Title

Relapse after cessation of weekly tocilizumab for giant cell arteritis: a multicentre service evaluation in England.

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Abstract

Background/Objectives

The National Health Service in England funds 12 months of weekly subcutaneous tocilizumab (qwTCZ) for patients with relapsing or refractory giant cell arteritis (GCA). During the COVID-19 pandemic, some patients were allowed longer treatment. We sought to describe what happened to patients after cessation of qwTCZ.

Methods

Multi-centre service evaluation of relapse after stopping qwTCZ for GCA. The log-rank test was used to identify significant differences in time to relapse.

Results

336 GCA patients were analysed from 40 centres, treated with qwTCZ for a median (interquartile range, IQR) of 12 (12-17) months. At time of stopping qwTCZ, median (IQR) prednisolone dose was 2 (0-5) mg/day. By 6, 12 and 24 months after stopping qwTCZ, 21.4%, 35.4% and 48.6% respectively had relapsed, requiring an increase in prednisolone dose to a median (IQR) of 20 (10-40) mg/day. 33.6% of relapsers had a major relapse as defined by EULAR. Time to relapse was shorter in those that had previously also relapsed during qwTCZ treatment (P=0.0017); in those not in remission at qwTCZ cessation (P=0.0036); and in those with large vessel involvement on imaging (P=0.0296). Age ≥65, gender, GCA-related sight loss, qwTCZ treatment duration, TCZ taper, prednisolone dosing, and conventional synthetic DMARD use were not associated with time to relapse.

Conclusion

Up to half our patients with GCA relapsed after stopping qwTCZ, often requiring a substantial increase in prednisolone dose. One third of relapsers had a major relapse. Extended use of TCZ or repeat treatment for relapse should be considered for these patients.

Key words

giant cell arteritis, vasculitis, tocilizumab, NICE guidance, service evaluation, relapse.

Key messages

(1) Up to half of patients relapsed after stopping tocilizumab; one in three relapses were major.

(2) Relapses after stopping tocilizumab required a substantial increase in prednisolone dose.

(3) Patients who had already relapsed during tocilizumab therapy were more likely to relapse after stopping.

Introduction

Giant cell arteritis (GCA) is a primary systemic vasculitis treated with long-term glucocorticoid to prevent ischaemic complications such as visual loss [1]. Relapses require treatment escalation [2], which can cause significant glucocorticoid toxicity [3]. Weekly subcutaneous tocilizumab (qwTCZ) is licensed for GCA on the basis of clinical trial evidence of reduced relapse rate and cumulative glucocorticoid requirements [4,5].

Following approval by The National Institute for Health and Care Excellence (NICE), 12 months' treatment with TCZ for patients with refractory or relapsing GCA has been available through the English National Health Service (NHS) since July 2018 (Technology Appraisal TA518) [6] (Fig. S1 online). Treatment beyond 12 months is not currently funded in England. From July 2020, during the COVID-19 pandemic, NHS England permitted more than 12 months' treatment for GCA patients believed to be at higher risk of relapse (LV-GCA on imaging or biopsy, history of critical ischaemia, or active disease between months 6-12 on TCZ with eventual disease control); this arrangement ceased on 31st March 2022.

We designed a multi-centre service evaluation to describe clinical outcomes after qwTCZ cessation in patients with GCA in England, focusing on the time to first relapse.

Methods

Inclusion criteria

From November 2022 to January 2023, NHS rheumatology departments (centres) in England were invited to take part in TOC STOP by submitting anonymised data on all their GCA patients who had completed at least one month of qwTCZ and had at least one follow-up after qwTCZ had been stopped. Follow-up started when qwTCZ was stopped. One dose of intravenous TCZ 8mg/kg was considered equivalent to four weeks' subcutaneous TCZ 162mg/week.

Data collection and information governance

Approval from an ethics committee and patient consent were not required as TOC STOP was defined as a service evaluation with the Health Research Authority decision tool following advice from the Chair of the Oxford A (UK) Research Ethics Committee. Each participating centre registered TOC STOP with their audit department, identified relevant patients using local databases, and reviewed their patients' medical records. Data were recorded on a standardised Microsoft Excel spreadsheet, supported by a Frequently Asked Questions list generated during a pilot of 62 patients conducted at two participating centres (Luton and Leeds). To minimise the risk of inadvertent patient identification and for reasons of feasibility and parsimony, data collection was kept to core variables, all durations were rounded to nearest month, and the only patient demographics collected were gender and age ≥65 years. Each centre obtained local Caldicott Guardian approval to export their anonymised data to Luton and Dunstable Hospital, UK, for amalgamation. All identifiable data were removed before export. Data queries were completed and centre identifiers removed to create the final dataset for analysis.

Definitions

Remission was defined as absence of signs or symptoms of GCA with centre-defined normal laboratory markers of inflammation (CRP, ESR, or plasma viscosity).

