Title: Real-world risk of relapse of giant cell arteritis treated with tocilizumab: A retrospective analysis of 43 patients

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Abstract

Objectives

Tocilizumab (TCZ), an IL-6 receptor antagonist, is approved for giant cell arteritis (GCA) as a cortisone-sparing strategy and in refractory patients. This study assessed the real-world efficacy, safety, and long-term outcomes of GCA patients treated with TCZ.

Methods

We conducted a multicenter retrospective observational study at three French centers. All patients ≥ 50 years, meeting the American College of Rheumatology (ACR) criteria, and had received at least one dose of TCZ were included. Relapse was defined by therapeutic escalation, such as increased doses of CS, resumption of CS after weaning, or introduction or intensification of adjuvant therapy.

Results

Between 2013 and 2019, 43 patients were included. Patients were followed-up in median 511 days between GCA diagnosis and inclusion with 34/43 (72%) patients experiencing relapses. At inclusion, median age was 77 years and median dose of corticosteroid (CS) was 15 mg/day. After inclusion, the mean cumulative dose of CS was 2.1g/year versus 9.4g/year before inclusion ($p<2.10^{7}$) with 12/43 (28%) patients experiencing relapses on TCZ. Among 29 patients undergoing TCZ discontinuation, 18 (62%) experienced relapse. Factors associated with relapse after inclusion were introduction of TCZ > 6 months after diagnosis (p=0,005), absence of ischemic signs at diagnosis (p=0,006), relapse rate >0.8/year (p=0.03) and absence of CS tapering ≤ 5 mg/day

(p=0,03) before inclusion. Serious adverse events occurred in 18/43 patients (42%), including four deaths.

Conclusion

Our results confirm the effectiveness of TCZ for CS-sparing, but after discontinuation of treatment, TCZ allows for a prolonged remission in less than 50% of patients. Attention must be paid to the tolerance of this long-term treatment in this elderly and heavily treated population.

Introduction

Giant cell arteritis (GCA) is a granulomatous vasculitis affecting large and intermediate sized blood vessels. It is the most common vasculitis in subjects aged > 50 years old (1). Corticosteroids (CS) are the standard treatment for this disease (1). However, relapse is common, with an overall relapse rate recently estimated at 47% in a meta-analysis (2). With cumulative doses of CS in studies reaching almost 10 g by the end of follow-up (3), 52.5–86% of elderly patients with GCA experience CS side effects (4). The development of CS-sparing therapy for the treatment of GCA is therefore a priority. To achieve this goal, methotrexate (MTX) has been used, which has shown moderate efficacy (1).

IL-6 plays a key role in the pathogenesis of GCA, and two trials on tocilizumab (TCZ), a humanized monoclonal IgG1 specifically targeting soluble and membranous IL6 (IL-6R), have demonstrated its remarkable efficacy in GCA and primary aortitis (PA), in particular in reducing the number of relapses and cumulative doses after one year of treatment (5, 6). Therefore, TCZ is the treatment of choice as a CS-sparing strategy and in refractory patients (7). Nevertheless, real-world data on the use of TCZ remain sparse, and no studies have assessed the long-term efficacy and safety of TCZ in these elderly patients. Two recent small observational studies reported that almost half of patients relapsed upon discontinuation of TCZ treatment, but no predictive factors for relapse have been identified (8, 9). Although data on the use of TCZ in rheumatoid arthritis are reassuring, a recent publication suggests a less favorable safety profile for older GCA patients and with intensive use of CS (10). Therefore, it is necessary to reevaluate the real-world tolerance of TCZ in GCA, with more refractory patients. Hence, in this study, we assessed GCA patients treated with TCZ.

Patients and Methods

We conducted a multicenter retrospective study at three hospitals in France. Data were collected from January to August 2019. All GCA or PA patients treated with TCZ since January 2013 were the subject of a medical records search to assess if they met the criteria of the study. All patients were screened from the hospital pharmacy registry or other clinical unit registry.

Patients had to be ≥ 50 years old at the time of diagnosis, have received at least one TCZ injection, and meet ACR criteria (11) defining GCA or PA according to criteria recognized by the radiology and nuclear imaging community (12, 13). Patients whose initial data were missing were not included in the study, nor were those whose follow-up after introduction of TCZ was < 6 months. For patients who were no longer being followed at the clinical center, the attending physician was contacted to collect all of the missing information until the last follow-up.

