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Interleukin-6: a promising target for the treatment of polymyalgia rheumatica or giant cell arteritis?

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Polymyalgia rheumatica (PMR) is a chronic inflammatory disease of unknown aetiology affecting people aged over 50. The hallmark manifestations of PMR are pain and stiffness affecting the neck and shoulder and pelvic girdles. There is no specific laboratory test for the disease, and thus the diagnosis of PMR depends on a combination of clinical symptoms, raised acute phase reactants, the exclusion of other diagnoses and response to glucocorticoids (GCs).[1] For classification purposes, a number of criteria have been proposed and the most recent were collectively drawn up by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR).[2]

Giant cell arteritis (GCA) is a type of vasculitis of large-sized and medium-sized arteries affecting people aged over 50. The disease usually involves aorta, supra-aortic branches and the extracranial branches of the carotid artery. The clinical manifestations include headaches, temporal artery or scalp tenderness, jaw claudication, visual symptoms, constitutional symptoms and PMR manifestations.[3] At the time of diagnosis, the most serious consequence of GCA is the occurrence of visual loss in 12–14% of patients.[4] Aortic aneurysm or dissection may develop during follow-up and can be potentially life-threatening. The gold standard for the diagnosis of GCA remains temporal artery biopsy (TAB). Approximately 60–80% of TABs show evidence of vasculitis with a mononuclear cell infiltrate, disruption of the internal elastic lamina and multinucleated giant cells, the hallmark of the disease, in ~50% of patients.[5] However, ACR classification criteria were developed in patients who already have evidence of vasculitis and do not take into account the additional value of imaging techniques.[6] Indeed, ultrasonography of TAB may reveal a hypoechoic halo sign and is considered to be highly specific for GCA diagnosis despite interobserver and interstudy discrepancies.[7] In addition, positron emission tomography (PET) is a valuable method for the detection of occult arterial involvement of the aorta or large vessels in patients with GCA.[8]

The first-line treatment for PMR is GC, and EULAR/ACR recommend its use at the minimum effective daily dose, ranging from 12.5 to 25 mg prednisone as the initial treatment.[9] GCs are also the treatment of choice for GCA, with a starting dose of 0.7 mg/kg for patients without ocular symptoms.[10] Despite its efficacy, GC therapy is associated with well-described adverse events. Indeed, it has been estimated that up to 65–86% of patients with PMR and GCA, respectively, develop GC-related adverse events.[10] In addition, after a mean follow-up of 104 weeks, 46% of patients with GCA experience relapse. Some patients with PMR may need low-dose GC for several years. Alternatives to GC have thus been evaluated both in PMR and GCA but remain unsatisfactory.[1 3] Methotrexate (MTX) is recommended as a steroid-sparing agent for patients with PMR at high risk of relapse and/or prolonged therapy, experiencing GC-related events or with comorbidities, limiting the use of this drug class.[9] However, the results of MTX therapy in PMR are still a subject of debate.[1] The role of MTX in GCA is limited, because this drug showed only modest efficacy in improving outcomes.[11 12] Antitumour necrosis factor (TNF)α agents did not prove to be effective in PMR[1] and failed to demonstrate efficacy in patients with GCA.[3] Thus, in these different clinical settings, alternatives to GC are still required.

