

# Successful Treatment of Giant Cell Arteritis with Tocilizumab: Report of 2 Cases with Review of the Literature

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## Abstract

Giant cell arteritis (GCA) is a systemic vasculitis of medium and large vessels. Corticotherapy is the cornerstone treatment, but most patients fail to reach remission or relapse during the weaning of Glucocorticoids (GC). Here we report 2 patients with corticoid dependent GCA, successfully treated with Tocilizumab (TCZ), with a rapid clinical and biological outcome allowing the tapering of GC, and we review the literature of the treatments used in GCA.

**Keywords:** Giant cell arteritis; Interleukin- 6; Large vessels vasculitis; Tocilizumab

## Introduction

Giant cell arteritis (GCA) is the most common form of systemic vasculitis in adults [1], affecting preferentially medium-large size arteries especially the extracranial branches of the carotid artery. The most common manifestations of GCA are constitutional symptoms, headache, visual symptoms, jaw claudication, and Polymyalgia Rheumatica (PMR) [2] and the most feared complication is irreversible loss of vision [3]. Numerous disease modifying drugs have been used in controlling disease and tapering Glucocorticoids (GC) that represent the mainstay of Giant cell arteritis treatment [4-6].

Tocilizumab (TCZ), an interleukin 6 receptor antibody, was considered, on the basis of pathogenic and pathologic data of GCA, as a potentially effective treatment for this disease. The drug showed efficacy in few case reports and small series [7-17]. Here we report 2 cases with Giant cell arteritis that was dependent to corticoids, successfully treated by TCZ.

## Cases

### Case 1

A 72 year- old woman, having hypertension on Ramipril and Atenolol, asymptomatic hyperuricemia, osteopenia and stage 3 chronic kidney disease, who was previously treated with steroids at a starting dose of 20 mg/day for a PMR since 7 months, with a good response. At the dose of 5 mg/day, she consulted in our department for relapse of her symptoms, she didn't report headache neither jaw claudication nor visual symptoms.

The physical examination revealed abolition of the radial pulse in the right side, vascular murmur of the right axillary artery and limitation of the left shoulder abduction.

The laboratory tests demonstrated acute phase responses (ESR: 100 mm at the first hour, CRP: 70 mg/l) with anemia of chronic disease (Hb: 9.5 g/dl, MCV: 83). The workup of the inflammatory syndrome, including chest X-ray, thoracic-abdominal scan, serum protein electrophoresis and medulogram, was normal, also the immunologic (RA test, ANA, ANCA) and serologic tests for HCV, wright, widal and CMV were negative. The ultrasound of the shoulders showed a subtotal tear of the left supraspinatus tendon with left sub-acromial bursitis. The arterial Doppler ultrasound of the upper and lower limbs showed severe stenosis of the right subclavian artery, occlusion of the right axillar artery with chronic distal ischemia, severe stenosis of the left

axillar artery and multiple bilateral stenosis of the arteries of the lower limbs. The temporal artery biopsy demonstrated typical histological lesions compatible with GCA.

Aspirin 100 mg/day with GC at the dose of 60 mg/day was started for 6 weeks with a reduction of 5 mg every 2 weeks, which brought the patient in clinical and biological remission (ESR: 2 mm at the first hour, CRP: 1 mg/l).

During the follow up, the patient consulted for chest pain with orthopnea, she has been diagnosed with a coronary artery disease and she underwent a coronary artery bypass. Few months later, the scar of the operation in the right thigh was complicated by lymphocele and infection opposite the saphenous vein, a prolonged course of oral antibiotics was necessary to cure the infection.

The patient became steroid dependent at the dose of 15 mg/day, the ESR has risen to 111 at the first hour and the CRP to 13 mg/l; she complained of retrosternal burning, the Positron emission tomography (PET) scan was normal apart from hyper fixation of the esophagus, the patient refused to do a gastroscopy, the diagnosis of a probable mycotic esophagitis was considered, a treatment by nystatin was conducted which led to disappearance of the symptoms. A new Doppler ultrasound of the four limbs was similar to the first one done at the initial workup, in addition to aneurysms of the lower limbs arteries.

The treatment by GC was complicated by diabetes requiring insulin therapy, proximal myopathy leading to frequent falls, physical therapy with Adenosine Triphosphate was advised, and bilateral cataract that was removed surgically, also the bone mineral density at the femoral neck has deteriorated, a treatment by Alendronate 70 mg/week was prescribed.