The date of diagnosis was defined as the first day of CS therapy. The date of inclusion in the study was defined as the first day of TCZ treatment. The duration of the first treatment was defined as between the first injection and 4 weeks (intravenous, IV) or 1 week (subcutaneous, SC) after voluntary discontinuation. Therapeutic breaks < 3 months, particularly for infectious reasons or surgical procedures and mentioned as such, were not considered an end of treatment.

A relapse was defined as therapeutic escalation, such as increased doses of CS, resumption of CS after weaning, or introduction or intensification of adjuvant therapy. A major relapse was defined according to the latest European guidelines (7). Response to treatment was complete if all clinical signs disappeared in the first month after therapy introduction. Serious adverse events (including severe infections) and causes of death were recorded during follow-up. Reasons for TCZ

introduction could be CS dependence, CS toxicity or primary prevention according to the physician's motivation to introduce the treatment.

In order to assess the spacing or reduction of doses of TCZ performed in real life, we measured the daily dose of TCZ received by calculating the ratio between the dose received by the number of days between the injections. The SC dose/day was weighted by its bioavailability (79.5%) (14).

Given the retrospective and observational methodology of the study, no specific patient consent was collected, and no ethics board approval was required in accordance with French laws.

Statistical analyses

The results are expressed as means and confidence intervals (CIs) or median and interquartile range (IQR) according to the relevance for each situation. The Student's paired t-test was used to compare continuous variables before and after inclusion. To identify risk factors for relapse in univariate analyses, the Fisher's exact test was used, with the odds ratio calculation, where the confidence interval is given by the Baptista-Pike method. Relapse-free survivals were summarized by means of Kaplan–Meier curves and groups were compared with the log-rank test. The analyses were performed using the Prism 8 software (Prism version 8.20 for MacOS, GraphPad Software, La Jolla California USA, www.graphpad.com).

Results

Diagnostic data

A total of 43 patients (35 female, 81%) were considered, including 37 with GCA and 6 with PA. The date of initial diagnosis ranged from May 2007 to January 2019. The median age at diagnosis was 76 years (IQR [67-81]). All 37 ACG patients met the ACR criteria. For 18 of the patients for whom imaging was performed, 10/18 (56%) had aortitis. 34/37 (92%) patients had at least one imaging test or temporal arterial biopsy (TAB) supporting the diagnosis. The main manifestations at diagnosis were asthenia 29/43 (67%), headache 28/43 (65%), scalp tenderness 18/43 (42%) and weight loss 16/43 (37%). The CRP median at diagnosis was 89 mg/l (IQR [44-143]). Corticosteroid therapy was started at a median dose of 50 mg/day (IQR [40-60]). The main clinical and laboratory characteristics of the patients are summarized in table 1.

Data from diagnosis to initiation of TCZ

Before study inclusion, patients were followed for a median of 511 days (IQR [143–1292]), (95 person-years). For 31/43 (72%) patients, adjuvant therapy was started during this period, including for 26 (60%) with methotrexate. Overall, 26/43 (60%), 21/43 (49%), and 11/43 (26%) patients received CS doses < 10 mg, ≤ 5 mg, or achieved complete withdrawal before inclusion, with a median to achieve these goals of 340 days, 506 days, and 792 days respectively. The media cumulative doses to achieve these goals were 8.1g, 10.2g, and 9.6g, respectively.

Before inclusion, 79 relapses were recorded (including 6 major relapses) in 34 (79%) patients, with an average of 1.26 relapse/year (95% CI [0.79–1.73]). Of these, the main clinical findings during relapse were PMR (34/79 (33%)) and headache (30/79 (29%)), and the median level of C-reactive protein (CRP) was 26 mg/L (IQR [17–43]). The mean cumulative dose per year of CS was 9.4 g/year (95% CI = [6.9–12.0]), and the total cumulative dose was 11.5 g (95% CI [8.9-14.2]).

Data at inclusion (introduction of TCZ treatment)

On the day of the first administration of TCZ, all patients were on CS with a median dose of 15 mg/day (IQR [10–29]). The reasons for the introduction of TCZ were CS dependence in 32 patients (74%), CS toxicity in 7 patients (16%; 4 neuropsychiatric effects, 2 diabetes decompensations, 1 osteonecrosis), and primary prevention of CS adverse effects in 4 (9%).