Relapse was either documented by a consultant or confirmed by consultant review of the medical notes, and defined as an increase in disease activity of sufficient severity to require a change of treatment plan such as slowed glucocorticoid taper, glucocorticoid dose increase, or addition of conventional synthetic disease modifying antirheumatic drug (csDMARD). This definition allowed inclusion of those not in remission at qwTCZ cessation, who may still have responded over their treatment course: GCA disease states are not binary; there exists a continuum where patients are neither in full remission nor in acute relapse, e.g., stable low disease activity. Time of relapse was defined as time of treatment plan change, rounded to the nearest month.

Major relapse was defined as relapse with clinical features of ischaemia e.g., jaw claudication, visual symptoms, visual loss, scalp necrosis, stroke, limb claudication and/or evidence of active aortic inflammation causing progressive aortic or large

vessel stenosis, dilatation, or dissection [7]; and could occur at any time during follow-up.

Large vessel (LV-) GCA was defined as GCA involving the aorta and/or its major branches such as the axillary, subclavian or carotid arteries and confirmed by imaging at any time since diagnosis (wall thickening, oedema, increased tracer uptake, or stenosis deemed to be due to vasculitis). Cranial GCA could include headache, scalp tenderness, jaw or tongue claudication, scalp necrosis or abnormality of temporal arteries on examination, biopsy or imaging. GCA phenotype was classified as pure cranial, pure LV-GCA, or mixed (both cranial and LV-GCA).

csDMARD was defined as any of oral/subcutaneous methotrexate, leflunomide, azathioprine, mycophenolate mofetil or cyclophosphamide given for GCA. Specific csDMARDs were not collected.

Optional variables, if collected by a centre, were required for all patients submitted by that centre; these included GCA relapse whilst on qwTCZ and death during follow-up.

For the purpose of this analysis, patients were deemed to fulfil the pandemic extension criteria if they had at least one of LV-GCA, GCA-related sight loss, or GCA relapse whilst on qwTCZ.

Statistical analysis

Categorial variables were shown as numbers and percentages. Continuous variables were shown as the median with interquartile range, as the data were not normally distributed. Baseline characteristics of relapsers and non-relapsers after qwTCZ cessation were compared with the 2-tailed *Z*-test or non-parametric *t*-test to identify variables of interest for time to first relapse analysis.

In further data exploration, correlations between variables were analysed with polyserial (categorical vs continuous variables) or tetrachoric correlation (categorical vs categorical variables).

For time to first relapse analysis, we plotted Kaplan-Meier curves with 95% Hall-Wellner bands. We also plotted curves for variables of interest identified *a priori* or

from the data exploration phase. A log-rank test was used to compare time to relapse between subgroups.

In an exploratory multivariable analysis, we fitted a Cox proportional-hazard model to investigate the association between relapse after qwTCZ cessation and a number of variables.

A *P*-value <0.05 was considered statistically significant. Statistical analysis was performed with SAS version 9.4.

Results

Data from 379 patients from 40 centres across England were submitted. Centres submitted a median of 5 (IQR 2-12) patients; 7 centres submitted 20 or more.

43 patients were excluded from the analysis. 23/43 did not fulfil the inclusion criteria as they had no follow-up after qwTCZ cessation, whilst 20/43 had commenced TCZ treatment before publication of NICE TA518 [5] so criteria for commencement and cessation may have differed. 336 patients remained for the analysis. There were no missing values in the compulsory dataset.

Patients and treatments up to the time of stopping qwTCZ

Patient characteristics are shown in Table 1, which also includes a comparison between those with and without GCA relapse after qwTCZ cessation. 61.3% had evidence of LV-GCA on imaging during their disease course, likely reflecting a propensity for LV involvement in relapsing/refractory patients. 43.2% were co-prescribed a csDMARD during the last three months of qwTCZ.

Median prednisolone dose at start of treatment with qwTCZ was 20 (10-40) mg/day, and 2 (0-5) mg/day at qwTCZ cessation, *P*=0.0001.

Median duration of qwTCZ was 12 (12-17) months. 78/336 (23.2%) patients received <12 months, 96/336 (28.6%) received 12 months, and 162/336 (48.2%) received >12 months qwTCZ (Graph S1 online).

286/336 (85.1%) patients were in remission at the time they stopped qwTCZ. For the patients where these optional data were collected, 47/285 (16.5%) patients had relapsed whilst receiving qwTCZ.

Treatments during follow-up after qwTCZ cessation

Median duration of follow-up after qwTCZ cessation was 10 (5-18) months (Graph S2 online).

After cessation of qwTCZ, 57/336 (17.0%) “tapered” their TCZ treatment by taking it at intervals greater than one week. Therefore, 17% patients took tapered dose TCZ for a proportion of their follow-up (as follow-up started when qwTCZ was stopped). Median duration of tapered TCZ was 6 (2-13) months; 41/57 patients took tapered TCZ for 3 months or more. Median duration of qwTCZ in those that tapered was 12 (7-16.5) months.

