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Relapse risk and safety of long-term tocilizumab use among patients with giant cell arteritis: a single-enterprise cohort study

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Abstract

Objectives: Evaluate safety and efficacy of tocilizumab (TCZ) in giant cell arteritis (GCA) among a large North American cohort.

Methods: Patients with GCA treated with TCZ between 1/Jan/2010 and 15/May/2020 were retrospectively identified. Kaplan-Meier methods were used to estimate time to TCZ discontinuation and time-to-first relapse after TCZ discontinuation. Poisson regression models were used to compare annualized relapse rates (ARR) before, during, and after TCZ use. Age- and sex-adjusted risk factors associated with relapse on/off TCZ and development of adverse event of significant interest (AESI) were examined using Cox models.

Results: 114 patients (60.5% female) were included with mean±SD age 70.4±8.2 years. Median duration from GCA diagnosis to TCZ start was 4.5 months. Median overall duration of TCZ treatment was 2.3 years. Relapse-rate prior to TCZ start (0.84 relapses/person-year) was 3-fold reduced while on TCZ (0.28 relapses/person-year, $p<0.001$) but increased to 0.64 relapses/person-year after TCZ stop. Fifty-two patients stopped TCZ after median 16.8 months; 27 relapsed after

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discontinuation (median: 8.4 months; 58% relapsed within 12 months). Only 14.9% of patients stopped TCZ due to AESI. Neither dose/route of TCZ, presence of large-vessel vasculitis, nor duration of TCZ therapy prior to discontinuation predicted relapse after TCZ stop.

Conclusion: TCZ is well-tolerated in GCA with low rates of discontinuation for AESI. However, relapse occurred in >50% despite median treatment >12 months. Since the duration of TCZ prior to discontinuation did not significantly impact subsequent risk of GCA recurrence, further research is needed to determine the optimal duration of therapy.

Keywords

Vasculitis; giant cell arteritis; tocilizumab; treatment; outcome

INTRODUCTION

Giant Cell Arteritis (GCA) is a primary vasculitis occurring in patients ≥ 50 years, with a predilection for the aorta and its major branches (1). The mainstay of treatment over the past seven decades has been glucocorticoid monotherapy. Unfortunately, relapses occur in 50–75% of patients receiving glucocorticoids alone (2, 3). Furthermore, the cumulative glucocorticoid amount required for GCA management results in a high burden of treatment-associated adverse events (AE), which occur in 86–100% of patients (4, 5).

Tocilizumab (TCZ), an interleukin-6 receptor alpha inhibitor, demonstrated superiority over placebo plus glucocorticoids in two randomized controlled trials with achieving sustained remission and reducing cumulative glucocorticoid exposure (6, 7). TCZ is the first, and currently only, medication to receive U.S. FDA approval for treatment of GCA. Consequently, the 2021 American College of Rheumatology (ACR) guidelines on the management of GCA have conditionally recommended starting TCZ with glucocorticoids as opposed to initiating glucocorticoids alone in patients with newly diagnosed GCA (8).

TCZ has shown efficacy and safety in randomized controlled trials at a duration of 52-weeks but relapse after discontinuation has been observed in 47–58% of patients during follow-up extension (9–11). Therefore, optimal duration of TCZ therapy for ongoing control in GCA remains largely unknown. Evaluation of long-term safety and efficacy in real-world clinical experience has been restricted by cohort size (12–14) and follow-up duration (12, 15, 16). Additionally, it is increasingly understood that GCA is more heterogenous than previously conceived, with patients exhibiting different dominant clinical patterns of disease presentation (17, 18). Comparison of outcomes among patients with GCA receiving TCZ based on disease presentation and clinical characteristics are limited (16, 19) and more information is necessary to guide clinicians in the real-world use of TCZ. This study aimed to describe a large single-enterprise, real-world cohort of GCA patients treated with TCZ with long-term follow-up, with outcome comparison by initial GCA features and characteristics at TCZ initiation.

METHODS

Study design and patient selection

This retrospective chart review study was approved by the Mayo Clinic Institutional Review Board (IRB:20–005144). Patients evaluated at one of the Mayo Clinic Enterprise sites (Rochester, Minnesota; Scottsdale, Arizona; Jacksonville, Florida, or in the Mayo Clinic Health System) between 1/1/2010 and 15/5/2020 with at least one international classification of diseases (ICD) ninth or tenth revision code for GCA (ICD-9:446.5, ICD-10:M31.6) and at least one intravenous infusion order or pharmaceutical prescription for subcutaneous injection of TCZ were manually reviewed. Patients were considered eligible for inclusion in this cohort if they met all of these criteria: 1) Age ≥50 years at onset of symptoms, 2) diagnosis of GCA based on temporal artery biopsy confirmation, positive arterial imaging consistent with large vessel vasculitis or clinical diagnosis by a Mayo rheumatologist with fulfillment of either the 1990 ACR (20) or the 2022 ACR/EULAR (European Alliance of Associations for Rheumatology) Classification Criteria for GCA (21), 3) treated with intravenous or subcutaneous TCZ for a minimum of three consecutive months, 4) six months of follow-up after TCZ initiation.