TCZ was started via SC access in 4 patients and IV in 39 patients.

Data after inclusion (after TCZ initiation)

Patients were followed for a median of 842 days (IQR [568–1434]) (112 person-years). The mean cumulative CS was 2.1 g/year (95%CI = [1.5–2.7]); ($p < 2x10^{-7}$ when compared to the first phase of treatment) and the total cumulative dose was 4.2 g (95% CI [1.5 to 5.2]).

In a subgroup of 10 patients for whom TCZ treatment was started early in the first 90 days of the disease, cumulative CS doses after inclusion averaged 2.92 g/year.

Patients received a median of 17.4 mg/day of TCZ at the start of treatment (IQR [14.4-19.5]). At 12 months and 18 months, 23 patients and 9 were still on TCZ, at 11.7 mg/day (IQR [8.9-18.3]) and 11.3 mg/day (IQR [8.3-17.3]), respectively. The doses at 12 and 18 month were significantly decreased compared to the initial dose ($p <0.01$, $p <0.02$). Concretely, 12/23 and 5/9 patients had a decreased dose at 12 and 18 month.

At inclusion, all patients were treated with CS including 39 with CS > 5 mg/day and 28 with CS > 10 mg/day. At the final follow-up, all of the 28 patients' ≥ 10 mg/day of CS were tapered < 10 mg for a median of 81 days, 37 of the 39 patients' > 5 mg/day of CS were tapered ≤ 5 mg for a median of 129 days, and 26 of the 43 patients treated discontinued CS for a median of 279 days. There was no difference in the risk of relapse according to the capacity to quickly reduce the dose of CS or not: 15/27 patients relapsed if CS was reduced to 5 mg within 6 months, versus 11/16 if not, OR = 0.57 (CI 95%[0.12-2.44], p=0,52).

During follow-up, 12 patients (28%) received MTX in addition to TCZ and CS.

A total of 26 patients (60%) experienced at least one relapse during follow-up after inclusion: 14 patients relapsed after stopping TCZ, 8 still treated with TCZ and 4 during both periods.

Overall, we observed 47 relapses (including 7 major relapses), representing 0.44 relapse/year (95% CI [0.25–0.62]), ($p < 6x10^{-4}$ compared to the period before inclusion). The median time to onset of a first relapse was 310 days (IQR [242–498]).

Twenty-four relapses were recorded on TCZ and 23 after TCZ discontinuation. Regarding the 24 relapses on TCZ, the patients had a median of 5 mg of CS (IQR [1-8]) and 8/24 (33%) relapses occurred when TCZ dose was reduced ; 13/24 maintained the same doses of CS but the dose of TCZ was increased; 11/24 undergoing an increase in the dose of CS of +5 mg (IQR [+3.5-+29]). Regarding the 23 relapses during periods of TCZ withdrawal, the patients had a median of 0 mg of CS (IQR [0-4.5]). The CS doses were increased for 17/23 relapses by a median of +6 mg (IQR [+2-+21]), and the TCZ was restarted for 11/23 relapses. All these measures made it possible to control relapses.

The main characteristics of relapses before inclusion, after inclusion on TCZ and after inclusion when TCZ was stopped are summarized in table 2.

Concerning the 6 AP patients, 5/6 relapsed after the introduction of TCZ, with a median incidence of relapses at 0.95/year of follow-up. Of the 18 relapses recorded in these patients, 11 presented constitutional symptoms or PMR, and the other seven relapses, of which five under TCZ were related to elevated inflammatory marker.

After inclusion, we noted that CRP levels at relapse were 10 mg/L (IQR [2.5–63]) for patients still on TCZ and 42 mg/L (IQR [18–54]) for relapses after TCZ discontinuation. Among 14 relapses on TCZ with increased CRP level, 7 (50%) occurred when TCZ dose was reduced versus 1/7 (14 %) relapses with low CRP level occurred when TCZ dose was reduced. For 3 relapses on TCZ, CRP measurement was missing.

