


Original article

Tocilizumab for the treatment of giant cell arteritis in Scotland: a report on behalf of the Scottish Society for Rheumatology standards subgroup

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Abstract

Objectives. The aim was to describe a modern National Health Service (NHS) Scotland cohort of patients with GCA over 12 months of care to include clinical presentation, practices relating to assessment and treatment, and specifically, the use of tocilizumab.

Methods. A multicentre audit of patients newly diagnosed with GCA between November 2019 and October 2021 was established on behalf of the Scottish Society for Rheumatology. Clinical data were collected retrospectively by rheumatology teams at participating NHS centres using electronic patient records. An extended cohort of patients from NHS Lothian was examined to investigate outcomes of tocilizumab use for >1 year.

Results. Sixty-three patients from three NHS Scotland health boards were included, with analysis of data from 216 clinic episodes. Mean follow-up was 371 days. Mean age was 71 years; 62% were female. The most common presenting features were headache (93.6%), scalp tenderness (82.5%) and ocular symptoms (24%). At baseline, 63% of patients had at least one existing risk factor for adverse outcomes from high-dose CS use, namely hypertension (57.1%), diabetes (24%) and osteoporosis (11%). Thirty per cent of all patients (19 of 63) received tocilizumab, with only 11% (7 of 63) receiving tocilizumab owing to glucocorticoid risk factors at baseline. One-quarter of all patients (16 of 63) experienced relapse of GCA during follow-up, of whom six were subsequently treated with tocilizumab.

Conclusion. This multicentre audit demonstrates that despite its availability for patients with risk factors for CS adversity and those who suffer relapse of GCA, tocilizumab is used in less than one-quarter of patients who might benefit. The reasons for this require further exploration.

Key words: GCA, temporal arteritis, IL-6, ultrasonography, vasculitis

Key messages

- Among newly diagnosed GCA patients in Scotland, 30% have been started on tocilizumab.
- Tocilizumab is under-utilized in patients at risk of glucocorticoid-related adverse events.
- Rates of CS-free remission appear higher in patients receiving tocilizumab for ≥ 12 months.

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Introduction

Over the last decade, the assessment and management of GCA has evolved. Development of fast-track pathways across the National Health Service (NHS) has facilitated prompt access to specialist assessment in addition to non-invasive diagnostic tests, such as vascular US and PET-CT [1–3]. Furthermore, the advent of biologic therapy for GCA in the form of the IL-6 receptor inhibitor, tocilizumab, has provided an effective treatment option for medical management.

Traditional treatment of GCA entails prolonged use of glucocorticoids, usually commencing at doses of 40 to 60 mg of prednisolone, often for 1 year or longer [4]. However, this significant CS exposure frequently results in unwanted and serious side effects that impact physical and mental health and quality of life for patients (e.g. osteoporosis, psychiatric disturbance, weight gain, insulin resistance) [5]. The Giant Cell Arteritis Actemra (GiACTA) study, published in 2017, was a phase 3 trial of patients with relapsed or newly diagnosed GCA [6]. The trial demonstrated superiority of tocilizumab alongside a more rapid, 26-week glucocorticoid tapering regimen, vs placebo alongside a 26-week CS taper in obtaining CS-free GCA remission after 1 year.

In August 2018, after review of these data, the Scottish Medicines Consortium (SMC) approved the use of weekly s.c. injections of tocilizumab for 1 year in combination with tapering CS therapy for the treatment of GCA in Scotland [7]. This SMC guidance suggested that treatment with tocilizumab could be of value in those patients with GCA relapse or in those considered to be at risk from treatment with high doses of glucocorticoids. This allowed Scottish patients at risk of CS-related complications access to tocilizumab for newly diagnosed GCA, unlike National Institute for Clinical Excellence (NICE) guidance, which restricted use only to relapsed or refractory disease.

Few data exist relating to outcomes of patients treated with tocilizumab for GCA outside of clinical trials. In 2019, the Scottish Society for Rheumatology (SSR) standards subgroup set out to examine current practices in Scotland relating to treatment of GCA, particularly the use of tocilizumab. Furthermore, locally at the Rheumatic Diseases Unit in Edinburgh, additional review of our patient cohort examined real-world outcomes relating to tocilizumab use for >1 year.