Data collection

Patient demographics, clinical features, laboratory, examination findings and medications at the time of GCA diagnosis and tocilizumab initiation were abstracted. Fulfillment of the 1990 ACR and/or the 2022 ACR/EULAR classification criteria for GCA were recorded. The number of relapses from the time of GCA diagnosis to TCZ initiation and from TCZ initiation to last follow-up were recorded. Study-defined adverse events of special interest (AESI) adapted from Gale et al. (22) were documented. Study definitions for arterial imaging consistent with GCA, disease activity, and AESI are listed in supplemental table S1.

Statistical analysis

Descriptive statistics (means, standard deviations [SD], medians, interquartile ranges [IQR), etc.) were used to summarize the data. Kaplan-Meier methods were used to estimate time to TCZ discontinuation and time to first relapse after TCZ discontinuation. Poisson regression models were used to compare annualized relapse rates (ARR) before and after TCZ initiation. Age- and sex-adjusted Cox models were used to examine the associations of risk factors with relapse on/off TCZ and development of AESI. A p-value of <0.05 was considered statistically significant for all analyses. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline demographics

The study included 114 patients with GCA treated with TCZ. Baseline characteristics are described in Table 1. The cohort had a mean age at diagnosis of GCA of 70.4 years (SD:8.2), comprised of 69 females and 45 males and was predominantly white (99.1%). The overall cohort had a median follow-up duration of 34.5 [IQR:19.5–54.8]

months. GCA was diagnosed by positive temporal artery biopsy (53/114, 46.5%), imaging evidence of vasculitis (41/114, 36.0%), both positive temporal artery biopsy and imaging evidence (7/114, 6.1%) or a clinical diagnosis (13/114, 11.4%). Of patients that were clinically diagnosed, 12/13 (92%) fulfilled the 1990 ACR classification criteria for GCA. The clinically diagnosed patient in our cohort that did not fulfill the 1990 ACR criteria, did meet the 2022 ACR/EULAR criteria. Of note, among patients diagnosed with large-vessel vasculitis by imaging alone, only 22% (9/41) met the 1990 ACR and 59% (24/41) met the 2022 ACR/EULAR criteria. Seventeen patients in the imaging only group did not meet 1990 ACR or 2022 ACR/EULAR criteria which was due in all cases to the confirmed radiographic large-vessel pathology on computed tomography or magnetic resonance angiography being outside of the bilateral axillary artery requirement of the 2022 ACR/EULAR classification criteria. Distribution of the arterial involvement in these patients is outlined in supplemental table S2.

Signs and symptoms at GCA diagnosis

The median time from GCA symptom onset to diagnosis was 1.2 [IQR:0.6–3.8] months. The most common symptoms at disease onset were headache (70.8%), polymyalgia rheumatica (38.1%) and jaw claudication (35.7%) (Table 1). Vision changes included blurring (20.4%), diplopia (12.4%), amaurosis fugax (10.6%) and permanent vision loss (8.8%). Forty-seven patients had confirmed radiographic evidence of large-vessel vasculitis. Locations of radiographic involvement included the thoracic aorta (26%), subclavian/axillary arteries (18%), abdominal aorta (16%), iliac/femoral/popliteal arteries (10%) and carotid/vertebral arteries (8%).

Tocilizumab and glucocorticoids

The median time from GCA diagnosis to TCZ initiation was 4.5 [IQR:1.2–21.0] months. The majority of patients were started on TCZ within 0–3 months (50/114, 43.9%), whereas 36.8% of patients were started >12 months after GCA diagnosis. The median number of relapses prior to TCZ start was 1.0 [IQR:0.0–2.0]. The most common dose/route used at initiation was 162mg subcutaneous weekly (n=47), followed by intravenous 4mg/kg/month (n=32), 162mg subcutaneous every other week (n=18), intravenous 8mg/kg/month (n=14), and three patients with other dosing regimens (e.g., intravenous 6mg/kg/month). High-dose TCZ (162 mg subcutaneous weekly or 8 mg/kg IV monthly) was initiated in 55.0% of patients while low-dose (162 mg subcutaneous every other week or 4mg/kg IV monthly) was started in 45.0% of patients. The median duration of glucocorticoid therapy prior to TCZ initiation was 8.0 [IQR:2.0–24.0] months with a median dose of prednisone of 30.0 mg [IQR:15.0–40.0] at TCZ start. There were no significant differences between GCA diagnostic groups when comparing time from GCA diagnosis to TCZ initiation, use of high- or low-dose TCZ, prednisone dose at TCZ initiation, or inflammatory markers at TCZ initiation (Table 2). Factors including symptoms at GCA diagnosis, symptoms at TCZ initiation, glucocorticoid dose, glucocorticoid duration, prior use of glucocorticoid-sparing treatment, relapses prior to TCZ treatment and presence of large-vessel involvement were compared, but none were significantly associated with the initiation of high- or low-dose TCZ (Table 3).

