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TOCILIZUMAB IN GIANT CELL ARTERITIS. OBSERVATIONAL, OPEN-LABEL MULTICENTER STUDY OF 134 PATIENTS IN CLINICAL PRACTICE

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TOCILIZUMAB IN GIANT CELL ARTERITIS. OBSERVATIONAL, OPEN-LABEL MULTICENTER STUDY OF 134 PATIENTS IN CLINICAL PRACTICE

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Running Title: *GCA and TCZ in clinical practice*.

Key indexing terms: tocilizumab, giant cell arteritis, biological therapy, large-vessel vasculitis.

ABSTRACT

Objective: Tocilizumab (TCZ) has shown efficacy in clinical trials on giant cell arteritis (GCA). Real-world data are scarce. Our objective was to assess efficacy and safety of TCZ in unselected patients with GCA in clinical practice

Methods: Observational, open-label multicenter study from 40 national referral centers of GCA patients treated with TCZ due to inefficacy or adverse events of previous therapy. Outcomes variables were improvement of clinical features, acute phase reactants, glucocorticoid-sparing effect, prolonged remission and relapses. A comparative study was performed: **a)** TCZ route (SC vs. IV); **b)** GCA duration (≤6 vs. >6 months); **c)** serious infections (with or without); **d)** ≤15 vs. >15 mg/day at TCZ onset.

Results: 134 patients; mean age, 73.0±8.8 years. TCZ was started after a median [IQR] time from GCA diagnosis of 13.5 [5.0-33.5] months. Ninety-eight (73.1%) patients had received immunosuppressive agents. After 1 month of TCZ 93.9% experienced clinical improvement. Reduction of CRP from 1.7 [0.4-3.2] to 0.11 [0.05-0.5] mg/dL ($p<0.0001$), ESR from 33 [14.5-61] to 6 [2-12] mm/1st hour ($p<0.0001$) and decrease in patients with anemia from 16.4% to 3.8% ($p<0.0001$) were observed. Regardless of administration route or disease duration, clinical improvement leading to remission at 6, 12, 18, 24 months was observed in 55.5%, 70.4%, 69.2% and 90% of patients. Most relevant adverse side-effect was serious infections (10.6/100 patients-year), associated with higher doses of prednisone during the first three months of therapy.

Conclusion: In clinical practice, TCZ yields a rapid and maintained improvement of refractory GCA. Serious infections appear to be higher than in clinical trials.

1. INTRODUCTION

Giant cell arteritis (GCA) is a large-vessel vasculitis (LVV) which affects medium and large sized arteries. It is common in European people older than 50 years as well as in North American of European ancestry **(1-3).** Although blindness is the most feared complication, other severe manifestations such as stroke and aneurysms can also occur **(4-7).**

The mainstay treatment of GCA are glucocorticoids **(8,9).** However, adverse events related to these drugs are common **(9-11).** Besides, relapses are relative frequent in GCA patients **(12,13).** Therefore, other medications such as leflunomide, azathioprine or cyclophosphamide have been used with no efficacy (**14-16**). For methotrexate, results are controversial but a metaanalysis confirmed its efficacy (**17)** Although the etiology of GCA remains unknown, different proinflammatory cytokines including TNFα and IL-6 act as soluble pathogenic factors **(18).** However, prospective, double-blind studies with monoclonal TNFα inhibitors led to poor results **(19).**

In contrast, several case series suggested that tocilizumab (TCZ), a humanized monoclonal antibody against the IL-6 receptor, may be a good therapeutic option in GCA **(20-27).** In this regard, two recent randomized clinical double-blinded Phase II and III studies showed efficacy of TCZ in patients with GCA **(28,29)**. Consequently, TCZ has been approved by the *European Medicines Agency* (EMA) and the *Food and Drug Administration* (FDA) for the treatment of patients with GCA. However, it is not uncommon to see that patients are often excluded from clinical trials due to comorbidities. Also, many of the individuals included in these two trials were patients with a recent diagnosis of GCA and some others had a relative short period of follow-up with TCZ therapy **(29)**. In this regard, 23 of 30 (77%) patients in a Phase II study,

and 119 of 251 (47%) in a Phase III study were patients with GCA of recent onset **(28,29).** In the GiACTA trial, newly diagnosed GCA was defined if diagnosis was done ≤ 6 weeks before baseline, with a mean± SD time between diagnosis and TCZ onset of 0.5±0.5 months **(29)**. However, in a real-world scenario, TCZ will probably be more frequently used in patients with GCA refractory to conventional treatment or in those who experience side effects, including also GCA patients with one or several comorbidities. Therefore, in real life, patients with GCA undergoing TCZ therapy have longer disease duration, being often relapsing patients who are refractory to conventional immunosuppressive drugs. In addition, in the phase II study TCZ was prescribed intravenously (IV) whereas in the phase III GiACTA trial TCZ was given subcutaneously (SC) **(28,29)**. Moreover, the recommended dose of prednisone at the onset of TCZ therapy has not clearly established.

Taking all these considerations into account, the aim of the present study was to assess the usefulness and safety of TCZ in GCA patients from a real clinical setting with refractory disease and/or with unacceptable side effects due to conventional treatment.

2. PATIENTS and METHODS

2.1 Patients, Enrollment Criteria and Study protocol

We set up an observational, retrospective open-label multicenter study that included 134 GCA patients treated with TCZ in real clinical practice and followed-up, in some cases, up to 48 months. Before TCZ onset, all of them had received high-dose glucocorticoids, and 98 (73.1%) conventional synthetic and/or other biologic immunosuppressive drugs. To reduce selection bias, in the present study we included all the patients who had received at least one TCZ dose, regardless of the

outcome. Preliminary, partial data on 22 patients were previously reported **(21).** The study was approved by the Clinical Research Ethics Committee of University Hospital Marqués de Valdecilla from Santander (Cantabria, Spain).

Patients were diagnosed with GCA at the Rheumatology or Autoimmune Units of 40 national referrals centers. GCA diagnosis was based on **a)** American College of Rheumatology (ACR) criteria **(30)**, **b)** a positive biopsy of temporal artery, and/or **c)** presence of imaging techniques consistent with large vessel vasculitis (LVV) in patients with cranial symptoms of GCA. The main imaging techniques used for LVV diagnosis were ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) scan, magnetic resonance imaging angiography (MRI-A), computed tomography angiography (CT-A), and helical CT scan.

Treatment of GCA was based on the classic pharmacological therapy, starting on high dose of glucocorticoids, generally an initial dose of prednisone between 40 to 60 mg/day, which was gradually tapered. Conventional immunosuppressive drugs and biologic therapy were used to spare glucocorticoid dose, mainly in patients with relapsing disease or in those cases with adverse side effect related to glucocorticoid therapy. The doses of conventional immunosuppressive drugs and biological agents used prior to TCZ were as follows: methotrexate (MTX) (7.5-30 mg/SC/week or 7.5-25 mg/per os/week), leflunomide (LFN) (10-30 mg/per os/day), hydroxychloroquine (HCQ) (400 mg/per os/day), azathioprine (AZA) (50-150 mg/per os/day), cyclophosphamide (CYC) (75-125 mg/per os/day), mycophenolate mofetil (MMF) (2 g/ per os/day), etanercept (ETN) (50 mg/SC/week), infliximab (IFX) (3 mg/kg/IV/8 weeks), rituximab (RTX) (2 g/IV/6 months) and abatacept (ABT) (10 mg/kg/IV at 0, 2, 4 weeks and later every 4 weeks).