Interleukin-6 (IL-6) is a pleiotropic cytokine that has a wide range of biological activity. IL-6 is associated with the production of acute phase proteins in hepatocytes, immunoglobulin induction in B lymphocytes, cytotoxic T-cell differentiation and Th17 differentiation in T cells.[13] Weyand *et al*[14] showed that IL-6 was expressed both in the temporal artery wall of patients with GCA and isolated PMR without manifestations of GCA. Since this initial study, there is now substantial evidence suggesting the involvement of IL-6 in the pathophysiology of PMR and GCA.[13] Genetic studies performed in GCA suggest that the IL-6 174 C polymorphism may contribute to the phenotypic presentation of GCA, although this was not confirmed in another study.[15 16] Despite variations between patients, IL-6 is elevated in the serum of patients with PMR and GCA and IL-6 levels correlate to disease activity.[17 18] A correlation was found between oscillation of IL-6, erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) during follow-up of patients with GCA.[17] High IL-6 mRNA levels in TABs were mainly reported in patients with GCA with systemic inflammatory response markers (including weight loss, fever, haemoglobin <11.0 g/dL and ESR>85 mm).[19] Interestingly, in a previous study, the same authors also demonstrated that these patients experienced more relapses and required a higher dose of GC during follow-up.[20] Therefore, this suggests that patients with a high IL-6 level may require a higher GC dose. Disease progression under treatment varies between patients and IL-6 remains above the normal range in a majority of patients, even in the absence of clinical disease activity.[17 18] Finally, during follow-up of patients with PMR, there is an increased risk of relapse in patients with persistently elevated levels of IL-6 or soluble IL-6 receptor.[13] In temporal arteries, CD4-T cells are recruited by local dendritic cells and differentiate in Th1, Th17 and Th1Th17 cells in the local environment containing IL-6, IL-12, IL-18, IL-21, IL-23 and IL-1β. Recent data indicate that Th17 cells are implicated in GCA and PMR, with an increased percentage of these cells in peripheral blood as compared with healthy controls. In addition, a massive infiltration of Th1 and Th17 cells is observed in TAB specimens of patients with GCA.[21] CD161+ CD4+ peripheral T cells (considered as precursors of Th17 cells) from patients with GCA or PMR were found to produce a high amount of IL-17 compared with those isolated from healthy controls.[21] Differentiation of CD161+ CD4+ peripheral T cells in Th17 cells with IL-6 underline the potential effect of IL-6 inhibitors.

All these data strongly support the rationale for targeting IL-6 in PMR and/or GCA. Thus, tocilizumab (TCZ), a humanised monoclonal antibody directed against the IL-6 receptor, has recently been evaluated in the treatment of patients with isolated PMR, GCA or both.

Results on the effects of TCZ in the treatment of patients with PMR are limited and based on case series or open-label studies (table 1).[22–27]

Most of the patients who received TCZ had a disease that required inappropriate use of GC or significant comorbidities that limit the use and/or dosage of GC. TCZ was mostly used at an 8 mg/kg dosage and as a monotherapy. Around 65% of patients received immunosuppressants or TNFα inhibitors before TCZ

Table 1 Characteristics of patients with **PMR** treated by TCZ

Author/reference	N	Age (years)/ sex	Immunosuppressive agent before starting TCZ	Prednisone-equivalent/day before starting TCZ	TCZ dosage and duration of treatment	Results	Onset of response	Adverse events
Macchioni *et al*[22]	2	79, F 87, F	No	No CS (declined by the patients)	8 mg/kg 2–6 months	1 responder	2 months	No
Mori and Koga[23]	3	55, F 67, F 55, F	MTX=1 (8 mg/week) SLZ=1	5–10 mg	8 mg/kg 2–6 months	Remission	1 month	No
Unizony *et al*[24]	1	ND	No	20 mg	8 mg/kg ND	Remission	2–3 months	No
Hagihara *et al*[25]	1	65, F	No	10 mg	8 mg/kg ND	Remission	1 month	No
Izumi *et al*[26]	13	74 (mean), 11F, 2 M	MTX=7 (mean 8.3±2.1) mg/week	6 mg	8 mg/kg 12–96 months	Remission for all	2 months	1 infection, 1 thrombocytopaenia, 1 leucopaenia
Toussirot *et al*[27]	7	73 (mean) 1F, 6 M	MTX=6 (mean 12.5±1.5) LFM=1, anti-TNF=2	20.5 mg	8 mg/kg 2–22 months	5 responders	1–3 months	No
Devauchelle-Pensec *et al*[28]	20	66.9 (median) 7 F, 13 H	No	0 (0.15 mg/kg after 3 months of TCZ)	8 mg/kg 3 months	20 responders PMR-AS≤10 at week 12	2 months	3 neutropaenia, 5 leucopaenia

CS, corticosteroids; F, female; LFM, leflunomide; M, male; MTX, methotrexate; PMR, polymyalgia rheumatica; PMR-AS, polymyalgia rheumatica activity score; SLZ, sulfasalazine; TCZ, tocilizumab.