Thirty-seven patients (32.5%) were on a glucocorticoid-sparing agent prior to initiation of TCZ. The most common agent was methotrexate (25/37, 68%). Twenty (17.5%) patients were on a steroid-sparing agent at initiation of TCZ, 12 of which (all methotrexate) remained on treatment for > 3 months after TCZ initiation.

The median overall duration of TCZ treatment during the study period was 2.3 years (Figure 1A) with maximum duration of 66 months. The median (IQR) duration of follow up after TCZ initiation was 2.2 (1.2–3.0) years with the longest follow up being 7.9 years. During the course of TCZ treatment 49% of patients remained on the same TCZ dose/frequency, 31% underwent a reduction of TCZ dose/frequency and only 4% of patients required TCZ dose/frequency increase. The remainder had both increase and decrease in the dose/frequency at some point during treatment. Glucocorticoids were able to be discontinued in 65 (57.0%) patients following TCZ start. TCZ was discontinued in 52 (45.6%) patients. Among patients discontinuing TCZ, the median duration time from TCZ start to first TCZ stop was 16.8 (IQR:10.3–28.0) months.

Relapse

Sixty-eight patients had at least one relapse following TCZ initiation; 41 while receiving TCZ, 13 after TCZ disontinuation and 14 with relapse on TCZ who also had subsquent relapse after TCZ discontinuation. Among relapses on TCZ, 45 occurred on prednisone with median dose of 8.0 mg/day (IQR 5.0–18.0). Among relapses following TCZ discontinuation, 18 occurred on prednisone with median dose of 8.8 mg/day (IQR 6.0–10.0).

Relapses while receiving TCZ were more commonly characterized by recurring GCA symptoms without inflammatory marker elevation (59%) followed by GCA symptoms with inflammatory marker elevation (24%), inflammatory marker changes only (13%) and worsening/progression of large-vessel vasculitis on imaging (4%). Characteristics between those relapsing on TCZ and those relapsing after TCZ discontinuation were compared. The only statistically significant difference between the two groups were inflammatory markers during relapse which were lower in the group of patients relapsing on TCZ compared to the group relapsing after TCZ discontinued (median ESR 26.0 mm/hr [IQR:12.0–37.0] vs 3.5 mm/hr [IQR:1.0–10.0] and CRP 16.1 mg/L [IQR:4.7–25.9] vs 3.0 mg/L [IQR:3.0–8.5]). There were two relapses of transient vision loss while on TCZ which recovered with glucocorticoid therapy. No permanent vision loss or stroke was noted during relapse on TCZ or relapse following TCZ discontinuation.

The ARR prior to TCZ was 0.84 relapses/person-year. The ARR while receiving TCZ significantly decreased to 0.28 relapses/person-year ($p<0.001$). Cranial symptoms of GCA at diagnosis was the only risk factor predicting relapse (HR:2.29; 95%CI:1.07–4.91; Supplemental table S3). Among the 52 patients in which TCZ was discontinued, 27 patients had a relapse. Median time to first relapse after TCZ discontinuation was 8.4 months (Figure 1B). ARR following TCZ discontinuation was 0.64 relapses/person-year. Among patients who relapsed after TCZ discontinuation, treatment following first relapse included prednisone only (n=6), TCZ only (n=7), prednisone/TCZ (n=7), prednisone/methotrexate (n=4), TCZ/methotrexate (n=1).

Only the presence of statin therapy at GCA diagnosis was associated with a reduced risk of relapse among patients discontinuing TCZ (HR:0.38; 95%CI:0.15–0.97). Neither TCZ route, TCZ dose, TCZ duration prior to discontinuation, nor any of the additional risk factors assessed were significantly associated with an increased risk of relapse among patients discontinuing TCZ (Supplemental table S3).