As indicated by the Spanish National Guidelines for the administration of biologic

therapy in patients with rheumatic diseases, the presence of infectious diseases had to be ruled out, including tuberculosis and hepatitis B or hepatitis C infection, before the onset of biologic therapy, as previously described **(31).**

To exclude latent tuberculosis, a tuberculin skin testing (PPD) and/or an interferon assay (quantiFERON) as well as a chest radiography were performed. In positive cases, prophylaxis with isoniazid was initiated at least 4 weeks before the onset of the biological agent and it was maintained for 9 months. The presence of malignancies was also excluded in all the patients.

TCZ was prescribed IV at standard dose (8 mg/kg/4 weeks) or SC (162 mg/week). It was given due to lack of efficacy and/or unacceptable adverse side-effects related to previous therapy. In most cases, TCZ was prescribed off-label since it was indicated before its approval by the EMA and the FDA for the treatment GCA. Therefore, a written informed consent was obtained in these cases.

2.2 Clinical definitions and laboratory data

Fever was considered to be present if temperature was ≥ 38ºC. *Constitutional symptoms* included asthenia, anorexia and weight loss greater than 5% of the normal body weight over the last 6 months before disease diagnosis. *Headache* if it was of recent development or had different characteristics than usual. *Visual manifestations* include blurred vision, diplopia, amaurosis fugax, unilateral or bilateral hemianopsia and permanent unilateral or bilateral blindness. *Polymyalgia rheumatica* (PMR) was defined according to the classification criteria proposed by EULAR/ACR 2012 **(32**). Definition of other clinical manifestations were reported elsewhere **(33)**.

Serum C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), renal and liver function tests, as well as a full blood cell count were obtained at the time of TCZ

onset and then at each visit. A Serum CRP value was considered to be increased when it was higher than 0.5 mg/dL. An ESR value greater than 20 mm/h in men or > 25 mm/h in women was also considered abnormal. *Anemia* was defined as a hemoglobin level ≤11 g/dL.

A *serious infection* was considered to be present when a life-threatening infection, fatal, or requiring hospitalization occurred, intravenous antibiotics were required, or the infectious process led to persistent or significant disability.

Large vessel involvement was considered to be present if vasculitis involvement of the aorta and/or its major branches was disclosed by imaging techniques such as ^{18}F-FDG PET-CT scan, MRI-A, CT-A, or helical CT-scan. Assessment of large vessel vasculitis was performed in each of the recruiting centers. Nuclear medicine radiologists or angiography or angio/ interventional radiology staff members experts in the field from each hospital confirmed the presence of large vessel vasculitis.

Remission was defined if the patients was free of symptoms and had normalization of the acute phase reactants (CRP and ESR).

Prolonged remission was defined if the patients persisted asymptomatic with normal acute phase reactant for at least 6 months.

Relapse was defined as the recurrence of signs or symptoms of GCA along with ESR >20 mm/h in men or >25 mm/h in women and/or serum CRP >0.5 mg/dL.

2.3 Data collection

Information was retrieved from the patient's clinical records according to a specific designed protocol, including data on clinical and laboratory parameters at diagnosis, drugs used for the management of GCA, presence of relapses and side effect related to therapy different from TCZ, response to TCZ and development of side

effects while patients were undergoing TCZ therapy. To minimize entry error, all the data were double checked. Information was stored in a computerized database.

2.4 Statistical Analysis

All continuous variables were tested for normality, and results were expressed as mean± standard deviation (SD) or as median and interquartile range (IQR) as appropriate. Student's t test or Mann-Whitney U-test were used to compare continuous variables, and χ^2-test to compare categorical variables.

To assess the effect of TCZ on serum CRP levels, ESR and dose of prednisone between TCZ onset and the different follow-up visits we used the Wilcoxon's signed rank test.

A comparative study between the following groups was done: **a)** patients receiving IV or SC TCZ; **b)** TCZ efficacy in GCA patients with a disease duration ≤6 months or >6 months; **c)** TCZ in GCA patients with and without serious infections; and **d)** patients receiving prednisone doses ≤15 mg/d or >15 mg/d at TCZ onset.

Analyses were performed by using STATISTICA software (StatSoft Inc. Tulsa, Oklahoma, USA).

2.5 Role of the Funding source

This *study* was not *funded* by any drug company. It was the result of an independent initiative of the investigators.

3. RESULTS

3.1 Baseline main clinical features prior to TCZ onset

We studied 134 patients (101 women/33 men); mean age 73.0±8.8 years, diagnosed with GCA and treated with TCZ. Of them, 119 (88%) fulfilled the 1990 ACR classification criteria for GCA **(30)**. The remaining patients were diagnosed by a

positive temporal artery for GCA in 9 cases. Six patients did not fulfil the ACR classification criteria for GCA and had a negative TAB. All of them were older than 50 years but had an ESR at the time of diagnosis lower than 50 mm/1st hour. Nevertheless, they presented cranial ischemic manifestations. In these patients, a diagnosis of GCA was confirmed by a positive imaging technique showing large vessel vasculitis involvement. In addition, other entities, such as connective-tissue diseases, IgG4 related disease or any other inflammatory conditions that may be associated with large-vessel vasculitis, were excluded. In addition, all of them exhibited a rapid response to prednisone dose (initial dose range between 40-60 mg/day). With respect to this, a positive temporal artery biopsy was positive in 72 (61.5%) of 117 patients in whom it was performed. Also, imaging techniques to identify the presence of LVV were performed in 75 patients. Of them 58 yielded positive results. With respect to this, 51 of these 58 patients with LVV also had cranial features of GCA.

The median [IQR] time from GCA diagnosis to TCZ onset was 13.5 [5.0-33.5] months. The main clinical features before TCZ onset were PMR (n=73) and headache (n=70), followed by constitutional symptoms (n=31) and jaw claudication (n=14). Twenty-eight patients from this series had visual manifestations at the time of GCA diagnosis. Besides glucocorticoids and before starting TCZ, 98 (73.1%) patients had received conventional immunosuppressive drugs: MTX (n=94), AZA (n=14), LFN (n=9), CYC (n=4), HCQ (n=2), MMF (n=1). Five of them had also received other biologic agents: IFX (n=2), ETN (n=1), RTX (n=1), and ABA (n=1) **(Table 1).** The median [IQR] number of immunosuppressive agents per patient, before TCZ onset was 1 [0.75-1.0].

3.2 Treatment with TCZ and outcome

TCZ was initiated due to refractory GCA (n=86) or unacceptable adverse events of previous therapy (n=48). It was administered IV to 106 (79.1%) patients and SC to 28 (20.9%). The initial dose was 8 mg/kg/IV/4 weeks or 162 mg/SC/week, respectively. The maintenance dose of TCZ ranged from 8 mg/IV/kg/4 weeks to 4 mg/IV/kg/8 weeks, and from 162 mg/SC/ week to 162 mg/SC/3 weeks. Regardless of glucocorticoids, TCZ was prescribed as monotherapy to 82 (62.2%) cases and combined with conventional immunosuppressive agents in 52 (38.8%) patients: MTX (n=48), AZA (n=3), and LFN (n=1).