To avoid more side effects due to GC, the use of an immunosuppressive drug was necessary; because of the chronic renal

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failure we could not add MTX, so we decided to put the patient on TCZ at the dose of 4 mg/kg/month (total dose 240 mg) instead of 8 mg/kg because of her weak general health status.

After the first infusion, the acute phase responses decreased dramatically (ESR: 30 mm at the first hour, CRP: 12 mg/l). TCZ was delayed for 4 months between the first and second infusions because of cellulitis of the left leg, for which the patient was hospitalized and received IV antibiotics with surgical drainage, it was delayed also between the 6<sup>th</sup> and 7<sup>th</sup> infusions because of a viral respiratory infection and between the 10<sup>th</sup> and 11<sup>th</sup> infusions because of a herpes zoster at the left D5-D6 dermatome, requiring a treatment by valaciclovir. The patient experienced also a bacterial cystitis after the 7<sup>th</sup> infusion, necessitating a course of antibiotics and a self-remitting gastroenteritis after the 11<sup>th</sup> infusion.

After 20 months of treatment (15 infusions in total: the first 4 ones at the dose of 4 mg/kg and the subsequent at the dose of 8 mg/kg), we could taper GC at the dose of 2.5 mg/day, with no clinical symptoms, also the inflammatory markers were normal at the last infusion (ESR: 9 mm at the first hour and CRP: 1mg/l) and the Hb has risen to 13, 5 g/dl.

## Case 2

A 62 years old woman with a medical history of hypertension well controlled on Bisoprolol, diabetes on Metformin and Glibenclamid, and dyslipidemia on Simvastatin, consulted in our department for a new onset headache with inflammatory pain of the shoulders, asthenia and low grade fever. The physical examination was unremarkable except for pain and limitation of the left wrist.

The inflammatory markers were very high (ESR: 120 mm at the first hour and CRP: 10.8 mg/l) with inflammatory anemia (Hb: 11 g/dl, MCV: 85), the immunologic tests (ANA, Anti-DNA, RA test, ACPA, ANCA) and the parvovirus B19 IgM were negative. The Doppler ultrasonography of the carotid and vertebral arteries was normal, and the Doppler ultrasonography of the temporal arteries showed stenosis of the left temporal artery. A biopsy of the left temporal artery was performed but the results were not concluding because of an inadequate sample. A thoracic-abdominal-pelvic scan was normal and the ophthalmologic examination didn't show any visual complication.

Because of the strong suspicion of GCA, we started GC at the dose of 60 mg/day with Aspirin 100 mg/day. A spectacular response was noted, with disappearance of the symptoms and normalization of the laboratory tests (ESR: 15mm at the first hour, CRP: 1.5 mg/l and Hb: 13.7). Quickly after starting the GC, the patient developed a weakness of the thighs due to a corticoid- induced myopathy, the treatment by Adenosine Triphosphate with physical therapy was very helpful, and she complained also of a dysphagia due to severe mycotic esophagitis confirmed by gastroscopy, a treatment by fluconazole 50 mg/day for 3 weeks was prescribed. The osteodensitometry showed a T score of -1.8 at the femoral neck, Alendronate 70 mg/week was started. Also, a cure by Clarithromycin then Moxifloxacin was necessary to control an acute febrile bronchitis.

Despite the addition of Leflunomide to the treatment, we could not taper the GC below the dose of 35 mg/day (relapse of the headache and shoulders pain with increase of the ESR: 90 at H1 and CRP: 6 mg/l and decrease of the Hb: 12.9 mg/dl). The PET scan didn't show any sign of malignancy, an ileocolonoscopy was normal also.

The first infusion of TCZ at the dose of 8 mg/kg (560 mg), allowed us to decrease the GC and stop Lefluomide, the symptoms disappeared

and the inflammatory markers have decreased (ESR: 22 mm at H1 and CRP: 0.93 mg/l).

We note that there was a delay of 10 days between the 3rd and 4th infusions because of a periungueal infection of the left thumb that required a course of Amoxicillin and Clavulanic acid.

The remission observed since the first infusion of TCZ, was sustained after 12 months of treatment, and we could taper the GC to the dose of 2.5 mg/day, the ESR at the last infusion was 14 mm/h and the CRP was 0.12 mg/l.

## Discussion

GCA or temporal arteritis is an inflammatory disease of medium- and large-sized arteries that affects individuals older than 50 years of age; it's the most common type of vasculitis in Europe and North America, especially in people above 70 years of age [1].