The primary aim of the present study was to characterize current use of tocilizumab in Scotland for the management of GCA in relationship to patient selection, the indications for starting the drug and CS tapering practices thereafter. A secondary aim of the study was to describe a modern NHS Scotland GCA cohort over 12–18 months of care. The remit was to describe the clinical presentation of the cohort, the imaging and diagnostic modalities used, medical treatment, including use of CS-sparing immunosuppressive drugs, and the clinical outcome (primarily GCA relapse). By analysing an extended cohort of patients treated at the Rheumatic

Diseases Unit in Edinburgh, the final aim was to evaluate rates of CS-free remission and relapse in patients treated with tocilizumab for >1 year.

Methods

Study design

After approval to conduct this audit from the SSR's standards subgroup, all rheumatology units across Scotland were invited to participate before data collection commenced. Local Health Board approval was required to collect data onto the audit tool spreadsheet saved according to local guidelines, which would be, at minimum, on a password-protected personal computer in the NHS Health Board. The spreadsheet was registered as an information asset. Once approved by the local Information Governance and Security Manager, an anonymized data sheet was shared with the authors for collation. This anonymized clinical reporting form was designed by the investigators (M.S., N.D.M. and O.C.). According to NHS Research Ethics Committee guidelines, this work was classed as service evaluation, and formal ethical approval was not required.

Key information to be collected included data relating to anonymized patient demographics, date of diagnosis, date of first rheumatology assessment and subsequent follow-up visits, symptoms at diagnosis and follow-up, relevant investigations performed, including baseline and follow-up inflammatory markers (CRP and ESR), dose of CS used at the clinic visit, and use of any additional immunosuppressants as treatment for GCA. The presence of co-morbidities and risk factors susceptible to deterioration with prolonged glucocorticoid exposure was also recorded (i.e. hypertension, osteoporosis, diabetes mellitus). Treatment and management of patients was at the discretion of the responsible Consultant Rheumatologist and was in no way influenced by the investigators. Collection of data was retrospective and applied to patients of participating centres during a fixed time period, as outlined below.

Data collection

The SSR GCA audit comprised a multicentre audit of newly diagnosed patients with GCA (cranial, large vessel or both). Patients with Takayasu's arteritis were not included in the study, nor were patients with a history of GCA before the audit commencement date. The audit was established in advance of its capture period commencing on 1 November 2019. Initially, the planned follow-up period had been for 1 year, but owing to the coronavirus disease 2019 pandemic, new patient data were recorded for patients diagnosed up to 31 October 2020, with recording of follow-up of clinic visits and patient outcomes until 30 April 2021. This ensured that all participants had a minimum of 6 months of follow-up from diagnosis. Time to relapse was defined as from the date of first starting CSs to the date of clinical review confirming relapse.

Participating centres were provided with the clinical reporting form in paper and electronic format (Microsoft Excel), and uniform methods of data collection were outlined to each unit. Data were collected by local rheumatology teams using electronic patient records (e.g. TRAKCARE) and anonymized accordingly. Participating centres were asked to include all eligible patients diagnosed with GCA during the audit epoch.

Prolonged tocilizumab outcomes after 1 year cohort (Edinburgh)

At the Rheumatic Diseases Unit in NHS Lothian, Edinburgh, patients commencing tocilizumab for the treatment of GCA were included in a subgroup analysis. Patients were identified via pharmacy records of those prescribed tocilizumab for GCA. This included patients commencing tocilizumab before and during the SSR audit capture period. This facilitated a longer follow-up of such patients and review of outcomes in patients who continued tocilizumab treatment for >1 year and outcomes in those who stopped after ≤1 year of treatment. Data were collected anonymously in a similar manner to the SSR audit using electronic patient records (i.e. TRAKCARE) but over a significantly longer time frame (commencing January 2017). Data from the Edinburgh cohort were collected by H.P., B.H. and B.K. and presented by duration of follow-up in three groups: those receiving tocilizumab for <12 months, those receiving the drug for 12 months and those receiving treatment for >12 months.