As described in **Table 2,** one month after TCZ onset, most patients (93.9%) achieved clinical improvement. At that time, significant reduction of the acute phase reactants was also observed. In this regard, the median serum CRP fell from 1.7 [0.4-3.2] to 0.11 [0.05-0.5] mg/dL ($p<0.0001$), and the median ESR from 33 [14.5-61] to 6 [2-12] mm/1st hour ($p<0.0001$). The percentage of patients with anemia decreased from 16.4% to 3.8% ($p<0.0001$), and the mean hemoglobin level increased from 12.3±1.5 g/dL to 13.1±1.3 g/dL ($p<0001$). Furthermore, the median dose of prednisone was reduced from 15 [10-30] to 13.75 [7.5-20] mg/day ($p<0.0001$) at month 1. Noteworthy, improvement of the clinical and laboratory parameters was observed throughout the follow-up. At the same time successful glucocorticoid tapering was achieved (**Table 2** and **Figure 1, panels A, B and C**). Persistent remission of the disease was observed in 27 (69.2%) of 39 patients followed-up for at least 2 years. At that time, the median level of the acute phase reactants in these 39 patients was within the normal range. Interestingly, the median prednisone dose after 2 years of follow-up in these 39 patients was 0 [0-5] mg/day. However, 7 of these 39 cases (17.9%) had relapses during the follow-up, usually mild, that were successfully treated following a small increase of prednisone dose.

With respect to these 7 relapsing patients, two of them were still receiving TCZ at 24 months of follow-up. From the remaining 5 patients, TCZ was withdrawn in 3 patients due to remission and because of severe adverse events in the other 2 patients.

No significant differences in the clinical response or in the acute phase reactants were observed when patients were stratified according to the duration of the disease prior to TCZ equal to or less than 6 months or longer than 6 months. It was also the case when patients were compared according to the route of TCZ administration (IV or SC) or when patients receiving more than 15 mg/day at the time of TCZ onset were compared with those receiving 15 mg/day or less **(Figure 2 panels B, C and D**).

3.3 Side effects

After a median follow-up of 12 [3-24] months, 32 (23.9%) patients developed relevant adverse events **(Table 3).** Seventeen of them required permanent discontinuation of TCZ therapy. The most frequent adverse events were infections and hematological abnormalities. Serious infections were observed in 16 patients (11.9%; 10.6 per 100 patients-year).

Five patients died during the follow-up due to stroke (n=2; one of them in the setting of an infective endocarditis), lung cancer (n=1), necrotizing gluteal ulcer (hyponatremia and cutaneous infection) (n=1), and of unknown cause (n=1).

We performed a comparative study between patients with serious infections (n=16) and those without (n=118). At TCZ onset, patients who experienced serious infections were slightly older (74.3±9.6 vs. 72.9±8.7 years; p=0.55) and had a non-statistically significant longer course of the disease (20 [4.25-45.8] vs. 13 [5-29.3] months; p=0.60). They were receiving a significantly greater prednisone dose at TCZ onset (29.1 [20-40] vs. 15 [10-30] mg/day; p=0.01) and also after 3 months from the

onset of TCZ (12.5 [10-20] vs. 7.5 [5.0-12.5] mg/day; p=0.003). Thirteen of the 66 patients that received more than 15 mg/day of prednisone at TCZ onset had serious infections (16.3 per 100 patients-year) compared to only 3 (4.2 per 100 patients-year) of 68 from the group on ≤15 mg/day (p=0.006). Nevertheless, clinical and acute phase reactants improvement was similar in both groups.

To analyze the safety and efficacy of TCZ, we made a comparative study regarding associated therapies and the duration of the treatment with TCZ. The biologic agent was prescribed as monotherapy (82, 62.2%) or combined with conventional immunosuppressants (52, 38.8%). The main immunosuppressants were MTX (n=48), AZA (n=3), and LFN (n=1). There were not statistically significant differences in terms of relevant adverse events (28% vs 17.3%, p=0.55) or serious infections between patients treated with TCZ in monotherapy and those treated with TCZ in combination with a conventional immunosuppressant (14.6% vs 7.7%, p=0.227). Likewise, a comparison according to duration of TCZ treatment (< 12 months in 68 [50.7%] patients and ≥ 12 months in 66 [49.3%] patients) was performed. Relevant adverse events were seen in 14 (20.5%) patients vs 18 (27.2%) patients respectively, p=0.366. More specifically, regarding serious infections, no significant differences were observed. In the first group (< 12 months) they occurred in 13.2% of patients whereas they were observed in 10.6% of the patients from the second group (≥ 12 months), p=0.640.

Figure 3 shows the flow-chart summarizing the 134 patients with GCA on TCZ regarding the dose of the biologic agent and the outcome of the patients.

4. DISCUSSION

We present the largest multicenter series of real-life GCA patients in whom short and long-term efficacy of TCZ was assessed. All of them were refractory and/or had unacceptable side effects due to conventional therapy. Our results show that TCZ yields a rapid and maintained clinical and laboratory improvement, regardless of GCA time course (≤ 6 months or > 6 months), TCZ administration route (IV vs SC) or prednisone dose at TCZ onset (≤ 15 mg/d or > 15 mg/day). However, the frequency of serious infections was higher than reported in the GiACTA clinical trial and in patients with rheumatoid arthritis (RA), especially in those GCA patients on higher doses of prednisone during the first three months of treatment **(29)**.

Glucocorticoids are the first line of treatment in GCA and they are usually effective at high doses **(9,10).** However, relapses are common when the dose is tapered, and side-effects are also frequent **(9,10,12).** For that reason, several synthetic immunosuppressive agents have been used for the treatment of GCA, but only MTX has shown positive although often contradictory result **(10,14).** Thus, the biologic therapy represents a new and promising alternative in the treatment of patients with GCA, although anti-TNFα agents showed negative results **(19).**

IL-6 has a wide range of pleiotropic effects, including production of acute phase reactants by hepatocytes, B lymphocyte differentiation and T lymphocyte subset differentiation. Th1 and Th17 are involved in GCA, and IL-6 blockade may correct the imbalance of Th17 and/or Th1 versus Treg lymphocytes **(18,34-38).**

TCZ is a humanized monoclonal antibody acting against soluble and membrane bound IL-6 receptor. TCZ has been approved for the treatment of inflammatory and autoimmune diseases, such as RA, systemic and polyarticular juvenile arthritis and Castleman's disease, including also vascular syndromes. A growing body of

evidence supports the potential use of TCZ in other autoimmune diseases such as uveitis and adult-onset Still's disease **(34,39-42).**

Several observational studies on the use of TCZ in GCA showed promising results, with clinical and laboratory data improvement and a glucocorticoid dose sparing **(20-22, 23-27,43,44).** Interestingly, a phase II, randomized, double-blind, placebo-controlled trial showed complete GCA clinical remission at week 12 in 85% of patients treated with TCZ (8 mg/kg/4 weeks IV), and a relapse-free survival in the same extent at week 52, with less cumulative glucocorticoid dose **(28).** Results of the GiACTA study **(29)**, a phase III, randomized, double-blind placebo-controlled trial, showed that the use of TCZ at a dose of 162 mg SC weekly or every other week (eow), plus a 26-week prednisone tapering regimen, allowed sustained remission in 56% and 53% of patients respectively, at 52 weeks. A decrease of the total cumulative dose of glucocorticoids was also possible **(29)**.