Adverse Events of Special Interest

While on TCZ, the most common treatment related AESI was infection requiring hospitalization (7.0%). Hepatotoxicity (2.6%), diverticulitis (1.8%), severe neutropenia (absolute neutrophil count <500/microL) (1.8%) and thrombocytopenia (0.9%) were less common. One patient with known diverticulosis had a colonic microperforation which resolved with antibiotics and bowel rest. Severe anemia (<8gm/dl or requiring transfusion), myocardial infarction, venous thromboembolism and stroke while on TCZ were not observed. Two patients had transient vision loss with recovery on glucocorticoid increase, however, no fixed visual loss was noted. Seventeen patients (14.9%) discontinued TCZ due to a study-defined AESI. Risk factors for AESI adjusted for age and sex were compared. Only vision changes at TCZ start were found to increase risk (HR:3.78; 95%CI:1.35–10.57). Initial TCZ dose, age ≥80 years at TCZ initiation, time from GCA diagnosis to TCZ treatment and steroid sparing agents at TCZ initiation, among other factors, were not found to significantly increase risk of AESI (Supplemental table S4). Three patients died during follow-up, none of the deaths were attributable to complications from GCA or TCZ.

DISCUSSION

We present the largest North American, single enterprise, cohort of patients with GCA treated with TCZ. Outside of randomized, placebo-controlled trials evaluating TCZ in GCA there have been several reports of the efficacy of TCZ through case series, small prospective studies, and a few real-world cohorts. Nevertheless, the majority of these reports include 60 patients or less (12–14, 16, 23–32) with few studies monitoring to 2 years of TCZ treatment (13, 14, 29). Comparable large cohorts of patients with GCA receiving TCZ have been reported in Spain (15) and Switzerland (33) with 134 and 186 patients, respectively. However, median time of observation on TCZ among the European cohorts was only 11–12 months. Therefore, the size and duration of follow-up presented in the current report provides critical insight into longer term safety and efficacy data of TCZ in GCA within a real-world setting and highlights the variability of clinical practice in regards to patients included and the dose and route of TCZ used.

Clinical trials evaluating TCZ in GCA have shown a 4-fold improvement in sustained remission (7) and relapse-free survival (6) at 52 weeks, in comparison to placebo. Uncontrolled observational studies have shown similar, but attenuated results. The current study reaffirms the efficacy of TCZ in real-world management of GCA as evidenced by a 3-fold reduction in the ARR while receiving TCZ compared to prior to TCZ initiation. Although the frequency of relapses prior to TCZ initiation were lower than other reported studies, our findings are comparable to the ARR observed in a real-world multicenter retrospective analysis in France (n=43) (13) where the ARR decreased from 1.26 to 0.44

relapses/year (2.86 fold reduction) as well as a single-institution American cohort (n=60) where the relapse rate decreased from 1.4 to 0.6 relapses/year (2.3 fold reduction) (16).

Tapering and discontinuation of glucocorticoids is a primary goal in GCA management. While TCZ has demonstrated a significant steroid-sparing effect, only slightly more than half the patients in our cohort were able to stop glucocorticoids while receiving TCZ. This has been similarly observed in other cohorts with 46–60% of patients able to discontinue glucocorticoid therapy during TCZ treatment (13, 16, 32).

Given the uncontrolled and retrospective nature of this study, it is not feasible to determine the rationale for ongoing use. Possible reasons include provider/patient preference, polymyalgia symptoms, relative adrenal insufficiency and smoldering disease activity among others. Our group has shown previously that glucocorticoid discontinuation among patients receiving glucocorticoid monotherapy was low with only 6% off at one year and 24% at two years after GCA diagnosis (3). While TCZ improves likelihood of glucocorticoid discontinuation, patients and providers should be aware that approximately half of patients may require ongoing use of glucocorticoids despite initiation of TCZ.

Due to the retrospective nature of this study, the dosing and route of TCZ was determined by the treating rheumatologist. Until recently, the only FDA approved formulation of TCZ for GCA management was 162 mg subcutaneous weekly. However, only 42% of patients received this dose and route at TCZ initiation. This study was completed prior to the recent approval of 6mg/kg intravenous monthly dosing. Consequently, this dose and route was the least frequently utilized in the current cohort. Similar variability in TCZ dosing has been demonstrated in other observational cohorts (14–16), raising the possibility that patient factors, provider preference, and medication formulation availability likely play a role in the decision of TCZ dosing. High-dose and low-dose regimens were compared to see if the decision to start TCZ was influenced by prior steroid-sparing agents, prior relapses, presence of large-vessel vasculitis, symptoms (cranial, visual, PMR), prednisone dose, prednisone duration or inflammatory markers. Interestingly, none of these features appeared to be associated with the chosen dosing regimen. High-dose and low-dose regimens were also assessed for risk of relapse after the start of TCZ and after discontinuation. Neither dose nor route was found to be a risk factor for relapse at either point; unlike the results of the GiACTA trial which showed weekly subcutaneous TCZ had a lower risk of flare in the patients with relapsing disease (7, 11) compared to every other week dosing. Similar to our findings, Rossi and colleagues, showed significant efficacy of lower-dose TCZ in the elderly population with relapsing disease (34) and a comparably large multi-center Spanish cohort has also shown clinical benefit regardless of TCZ administration route or disease duration (15). Further research into which subtypes of patients may benefit from lower dose regimens is needed before routine use is considered.

