The Journal of Rheumatology 2021;xx:xxxx
doi:10.3899/jrheum.200952
First Release June 1 2021

The Journal of Rheumatology

Real-world Risk of Relapse of Giant Cell Arteritis Treated With Tocilizumab: A Retrospective Analysis of 43 Patients

Jérémy Clément[1], Pierre Duffau[2], Joel Constans[3], Thierry Schaeverbeke[4], Jean-Francois Viallard[5], Damien Barcat[6], Jean-Philippe Vernhes[7], Laurent Sailler[8], and Fabrice Bonnet[9]

ABSTRACT. ***Objective.*** Tocilizumab (TCZ), an interleukin 6 (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 patients with GCA treated with TCZ.

Methods. We conducted a multicenter retrospective observational study at 3 French centers. All patients aged ≥ 50 years who met the American College of Rheumatology (ACR) criteria, and had received at least 1 dose of TCZ were included. Relapse was defined by therapeutic escalation, such as increased doses of corticosteroids (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 for a median 511 days between GCA diagnosis and inclusion, with 34/43 (79%) patients experiencing relapses. At inclusion, median age was 77 years, and median dose of CS was 15 mg/day. After inclusion, the mean cumulative dose of CS was 2.1 g/year vs 9.4 g/year before inclusion ($P < 2 \times 10^{-7}$), with 12/43 (28%) patients experiencing relapses on TCZ. Among 29 patients undergoing TCZ discontinuation, 18 (62%) experienced relapses. 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 4 deaths.

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

Key Indexing Terms: aortitis, giant cell arteritis, tocilizumab

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.[1] Corticosteroids (CS) are the standard treatment for this disease.[1] However, relapse is common, with an overall rate estimated at 47% in a recent metaanalysis.[2] With cumulative doses of CS reaching almost 10 g by the end of follow-up in studies,[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 and has shown moderate efficacy.[1]

Interleukin 6 (IL-6) plays a key role in the pathogenesis of GCA, and 2 trials on tocilizumab (TCZ), a humanized monoclonal IgG1 specifically targeting soluble and membranous IL-6 receptor, have demonstrated its remarkable efficacy in GCA and primary aortitis (PA), in particular in reducing the number of relapses and cumulative doses after 1 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 (RA) are reassuring, a recent publication suggests a less favorable safety profile for older patients with GCA 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 patients with GCA treated with TCZ.

[1]J. Clément, MD, CHU de Bordeaux, Service de Médecine Interne et Maladies Infectieuses, Bordeaux; [2]P. Duffau, MD, PhD, CHU de Bordeaux, Service de Médecine Interne, Bordeaux; [3]J. Constans, MD, PhD, CHU de Bordeaux, Service de Médecine Vasculaire, Hôpital Saint-André, Bordeaux; [4]T. Schaeverbeke, MD, PhD, CHU de Bordeaux, Service de Rhumatologie, Bordeaux; [5]J.F. Viallard, MD, PhD, CHU de Bordeaux, Service de Médecine Interne et Maladies Infectieuses, Hôpital Haut-Lévêque, Pessac; [6]D. Barcat, MD, CH de Libourne, Service de Médecine Interne, Libourne; [7]J.P. Vernhes, MD, CH de Libourne, Service de Rhumatologie, Libourne; [8]L. Sailler, MD, PhD, CHU de Toulouse, Département de Médecine Interne, Toulouse; [9]F. Bonnet, MD, PhD, CHU de Bordeaux, Service de Médecine Interne et Maladies Infectieuses, Hôpital Saint-André, Bordeaux, and Université de Bordeaux, INSERM U1219, Bordeaux Population Health Research Center, Bordeaux, France.

The authors declare no conflicts of interest.

Address correspondence to Dr. F. Bonnet, Service de Médecine Interne et Maladies Infectieuses, Hôpital Saint-André, CHU de Bordeaux, 1 rue Jean Burguet, 33075 Bordeaux, France. Email: fabrice.bonnet@chu-bordeaux.fr.

Accepted for publication January 26, 2021.

METHODS

We conducted a multicenter retrospective study at 3 hospitals in France. Data were collected from January to August 2019. A medical records search was conducted for all GCA or PA patients treated with TCZ since January 2013 to determine if they met the study criteria. All patients were screened from the hospital pharmacy registry or other clinical unit registry.

Inclusion criteria were age ≥ 50 years at the time of diagnosis, having at least 1 TCZ injection, and meeting the American College of Rheumatology (ACR) criteria[11] for GCA or meeting criteria recognized by the radiology and nuclear imaging community fo PA.[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 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 the first day of TCZ treatment. The duration of the first treatment was defined as the time 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, were not considered 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 introduction of therapy. Serious adverse events (SAEs; 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.