Clinical features of GCA are mainly due to involvement of the cranial arteries [18]. Headache is the most common symptom in GCA, being present in nearly three quarters of patients, PMR manifestations are observed in approximately one third of patients [19]; constitutional symptoms, such as fever, anorexia, weight loss and fatigue, are present in one-third to two-thirds of GCA patients [20]; visual symptoms are common, especially loss of vision and diplopia [21]. Large vessel vasculitis is present in one third of GCA patients; it can be complicated by vascular stenosis, dissections and aneurysms [22].

Temporal artery biopsy is the gold standard for diagnosing GCA [23], although numerous tests support the diagnosis; such as raised inflammatory markers like ESR and CRP that can also be used to monitor disease activity [18]. The halo sign in the inflamed temporal arteries, documented by the arterial echo Doppler has a specificity of 82 to 100% and a sensitivity of 55 to 73% for the diagnosis of GCA [24,25]. MRI could be able to demonstrate the inflammation in the temporal arteries [26], while the PET scan can be useful for the diagnosis of GCA with large vessel involvement [27].

The diagnosis of GCA requires the fulfillment of 3 of the 5 ACR 1990 criteria: age greater than or equal to 50 years at disease onset, new onset of localized headache, temporal artery tenderness or decreased temporal artery pulse, elevated erythrocyte sedimentation rate greater than or equal to 50 mm/hour, and biopsy sample including an artery, showing necrotizing arteritis, characterized by a predominance of mononuclear cell infiltrates or a granulomatous process with multinucleated giant cells [28].

Our two patients fulfilled the criteria of Giant cell arteritis, with a biopsy proven diagnosis in one of them.

Glucocorticoids (GCs) are the drugs of choice in treatment of GCA [29]. In a cohort of 120 patients with Giant cell arteritis treated with GC, the improvement of symptoms was noted within hours or days of the first dose; the median duration required to reach 5 mg/day was 7.5 months; a drug free remission was achieved in 86 patients, the median time to reach it was 21.6 months. Adverse events related to GC was observed in 86%, these included bone fractures in 46 patients, avascular necrosis of the hip in 3, diabetes mellitus in 11, infections in 37, gastrointestinal bleeding in 5, posterior sub capsular cataract in 49, and hypertension in 26; increasing age and larger cumulative dose increased the risk for adverse effects [30].

As in the published literature, the response to the treatment by GC in our patients was quick, also were the complications, we observed

proximal myopathy, mycotic esophagitis and infection in the two patients, plus diabetes and cataract in the first one, and corticoid induced osteoporosis in the second.

Even with a gradual reduction of prednisone, more than 50% of patients experience flares of disease activity during the first year [4]. In a study of 174 patients with biopsy proven GCA, the relapse rate was 40.8%, it manifested as headaches in 52%, PMR in 30% and never as visual loss [31].

It was the case of our 2 patients; the first one relapsed at the dose of 20 mg/day and the second one at the dose of 35 mg/day. Thus the weaning from GCs was suitable and there was a need for a more efficacious and less toxic treatment, numerous disease-modifying anti-rheumatic drugs were studied.

Methotrexate (MTX) was assessed in 3 randomized controlled trials, the results are conflicting. Spiera et al. [5] studied 12 patients treated with MTX starting at 7.5 mg/week with 9 patients treated with placebo, at the end of the study, there were no significant differences between MTX and placebo-treated patients concerning the cumulative corticosteroid dose and number of weeks to taper off corticosteroids. Jover et al. [32] found that the treatment of 42 patients with biopsy proven GCA with MTX 10 mg/week along with a starting dose of Prednisone 60 mg/day reduced the rate of relapse of GCA and mean cumulative dose of prednisone dose in MTX-treated patients compared with the placebo treated patients, with no difference in the rate and severity of side effects. A larger number of patients were included in the study of Hoffman et al. [4], they enrolled 98 patients with GCA, treated by Prednisone alone or in combination with MTX at a median dose of 15 mg/week, the incidence of treatment failure was comparable in both groups, there was no difference between the groups, in terms of rate of failure, cumulative corticoids dose or side effects.

Azathioprine was studied in a small series of 31 patients with GCA or PMR or both [33], a significant difference reduction of the mean prednisone dose was noted at the end of 52 weeks.

Leflunomide was evaluated in two case series. Adizie et al. found that the treatment of 9 patients with refractory GCA, allowed a complete or partial response in all the patients [34]. Diamantopoulos et al. demonstrated that the treatment by Leflunomide was steroid sparing in 11 patients with GCA [35].