However, clinical trials do not always exemplify a real-world clinical scenario, since they often include selected patients with very specific inclusion and exclusion criteria and limited follow-up over time. For example, patients with specific comorbidities are usually excluded and only a small proportion of patients included in the GiACTA trials had previously received immunosuppressive drugs **(29)**. On the other hand, information on the long-term efficacy and safety of TCZ in GCA patients treated in daily clinical practice is scarce. In this regard, the overall safety profile of TCZ in GCA is consistent with the known safety in other conditions such as RA **(45).** In the GiACTA study **(29)**, serious infections occurred in 7% of the patients that received TCZ weekly, 4% in the group on TCZ eow and 4% in the group that followed the 26-week tapering protocol **(29)**. In our series, serious infections occurred in 11.9% of patients (10.6 per 100 patients-year). In contrast, in clinical practice this incidence in

RA patients was 4.7 per 100 patients-year **(45).** The older age as well as the higher prednisone dose used in our series of GCA patients at the time of TCZ onset may explain the increased frequency of serious infections when compared with RA. Therefore, we feel that several features of the patient should be considered before using TCZ in the clinical practice. They include the age at the beginning of therapy, the cumulative dose of corticosteroids and the presence of comorbidities that predispose to infections.

Our study represents the largest real-world study on refractory GCA treated with TCZ. However, it has potential limitations derived from its observational and retrospective nature. In addition, during the follow-up several patients were lost. Moreover, although the study included 134 cases, only 39 of them reached a follow-up of 24 months. Also, in our study we did not use TCZ in newly diagnosed patients, but only in those who were refractory to conventional therapy; being this a limitation when compared with the GiACTA trial. Another limitation of this study was that the definition of relapse used by authors might not be accurate for a study assessing the efficacy of TCZ since this monoclonal antibody acts suppressing CRP, ESR and fibrinogen. This limitation was also present in the GiACTA trial. However, in an attempt to compare real life data with the GiACTA trial, the investigators of our study decided to include in the definition of relapse the presence of an increase of acute phase proteins, in a similar way to that used in the GiACTA trial.

Our results are consistent with those observed in clinical trials, confirming the efficacy of TCZ in the treatment of GCA. Interestingly, in our series clinical and laboratory improvement was unrelated to disease duration, administration route or a dose of prednisone at TCZ onset greater than or lower than 15 mg/day.

5. CONCLUSION

Taken together our findings and the results of the randomized control trials, TCZ seems to be an excellent therapeutic option in GCA, regardless of the administration route and GCA duration, helping to minimize the glucocorticoid exposure over time. The most relevant side effects are serious infections that seem to be higher than in the GiACTA trial.

In conclusion, TCZ improves clinical manifestations, acute-phase reactants and imaging findings. However, GCA patients treated with TCZ may have normal levels of CRP even though active disease may be still present. Therefore; an important issue to be addressed is how we can be sure that TCZ-treated patients have a “true” remission of the disease. Therefore, we feel that the definition of relapse in future studies on patients undergoing biologic therapy, in particular in those treated with anti-IL-6 receptor agents, should be reconsidered. Because of that, based on previous observations of our group (46), the definition of relapses in patients undergoing biologic therapy should be based on the presence of clinical features and confirmed by an imaging technique (for example a PET/CT-scan).

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REFERENCES

1. Salvarani C, Cantini F, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis. Lancet Lond Engl. 2008; 372:234-45.
2. Gonzalez-Gay MA, Vazquez-Rodriguez TR, Lopez-Diaz MJ, Miranda-Filloy JA, Gonzalez-Juanatey C, Martin J, Llorca J. Epidemiology of giant cell arteritis and polymyalgia rheumatica. Arthritis Rheum. 2009; 61:1454-61.
3. Hoffman GS. Giant Cell Arteritis. Ann Intern Med. 2016; 165:65-80.
4. Salvarani C, Pipitone N, Versari A, Hunder GG. Clinical features of polymyalgia rheumatica and giant cell arteritis. Nat Rev Rheumatol. 2012; 8:509-21.
5. Soriano A, Muratore F, Pipitone N, Boiardi L, Cimino L, Salvarani C. Visual loss and other cranial ischaemic complications in giant cell arteritis. Nat Rev Rheumatol. 2017; 13:476-84.
6. González-Gay MA, García-Porrúa C, Llorca J, Hajeer AH, Brañas F, Dababneh A, et al. Visual manifestations of giant cell arteritis. Trends and clinical spectrum in 161 patients. Medicine (Baltimore). 2000; 79:283-92.

7. Gonzalez-Gay MA, Garcia-Porrua C, Piñeiro A, Pego-Reigosa R, Llorca J, Hunder GG. Aortic aneurysm and dissection in patients with biopsy-proven giant cell arteritis from northwestern Spain: a population-based study. Medicine (Baltimore). 2004 Nov;83(6):335-41.

8. Gonzalez-Gay MA, Martinez-Dubois C, Agudo M, Pompei O, Blanco R, Llorca J. Giant cell arteritis: epidemiology, diagnosis, and management. Curr Rheumatol Rep. 2010; 12:436-42.

9. Proven A, Gabriel SE, Orces C, O'Fallon WM, Hunder GG. Glucocorticoid therapy in giant cell arteritis: duration and adverse outcomes. Arthritis Rheum. 2003; 49:703-8.

10. González-Gay MA, Pina T, Prieto-Peña D, Calderon-Goercke M, Blanco R, Castañeda S. Current and emerging diagnosis tools and therapeutics for giant cell arteritis. Expert Rev Clin Immunol. 2018; 14:593-605.

11. Petri H, Nevitt A, Sarsour K, Napalkov P, Collinson N. Incidence of giant cell arteritis and characteristics of patients: data-driven analysis of comorbidities. Arthritis Care Res. 2015; 67:390-5.

12. Martinez-Lado L, Calviño-Díaz C, Piñeiro A, Dierssen T, Vazquez-Rodriguez TR, Miranda-Filloy JA, et al. Relapses and recurrences in giant cell arteritis: a population-based study of patients with biopsy-proven disease from northwestern Spain. Medicine (Baltimore). 2011; 90:186-93.

13. Kermani TA, Warrington KJ, Cuthbertson D, Carette S, Hoffman GS, Khalidi NA, et al. Disease Relapses among Patients with Giant Cell Arteritis: A Prospective, Longitudinal Cohort Study. J Rheumatol. 2015; 42:1213-7.

14. Yates M, Loke YK, Watts RA, MacGregor AJ. Prednisolone combined with adjunctive immunosuppression is not superior to prednisolone alone in terms of efficacy and safety in giant cell arteritis: meta-analysis. Clin Rheumatol. 2014; 33:227-36.

15. Mahr AD, Jover JA, Spiera RF, Hernández-García C, Fernández-Gutiérrez B, Lavalley MP, et al. Adjunctive methotrexate for treatment of giant cell arteritis: an individual patient data meta-analysis. Arthritis Rheum. 2007; 56:2789-97.

16. Diamantopoulos AP, Hetland H, Myklebust G. Leflunomide as a corticosteroid-sparing agent in giant cell arteritis and polymyalgia rheumatica: a case series. BioMed Res Int. 2013; 2013:120638.

17. Mahr AD, Jover JA, Spiera RF, Hernández-García C, Fernández-Gutiérrez B, Lavalley MP, Merkel PA. Adjunctive methotrexate for treatment of giant cell arteritis: an individual patient data meta-analysis. Arthritis Rheum. 2007; 56: 2789-97.