In order to assess the spacing or reduction of doses of TCZ performed in real life, we measured the daily TCZ dose 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 mean and CI, or median and IQR, according to the relevance for each situation. The paired *t* test was used to compare continuous variables before and after inclusion. To identify risk factors for relapse in univariate analyses, the Fisher exact test was used, with the OR calculation, where the CI 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).

RESULTS

Diagnostic data. The date of initial diagnosis ranged from May 2007 to January 2019. The main clinical and laboratory characteristics of the patients are summarized in Table 1. A total of 43 patients (35 female, 81%) were considered, including 37 with GCA and 6 with PA. All 37 patients with GCA met the ACR criteria. Of the 18 patients for whom imaging was performed, 10 (56%) had aortitis. Of the 37 patients with GCA, 34 (92%) had at least 1 imaging test or temporal arterial biopsy supporting the diagnosis. The median age at diagnosis for the entire cohort was 76 years (IQR 67–81). Among the 43 patients, the main manifestations at diagnosis were asthenia (29, 67%), headache (28, 65%), scalp tenderness (18, 42%), and weight loss (16, 37%). The median C-reactive protein (CRP) 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 [PY]). For 31 (72%) patients, adjuvant therapy was started during this period, including 26 (60%) with MTX. Overall, 26 (60%), 21 (49%), and 11 (26%) patients received CS doses < 10 mg, CS ≤ 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 median cumulative doses to achieve these goals were 8.1 g, 10.2 g, and 9.6 g, respectively (data not shown).

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 polymyalgia rheumatica (PMR; 34/79, 43%) and headache (30/79, 38%), and the median level of CRP was 26 mg/L (IQR 17–43; Table 2). 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 through SC access in 4 patients and IV in 39 patients (data not shown).

Data after inclusion (after TCZ initiation). Patients were followed for a median of 842 days (IQR 568–1434, 112 PY). The mean cumulative CS was 2.1 g/year (95% CI 1.5–2.7, $P < 2 \times 10^{-7}$) when compared to the first phase of treatment, and the total cumulative dose was 4.2 g (95% CI 1.5–5.2; data not shown).

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 patients 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 months and 18 months were significantly decreased compared to the initial dose ($P < 0.01$, $P < 0.02$). Specifically, 12/23 and 5/9 patients had a decreased dose at 12 months and 18 months.

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 28 patients taking CS ≥ 10 mg/day were tapered < 10 mg for a median of 81 days, and 37 of the 39 patients taking CS > 5 mg/day were tapered ≤ 5 mg for a median of 129 days; 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, vs 11/16 if CS dose was not reduced (OR 0.57, 95% CI 0.12–2.44, $P = 0.52$).

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

Table 1. Characteristics of the patients at diagnosis of giant cell arteritis or primary aortitis (n = 43).

	Median (IQR)	n (%)
Demographics		
Women		35 (81)
Age, yrs	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[a]		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), stroke (n = 2), dementia (n = 2), diabetes (n = 2)
CV risk (high and very high)		14 (33)
Diagnosis		
Giant cell arteritis		37 (86)
Positive TAB		22/29 (76)
Positive TAB/TAD		30/36 (83)
Positive TAB/TAD/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)

[a] Ischemic signs: jaw claudication, peripheral arterial disease, superficial signs of temporal artery injury, scalp tenderness or necrosis, blindness. ACR: American College of Rheumatology; CRP: C-reactive protein; CV: cardiovascular; TAB: temporal artery biopsy; TAD: temporal artery Doppler.

A total of 26 patients (60%) experienced at least 1 relapse during follow-up after inclusion: 14 patients relapsed after stopping TCZ, 8 were still being treated with TCZ, and 4 during both periods. Overall, we observed 47 relapses (including 7 major relapses), representing 0.44 relapses/year (95% CI 0.25–0.62, $P < 6 \times 10^{-4}$) compared to the period before inclusion. The median time to onset of a first relapse was 310 days (IQR 242–498).

The main characteristics of relapses before inclusion, after inclusion on TCZ, and after inclusion when TCZ was discontinued are summarized in Table 2. 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. 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, and TCZ was restarted for 11/23 relapses. All these measures made it possible to control relapses.

Concerning the 6 PA 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; the other 7 relapses were related to elevated inflammatory markers (5 of them were on TCZ).