Data analysis

At the end of the follow-up period, data from participating centres were anonymously collated into a single cohort of Scottish GCA patients. The investigators (O.C., H.F. and N.D.M.) analysed the SSR GCA audit data, while H.P. and B.H. analysed the Edinburgh prolonged tocilizumab group. Depending on the data type and distribution, data were described as the total number (*n*), percentage (%), mean with standard deviation (s.d.) in parentheses or median with inter-quartile ranges (IQR) or minimum and maximum values. Owing to the retrospective collection of data, some missing data occurred. This was applicable to inflammatory markers (CRP and ESR) and to BMI, which was not measured routinely in all centres or at all visits. No imputation of missing data was planned, and where applicable, a reduced number for the given variable is stated.

Results

Incidence and baseline clinical characteristics in the SSR GCA audit cohort

Patients attending the Rheumatology Departments at NHS Dumfries and Galloway, NHS Forth Valley and NHS Lothian were included in the audit. These areas serve a total population of 1,283,151 people, of whom 284,124 are aged ≥60 years (23.1%) [8]. In Scotland, 23.2% of

the population are aged ≥60 years, similar to the proportion of the population aged ≥60 years in England and Wales [9]. A total of 63 patients with a new diagnosis of GCA were included in the SSR GCA audit over the 12 month audit entry period. This suggested an incidence of new GCA diagnosis in these areas in Scotland in people aged ≥60 years of 22.1 per 100 000 population. Data from 216 individual clinical episodes were analysed. The mean age was 71 (8.3) years, and 62% of those included were female. Seventeen per cent of patients were current smokers and 31.2% former smokers. Baseline BMI data were available for 45 patients, who had a mean BMI of 27.6 (6.2) kg/m², with 49% of patients being in the obese category (BMI >30 kg/m²). Mean (s.d.) follow-up was for 371 (118) days.

Patient symptoms reported at baseline assessment are outlined in Table 1. The three most common presenting features were headache, scalp tenderness and ocular disturbance. The mean pre-diagnosis CRP was 73 (68) mg/l and ESR 57 (28) mm/h. The most commonly used investigation to aid diagnosis was vascular US (temporal ± axillary artery). This was performed in 42 of 63 patients (66.6%). US was positive in 73.8% of cases where used. The next most common tertiary investigation was temporal artery biopsy, which was used in 19% of cases (*n* = 12). Biopsy was positive in 66.6% of cases when used. Three patients underwent PET-CT, and two patients were investigated at baseline using MR angiography to assess for large vessel GCA involvement.

CS treatment and relapse characteristics in the SSR GCA audit cohort

Forty-six per cent (*n* = 29) of patients had been commenced on 60 mg of oral prednisolone daily before the initial rheumatology review (i.e. prescribed in primary care or accident and emergency). Twenty-five patients (39.6%) had been commenced on 40 mg of oral prednisolone daily before review. Nine patients (14.2%) had not been commenced on prednisolone before rheumatology review. Cessation of long-term CS treatment was achieved in five patients (8%). This occurred within 5 months in two cases, both of whom subsequently had a relapse while no longer on CSs. In the other three patients, CSs were stopped by months 8, 9 and 11 after commencement.

During the follow-up period, 16 patients (25.4%) suffered a relapse of GCA activity. The percentage of females who relapsed was 56.2%, and the mean (s.d.) prednisolone dose on relapse was 19 (20) mg. The mean (s.d.) CRP at relapse was 11.9 (24.7) mg/l, and mean (s.d.) ESR was 20.2 (24.8) mm/h. The median time to relapse was 172 days (minimum 24 days, maximum 363 days). The frequency of symptoms of GCA at relapse mirrored those at baseline assessment, with headache (62.5%), scalp tenderness (37.5%) and ocular disturbance (25%) representing the three most reported symptoms (Table 2). Of the 16 patients who experienced a GCA relapse during the follow-up, six patients were