18. Ciccia F, Rizzo A, Ferrante A, Guggino G, Croci S, Cavazza A, et al. New insights into the pathogenesis of giant cell arteritis. Autoimmun Rev. 2017; 16:675-83.

19. Hoffman GS, Cid MC, Rendt-Zagar KE, Merkel PA, Weyand CM, Stone JH, Salvarani C, Xu W, Visvanathan S, Rahman MU; Infliximab-GCA Study Group. Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis: a randomized trial. Ann Intern Med. 2007; 146:621-30.

20. Seitz M, Reichenbach S, Bonel HM, Adler S, Wermelinger F, Villiger PM. Rapid induction of remission in large vessel vasculitis by IL-6 blockade. A case series. Swiss Med Wkly. 2011; 141: w13156.

21. Loricera J, Blanco R, Hernández JL, Castañeda S, Mera A, Pérez-Pampín E, et al. Tocilizumab in giant cell arteritis: Multicenter open-label study of 22 patients. Semin Arthritis Rheum. 2015; 44:717-23.

22. Loricera J, Blanco R, Castañeda S, Humbría A, Ortego-Centeno N, Narváez J, et al. Tocilizumab in refractory aortitis: study on 16 patients and literature review. Clin Exp Rheumatol. 2014; 32:79-89.

23. Pazzola G, Padovano I, Boiardi L, Versari A, Pipitone N, Catanoso M, et al. Tocilizumab in glucocorticoid-naïve large-vessel vasculitis. Clin Exp Rheumatol. 2013; 31:59-61.

24. Beyer C, Axmann R, Sahinbegovic E, Distler JH, Manger B, Schett G, et al. Anti-interleukin 6 receptor therapy as rescue treatment for giant cell arteritis. Ann Rheum Dis. 2011; 70:1874-5.

25. Salvarani C, Magnani L, Catanoso M, Pipitone N, Versari A, Dardani L, et al. Tocilizumab: a novel therapy for patients with large-vessel vasculitis. Rheumatolgy (Oxford). 2012; 51:151-6.

26. Unizony S, Arias-Urdaneta L, Miloslavsky E, Arvikar S, Khosroshahi A, Keroack B, et al. Tocilizumab for the treatment of large-vessel vasculitis (giant cell arteritis, Takayasu arteritis) and polymyalgia rheumatica. Arthritis Care Res. 2012; 64:1720-9.

27. Sciascia S, Rossi D, Roccatello D. Interleukin 6 Blockade as Steroid-sparing Treatment for 2 Patients with Giant Cell Arteritis. J Rheumatol. 2011; 38:2080-1.

28. Villiger PM, Adler S, Kuchen S, Wermelinger F, Dan D, Fiege V, et al. Tocilizumab for induction and maintenance of remission in giant cell arteritis: a

phase 2, randomised, double-blind, placebo-controlled trial. Lancet. 2016; 387:1921-7.

29. Stone JH, Tuckwell K, Dimonaco S, Klearman M, Aringer M, Blockmans D, et al. Trial of Tocilizumab in Giant-Cell Arteritis. N Engl J Med. 2017; 377:317-28.

30. Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum. 1990; 33:1122-8.

31. Calvo-Río V, Blanco R, Beltrán E, Sánchez-Bursón J, Mesquida M, Adán A, et al. Anti-TNF-α therapy in patients with refractory uveitis due to Behçet's disease: a 1-year follow-up study of 124 patients. Rheumatology (Oxford). 2014; 53:2223-31.

32. Dasgupta B, Cimmino MA, Maradit-Kremers H, Schmidt WA, Schirmer M, Salvarani C, et al. 2012 provisional classification criteria for polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. Ann Rheum Dis. 2012; 71:484-92.

33. Gonzalez-Gay MA, Barros S, Lopez-Diaz MJ, Garcia-Porrua C, Sanchez-Andrade A, Llorca J. Giant cell arteritis: disease patterns of clinical presentation in a series of 240 patients. Medicine (Baltimore). 2005; 84:269-76.

34. Ogata A, Tanaka T. Tocilizumab for the treatment of rheumatoid arthritis and other systemic autoimmune diseases: current perspectives and future directions. Int J Rheumatol. 2012; 2012:946048.

35. Weyand CM, Younge BR, Goronzy JJ. IFN-γ and IL-17: the two faces of T-cell pathology in giant cell arteritis. Curr Opin Rheumatol. 2011; 23:43-9.

36. Manel N, Unutmaz D, Littman DR. The differentiation of human T(H)-17 cells requires transforming growth factor-beta and induction of the nuclear receptor RORgammat. Nat Immunol. 2008; 9:641-9.

37. Weyand CM, Goronzy JJ. Immune mechanisms in medium and large-vessel ……vasculitis. Nat Rev Rheumatol 2013; 9:731-40.

38. Deng J, Younge BR, Olshen RA, Goronzy JJ, Weyand CM. Th17 and Th1 T-cell ……responses in giant cell arteritis. Circulation. 2010; 121:906-15.

39. Calvo-Río V, Santos-Gómez M, Calvo I, González-Fernández MI, López-Montesinos B, Mesquida M, et al. Anti-Interleukin-6 Receptor Tocilizumab for Severe Juvenile Idiopathic Arthritis-Associated Uveitis Refractory to Anti-Tumor Necrosis Factor Therapy: A Multicenter Study of Twenty-Five Patients. Arthritis Rheumatol. 2017; 69:668-75.

40. Calvo-Río V, Blanco R, Santos-Gómez M, Díaz-Valle D, Pato E, Loricera J, et al. Efficacy of Anti-IL6-Receptor Tocilizumab in Refractory Cystoid Macular Edema of Birdshot Retinochoroidopathy Report of Two Cases and Literature Review. Ocul Immunol Inflamm. 2017; 25:604-9.

41. Atienza-Mateo B, Calvo-Río V, Beltrán E, Martínez-Costa L, Valls-Pascual E, Hernández-Garfella M, et al. Anti-interleukin 6 receptor tocilizumab in refractory uveitis associated with Behçet's disease: multicentre retrospective study. Rheumatology (Oxford). 2018; 57: 856-864.

42. Ortiz-Sanjuán F, Blanco R, Calvo-Rio V, Narvaez J, Rubio Romero E, Olivé A, et al. Efficacy of tocilizumab in conventional treatment-refractory adult-onset Still's disease: multicenter retrospective open-label study of thirty-four patients. Arthritis Rheumatol. 2014; 66:1659-65.

43. Régent A, Redeker S, Deroux A, Kieffer P, Ly KH, Dougados M, et al. Tocilizumab in Giant Cell Arteritis: A Multicenter Retrospective Study of 34 Patients. J Rheumatol. 2016; 43:1547-52.

44. Evans J, Steel L, Borg F, Dasgupta B. Long-term efficacy and safety of tocilizumab in giant cell arteritis and large vessel vasculitis. RMD Open. 2016; 2:e000137.

45. Morel J, Constantin A, Baron G, Dernis E, Flipo RM, Rist S, et al. Risk factors of serious infections in patients with rheumatoid arthritis treated with tocilizumab in the French Registry REGATE. Rheumatology (Oxford). 2017; 56:1746-1754.