After inclusion, we noted that CRP levels at relapse were

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

	Relapses Before Inclusion, n = 79 (34 Patients)	Relapses After Inclusion on TCZ, n = 24 (12 patients)	Relapses After Inclusion and TCZ Discontinuation, n = 23 (18 patients)
CS dose, mg/d, median (IQR)	8 (5–15)	5 (1–8)	0 (0–4.5)
MTX using when relapse occurred, n/N (%)	21/79 (27)	3/24 (13)	3/23 (13)
CRP level, mg/L, median (IQR)	26 (17–43)	10 (2.5–63.5)	42 (18–54)
Main manifestations, n/N (%)	PMR, 34/79 (43) Headaches, 30/79 (38)	Weakness, 6/24 (25) Headaches, 6/24 (25) PMR, 5/24 (21)	PMR, 10/23 (43) Headaches, 9/23 (39)
Major events, n/N (%)	6/79 (8)	3/24 (13)	4/23 (17)
Increase in CS dose, mg/d, mean (IQR)	7 (2–10)	0 (IQR 0–5)	6 (IQR 2–21)

CRP: C-reactive protein; CS: corticosteroids; MTX: methotrexate; PMR: polymyalgia rheumatica; TCZ: tocilizumab.

10 mg/L (IQR 2.5–63.5) 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 levels, 7 (50%) occurred when TCZ dose was reduced, vs 1/7 (14%) relapses with low CRP level that occurred when TCZ dose was reduced. For 3 relapses on TCZ, CRP measurements were 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 the end of treatment plan 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.

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, 4 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, 95% CI 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 not reported [NR], 95% CI 1.6–NR, $P = 0.03$), and introduction of TCZ > 6 months after diagnosis (OR 8.6, 95% CI 1.8–33, $P = 0.005$; data not shown).

The presence of 2 or more of these 4 criteria was associated with an 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 2.3–15.6, $P = 0.006$; Figure 1B).

Safety. Before inclusion, treatment-related adverse events (AEs) were found in 36/43 (84%) patients, including 8 (19%) with severe AEs (SAEs): 3 severe infections, 3 osteoporotic fractures, 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 (23%) osteoporotic fractures, 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 in patients 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 dose of 9.4 g/year, compared to the Giant-Cell Arteritis Actemra (GiACTA) trial, where only 53% of patients were CS-dependent.[6]

According to the latest European recommendations,[7] CS dependence remains the main indication for the introduction of TCZ; this probably explains we included more CS-dependent patients in our real-world cohort of patients than in the GiACTA cohort. However, in our cohort, we noticed that for 10 patients for whom treatment with TCZ was started early in the disease course, there was a benefit on the cumulative doses of CS, with an average of only 2.92 g/year during follow-up.

The results confirm the efficacy of TCZ for decreasing the risk of relapse in heavily treated patients, with an incidence of relapse 3-times lower in patients when treated with TCZ. However, 28% of patients experienced relapse (including major relapses) while on TCZ treatment, a prevalence higher than in the GiACTA cohort (24%), but with a much longer period of follow-up for our cohort. An observational study reported only 7/39 (18%) patients relapsing in 2 years, but that could be explained by their definition of relapse, which implied an increase only in CRP levels.[15]

Since the TCZ dosing was not standardized, we acknowledge that the TCZ dosing and strategy may affect the prognosis and

