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Long-term effect of tocilizumab in patients with giant cell arteritis: open-label extension phase of the Giant Cell Arteritis Actemra (GiACTA) trial

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Summary

Background The combination of tocilizumab plus a glucocorticoid taper is effective in maintaining clinical remission without requiring additional glucocorticoid therapy in patients with giant cell arteritis, as shown in part one of the Giant Cell Arteritis Actemra (GiACTA) trial. However, the duration of the tocilizumab effect after discontinuation is unknown. Here, we explored the maintenance of efficacy 1 year after discontinuation of tocilizumab treatment, the effectiveness of retreatment with tocilizumab after relapse, and the long-term glucocorticoid-sparing effect of tocilizumab.

Methods In part one of the GiACTA trial, 251 patients were randomly assigned (2:1:1:1) to receive subcutaneous tocilizumab (162 mg) once a week or every other week, combined with a 26-week prednisone taper, or placebo combined with a prednisone taper over a period of either 26 weeks or 52 weeks. Patients in clinical remission stopped masked injections at 1 year (the conclusion of part one). In part two, treatment was at the investigators' discretion and could consist of no treatment, tocilizumab, glucocorticoids, methotrexate, or combinations of these, for two years. Maintenance of efficacy as assessed by clinical remission (defined as absence of relapse determined by the investigator), cumulative glucocorticoid dose, and long-term safety were exploratory objectives in part two of the trial. This trial is registered at ClinicalTrials.gov, NCT01791153.

Findings 215 patients participated in part two of the trial; 81 patients who were randomly assigned to tocilizumab once a week in part one were in clinical remission after 1 year, of whom 59 started part two on no treatment. 25 of these 59 patients (42%) maintained tocilizumab-free and glucocorticoid-free clinical remission throughout part two. Median (95% CI) cumulative glucocorticoid doses over 3 years were 2647 mg (1987–3507) for tocilizumab once a week, 3948 mg (2352–5186) for tocilizumab-every-other-week, 5277 mg (3944–6685) for placebo with a 26-week prednisone taper, and 5323 mg (3900–6951) for placebo with a 52-week prednisone taper (van Elteren $p \leq 0 \cdot 001$, tocilizumab once a week *vs* placebo groups; $p < 0 \cdot 05$, tocilizumab-every-other-week *vs* placebo groups). Tocilizumab-based regimens restored clinical remission among patients who experienced relapse in part two and were treated (median time to remission: 15 days for tocilizumab alone [n=17]; 16 days for tocilizumab plus glucocorticoids [n=36]; and 54 days for glucocorticoids alone [n=27]). No new or unexpected safety findings were reported over the full 3 years of the study.

Interpretation Giant cell arteritis remains a chronic disease that entails ongoing management and careful vigilance for disease relapse, but continuous indefinite treatment with immunosuppressive drugs is not required for all patients. A substantial proportion of patients treated with tocilizumab for one year maintain drug-free remission during the two years after tocilizumab cessation. For patients who experience relapse, tocilizumab can be used to manage relapses, but it remains prudent to include prednisone for patients who experience relapse because of the risk for vision loss.

Funding F Hoffmann-La Roche.

Introduction

Giant cell arteritis is a chronic disease associated with vision loss, headaches, polymyalgia rheumatica, jaw and limb claudication, and aortic aneurysms.[1,2] In part one of the Giant Cell Arteritis Actemra (GiACTA) trial,[3] a 52-week randomised, double-blind trial, treatment with tocilizumab (an interleukin-6 receptor [IL-6R] antagonist) plus blinded prednisone taper was more effective than was placebo plus blinded prednisone taper for inducing sustained remission;[3] however, the duration of the effects of tocilizumab is unknown. Patients with giant cell arteritis might experience continued benefit after discontinuation of successful initial therapy. In a previous phase 2 trial, among 17 of 20 patients randomly assigned to receive intravenous tocilizumab, all were in remission after 1 year and all stopped tocilizumab treatment; nine of the patients remained in remission for a mean of 29·3 months after stopping tocilizumab.[4] In another randomised controlled

Research in context

Evidence before this study

Part one of this study was a 1-year phase 3 randomised controlled trial in which subcutaneous tocilizumab plus prednisone tapering was superior to prednisone tapering alone for achieving sustained glucocorticoid-free remission in patients with giant cell arteritis. However, the duration of tocilizumab treatment in reported clinical trials has been arbitrary, and the optimal length of tocilizumab therapy and the effect after 1 year of treatment are not known. We searched PubMed from inception to March, 2020, for clinical trial articles including the terms "giant cell arteritis" AND "remission" and found 19 articles. In one phase 2 randomised controlled trial, nine of 17 patients who achieved remission after 1 year of intravenous tocilizumab and then stopped treatment remained in remission for a mean of 29 months. Another randomised controlled trial reported that a larger proportion of patients treated with initial high-dose methylprednisolone achieved sustained remission and had lower cumulative prednisone exposure up to 78 weeks than those treated with placebo induction therapy (initial high-dose methylprednisolone pulse therapy, however, is not in giant cell arteritis treatment recommendations). Available data suggest that further investigation is needed into the concept that patients with giant cell arteritis might experience sustained remission and reduced glucocorticoid exposure after discontinuation of successful initial therapy.