46. Prieto-Peña D, Martínez-Rodríguez I, Loricera J, Banzo I, Calderón-Goercke M, Calvo-Río V, González-Vela C, et al. Predictors of positive (18)F-FDG PET/CT-scan for large vessel vasculitis in patients with persistent polymyalgia rheumatica. Semin Arthritis Rheum. 2018 May 18. pii: S0049-0172(18)30215-4. doi:10.1016/j.semarthrit.2018.05.007. [Epub ahead of print] PubMed PMID: 29903537

FIGURE LEGENDS

FIGURE 1. Reduction of acute phase reactants and glucocorticoid dose in 134 patients with refractory giant cell arteritis (GCA) following tocilizumab therapy. **A)** Serum C-reactive protein (CRP) evolution; **B)** Erythrocyte sedimentation rate (ESR); **C)** Glucocorticoid dose. Bars represent median values with 95% confidence intervals; *p*-compared with baseline, *p<0.05.

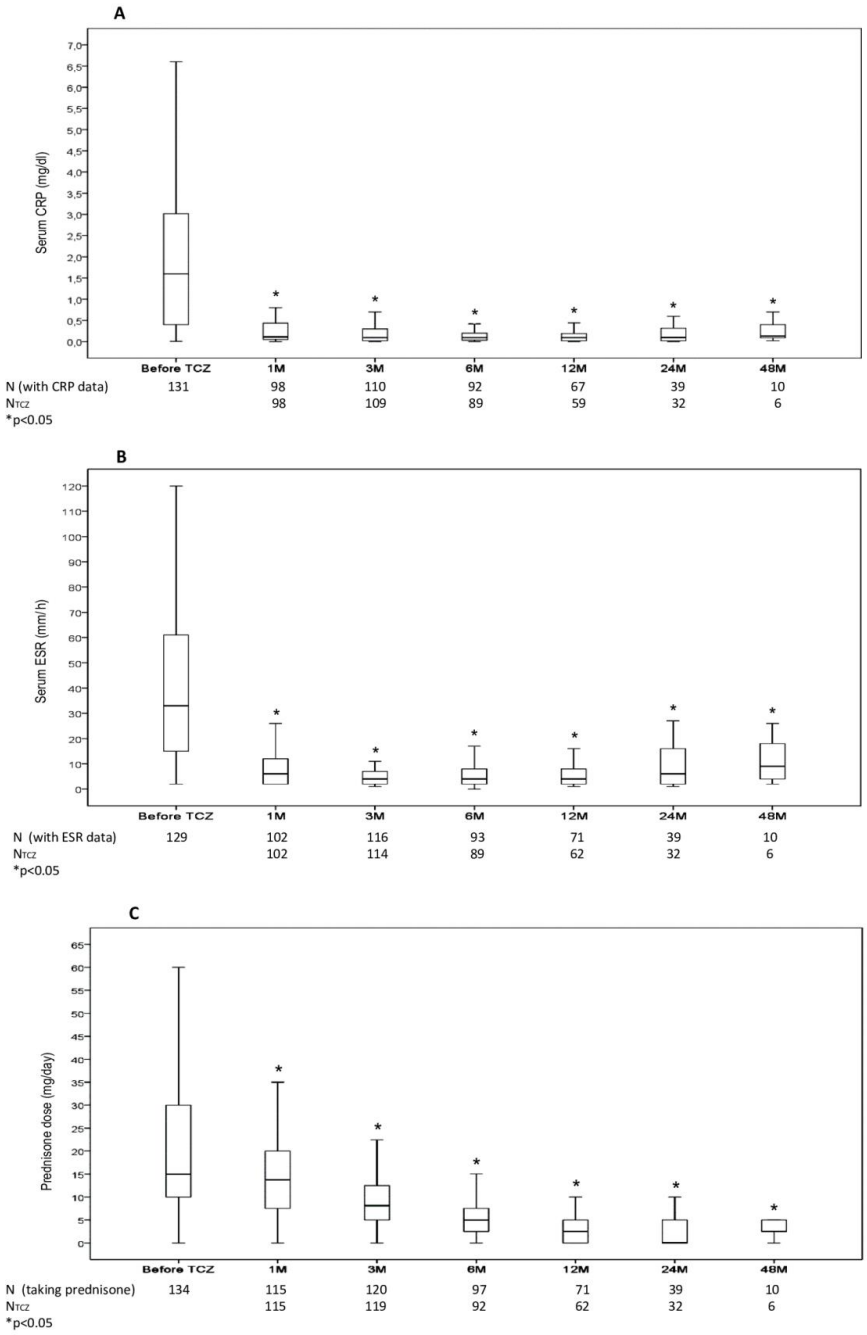

FIGURE 2. Percentage of responders according to clinical and/or therapeutic characteristics (n=134). **A)** In the whole series; **B)** According to type of therapy (IV or SC tocilizumab administration); **C)** According to giant cell arteritis (GCA) duration (≤6 months or >6 months); **D)** Regarding prednisone dose at tocilizumab onset (≤15 mg/d or >15 mg/d).

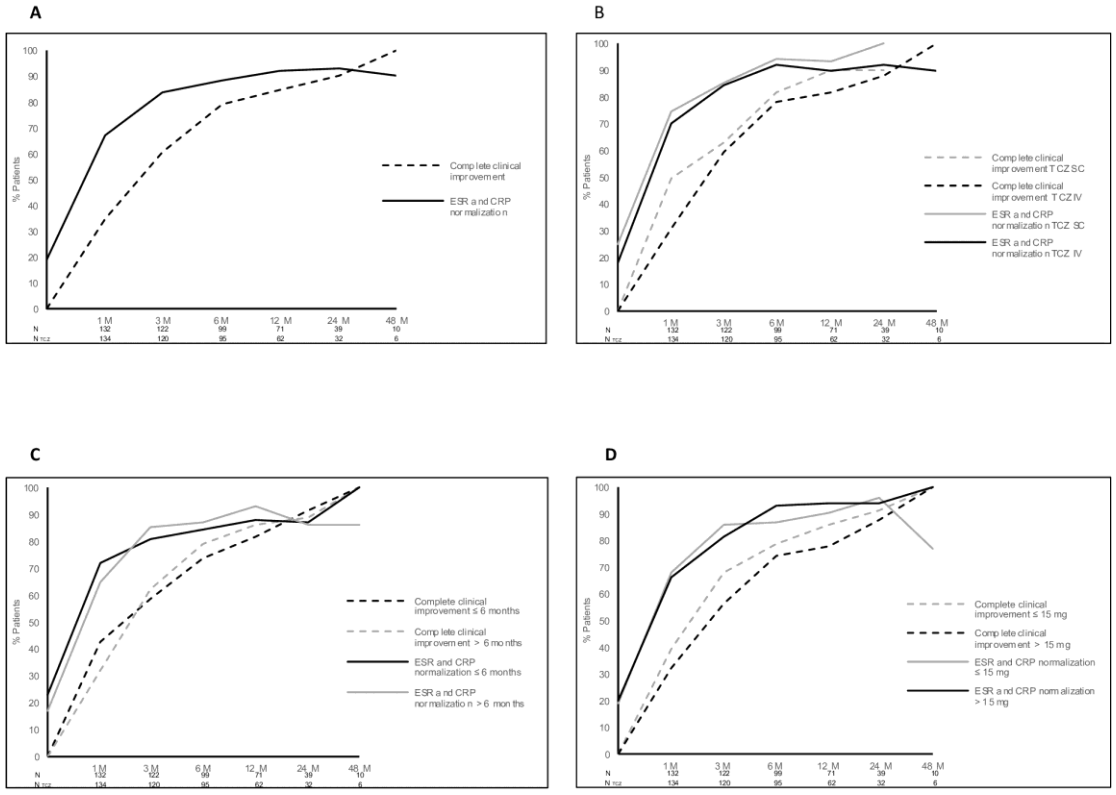

FIGURE 3. Flow chart of 134 patients with giant cell arteritis treated with tocilizumab.