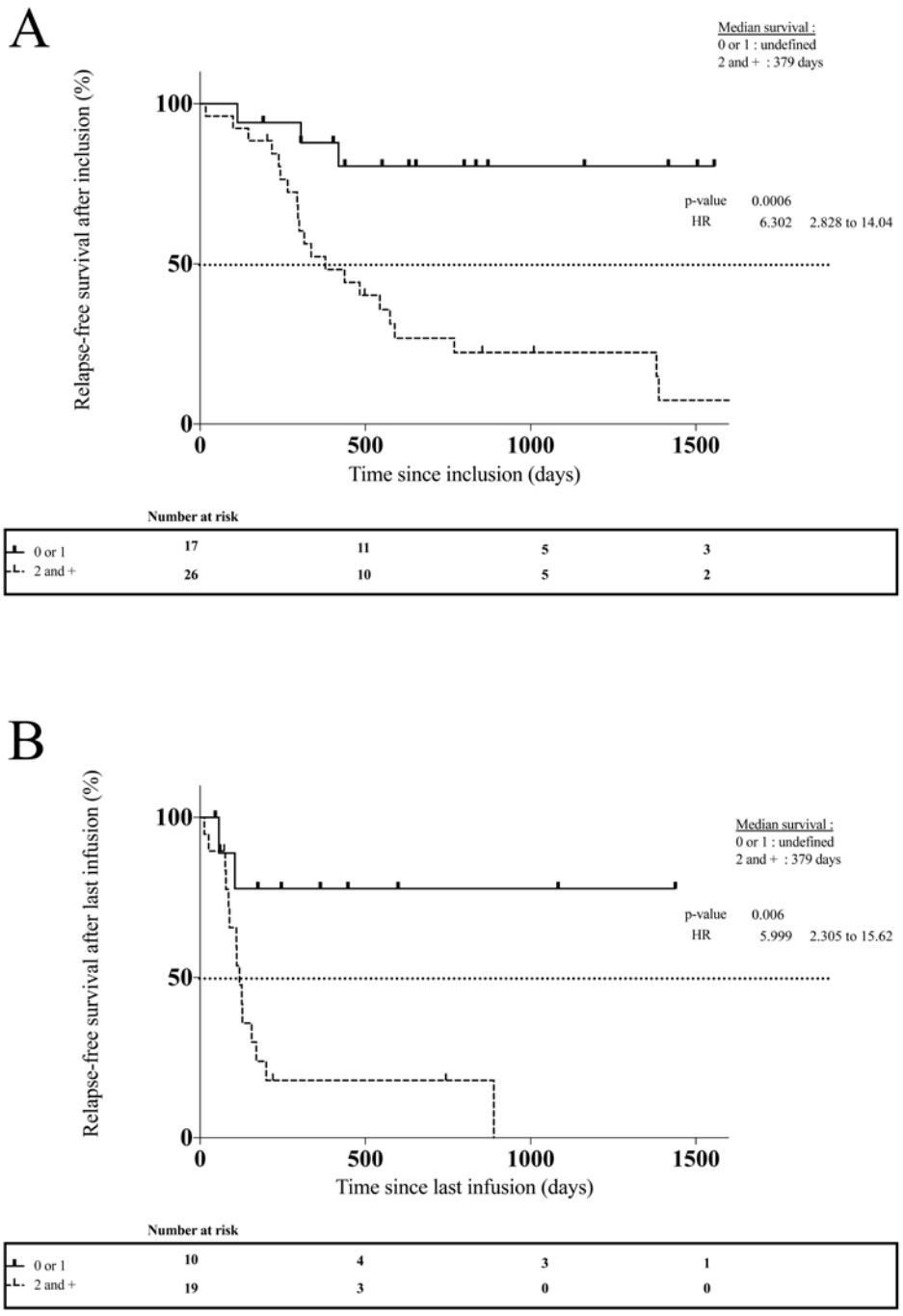

Figure 1. Kaplan-Meier curve for relapse-free survival (A) after inclusion, and (B) after TCZ discontinuation, according to number of identified risk factors. Continuous line: patients with ≤ 1 risk factor; dotted line: patients with ≥ 2 risk factors.

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 on its own, independent of treatment, 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

Table 3. Adverse events recorded before and after tocilizumab start.

Adverse Event	Preinclusion, Median Follow-up 511 days (IQR 143–1292)	Postinclusion, 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
Thrombocytopenia	0 (0)	6 (14)
Aminotransferase increase	0 (0)	2 (5)
Other	0 (0)	8 (19)
Headache	0 (0)	2
Digestive disorder	0 (0)	2
Cutaneous vasculitis	0 (0)	2
Renal cell carcinoma	0 (0)	1
Aphthous ulcers	0 (0)	1

during relapse. We therefore insist on maintaining the monitoring of this marker under TCZ, especially when infusions are spaced out 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.[8,9]

The early onset of relapse upon discontinuation of treatment is, for many clinicians, proof that TCZ is only a suspensive treatment. We think that only a subgroup at risk could relapse after TCZ discontinuation. We identified 4 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 in a previous study.[8] The last 3 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 cell-mediated 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 Th17 immune response; this is a method that has yet to be studied and confirmed. We relied on the works by Weyand and Goronzy[17], as well as Conway, *et al*,[18] who established that the ischemic manifestations are associated with an exacerbated Th1 immune response and that the constitutional/PMR manifestations are associated with an exacerbated Th17 immune response. 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 for relapses. To our knowledge, for patients with GCA, there are no studies that have analyzed risk factors of relapse in the form of clinical profiles.

Finally, by combining these 4 factors, we identified patients with a high risk of relapse (≥ 2 factors) after TCZ introduction, and particularly after its discontinuation.