Outcomes after discontinuing TCZ

A total of 29 patients were observed after discontinuing TCZ. The median duration before discontinuation was 355 days (IQR [219–507]). The median duration of observation after TCZ discontinuation was 495 days (IQR [220–1083]). The reason for TCZ discontinuation was planned in 23 (79%) cases, toxicity in 5 (17%) cases, and treatment failure in 1 (4%) case. Effects that led to the discontinuation of TCZ were cutaneous vasculitis (2), severe infection (2) and renal cancer with rapid growth.

After TCZ discontinuation, 23 relapses (with 4 major events) were recorded among 18 patients (62%), after a median time of 110 days (IQR [77–163]) and a maximum of 1112 days. The median dose of CS at relapse was 0 mg (IQR [0–4.5]).

At the final follow-up, among the 43 initial patients, 14 had not discontinued TCZ after a median time of 647 days (IQR 430–845), and 14 others had discontinued TCZ and remained off TCZ after a median time of 350 days (IQR: 219–507). The other 15 patients had discontinued TCZ at least once, but had to restart because of relapse (of which 11 were still on TCZ and only 4 were no longer being treated at the final follow-up).

Risk factors for relapse

Of the factors studied in univariate analyses, four were identified as increasing the risk of relapse after inclusion (TCZ introduction): absence of ischemic signs (jaw claudication, peripheral arterial disease, superficial signs of temporal artery injury, scalp tenderness or necrosis, blindness) at the initial clinical presentation (OR = 13.7 [1.7–150], p = 0.006), relapse before TCZ > 0.8/year (OR = 4.5 [1.3–16.7], p = 0.03), absence of tapering ≤ 5 mg CS for patients treated at least 6 months before inclusion (OR NR [1.6–NR], p = 0.03), and introduction of TCZ > 6 months after diagnosis (OR = 8.6 [1.8–33], p = 0.005).

The presence of two or more of these four criteria was associated with a hazard ratio (HR) for relapse of 6.3 (95% CI [2.8–14], p = 0.0006) after introduction of TCZ (Figure 1A).

We extrapolated this risk assessment to the period after TCZ discontinuation for 29 patients, with an HR to relapse of 6.0 (95% CI [2.3–15.7], p = 0.006) (Figure 1B).

Safety

Before inclusion, treatment-related adverse events were found in 36/43 (84%) of patients, including 8 (19%) with severe adverse events (SAE): 3 severe infections, 3 osteoporotic fracture, 1 osteonecrosis and 1 cardiovascular event.

After inclusion, adverse events related to CS and/or TCZ occurred in 41 (95%) patients, including 18 (42%) with SAE (4 leading to death: 3 from severe infection and 1 from renal cancer). Among the 18 patients with SAE we recorded 8 (19%) severe infections, 10 (7%) osteoporotic fracture, 2 (5%) grade III or IV neutropenia, 1 (2%) osteonecrosis, 1(2%) cardiovascular event, 1 (2%) grade III thrombocytopenia and 1 (2%) fast-growing renal cancer (table 3).

Discussion

In this retrospective study, we obtained long-term follow-up data, with patients having been observed for > 6 years after introduction of TCZ).

Patients included in this cohort were particularly difficult to treat since 74% of them were CS-dependent and had received an average of 9.4 g/year of CS. For comparison, in the GiACTA trial, only 53% of patients were CS-dependent (6).

CS-dependence in the latest European recommendations remains the main indication for the introduction of TCZ which probably explains this proportion of patients (7). However, in our cohort, we noticed for the 10 patients for whom treatment with TCZ was started early in the

diseases course, a benefit on the cumulative doses of CS, with an average of only 2.92 g/year during follow-up after initiation of TCZ.

The results confirm the efficacy of TCZ for decreasing the risk of relapse in heavily treated patients, with an incidence of relapse three times lower in patients when treated with TCZ. However, more than 30% of patients experienced relapse (including major relapses) while on TCZ treatment, a prevalence higher that in the GiACTA cohort (24%) with a shorter period of follow-up. An observational study reported only 7/39 (17.9%) patients relapsing in 2 years, but that could be explained by their definition of relapse, which implied only an increase in CRP level (15).

Since the TCZ dosing was not standardized, we acknowledge that the TCZ dosing and strategy may impact the prognosis and the flare rates on and after TCZ. Strategies with a progressive dose reduction of TCZ before stopping have already been tested prospectively with reassuring results in terms of prognosis without any relapse after 1 year of treatment (16).