Added value of this study

Part two of the GiACTA study provides data on the maintenance of efficacy in patients who discontinued tocilizumab treatment after achieving remission and on the long-term glucocorticoid-sparing effect provided by tocilizumab treatment. Among patients who achieved clinical remission within 1 year of weekly tocilizumab treatment plus a 6-month prednisone-tapering schedule, 42% were able to maintain tocilizumab-free and glucocorticoid-free clinical remission for another 2 years after withdrawal of all giant cell arteritis treatment. Patients who did experience relapse regained remission after restarting treatment with tocilizumab once a week.

Implications of all the available evidence

A substantial proportion of patients with giant cell arteritis who achieve remission with tocilizumab treatment can maintain tocilizumab-free and glucocorticoid-free remission for another 2 years after stopping treatment. Tocilizumab can be used to manage relapses, but it remains prudent to include prednisone for patients who experience relapse because of the risk for vision loss. The results of this study support the principle that continuous indefinite treatment with immunosuppressive drugs is not required to maintain disease control for all patients with giant cell arteritis.

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trial that included 27 patients with giant cell arteritis, initial high-dose intravenous methylprednisolone treatment led to more patients achieving sustained remission and lower cumulative prednisone exposure up to 78 weeks than did standard prednisone taper alone.[5] Observational studies suggest that although between 40% and 74% of patients treated with glucocorticoids are at risk for relapse, some can successfully taper or discontinue treatment entirely.[6–10] These studies support the concept that patients might experience sustained remission and reduced glucocorticoid exposure after successful initial therapy.

Glucocorticoids still have an important role in managing giant cell arteritis. Many patients undergo lengthy glucocorticoid courses intended to prevent relapses;[8,11–15] however, relapses occur in some patients even at moderate glucocorticoid doses.[16] In part one of the GiACTA trial, relapses occurred within 1 year after treatment cessation in 58% of patients treated with prednisone alone; 49% of those relapses occurred in patients receiving more than 5 mg per day.[16]

Part two of the GiACTA trial was designed to describe the long-term safety and maintenance of efficacy after 52 weeks of tocilizumab treatment in patients with giant cell arteritis. The aims were to explore the maintenance of efficacy after tocilizumab treatment was discontinued, the effectiveness of retreatment with tocilizumab therapy in patients who experienced relapse, and the possible long-term glucocorticoid-sparing effect of tocilizumab. Although part two of the GiACTA trial was not randomised, it is, to our knowledge, the first large phase 3 trial to report the longer-term efficacy and safety of a novel therapy for giant cell arteritis.

Methods

Study design and participants

The study design of the GiACTA trial and results from part one of the trial have been published previously.[3,17] Briefly, in part one, patients with newly diagnosed or relapsing giant cell arteritis were randomly assigned (2:1:1:1) to one of the four treatment groups: once a week subcutaneous tocilizumab 162 mg plus a 26-week prednisone taper (tocilizumab once-a-week), every-other-week subcutaneous tocilizumab 162 mg plus a 26-week prednisone taper (tocilizumab-every-other-week), once-a-week subcutaneous placebo plus a 26-week prednisone taper, or once-a-week subcutaneous placebo plus a 52-week prednisone taper.

Patients who completed the 52-week double-blind part of the study were eligible to enter part two, which was a 104-week, open-label, non-randomised follow-up period. Patients stopped their masked injections at the end of part one, but original treatment assignments remained masked throughout part two. Investigators could adjust patients' treatments at any time during part two, including at the start. There were two reasons for this design. First, serum IL-6 concentrations increase after tocilizumab

initiation.[18] Because the effect of abrupt discontinuation of IL-6R blockade on giant cell arteritis activity was unknown, there was concern that relapse could threaten a patient's vision. Second, the treatment received in part one of the trial largely dictated the patient's clinical status at the beginning of part two; some patients were in remission and off all treatments, some were in remission but remained on treatment, and some were not in remission and could be on or off treatment. Therefore, implementation of a randomised trial design was not possible for part two. Rather, investigators were permitted to treat patients with no treatment, open-label tocilizumab once a week (162 mg), prednisone or methotrexate, or any combination of these, at their discretion.

The GiACTA protocol was approved by the institutional review board at each site, and the study was done in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent.