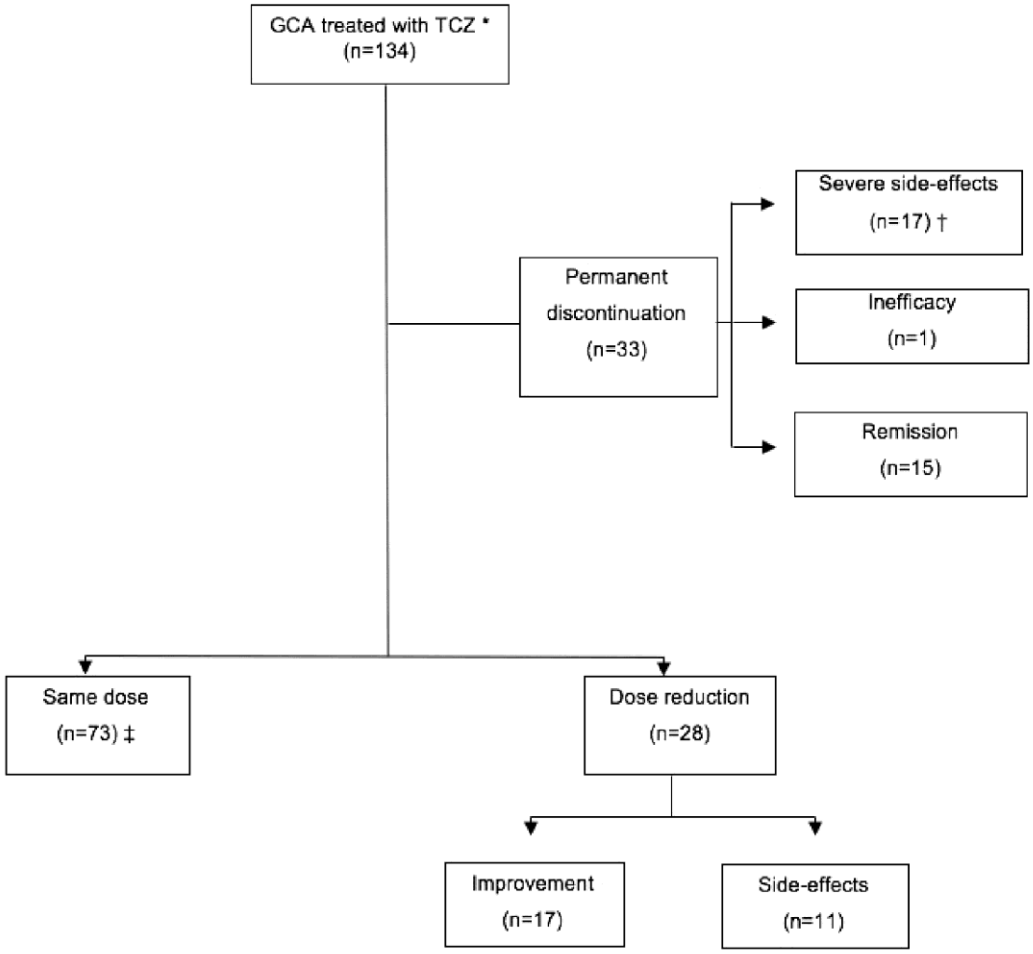

TABLE 1. Main features of 134 patients with refractory Giant Cell Arteritis who were treated with TCZ.

	Overall n= 134	**GCA fulfilling ACR 1990 criteria n= 119**	**Biopsy-proven GCA n= 72**	**Cranial symptoms plus LVV* n= 51**
Age, years, mean± SD	73 ± 8.8	73.4 ± 8.5	75.7 ± 7.1	71.5 ± 8.9
Sex, female/male n (%)	101 / 33	88 / 31	57 / 15	43 / 8
Time from GCA diagnosis to TCZ onset (months), median [IQR]	13.5 [5.0-33.5]	14.0 [5.0-35.0]	14.5 [6.5-44.8]	14.0 [7.0-35.8]
SYSTEMIC MANIFESTATIONS				
Fever, n (%)	9 (6.7%)	8 (6.7%)	4 (5.5%)	4 (7.8%)
Constitutional syndrome, n (%)	31 (23.1%)	25 (21%)	14 (19.4%)	11 (21.6%)
PMR, n (%)	73 (54.4%)	73 (61.3%)	40 (55.5%)	29 (56.8%)
ISCHEMIC MANIFESTATIONS				
Headache, n (%)	70 (52.2%)	64 (53.7%)	33 (45.8%)	29 (56.8%)
Jaw claudication, n (%)	14 (10.4%)	12 (10.0%)	11 (15.2%)	6 (11.7%))
Stroke, n (%)	1 (0.7%)	-	-	1 (1.9%)
Visual involvement, n (%)	28 (20.9%)	17 (14.2%)	13 (18%)	7 (13.7%)
AORTITIS AND ANOTHER LVV involvement, n (%)	58 (43.2%)	46 (38.6%)	36 (50.0%)	51 (100%)
ACUTE PHASE REACTANTS at the onset of TCZ				
ESR, mm/1st hour, mean (SD)	40.5 ± 31.2	39.3 ± 31.2	39.3 ± 31.2	40.5 ± 33.6
CRP, mg/dL mean (SD)	3 ± 5.3	3.3 ± 5.6	3.2 ± 6.5	4.2 ± 7.6
Hemoglobin, g/dL, mean (SD)	12.3 ± 1.5	12.2 ± 1.4	12.2 ± 1.4	12 ± 1.2
POSITIVE TEMPORAL ARTERY BIOPSY, n (%)	72 (53.7%)	64 (53.7%)	72 (100%)	35 (68.6%)
IMAGING TECHNIQUES				
Positive CTA, n/n performed (%)	4/9 (44.4%)	4/9 (44.4%)	2/5 (40.0%)	3/5 (60.0%)
Positive PET/CT, n/n performed (%)	52/57 (91.2%)	43/47 (91.5%)	30/31 (96.8%)	46/46 (100%)
Positive MRA, n/n performed (%)	9/12 (75%)	8/11 (72.7%)	3/5 (60%)	2/4 (50%)
Patients with previous traditional DMARDs, n (%)	98 (73.1%)	85 (71.4%)	51 (70.8%)	42 (82.3%)
MTX, n (%)	94 (70.1%)	82 (68.9%)	51 (70.8%)	32 (62.7%)
AZA, n (%)	14 (10.4%)	14 (11.7%)	4 (5.5%)	6 (11.7%)
LFN, n (%)	9 (6.7%)	8 (6.7%)	2 (2.7%)	2 (3.9%)
CYC, n (%)	4 (2.9%)	3 (2.5 %)	2 (2.7%)	1 (1.9%)
HCQ/CQ, n (%)	2 (1.4%)	2 (1.6%)	-	1 (1.9%)
MMF n (%)	1 (0.7%)	1 (0.8%)	-	-
Patients with previous biologic therapy, n (%)	3 (2.2%)	4 (3.3%)	2 (2.7%)	1 (1.9%)
IFX, n (%)	2 (1.4%)	2 (1.6%)	1 (1.3%)	-
ETN, n (%)	1 (0.7%)	1 (0.8%)	1 (1.3%)	1 (1.9%)
RTX, n (%)	1 (0.7%)	1 (0.8%)	1 (1.3%)	-
ABA, n (%)	1 (0.7%)	1 (0.8%)	1 (1.3%)	-
CORTICOSTEROIDS AT TCZ ONSET				
Patients on corticosteroids, n (%)	129 (96.2%)	116 (97.4%)	69 (95.8%)	48 (94.1%)
Prednisone dose, mg/d	21.7±16.1	21.7 ±15.6	22.0 ±15.6	19.2 ±15.5