Our study also confirms the real-world CS-sparing effect of TCZ, with yearly doses of CS dramatically reduced after introduction from 9.4 g/year to 2.1 g/year. A progressively favorable course of the disease by itself may also play a role in promoting decreases in cumulative doses of CS.

The CRP level during relapse in patients treated with TCZ was normal in 8 out of 20 cases (40%). Although CRP is a poor marker for identifying relapses during TCZ treatment, it was eventually increased in > 60% of our cohort. This can be partly explained by the real-world use of lower-dose TCZ (spacing of injections, decreased doses injected), allowing CRP elevation during relapse. We

therefore insist on maintaining the monitoring of this marker under TCZ, especially when infusion are spaced or when doses of infusion are reduced.

Of the 29 patients seen after TCZ discontinuation, we documented 23 relapses in 18 patients (62%). This is slightly higher than reports from smaller cohorts addressing this question (8, 9).

The early onset of relapse upon discontinuation of treatment is, for many authors, proof that TCZ is only a suspensive treatment. We think that only a subgroup at risk could relapse after TCZ discontinuation. We identified four factors associated with an increased risk of relapse after TCZ introduction: no ischemic signs at diagnosis, introduction of TCZ > 6 months, relapse rate > 0.8/year, and inability to wean patients < 5 mg CS. The late introduction of TCZ as a risk factor for relapse has already been identified by others (8). The last three factors are clearly associated with CS dependence.

The absence of ischemic signs at diagnosis as a risk factor for relapse is an interesting finding. In the absence of the possibility of an in-vitro evaluation of T-immune response in this retrospective study, we tried to establish groups of patients based on clinical criteria, to study the risk depending on whether the patients have a stronger Th1 or a Th17 immune response, a method which remains exploratory. We relied on the works by Conway and Weyand, establishing that the ischemic manifestations are associated to an exacerbated Th1 immune response and that the constitutional / PMR manifestations are associated to an exacerbated Th17 immune response (17, 18). Our indirect conclusion is therefore that, after introduction of TCZ, patients presenting a clinical pattern for a stronger Th17 response (absence of ischemic signs) are more at risk of relapses. To our knowledge,

we do not have an identical analysis in the literature that was searched for clinical profiles at risk of relapse.

Finally, by combining these four factors, we identified patients with a high risk of relapse (≥2 factors) after TCZ introduction and more particularly after its discontinuation.

Long-term safety is also challenging in elderly people. In our cohort, 18/43 (42%) of patients experienced serious adverse events, including 8 (19%) with serious infections; also, 3 patients died of sepsis. This is consistent with a previous study that suggested a higher rate of severe infection in older patients with GCA versus those with rheumatoid arthritis (10). The high prevalence of severe adverse events, particularly severe infections, seems to be closely related to the characteristics of our population, heavy pre-treated, since the GiACTA cohort found a trend toward less toxicity with TCZ. Some authors also found that sever infections on TCZ are correlated with high dose of CS (10, 15).

This exploratory work is intended to provide additional insights to guide research. We acknowledge that our study had some limitations, notably related to its retrospective design. Our results came from a small cohort of patients which limits both the power of the results obtained and the interpretation that can be made of the results. Followed patients came from only three centers in France, which limits the applicability internationally, although patients are followed as closely as possible to national and European recommendations, particularly as regards the prevention of infectious risks. Finally, some risk factors of relapse were determined post hoc, which limits the level of evidence for the results.

Conclusions

Our results confirm the effectiveness of TCZ for CS-sparing, as well as a decrease in the number of relapses in a particularly refractory population. However, after discontinuation of treatment, TCZ allows for prolonged remission in less than 50% of patients. This study clearly identified factors predicting the risk of relapse while undergoing TCZ treatment and after its discontinuation. To note, level of CRP under TCZ, at the time of relapse, in real life, remains increased in most cases. Finally, attention must be paid to the tolerance of this long-term treatment in this elderly population, particularly in refractory patients, who are already heavily treated.

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Table 1: Characteristics of the patients at diagnosis of Giant cell arteritis or primary aortitis.

Table 1 was uploaded as separate files.

TAB, temporal artery biopsy; TAD, temporal artery Doppler

Ischemic signs: jaw claudication, peripheral arterial disease, superficial signs of temporal artery injury, scalp tenderness or necrosis, blindness

Table 2: Main characteristics of giant cell arteritis or aortitis relapses before inclusion, after inclusion on TCZ and after inclusion when TCZ was discontinuated.