Reflecting prescribing patterns in England, 53.3% received a csDMARD during the first 4 weeks after cessation of qwTCZ.

Relapse during follow-up after qwTCZ cessation

110/336 patients (32.7%) relapsed after stopping qwTCZ. Of these, 37/110 (33.6%) had a major relapse, representing 11.0% (37/336) of analysed patients. Median peak prednisolone dose used to treat relapse after qwTCZ cessation was 20 (10-40) mg/day. In those with major relapse, median peak prednisolone dose was 30 (15-60) mg/day. As expected, those that relapsed after stopping qwTCZ had been followed up for longer than non-relapsers. Where these optional data were collected,17/301 (5.65%) died during the follow-up period after qwTCZ cessation.

Relapse after qwTCZ cessation occurred in 52/243 (21.4%), 55/155 (35.4%), 45/100 (45.0%) and 35/72 (48.6%) of those followed up for 6, 12, 18 and 24 months respectively (Kaplan-Meier curve, Fig. 1a).Time to relapse was significantly shorter in those with LV-GCA (*P*=0.0296) (Fig. 1b), in those who had relapsed during qwTCZ (*P*=0.0017) (Fig. 1c), and in those not in remission at qwTCZ cessation (*P*=0.0036) (Fig. 1d).

There was no clear relationship between time to relapse and qwTCZ duration, TCZ tapering, or csDMARD use (Fig. S1e-f online).

20/57 (35.1%) patients that tapered TCZ relapsed after stopping qwTCZ. 12/57 (21.1%) relapsed whilst on their TCZ taper.

Exploratory descriptive correlations and multivariable Cox regression are shown in supplementary tables online.

Status at last follow-up

Patients who had relapsed following qwTCZ cessation were taking a higher dose of prednisolone at last follow-up than those who had not relapsed (median 6 (3-15) mg/day vs 0 (0-5) mg/day).

Discussion

In this multicentre service evaluation of 336 patients who received qwTCZ for relapsing or refractory GCA, 35.4% had relapsed by one year and 48.6% by two years after qwTCZ cessation, requiring substantial prednisolone dose escalation back to ranges comparable to those taken at the start of TCZ treatment: median 20 (10-40) mg/day. 33.6% relapsers had a major relapse. Time to relapse was shorter for those who had relapsed during qwTCZ therapy although this was an optional variable collected in only 85% patients. Time to relapse was shorter for those with LV involvement, although as we allowed LV-GCA to be detected at any time, there may have been more vascular imaging in relapsing patients compared to non-relapsers. Finally, time to relapse was shorter in patients who were not in remission at qwTCZ cessation.

Age ≥65, gender, GCA-related sight loss, qwTCZ treatment duration, TCZ taper, prednisolone dosing and csDMARD use were not associated with relapse, in contrast to some previous reports [2,8,9,10,11,12,13]. However, patient heterogeneity and variations in clinical practice in our non-randomised evaluation may have obscured a real association (e.g., extended duration TCZ was restricted to those fulfilling criteria believed to be associated with relapse; and GCA monitoring/treatment practices may have changed during/after COVID-related local and national lockdowns).

The strengths of this study include the large representative sample. Feasibility and generalisability were maximised by the strong incentive to keep accurate lists of GCA

patients prescribed TCZ to ensure central reimbursement; the standardised prescribing mandated by NHS England; and the focused data collection.

Our definition of relapse (worsening of disease activity requiring treatment change) was less restrained than EULAR's (return of disease activity) [7], and patients were selected for severity as NHS England restricts TCZ to relapsing or refractory GCA [6]. Despite this, our relapse rate of approximately 50% at two years was similar to meta-analyses of GCA patients treated with glucocorticoid alone [14] and methotrexate [2], the open label extension of the GiACTA trial [15], and other TCZ studies [12,16]. However, major relapse occurred more often (11.0%) than was reported in a meta-analysis of 2745 GCA patients (3.3%) [17].

Limitations of the retrospective design and reliance on clinical records meant that some variables, such as cumulative prednisolone dose, were not possible to calculate. Other than death, reasons for loss to follow-up were also not collected; nor did we collect data on reasons for early qwTCZ cessation or TCZ tapering, where this occurred.

In conclusion, TOC STOP provides descriptive real-world data on GCA patient outcomes in England after qwTCZ cessation. Relapse occurred in up to half of patients requiring a substantial increase in prednisolone dose. These data challenge the concept of GCA as a self-limiting disease and support a change to NHS England policy such as extended use of TCZ for GCA beyond 12 months or repeat treatment for GCA relapse.

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Data availability statement

Anonymised data are available upon reasonable request to the corresponding author.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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