initiation. Overall, there was a rapid improvement (between 1 and 3 months) after TCZ infusions in clinical symptoms, PMR-activity score (PMR-AS) and the acute phase reactants. In addition, GC dosage was reduced in some patients. We reported the efficacy of a monthly 8 mg/kg infusion of TCZ in a series of seven patients with isolated PMR. Interestingly, we observed that TCZ may be interrupted after remission achievement in patients who received TCZ 1–4 months after disease onset without subsequent relapse.[27] Similar efficacy was reported in a series of 13 patients from Japan.[26] All patients received TCZ 8 mg/kg monthly due to disease relapse or insufficient response to GC. TCZ treatment was associated with significant improvement of PMR symptoms and inflammation. The TENOR study is the first open-label trial that evaluated the effect of TCZ as a first-line therapy in patients with early and active PMR.[28] Twenty patients received three infusions of TCZ 8 mg/kg without GC during 3 months followed by GC at a 0.15 or 0.3 mg/kg daily dosage according to their response evaluated by PMR-AS at week 12. In this study, PMR-AS decreased after the first TCZ infusion and all the patients benefited from the lower GC dosage (0.15 mg/kg instead of the classical 0.3 mg/kg/day), thus resulting in a significant GC sparing effect compared with a theoretical dose of GC. All parameters of PMR-AS were ameliorated and a level of PMR-AS <10 was achieved for all patients with or without inclusion of the CRP level. Quality of life and imaging (PET) parameters were also significantly ameliorated after TCZ infusions. Thus, despite the fact that PMR-AS is a composite index of disease activity that includes CRP, TCZ improved different dimensions of the disease including clinical and imaging parameters. Finally, an open-label phase 2a study evaluated the rate of patients able to achieve remission under TCZ (ClinicalTrials.gov NCT01396317).

The effects of TCZ in patients with GCA have been documented in greater detail, with a huge number of single cases or large retrospective series (table 2).[24 29–36]

All patients with GCA received TCZ for unacceptable side effects of GC, as a steroid-sparing agent or alternatively for severe disease. Most of the patients had received one or several lines of immunosuppressants previous to TCZ, and a small number of them had received a TNFα inhibitor. GC dosage before TCZ initiation ranged from 6 to 60 mg daily of prednisone. TCZ monotherapy was given at 8 mg/kg, and was reduced for some patients to 4 mg/kg due to safety concerns (especially for neutropaenia).[35 36] For all these patients, clinical efficacy was observed between 1 and 3 months after the first TCZ infusion. A limited number of patients with GCA did not improve with TCZ treatment, especially those with ocular involvement who had persistent visual impairment.[35 36] One patient died from acute myocardial infarction following surgery, and autopsy revealed persistent vasculitis of the large-sized and medium-sized artery, despite clinical response to TCZ.[24] TCZ was also associated with a significant steroid-sparing effect in most cases. In addition, inflammation assessed by PET imaging also decreased.[24 31] TCZ was administered during a prolonged period for most of the patients (ranging from 3 to 17 months), but long-term follow-up was not described in most reports. Three large series of TCZ-treated patients with GCA have been reported. The first one was an open case series including eight patients from the UK.[34] All the patients had GC refractory disease or had developed GC side effects. They all had a good clinical response to TCZ and the GC dose was reduced from 24.6 to 4.7 mg. Regular TCZ administration was needed in this series and one patient developed infection (empyema) requiring the drug to be withdrawn. The second was a retrospective analysis of 22 Spanish patients who had active disease (including 2 with visual impairment) or GC-related side effects.[35] Nineteen patients were considered as responders to TCZ and the median daily GC dose was tapered from 18.75 to 5 mg. However, serious adverse events were reported including neutropaenia, pneumonia or cytomegalovirus infection, requiring TCZ discontinuation. One fatal case of stroke was reported in the setting of infective endocarditis. The third series enrolled 34 French patients to whom TCZ was given due to GC side effects or for a severe disease (visual loss or scalp necrosis in 2 patients).[36] In this series, 28 patients improved and 6 had persistent mild clinical symptoms. Visual impairment was not reversed despite treatment. After TCZ discontinuation in the responding patients, disease relapse was observed in 6/20 of them. Interestingly, all the patients for whom TCZ was initiated early in the course of the disease (<3 months) had a favourable clinical response and no relapse was observed after treatment interruption. Six patients experienced side effects: neutropaenia in three cases, infection in two cases including septic shock causing death and liver cytolysis in the other patient. Two randomised placebo-controlled trials have evaluated the efficacy of TCZ in patients with GCA. The first one was published recently.[37] This was a phase II randomised, double-blind, placebo-controlled trial that recruited 30 patients with new onset or relapsing GCA. Patients received either TCZ 8 mg/kg or placebo every 4 weeks until week 52. Patients in both groups also received 1 mg/kg/day prednisone that was tapered down to 0 mg according to a predefined reduction protocol. A significantly higher proportion of patients in the TCZ group were in remission at a 0.1 mg/kg GC dose at week 12 (85% vs 20% in the placebo group, p=0.03). In addition, there was a significant decrease in GC dosage at 6 and 12 months in the TCZ recipients as compared with the placebo group. Three major gastrointestinal complications were reported in the TCZ group, including gastric ulcer perforation, hepatopathy and gastrointestinal bleeding. The second trial is still ongoing: the GiACTA phase III placebo-controlled trial aims to evaluate the safety and efficacy of TCZ in patients with GCA.[38] The objective is to demonstrate