TABLE 1 Frequency of clinical features reported at baseline assessment

Symptom or clinical feature		Patients affected [n (%)]
		(n = 63 total)
Headache		59 (93.6)
Scalp tenderness		52 (82.5)
Ocular involvement	Any symptom	15 (23.8)
	Blurred vision	4 (6.3)
	Diplopia	3 (4.7)
	Amaurosis fugax	1 (1.5)
	Other (zig-zag lines, spots, discomfort, tunnel vision)	4 (6.3)
Jaw claudication		13 (20.6)
Polymyalgic symptoms		12 (19)
Temporal artery abnormality	Any abnormality	10 (15.8)
	Tender artery	8 (12.7)
	Thickened artery	3 (4.7)
Systemic symptoms		6 (9.5)
Large vessel involvement		3 (4.7)

TABLE 2 Frequency of clinical features reported at GCA relapse assessment

Symptom or clinical feature	Affected patients [n (%)]
(n = 16 total)	
Headache	10 (62.5)
Scalp tenderness	6 (37.5)
Ocular symptoms	4 (25)
Jaw claudication	3 (18.75)
Polymyalgic symptoms	3 (18.75)
Temporal artery tenderness	1 (6.25)

commenced on s.c. tocilizumab as a result of this relapse. Apart from tocilizumab, only one other CS-sparing agent was used in this cohort, when Methotrexate was used in a single patient.

Treatment with tocilizumab in the SSR GCA audit cohort

At GCA diagnosis, 63.4% of patients had at least one existing co-morbidity at risk of worsening with prolonged CS treatment (57% of patients had a documented history of hypertension, 16% had been diagnosed with diabetes mellitus and 11% had a known history of osteoporosis).

Of the 63 patients included in this analysis, 19 patients were treated with s.c. tocilizumab as adjunctive therapy for GCA during the audit follow-up period. The reasons provided for commencement of tocilizumab therapy are summarized in [Table 3](#).

Extended NHS Lothian cohort—tocilizumab beyond 1 year

A total of 36 patients were commenced on s.c. tocilizumab for the treatment of GCA in the NHS Lothian

TABLE 3 Indications provided for commencement of tocilizumab for GCA treatment

Indication provided	Number of patients (% of total cohort)
Risk of CS side effects at baseline or because of developing problems owing to CS treatment	7 (11)
GCA relapse	6 (9.5)
Difficulty in weaning off CSs	4 (6.3)
Unclear rationale	2 (3.2)

Rheumatic Diseases Unit, Edinburgh, between January 2017 and July 2020. All patients were treated initially with high-dose oral CSs. The mean (s.d.) age of this cohort was 69 (7) years, with 81% of patients being female. Patients had a mean (s.d.) BMI of 29.1 (6.4) kg/m². The reasons for commencing tocilizumab included disease relapse (47%), owing to the occurrence of side effects of CSs (36%) and owing to the risk of CS-related side effects (11%).

The mean follow-up of the total group was for 27.5 (10.9) months, but data are presented in three groups depending on the duration of tocilizumab treatment (<12 months, 12 months and >12 months). Five patients received tocilizumab for <12 months, nine patients received the drug for 12 months and 22 patients received treatment with tocilizumab for >12 months. Multiple reasons for continuing with tocilizumab treatment beyond 12 months were provided, including the presence of large vessel vasculitis (30% of cases), remaining on high-dose prednisolone (8.6%), existing unilateral visual loss (8.6%) and restarting of the drug after disease relapse (17.3%). All patients who continued tocilizumab beyond 12 months (outside SMC guidance) had additional approval, in line with Scottish medicines governance policies. The duration of tocilizumab treatment,

TABLE 4 Edinburgh extended cohort: outcomes for patients with GCA receiving tocilizumab for <12 months, for 12 months and for >12 months

Parameter	<12 months	12 months	>12 months
Number of patients receiving tocilizumab	5	9	22
Duration of treatment, mean (s.d.), months	5.5 (1.9)	12.1 (0.7)	25.9 (11.9)
Achieved CS-free remission, <i>n</i> (%)	0 (0)	7 (78)	9 (41)
Number relapsing while receiving tocilizumab	0	0	0
Number relapsing after discontinuing tocilizumab	4	1 (4 months after stopping tocilizumab)	1 (1 month after stopping tocilizumab)
Reason for early discontinuation	Hypertension, hypercholesterolaemia, neutropenia, diverticulitis	–	–

rates of achievement of CS-free remission and relapse rates during and after treatment with tocilizumab are provided in [Table 4](#).