Table 2 was uploaded as separate files.

CS: Corticosteroids; MTX: Methotrexate; CRP: C-Reactive Protein; TCZ: Tocilizumab, PMR : polymyalgia rheumatica

Table 3: Adverse events recorded before and after tocilizumab start

Table 3 was uploaded as separate files.

Figure 1: Kaplan-Meier curve for relapse-free survival after inclusion (A) and after TCZ discontinuation (B) according to number of identified risk factors.

Figure 1 was uploaded as separate files.

Legend:

HR: hazard ratio (log-rank test)

Continuous-line: patient with ≤ 1 risk factor

Dotted-line: patient whit ≥ 2 risk factors.

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Table 1.

	Median (IQR)	n (%)
Epidemiologic characteristics		
Women		35 (81)
Age (y)	76 (67–81)	
Weight (kg)	63 (56–70)	
Clinical signs, biology and comorbidities		
Weakness		29 (67)
Headache		28 (65)
Scalp tenderness		18 (42)
Weight loss		16 (37)
Jaw claudication		16 (37)
Polymyalgia rheumatica		15 (35)
Fever		13 (30)
Anterior ischemic optic neuropathy		4 (9)
No ischemic signs		13 (30)
Cholestasis		10 (23)
Hemoglobin (g/dL)	11.5 (10.2–12.2)	
Platelet count (10^9/L)	361 (285–463)	
CRP (mg/L)	89 (44–143)	
Charlson Comorbidity Index	1 (0–2)	
Comorbidities	Rheumatic disease, n=19 Chronic pulmonary disease, n=5 Renal disease, n = 5 Malignancy n = 6	Congestive heart failure, n=2 Stoke, n = 2 Dementia, n = 2 Diabetes, n =2

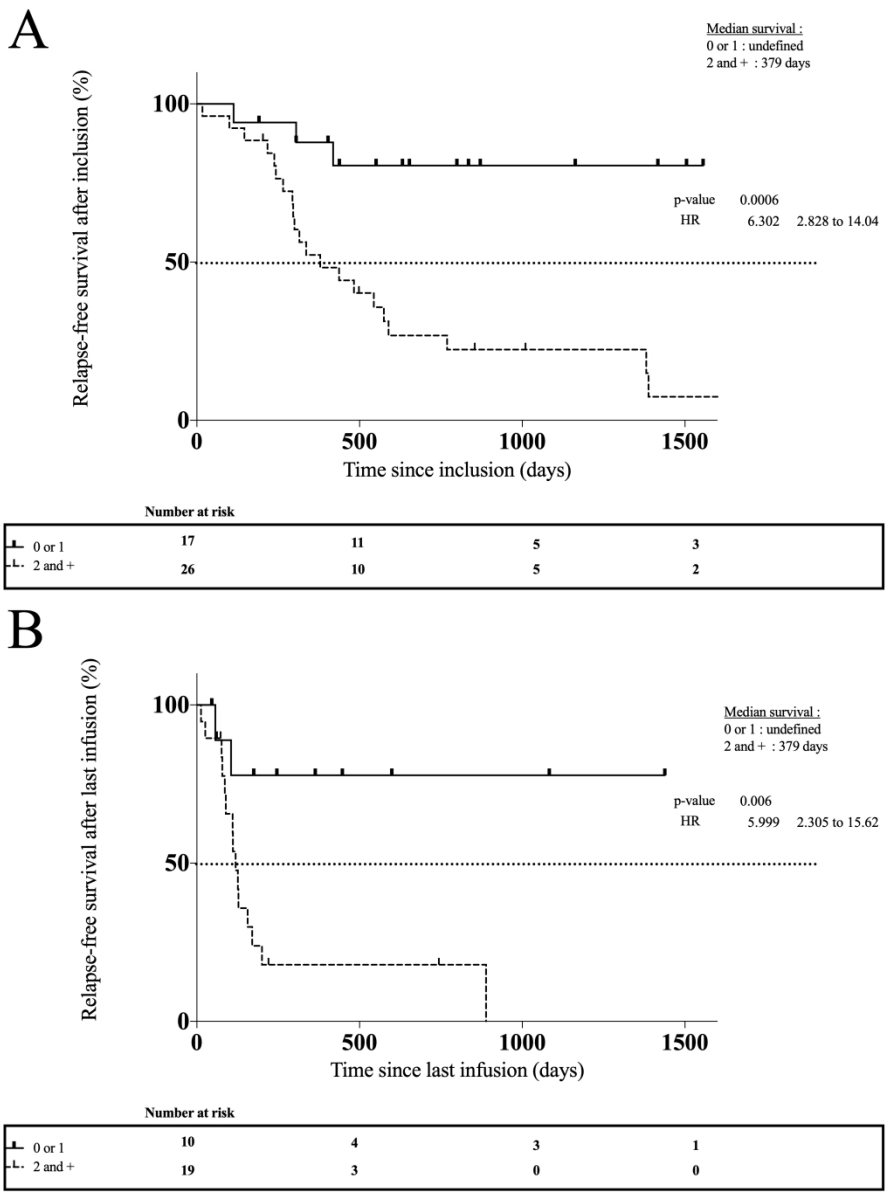
High and very high cardiovascular risk		14 (33)
Diagnosis		
Giant Cell Arteritis		37 (86)
Positive TAB		22/29 (76)
Positive TAB or TAD		30/36 (83)
Positive TAB or TAD or aortitis on imaging		34/37 (92)
ACR criteria = 3		19/37 (51)
ACR criteria = 4		12/37 (33)
ACR criteria = 5		6/37 (16)
Primary Aortitis		6 (14)
Corticosteroid treatment		
Prednisone use		42/43 (98)
Initial dose (mg)	50 (40–60)	
Initial dose/weight (mg/kg)	0.82 (0.71–0.98)	
Initial bolus use		6 (14)
Initial complete response to corticosteroids		40/43 (95)