In a report of 3 patients, Mycophenolate mofetil have been demonstrated to have steroid-sparing effects [36].

Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) levels have been reported to be elevated in GCA [37] and to be expressed in the granulomatous infiltrates in patients with GCA [38]. Thus, TNF- $\alpha$  inhibitors were evaluated in the treatment of GCA. In a randomized controlled trial of 44 patients, Infliximab failed to show efficacy as maintenance of glucocorticosteroid-induced remission in patients with newly diagnosed GCA [39]. In a case series of 4 patients with long standing GCA, 3 of them achieved complete remission after treatment by Infliximab [40]. In 15 patients with biopsy-proven GCA with side effects secondary to corticosteroids, after 1 year of treatment with Etanercept, the patients had a lower dose of accumulated prednisone [41]. Adalimumab was evaluated in a randomized controlled trial of 70 patients with newly diagnosed GCA; the addition of Adalimumab to corticoids did not increase the proportion of patients who were relapse free [6].

While Rituximab is approved for remission induction in ANCA associated vasculitis [42], there are only two cases that were reported

in GCA, the results were good in one case and were not reported in the other one [43,44]

The efficacy of TCZ has been assessed in several double blind controlled clinical trials in rheumatoid arthritis [45, 46], and in two randomized controlled trials in systemic juvenile idiopathic arthritis [47,48].

There is a strong rationale behind the use of TCZ in the treatment of GCA. Interleukin-6 (IL-6) is an inflammatory cytokine with a well-documented role in inflammation [49], it influences the function of many cell types, it is important for B- and T-lymphocyte differentiation, generation of Th17 cells, fibroblast proliferation and hepatic synthesis of acute-phase proteins, including C-reactive protein (CRP) [50]. IL 6 binds to a membrane bound IL-6 receptor (IL-6R) [49], it has been shown that IL 6 is expressed in the inflamed arteries [51], is elevated in the serum of patients with GCA [52], and its concentration correlates with disease activity [53,54]. Therefore, TCZ, a humanized monoclonal antibody that antagonizes IL-6 receptors, could be a new therapeutic option for refractory CGA.

Some published reports showed the ability of TCZ to induce remission or to reduce glucocorticoids [7-17,55]. The tapering of corticoids to less than 7.5 mg/day was obtained after 3 to 8 months of treatment by TCZ in some reports [7,9,10,13,55]. Seitz et al. [55] reported that prednisone dosage could be reduced within 3 months to a mean of 2.5 mg/day (range 0-10 mg/day) in 5 patients with GCA (two of them were newly diagnosed and not treated by corticoids before). Unizony et al. reported a series of 10 patients with large vessels vasculitis treated by TCZ, of whom 7 patients with refractory GCA to glucocorticoids [15], at the end of the follow up, 3 patients were free from corticoids and 4 patients were at a dose ranging from 1 to 6 mg/day. Kieffer et al. reported a case series of 3 patients with GCA treated with TCZ, they could stop corticoids after 4 months of treatment in one patient and 6 months in another patient [8]. More recently, Loricera et al. reported the largest series of GCA patients treated by TCZ, Of 22 patients, 19 achieved maintained clinical and biological improvement with tapering of Prednisone from a mean of 18.75 (10-45) to 5 (2.5-10) mg/day after a median follow-up of 9 months [17]. Unlike these reports, Beasda et al. has found that the clinical response to TCZ in a patient with large vessel GCA, was moderate, but rapid disappearance of the wall inflammation demonstrated by the echo doppler of the axillary and carotid arteries, was noted [16].

In our patients, the time required to reach a dose of 2.5 mg/day of corticoids after the use of TCZ, was 20 months in one patient, knowing that there was a delay of several months because of the development of infections, and 12 months in the other patient.

The safety of TCZ was largely studied in patients with RA; in the ACT-SURE study, the adverse events were reported in 77.4% of patients, and the most frequent were: nasopharyngitis (6.9%), increased cholesterol (6.2%), headache (5.6%), nausea (4.7%), upper respiratory tract infection (4.2%), diarrhea (4.1%) and increased alanine aminotransferase level (3.5%), infections were reported in 35.3% of the patients [56].

According to the published reports, as in our patients, the infusions of TCZ lead to a rapid clinical response with normalization of symptoms and inflammation markers (Figure 1).