Discussion

The use of tocilizumab in the treatment of GCA is relatively novel, with the landmark GiACTA study being published in 2017 [6]. There have been few other studies of the effectiveness of this treatment in the first 12 months after GCA diagnosis. A recent Cochrane review identified only one other high-quality, randomized controlled trial examining the effectiveness of tocilizumab alongside CSs for this indication [10]. This second study was a phase 2 trial including only 30 patients but did demonstrate a favourable outcome in patients receiving tocilizumab compared with placebo [11]. This highlights a need for further data, including real-world experiences, to monitor the use, the effectiveness and safety of this treatment, particularly beyond 12 months.

The primary aim of this audit was to assess current practices in Scotland in relationship to tocilizumab use for GCA treatment. Since SMC approval in 2018, tocilizumab has been available in Scotland. The current audit demonstrates that a minority of patients diagnosed with GCA between November 2019 and October 2020 were treated with tocilizumab therapy, but many who might benefit from a more rapid CS-tapering regime were not. This audit shows that at diagnosis, 63% of patients had a co-morbidity that would put the patient at increased risk of glucocorticoid side effects, but only 11% of patients were treated with tocilizumab for this indication. Furthermore, 25% of patients in this survey experienced a relapse of GCA, but only 9.5% of patients were commenced on tocilizumab after relapse.

The reasons for this hesitancy in prescribing tocilizumab in patients who might derive benefit is currently unclear. Possible reasons might include concern about use of biologic treatment in an older age group, the presence of valid contraindications or co-morbidities, such as previous history of diverticulitis, recurrent infections, concern regarding coronavirus disease 2019, previous malignancy, tuberculosis infection, or patient's choice. A

recent series of tocilizumab use for GCA in 21 patients >80 years of age revealed relatively encouraging results [12]. One-third of patients experienced an adverse event related to tocilizumab, mostly in the form of blood dyscrasias, such as hypercholesterolaemia, neutropenia and hepatic transaminitis, although there were cases of incident infections and one death after mesenteric infarction. Another report demonstrated infection rates higher than originally reported in clinical trials, particularly when patients were taking higher doses of glucocorticoids [13].

It might also require some time and further confidence in the effectiveness and safety of this treatment in a GCA population before traditional practices of glucocorticoid monotherapy are to change [14]. Early signs of this might be reflected by the fact that only one patient in this audit was commenced on a CS-sparing agent other than tocilizumab (i.e. Methotrexate). We accept that tocilizumab might not be a suitable treatment for all patients with GCA or those who relapse or have risk of glucocorticoid adversity. However, based on the present survey a significant proportion of patients might be missing out on the benefit of reduced CS exposure. The reasons for this do require further exploration and consideration.

Furthermore, a regularly encountered dilemma for treating rheumatologists who have used tocilizumab to treat GCA relates to a lack of certainty regarding the optimal strategy after 1 year of treatment, as was performed in the original GiACTA trial [6]. Follow-on data from the original GiACTA cohort suggest that ~50% of patients will relapse in the year after discontinuation of tocilizumab treatment [15]. The investigators advise careful vigilance for disease relapse in this scenario. Thankfully, re-introduction of tocilizumab treatment was effective in reinstating remission. In the present study, we took the opportunity to analyse a cohort of 36 patients from the Edinburgh Rheumatic Diseases Unit who were followed up beyond 1 year of treatment. None of the 36 patients receiving tocilizumab (for any duration) experienced relapse while taking the treatment, reflecting the high rates of remission seen in real-world data that are reported retrospectively by other centres [16, 17].