The optimum duration of TCZ treatment remains unknown. Among those stopping TCZ, the median duration of treatment was 16.8 months. Following TCZ discontinuation, 58% of patients had a subsequent relapse within 12 months. These findings are commensurate to frequencies reported among both clinical trial and observational studies with relapse rates of 33–62% after TCZ discontinuation (9, 11, 13, 23, 26, 27, 33). The time from TCZ

stoppage to first flare is also similar, median 8.4 months in the current cohort, compared to ranges of 2–9 months in other studies (13, 23, 26, 27). Long-term follow-up of patients after TCZ stoppage is limited, consequently ARR analysis following TCZ discontinuation has not been previously reported. In the current study, we observed the ARR following TCZ discontinuation to be 0.64 relapses/year which is greater than two times higher than the ARR on TCZ and nearing pre-TCZ initiation rates. Of importance, in the current study, the duration of TCZ therapy prior to discontinuation was not associated with subsequent risk of relapse. Taken together, these findings affirm the suppressive effect of TCZ but confirm that treatment extension beyond 12 months prior to discontinuation does not necessarily increase the likelihood for prolonged treatment free remission. Therefore, it is imperative that future research be focused on identifying the optimal duration of TCZ therapy in patients with GCA in order to determine which patients are best suitable for discontinuation. Among those for which TCZ therapy is discontinued, close observation at least to 6–12 months off therapy is strongly suggested to assess for disease recurrence.

Clinical features at the time of GCA diagnosis and the time of TCZ initiation have not been reliable predictors of future relapse. Prior studies have failed to demonstrate any specific baseline clinical, radiographic, or laboratory parameter that predicts risk of relapse either on TCZ or after discontinuation (9, 33). In the current study, the only feature associated with risk of relapse after TCZ start was the presence of cranial symptoms at time of GCA diagnosis. The pertinence of this finding is uncertain since it has not been observed in other cohorts and directly contrasts with the observation noted by Clement and colleagues where an absence of ischemic signs (jaw claudication, scalp tenderness/necrosis, blindness, peripheral arterial disease) was associated with increased risk of relapse after TCZ start (13). Use of statin at GCA diagnosis was the only factor associated with reduced risk for relapse after TCZ discontinuation. The pertinence of this is unknown as the impact regarding statin use and relapse has provided conflicting results and statins are not currently recommend specifically for treatment of newly diagnosed GCA unless a patient's cardiovascular risk warrants initiation (8). The ability to prognosticate relapse risk has also been elusive in the pre-TCZ era with individual groups identifying potential risk factors which have failed to be consistent across cohorts (3, 5, 35–37). This further highlights the need for research collaboration to establish methods of novel multi-variable analysis of large international cohorts and ongoing efforts to identify novel biomarkers suitable for risk stratification.

Overall, TCZ was generally well tolerated within this cohort with only 14.9% stopping TCZ due to a study defined AESI despite long-term follow-up and median TCZ treatment duration of 2.3 years. Total AE and serious adverse event (SAE) rates are notably variable among cohorts which is attributable to differences in study definitions (6, 7, 13, 16, 30, 32, 38). SAE resulting in permanent discontinuation of TCZ appears to be a more reasonable indicator of overall long-term safety with apparent greater uniformity and consensus among reporting cohorts. Reassuringly, discontinuation due to SAE are uncommon in observational trials reporting on cohorts with 20 or more patients with GCA with rates between 6–15% (14–16, 30, 38). Vitiello and colleagues noted a 25% discontinuation rate due to SAE; however, this study has limitations of generalizability due to the small cohort size (n=12) and greater frequency of methotrexate use (40%) while receiving TCZ (32). Understandably long-term biologic therapies in the elderly raises concern for both patients and providers.

We did not observe any new safety signals during our follow-up period beyond what has been previously noted. Colonic perforation was seen in only one patient in our cohort. While important to consider and discuss risk with patients, this highlights the rarity of this event which has been reinforced by healthcare claim analysis reviewing 4,804 patients with GCA showing gastrointestinal perforation rates of 0.55 per 100 person years of observation (22). We did not observe age (>80 years-old), route or dose of TCZ or DMARD as risk factors for AESI. Visual symptoms at time of TCZ initiation was the only item found to be a risk factor for AESI which likely reflects a subgroup of patients treated with a higher dose of prednisone as vision changes often require pulse dose intravenous glucocorticoids upfront.