Long-term safety is also challenging in elderly people. In our cohort, 18/43 (42%) patients experienced serious adverse events, including 8 (19%) with serious infections and 3 (7%) who died of sepsis. This is consistent with a previous study that suggested a higher rate of severe infection in older patients with GCA vs those with RA.[10] The high prevalence of SAEs, particularly severe infections, seems to be closely related to the characteristics of our population, heavy pretreated, since the GiACTA cohort found a trend toward less toxicity with TCZ. Some authors also found that severe infections on TCZ are correlated with high doses 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 from them. Although patients are followed as closely as possible according to national and European recommendations, particularly regarding the prevention of infectious risks, followed patients came from only 3 centers in France; this limits the generalizability of the results. Finally, some risk factors of relapse were determined posthoc, which limits the level of evidence for the results.

Our results confirm the effectiveness of TCZ for CS sparing, and for decreasing the number of relapses in a particularly refractory population. However, after discontinuation of treatment, TCZ allows for prolonged remission in < 50% of patients. This study clearly identified factors predicting the risk of relapse while undergoing TCZ treatment and after its discontinuation. It is important to note in real-world use of TCZ, CRP levels at the time of relapse remain increased in most cases. Finally, attention must be paid to the tolerance of long-term TCZ treatment in this elderly population, particularly in refractory patients who are already heavily treated.

ACKNOWLEDGMENT

We acknowledge our statistician, Dr. Thomas Barnetche, for the reviewing of our statistical methods and results.

REFERENCES

1. Weyand CM, Goronzy JJ. Clinical practice. Giant-cell arteritis and polymyalgia rheumatica. N Engl J Med 2014;371:50-7.
2. Mainbourg S, Addario A, Samson M, Puéchal X, François M, Durupt S, et al. Prevalence of giant cell arteritis relapse in patients treated with glucocorticoids: a meta-analysis. Arthritis Care Res 2020;72:838-49.
3. Gale S, Wilson JC, Chia J, Trinh H, Tuckwell K, Collinson N, et al. Risk associated with cumulative oral glucocorticoid use in patients with giant cell arteritis in real-world databases from the USA and UK. Rheumatol Ther 2018;5:327-40.

4. 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.
5. 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.
6. Stone JH, Klearman M, Collinson N. Trial of tocilizumab in giant-cell arteritis. N Engl J Med 2017;377:1494-5.
7. Hellmich B, Agueda A, Monti S, Buttgereit F, de Boysson H, Brouwer E, et al. 2018 update of the EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis 2020;79:19-30.
8. 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.
9. Adler S, Reichenbach S, Gloor A, Yerly D, Cullmann JL, Villiger PM. Risk of relapse after discontinuation of tocilizumab therapy in giant cell arteritis. Rheumatology 2019;58:1639-43.
10. Gale S, Trinh H, Tuckwell K, Collinson N, Stone JH, Sarsour K, et al. Adverse events in giant cell arteritis and rheumatoid arthritis patient populations: analyses of tocilizumab clinical trials and claims data. Rheumatol Ther 2019;6:77-88.
11. 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.
12. Blockmans D. PET in vasculitis. Ann N Y Acad Sci 2011; 1228:64-70.
13. Prieto-González S, Arguis P, Cid MC. Imaging in systemic vasculitis. Curr Opin Rheumatol 2015;27:53-62.
14. Abdallah H, Hsu JC, Lu P, Fettner S, Zhang X, Douglass W, et al. Pharmacokinetic and pharmacodynamic analysis of subcutaneous tocilizumab in patients with rheumatoid arthritis from 2 randomized, controlled trials: SUMMACTA and BREVACTA. J Clin Pharmacol 2017;57:459-68.
15. Calderón-Goercke M, Loricera J, Aldasoro V, Castañeda S, Villa I, Humbría A, et al. Tocilizumab in giant cell arteritis. Observational, open-label multicenter study of 134 patients in clinical practice. Semin Arthritis Rheum 2019;49:126-35.
16. Nannini C, Niccoli L, Sestini S, Laghai I, Coppola A, Cantini F. Remission maintenance after tocilizumab dose-tapering and interruption in patients with giant cell arteritis: an open-label, 18-month, prospective, pilot study. Ann Rheum Dis 2019; 78:1444-6.
17. Weyand CM, Goronzy JJ. Immune mechanisms in medium and large-vessel vasculitis. Nat Rev Rheumatol 2013;9:731-40.
18. Conway R, O'Neill L, McCarthy GM, Murphy CC, Fabre A, Kennedy S, et al. Interleukin 12 and interleukin 23 play key pathogenic roles in inflammatory and proliferative pathways in giant cell arteritis. Ann Rheum Dis 2018;77:1815-24.