Table 2 Clinical features of patients with giant cell arteritis treated by TCZ

Author/ reference	N	Age (years)/ sex	Immunosuppressive agent before starting TCZ	Prednisone-equivalent/day before starting TCZ	TCZ dosage and duration of treatment	Results	Onset of response	Adverse events
Kieffer *et al*[29]	3	73, F 70, F 7, F	MTX=2 (15 mg/week) anti-TNFα=1	6–30 mg	8 mg/kg 3–17 months	Remission	1–2 months	1 death caused by cardiogenic shock and septicaemia
Vinit *et al*[30]	1	63, F	MTX (20 mg/week)	20 mg	8 mg/kg 3 months	Remission	1 month	No
Unizony *et al*[24]	7	69 (NA)	MTX=3 (dosage ND) AZA=1 anti-TNFα=2 CYC=3	20 mg	8 mg/kg (4 mg/kg in 2 cases) ND	Remission	2–3 months	Leucopaenia N=4 liver cytolysis N=4 Death (myocardial infarction) N=1
Beyer *et al*[31]	3	79, F 72, F 71, F	AZA=1, mycophenolate mofetil=1	30 mg	8 mg/kg 6 months	Remission	Rapid (no precision)	NA
Seitz *et al*[32]	5	70 (mean) 3F, 2 M	No	30 mg	8 mg/kg 4–7 months	Remission	2 months	No
Christidis *et al*[33]	1	63, F	MTX (dosage ND), AZA	60 mg	8 mg/kg 6 months	Remission	1 month	neutropaenia
Evans *et al*[34]	8	70 (mean) 4 F, 4 M	LFM N=3	24.6 mg	8 mg/kg 34 months	Clinical improvement N=1	ND	1 neutropaenia 1 infection (empyema)
Loricera *et al*[35]	22	69 (mean) 17F, 5 M	Immunosuppressive drugs=19 (MTX=18 dosage ND; AZA=1; LFM=1) Anti-TNFα N=2 RTX=1 ABA=1	26 mg	8 mg/kg 12 months	Clinical improvement N=20 No change in visual impairment N=2	1 month	1 death (stroke) 2 neutropaenia 1 pneumonia
Régent *et al*[36]	34	70.5 (mean) 27 F, 7 M	Immunosuppressive drugs=20 (MTX=18 dosage ND; AZA=1; LFM=1; dapsone=1) anti-TNFα N=4 anti-IL-1=1	26 mg	8 mg/kg (4 mg/kg N=1) 13 months	Responders N=28 Non-responders N=6	1–2 months	Neutropaenia N=3 infections N=2 (one death due to septic shock) liver cytolysis N=1
Villiger *et al*[37]	30 (20 TCZ 10 placebo)	70 (mean) 21 F, 9 M	No	0.1 mg/kg	8 mg/kg 12 months	Remission TCZ 80% Placebo 20%	NA	TCZ: pyloric ulcer perforation N=1 Gastrointestinal bleeding N=1 Viral hepatitis N=1