The treatment by TCZ was well tolerated by the second patient except for a periungueal infection, while the first one has experienced multiple infections (cellulitis, herpes zoster, upper respiratory infection, cystitis and gastroenteritis).

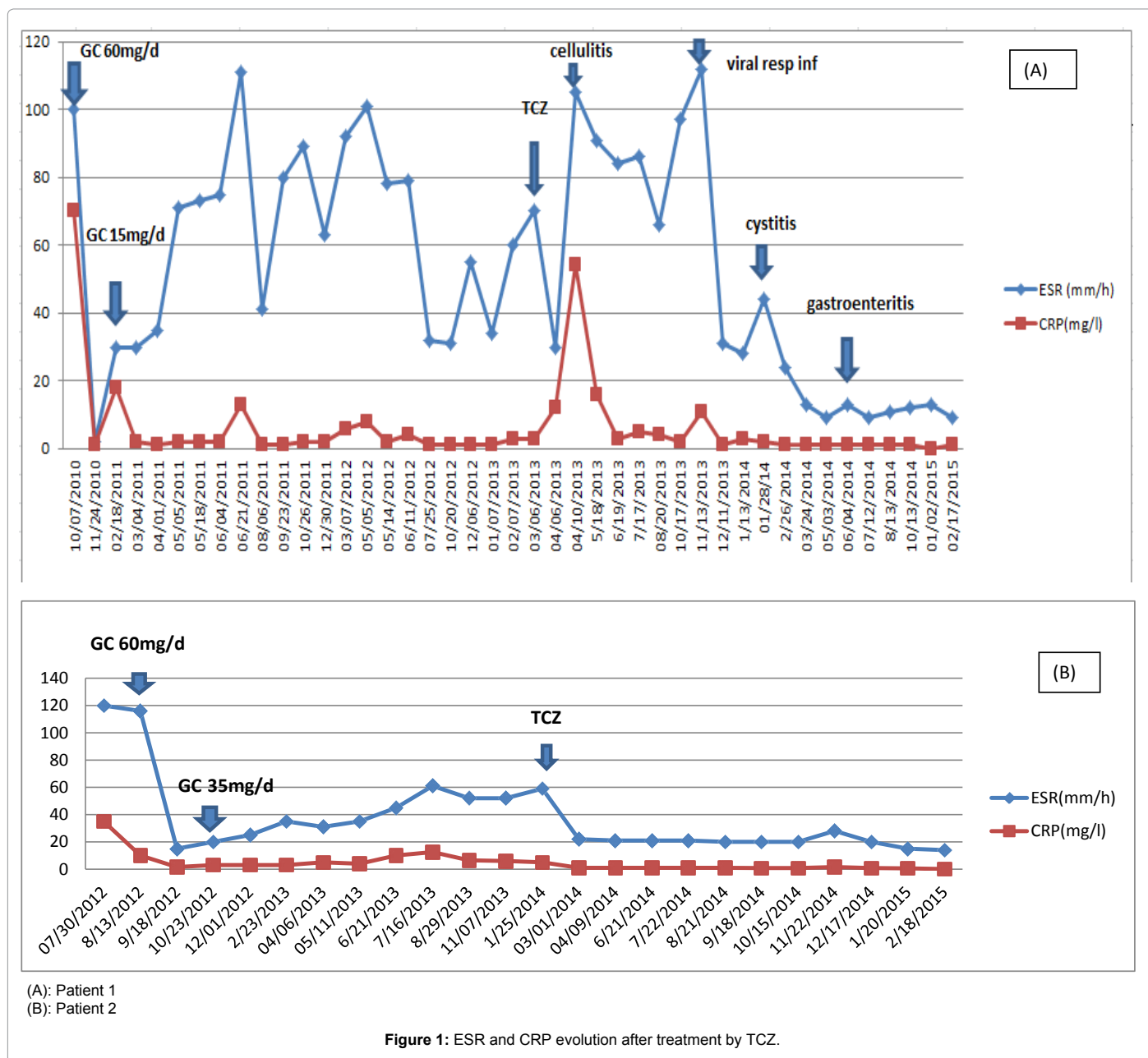


Figure 1: ESR and CRP evolution after treatment by TCZ.

Although the rapid clinical and biological efficacy in our two patients is promising, a randomized controlled trial is needed to confirm these results.

### Conclusion

Glucocorticoids are associated with significant adverse effects, and the poor efficacy of conventional and biologic immunosuppressive drugs together with the encouraging reported data about TCZ may justify its use as an alternative therapy in GCA.

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