***** Cranial symptoms of giant cell arteritis plus large vessel vasculitis (LVV) by imaging techniques.

Abbreviatios: ABA: abatacept; ACR: American College of Rheumatology; AZA: azathioprine; CQ: cloroquine; CRP: C-reactive protein; CTA: computed tomography angiography; CYC: cyclophosphamide; ESR: erythrocyte sedimentation rate; ETN: etanercept; GCA: giant cell arteritis; HCQ: hydroxychloroquine; IFX: infliximab; LFN: leflunomide; LVV: large vessel vasculitis; MMF: mycophenolate mofetil; MRA: magnetic resonance angiography; MTX: methotrexate; n: number; PET/CT: positron emission tomography/computed tomography; PMR: polymyalgia rheumatica; RTX: rituximab; SD: standard deviation; TCZ: tocilizumab.

TABLE 2. Main outcome variables of 134 patients with refractory Giant Cell Arteritis with tocilizumab therapy.

	Baseline	**Month 1**	**Month 3**	**Month 6**	**Month 12**	**Month 24**	**Month 48**
	n= 134	**n= 132**	**n= 122**	**n= 99**	**n= 71**	**n= 39**	**n= 10**
Clinical improvement, %		93.9%	94.2%	90.9%	92.9%	100%	100%
(n/n available cases)		(124/132)	(119/122)	(97/99)	(66/71)	(39/39)	(10/10)
Laboratory improvement							
CRP (mg/dL), median [IQR]	1.7 [0.4-3.2]	0.11 [0.05-0.5]*	0.09 [0.02-0.3]*	0.09 [0.03-0.2]*	0.09 [0.02-0.19]*	0.1 [0.02-0.34]*	0.13 [0.09-0.47]*
(n/n available cases)	(131/134)	(98/132)	(110/122)	(92/99)	(67/71)	(39/39)	(10/10)
ESR (mm/1st/h), median [IQR]	33 [14.5-61]	6 [2-12]*	4 [2-7.5]*	4 [2-8]*	4 [2-8]*	6 [2-16]*	9 [3-22]*
(n/n available cases)	(129/134)	(102/132)	(116/122)	(93/99)	(71/71)	(39/39)	(10/10)
Hemoglobin (g/dL), mean (SD)	12.3±1.5	13.1±1.3*	13.3±1.3*	13.4±1.4*	13.3±1.4 *	13.1±1.3*	13.3±1.1*
(n/n available cases)	(125/134)	(104/132)	(107/122)	(88/99)	(64/71)	(36/39)	(9/10)
Anemia (<11.0 g/dL), **%**	16.4%	3.8%	4.9%	3.0%	4.2%	5.1%	0%
(n/n available cases)	(22/134)	(5/132)	(6/122)	(3/99)	(3/71)	(2/39)	(0/10)
Prolonged remission † %,				55.5%	70.4%	69.2%	90%
(n/n available cases)	-	-	-	(55/99)	(50/71)	(27/39)	(9/10)
Relapses ‡ %,		3.0%	5.8%	5.1%	14.1%	17.9%	10%
(n/n available cases)	-	(4/132)	(7/122)	(5/99)	(10/71)	(7/39)	(1/10)
Prednisone dose, median [IQR]	15 [10-30]	13.75 [7.5-20]*	8.1 [5-12.5]*	5 [2.5-7.5]*	2.5 [0.0-5]*	0.0 [0.0-5]*	2.5 [1.3-7.5]*
(n/n available cases)	(134/134)	(115/132)	(120/122)	(97/99)	(71/71)	(39/39)	(10/10)

Abbreviations (in alphabetical order): CRP: C-reactive protein (mg/dL); ESR: erythrocyte sedimentation rate (mm/1st hour); IQR: interquartile range; n: number;

*p <0.01 vs. baseline (Wilcoxon test).

† Prolonged remission: remission was considered by absence of clinical symptoms and signs and normalization of the acute phase reactants (CRP and ESR) for at least 6 months. ESR <20 or 25 mm/h (in men and women, respectively) and/or CRP <0.5 mg/dL were considered normal.

‡ At least one relapse during follow-up.

TABLE 3. Relevant adverse events observed in our series of 134 patients with refractory Giant Cell Arteritis in treatment with tocilizumab.

	TCZ withdrawal (n=21)		Reduction TCZ dose (n=11)
	Permanent (n=17)	**Transient (n=4)**	
INFECTIONS			
Cytomegalovirus (bilateral pneumonia)	1 (4.8%)	-	-
Endocarditis	1 (4.8%) *	-	-
Facial Herpes Zoster Infection †	-	2 (40.0%)	-
Bacterial Infective Bursitis †	-	1 (20.0%)	-
Severe Infectious Cellulitis †	-	-	1 (7.7%)
Infectious Meningitis	1 (4.8%)	-	-
Infected ulcer †	1 (4.8%)	-	-
Infected Necrotizing ulcer	1 (4.8%) *	-	-
Pneumonia	3 (14.3%)	-	-
Recurrent urinary infection and sepsis †	-	1 (20.0%)	1 (7.7%)
Urinary sepsis	1 (4.8%)	-	1 (7.7%)
Anal abscess ‡	-	1 (20.0%)	-
HEMATOLOGICAL ALTERATIONS §			
Bicytopenia (anemia grade III & leukopenia gr. III)	-	-	1 (7.7%)
Myelodysplastic syndrome	1 (4.8%)	-	-
Neutropenia grade IV	1 (4.8%)	-	3 (23.1%)
Leukopenia grade III	-	-	1 (7.7%)
Thrombocytopenia grade III	-	-	1 (7.7%)
NEOPLASIA		-	
Colon adenocarcinoma	1 (4.8%)	-	-
Lung cancer	1 (4.8%) *		
CARDIOVASCULAR		-	
Atrioventricular blockade	1 (4.8%)	-	-
Hypertensive crisis	1 (4.8%)	-	-
OTHERS		-	
Alzheimer´s disease	1 (4.8%)	-	-
Diverticulitis	-	-	1 (7.7%)
Liver toxicity	1 (4.8%)	-	3 (23.1%)
Myopathy	1 (4.8%)	-	-
Stroke	2 (9.5%) *		
Unexpected death	1 (4.8) *		

These data are of adverse events, six patients presented more than one side-effect.

* Causes of death

† Requiring hospitalization and intravenous antibiotics

‡ Requiring surgical drainage

§ Cytopenias grade III were classified if hemoglobin was < 7.9 g/dL, leucocytes < 1900/mm^3, and/or platelet count < 49000/mm^3. Neutropenia grade IV was considered if neutrophils < 500/mm^3.