ABA, abatacept; AZA, azathioprine; CYC, cyclophosphamide; F, female; IL, interleukin; LFM, leflunomide; M, male; MTX, methotrexate; NA, not available; RTX, rituximab; TCZ, tocilizumab.

that TCZ is able to induce and maintain disease remission at week 52 in patients with GCA. Positive results were recently announced, showing that TCZ initially combined with a 6-month steroid regimen more effectively sustained remission through 1 year compared with a 6-month or 12-month steroid-only regimen in patients with newly diagnosed and relapsing GCA.[39] Finally, the HORTOCI study (ClinicalTrials.gov NCT0190038) is another clinical trial that aims to evaluate the immunological changes observed in patients with GCA while receiving TCZ, especially on the Th17 cell subset. This is an open-label study of 12 months duration with a 3-month TCZ treatment and a pre-established GC reduction dose.

Results from retrospective and prospective studies demonstrate the efficacy of TCZ in GCA and PMR. Patients had both a rapid and sustained clinical and laboratory improvement. However, TCZ is ineffective for ocular complications of GCA. Most of the treated patients had refractory disease (GC resistant or dependent) and long-standing disease and only a few of them were treated with TCZ as first-line therapy.

Specific questions remain, especially the best time to introduce this biological agent. The TENOR study and our retrospective study suggest that patients with early PMR (ie, with disease onset <3 months) may benefit from TCZ that allows a rapid reduction of GC dosage.[27 28] In addition, the TENOR study demonstrated well that TCZ given as first-line treatment is effective in PMR.[28] However, the results of a randomised placebo-controlled trial evaluating the efficacy and safety of TCZ in patients with isolated PMR are required. The same results were observed in the placebo-controlled trial of TCZ in GCA.[37] In our retrospective study, patients who were treated with TCZ early in the course of the disease did not experience relapses during follow-up.[36] This information supports the theory that early initiation of TCZ in the treatment of GCA and PMR is effective. The duration of TCZ treatment is not well defined and must be clarified. Indeed, some patients relapsed soon after TCZ discontinuation, suggesting that the drug may have only a suspensive effect. However, a point of concern is the safety and the infectious risk of TCZ therapy in this elderly population with comorbidities. Data from real practice showed that infections can occur in patients with PMR or GCA who had GC at the same time and had previously taken other immunosuppressants. A higher infection rate was not observed in the placebo-controlled trial, but this study only enrolled a limited number of selected patients.[37] The GiACTA trial will contribute some important information on this issue, but more data on real life will still be required regarding the safety of TCZ in these elderly participants. For some patients, TCZ dosage was reduced due to the haematological side effects.[24 36] Taken together, one may consider an initial reduced TCZ dose for patients with comorbidities, advanced age and previous use of various immunosuppressants (4 mg/kg intravenously every month or 162 mg subcutaneously at intervals longer than 2 weeks).

Should the results of the GiACTA be conclusive with a favourable benefit/risk ratio and a GC-sparing effect, TCZ could be considered for patients with GCA with or without PMR in the following situations:

- As a first-line treatment in combination with GC, in patients presenting serious comorbidities with the objective of rapidly reducing GC dosage.
- As a second-line agent in patients with PMR or GCA who require a second-line therapy and are intolerant or refractory to MTX.
- As a second-line treatment in patients with PMR or GCA after relapse during GC reduction or in the case of iterative relapses.

In conclusion, targeting IL-6 yielded promising results in PMR and GCA, and ongoing randomised placebo-controlled trials will soon be available to complete the current available data. However, it remains to be determined when this biological agent should be started and when it should be discontinued. Additional information on the safety of TCZ in this specific patient population is also required and will need longer follow-up in daily practice.

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