This study is the largest real-world single enterprise cohort of patients in North America with GCA treated with TCZ with extended follow-up. Nevertheless, this study must be viewed in context of its limitations. Since this was a cohort from a single enterprise, findings may not be applicable to other regions. However, patients were recruited from campuses in the midwest, southeast and southwest United States so we expect this impact to be limited. Given the observational, retrospective nature of this cohort, not all patients had the same amount of follow-up, and we were unable to confirm proper administration and adherence to prescribed medications, but rather relied on documentation of the treating clinician and confirmation of infusion records. Due to the referral nature of the practice, patients may represent those with more refractory disease and therefore may not be representative of the general GCA population. Seventeen patients with study-defined radiographic confirmation of large-vessel vasculitis did not fulfill either 1990 ACR or 2022 ACR/EULAR classification criteria; further evaluation is need to determine whether the treatment response to TCZ differs in this particular patient subset. Finally, due to the inclusion of patients before FDA approval of TCZ, there may be selection bias in what patients were treated with TCZ prior to this date and what dose and route was chosen.

Conclusion

Overall, this large real-world cohort with an extended duration of follow-up further affirms the safety and efficacy of TCZ in GCA. No differences were found between the groups of patients that were prescribed low- and high-dose TCZ. Additionally, neither the dose, nor the route was found to be associated with risk for relapse or adverse events of special interest. Relapse rates following TCZ discontinuation were similar to other series with shorter duration of treatment. Duration of TCZ prior to discontinuation was not associated with reduced risk of relapse. Further studies are needed to determine the optimal duration of TCZ therapy. Additional research is necessary to identify which subsets of patients are more likely to remain in prolonged remission following TCZ discontinuation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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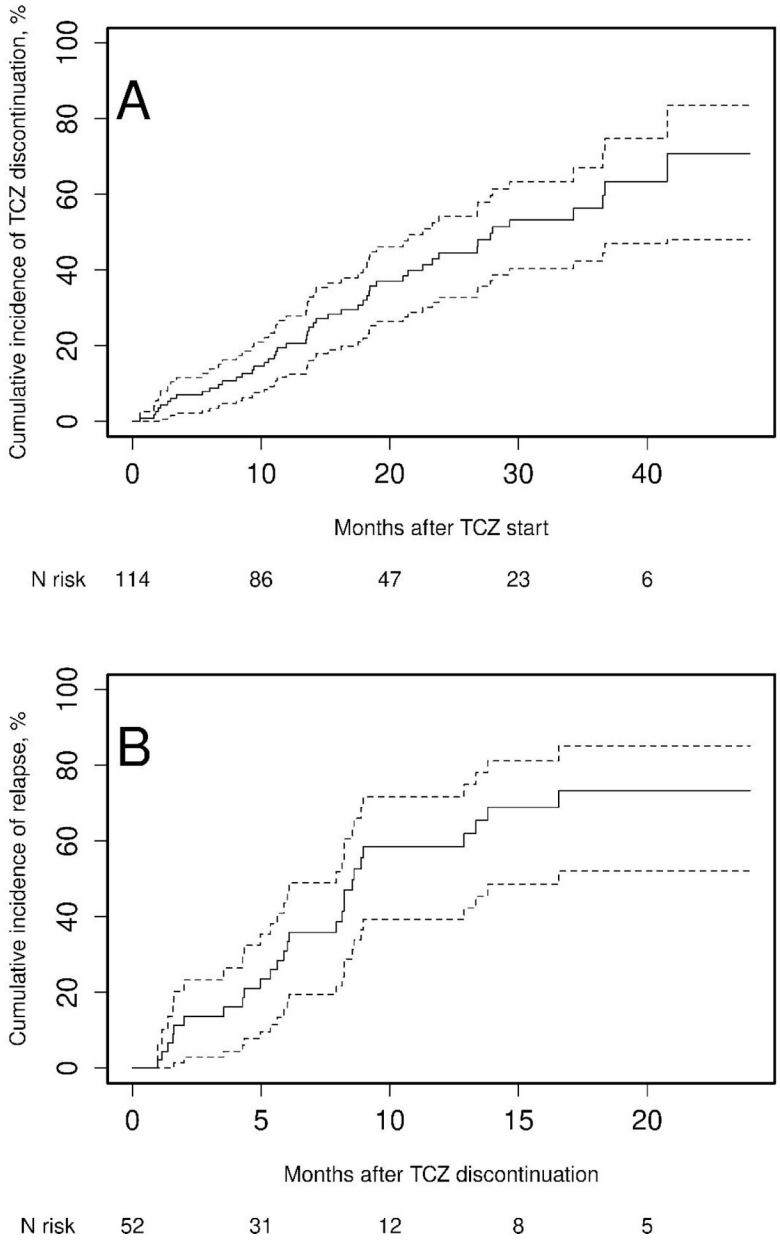

Figure 1.

