gold of treatment in GCA is still the limitation of the use of oral corticosteroids to avoid their deleterious systemic damage.

Key points:

- **Steroid-sparing strategies are needed for GCA long-term treatment**
- **Tocilizumab, anti-IL 6, is the only licensed biological drug for GCA**
- **Ustekizumab would be a promising therapeutic alternative**
- **Small molecules could have a place in GCA treatment scenario**

Figure 1. Mechanism of action of Tocilizumab

Figure 2. Mecanism of action of Jak Inhibitors

Abbreviations

GCA: giant cell arteritis;

TLR: toll-like-receptors;

ESR: erythrocyte sedimentation rate;

CRP: C reactive protein;

CS: systemic glucocorticoids

MTX: methotrexate

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GC: Conceptualization, Writing-original draft, Writing-review & editing.

AGL: Conceptualization, Writing-original draft, Writing-review & editing.

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The authors declare that they have no conflicts of interest.

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(**) Recommendations for treatment of GCA with strategies to achieve and maintain the treatment targets

(*) special interest

(**) outstanding interest