Four of the five patients who stopped tocilizumab treatment before 12 months of therapy experienced

relapse during subsequent follow-up. In those receiving tocilizumab for ≥ 12 months ($n=30$), only two relapses were recorded in 11 patients who had stopped tocilizumab treatment. On review of the 22 patients who received treatment with tocilizumab for >12 months, several reasons were provided for each patient to continue this treatment on an exceptional basis. Exceptional use was reserved for patients with resistant disease, with large vessel involvement or in those who had suffered unilateral sight loss. Some retrospective data suggest a reduced risk of visual symptoms when tocilizumab is used, but this requires clarification in prospective trials [17]. Only 41% of patients who were treated with tocilizumab for >1 year achieved CS-free remission, perhaps reflecting the fact that these patients had more resistant and severe disease.

This multicentre audit describes a contemporary cohort of patients in Scotland with a new diagnosis of GCA. The assessment and treatment of patients suspected of having GCA has evolved considerably over the last decade. Improvements in imaging techniques, such as vascular US and PET-CT, have led to a decrease in the reliance on temporal artery biopsy to confirm this clinical diagnosis. The present survey, spanning three separate rheumatology centres in Scotland, indicates that vascular US is now the first-line specialist test in the assessment of GCA in Scotland. The estimated incidence of GCA in Scotland from this analysis (22 per 100,000 people aged ≥ 60 years) is similar to that reported in other regions in Northern Europe, particularly Scandinavia (21.5 per 100,000 people aged ≥ 50 years) [18]. The clinical symptoms and manifestations at diagnosis reported in this audit are typical of most GCA cohorts, mirroring the symptoms reported in a recent large-scale meta-analysis [19]. Commencement of high-dose glucocorticoids in this SSR audit cohort was reasonably consistent with the recommendation from the 2010 British Society for Rheumatology's guideline to commence high-dose glucocorticoid treatment when clinical suspicion of GCA is raised [4]. However, in this cohort 14% of patients had not received CSs by the time of rheumatological assessment. The updated British Society for Rheumatology's guideline from 2020 provides more detail, advising that glucocorticoids should be started in cases 'strongly suspected' to have GCA by the treating clinician [20]. The reasons why these patients did not receive CSs in primary or emergency care are unclear but might be related to the availability of fast-track GCA pathways and rapid, same-day GCA assessment. However, this requires further exploration. The use of GCA probability scores, such as that devised by the Southend group, might inform guidance for primary care providers regarding when and when not to commence CSs before secondary care review [21].

The limitations of the present study are underlined by the retrospective nature of data collection and use of electronic patient records where all required information was not recorded. The accuracy of recording of prednisolone dosing at various time points (e.g. 6 or 12 months

post-treatment) was not robust enough to facilitate an analysis of whether CS requirement was reduced in patients who received tocilizumab compared with those who did not. The reported incidence calculation of GCA diagnosis is based on case reporting by rheumatologists, and factors such as missing reports of cases or GCA patients being treated in primary care might have led to underreporting of GCA cases. Additionally, the generalizability of this study to the whole of Scotland is not possible owing to the absence of patients from the North and West of Scotland. Furthermore, with respect to the Edinburgh cohort of extended tocilizumab use, the number of patients included is small; however, few cohorts exist that report these data, and it represents an area where guidance is urgently needed to inform practice.

Conclusions

Despite its availability for patients with GCA and co-existent risk factors for adverse reactions to prolonged, high-dose CSs, this audit demonstrates that tocilizumab is used in less than one-quarter of patients who might benefit. Furthermore, not all patients who experience disease relapse subsequently receive tocilizumab therapy. This study demonstrates that vascular US is now the most common first-line specialist investigation in the assessment of GCA in Scotland. Lastly, use of tocilizumab is associated with a very low relapse rate during treatment. Relapse rates when treatment with tocilizumab is for ≥ 12 months are lower than in those treated with tocilizumab for <1 year. Further research is required to understand why the rate of tocilizumab prescription in those with GCA relapse or at risk of CS toxicity at baseline is low.

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Data availability statement

Data underlying this article may be shared upon reasonable request and subsequent approval by the audit team and SSR's standards subgroup.

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