Table 2.

	Relapses before inclusion n = 79, 34 patients	**Relapses after inclusion on TCZ n = 24, 12 patients**	**Relapse after inclusion and TCZ discontinuation n = 23, 18 patients**
median dose of CS (mg/day)	8 (IQR [5-15])	5 (IQR [1-8])	0 (IQR [0-4,5])
MTX using when relapse occurred	21/79 (26%)	3/24 (12%)	3/23 (13%)
CRP level (mg/l)	26 (IQR [17-43])	10 (IQR [2,5-63,5])	42 (IQR [18-54])
Main Manifestations	PMR, 34/79 (33%) Headaches, 30/79 (29%)	Weackness, 6/24 (25%) Headaches, 6/24 (25 %) PMR, 5/24 (21%)	PMR, 10/23 (43%) Headaches 9/23 (39%)
Major events	6/79 (8%)	3/24 (12%)	4/23 (17 %)
median increase in dose of CS (mg/day)	+ 7 (IQR [+2-+10]).	+ 0 (IQR [+0-+5]).	+6 (IQR [+2-+21])

Table 3.

Adverse event n (%)	**Before inclusion** Median follow-up: 511 days (IQR [143-1292])	**After inclusion** Median follow-up: 842 days (IQR [568-1434])
Corticotropin deficiency	0 (0)	10 (23)
Hypertension	10 (23)	6 (14)
Diabetes	11 (26)	3 (7)
Central Obesity	18 (42)	1 (2)
Myopathy	9 (21)	3(7)
Osteoporotic Fracture	3 (7)	10 (23)
Osteonecrosis	1 (2)	1 (2)
Peptic Ulcer	2 (5)	0 (0)
Mood Change	17 (40)	1 (2)
Cataract	7 (16)	4 (9)
Cardiovascular event	1 (2)	1 (2)
Infection	15 (35)	29 (67)
Severe Infection	3 (7)	8 (19)
Neutropenia	0 (0)	10 (23)
Grade I/II	0 (0)	8
Grade III/IV	0 (0)	2
Thrombopenia	0 (0)	6 (14)
Aminotranferases increase	0 (0)	2 (5)
Other	0 (0)	8 (19) *Headaches (2)* *Digestive Disorders (2)* *Cuteneous Vascultis (2)* *Renal Cell Carcinoma(1)* Aphthous Ulcers *(1)*



Kaplan-Meier curve for relapse-free survival after inclusion (A) and after TCZ discontinuation (B) according to number of identified risk factors.