Kaplan-Meier curve of time from tocilizumab start to tocilizumab discontinuation (panel A) and time from tocilizumab discontinuation to first relapse after tocilizumab discontinuation (panel B). The solid line on each panel is the estimated cumulative incidence of the event and the dashed lines are the 95% confidence intervals.

Table 1.

Baseline characteristics at GCA diagnosis

Characteristic, n (%)	Total[d] N=114	Biopsy proven[a,d] N=60	Imaging only[b,d] N=41	Clinically diagnosed[c] N=13	P-value
Age, years[e]	70.4 (8.2)	72.0 (7.9)	66.8 (7.7)	74.1 (7.7)	0.002
Sex, female	69 (60.5)	36 (60)	26 (63)	7 (54)	0.82[g]
Time from GCA diagnosis to TCZ onset, mo.[f]	4.5 [1.2–21.0]	3.2 [1.2–19.7]	7.0 [1.2–23.7]	4.6 [1.5–16.3]	0.55
Length of follow-up, mo.[f]	34.5 [19.5–54.8]	31.8 [16.9–46.1]	44.5 [26.1–79.7]	34.0 [15.7–38.3]	0.02
Large Vessel Vasculitis	47 (41.2)	6 (10)	41 (100)	0 (0)	<0.001
Systemic Symptoms					
Fever	17/113 (15.0)	8 (13)	9/40 (23)	0 (0)	0.12
Weight loss (5 pounds or >10% premorbid weight)	22/113 (19.5)	11 (18)	11/40 (28)	0 (0)	0.09
Polymyalgia Rheumatica	43/113 (38.1)	22 (37)	15/40 (38)	6 (46)	0.81
Ischemic Manifestations					
Headache	80/113 (70.8)	52 (87)	16/40 (40)	12 (92)	<0.001
Jaw Claudication	40/112 (35.7)	32/59 (54)	4/40 (10)	4 (31)	<0.001
Arm Claudication	9 (7.9)	1 (2)	8 (20)	0 (0)	0.003
Leg Claudication	5/113 (4.4)	1 (2)	4/40 (10)	0 (0)	0.10
Temporal Artery Tenderness	19/113 (16.8)	12 (20)	2/40 (5)	5 (38)	0.01
Decreased temporal artery pulses	9/113 (8.0)	4 (7)	3/40 (8)	2 (15)	0.57
Decreased large artery pulses	7 (6.1)	0 (0)	7 (17)	0 (0)	0.001
Transient Vision loss	12/113 (10.6)	10 (17)	0/40 (0)	2 (15)	0.03
Permanent Vision loss	10/113 (8.8)	8 (13)	0/40 (0)	2 (15)	0.05
Classification Criteria					
Fulfilled 1990 ACR Criteria for GCA	76 (66.7)	55 (92)	9 (22)	12 (92)	<0.001
Fulfilled 2022 ACR/EULAR Criteria for GCA	95 (83.3)	59 (98)	24 (59)	12 (92)	<0.001
Did not meet 1990 ACR but met 2022 ACR/EULAR criteria	21/38 (55.3)	5/5 (100)	15/32 (47)	1/1 (100)	0.06
Did not meet either 1990 ACR or 2022 ACR/EULAR criteria[h]	17 (14.9)	0 (0)	17 (41)	0 (0)	---

ACR, American College of Rheumatology; EULAR, European Alliance of Associations for Rheumatology; GCA, giant cell arteritis; mo., month; TCZ tocilizumab.

[a] Biopsy proven with or without imaging

[b] Imaging showing evidence of large vessel vasculitis with either a negative biopsy or none performed

[c] Clinical diagnosis of GCA without imaging or biopsy positivity or none completed

[d] If data missing/unavailable, denominator listed if different from listed total

[e] mean±standard deviation

[f] median [interquartile range]

[g] Kruskal-Wallis p-value

[h] all patients had positive arterial imaging consistent with large-vessel vasculitis but patients included here had CT or MR angiography that was outside of the ‘bilateral axillary involvement’.

Table 2.

Baseline characteristics at TCZ initiation Between GCA Diagnostic Groups

Characteristic, n (%)	Total[d] N=114	Biopsy proven[a,d] N=60	Imaging only[b,d] N=41	Clinically diagnosed[c] N=13	P-value
Time GCA diagnosis to TCZ start					0.82
0–90 days	50 (43.9)	29 (48)	15 (37)	6 (46)	
91–182 days	14 (12.3)	7 (12)	5 (12)	2 (15)	
183–365 days	8 (7.0)	5 (8)	2 (5)	1 (8)	
>365 days	42 (36.8)	19 (32)	19 (46)	4 (31)	
Initial TCZ dose					0.82
High dose[f]	61/111 (55.0)	34/59 (58)	20/39 (51)	7 (54)	
Low dose[g]	50/111 (45.0)	25/59 (42)	19/39 (49)	6 (46)	
Prednisone dose at TCZ start [e]	30.0 [15.0–40.0]	30.0 [12.5–45.0]	20.0 [15.0–40.0]	40.0 [20.0–60.0]	0.13
Inflammatory Markers at TCZ start					
ESR (mm/Hr)[e]	16.0 [7.0–27.0]	17.0 [6.0–27.0]	16.0 [8.0–24.0]	37.0 [11.0–50.0]	0.45[h]
C-Reactive Protein (mg/L)[e]	9.1 [3.0–26.0]	5.7 [3.0–23.5]	9.7 [4.0–19.1]	26.3 [5.0–39.8]	0.11[h]

ESR, erythrocyte sedimentation rate; GCA, giant cell arteritis; IQR, interquartile range; TCZ, tocilizumab

[a] Biopsy proven with or without imaging

[b] Imaging showing evidence of large vessel vasculitis with either a negative biopsy or none performed

[c] Clinical diagnosis of GCA without imaging or biopsy positivity or none completed

[d] If data missing/unavailable, denominator listed if different from listed total

[e] median [interquartile range]

[f] High dose= 8mg/kg intravenous every 4 weeks or 162 mg subcutaneous weekly

[g] Low dose= 4mg/kg intravenous every 4 weeks or 162 mg subcutaneous every other week

[h] Kruskal-Wallis p-value

Table 3.

Patient Factors in the High and Low Dose TCZ Treatment Groups

Characteristic, n (%)	Total[c] N=111	High Dose TCZ[a,c] N=61	Low dose TCZ[b,c] N=50	P-value
Prior glucocorticoid-sparing agent	36 (32.4)	17 (28)	19 (38)	0.26
Relapses prior to TCZ start[d]	1.0 [0.0–2.0]	1.0 [0.0–2.0]	0.5 [0.0–2.0]	0.84[e]
Cranial Symptoms				
At GCA diagnosis	87 (78.4)	51 (84)	36 (72)	0.14
At TCZ start	37 (33.3)	22 (36)	15 (30)	0.50
Vision Changes				
At GCA diagnosis	46 (41.4)	28 (46)	18 (36)	0.29
At TCZ start	27 (24.3)	15 (25)	12 (24)	0.94
Large Vessel Vasculitis				
At GCA diagnosis	50 (45.0)	28 (46)	22 (44)	0.84
At TCZ start	47 (42.3)	25 (41)	22 (44)	0.75
Polymyalgia Rheumatica				
At GCA diagnosis	42/110 (38.2)	22 (36)	20/49 (41)	0.61
At TCZ start	17/110 (15.5)	8/60 (13)	9 (18)	0.50
Prednisone [f]				
Dose (mg/d) at TCZ start[d]	30.0 [15.0–40.0]	30.0 [15.0–40.0]	27.5 [15.0–40.0]	0.32[e]
Duration (days) prior to TCZ[d]	154.0 [44.5–555.5]	129.0 [39.0–522.0]	229.0 [59.0–665.0]	0.20[e]
Inflammatory Markers				
ESR (mm/hr) TCZ start[d,g]	16.0 [7.0–27.0]	13.0 [6.0–23.0]	20.0 [8.0–34.5]	0.10[e]
CRP (mg/L) TCZ start[d,h]	9.2 [3.0–26.0]	6.4 [3.0–17.5]	14.1 [3.7–27.4]	0.10[e]

CRP, c-reactive protein; ESR, erythrocyte sedimentation rate; GCA, giant cell arteritis; TCZ, tocilizumab

[a] TCZ intravenous 8mg/kg every 4 weeks or subcutaneous 162 mg weekly

[b] TCZ intravenous 4mg/kg every 4 weeks or subcutaneous 162 mg every other week

[c] 3 Patients were excluded if they received non-standard dosing (e.g. 6mg/kg intravenous monthly). If data missing/unavailable, denominator listed if different from listed total

[d] median [interquartile range]

[e] Kruskal-Wallis p-value

[f] Prednisone values were only available for 108 patients

[g] ESR values were only available for 94 patients

[h] CRP values were only available for 105 patients