Procedures

Efficacy was assessed every 12 weeks during part two in the intention-to-treat population. Additional visits could occur if patients had relapses or adverse events. Relapse in part two was defined as recurrent giant cell arteritis symptoms or signs or an erythrocyte sedimentation rate 30 mm/h or higher attributable to giant cell arteritis, as determined by the investigator. Clinical remission was defined as absence of relapse as determined by the investigator. In part one, remission also necessitated normalisation of C-reactive protein, but this was not part of the definition of clinical remission in part two. Maintenance of clinical remission in part two was defined as the absence of relapse throughout part two after the achievement of clinical remission at the end of part one. Treatment-free remission was defined as clinical remission without the use of tocilizumab or glucocorticoids. Methotrexate use was not considered in the definition of treatment-free remission because no patients newly started methotrexate at the beginning of part two, and none of the 23 patients receiving methotrexate in part one increased their dose at the start of part two (appendix p 7).

Outcomes

Maintenance of efficacy throughout part two was the main efficacy outcome. Treatment (no treatment, glucocorticoids only, tocilizumab only, or glucocorticoids plus tocilizumab) was assessed at the start of part two, before relapse, and

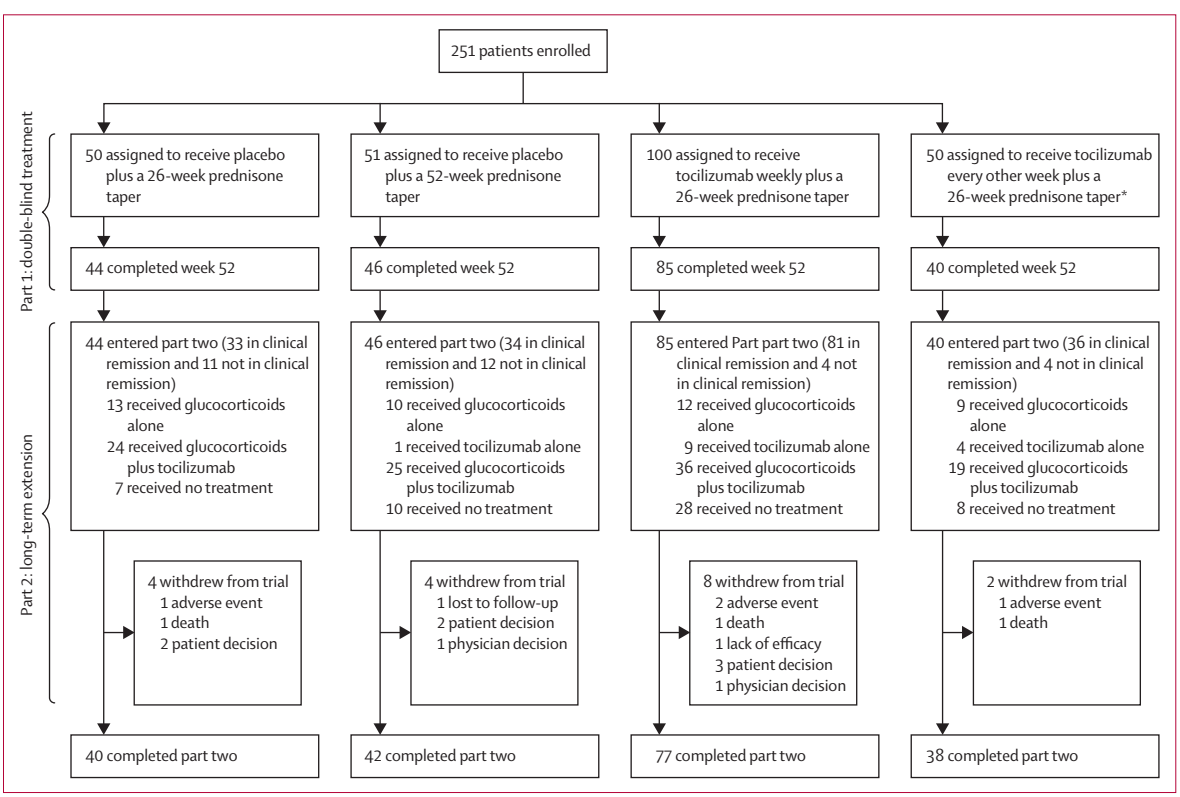

Figure 1: **Randomisation and follow-up during the double-blind (part one) and long-term extension (part two) periods of the GiACTA trial**
A report on the double-blind period has been published.[3] Treatment received during part two indicates the treatment during the entire 2 years of part two. Methotrexate was received by 31 patients in part two (placebo with 26-week prednisone taper n=5, placebo with 52-week prednisone taper n=10, tocilizumab-weekly n=12, tocilizumab-every-other-week n=4). One of the deaths, casued by an aortic aneurysm rupture in a patient randomly assigned to tocilizumab every other week, was considered related to giant cell arteritis by the investigator. *One patient was randomly assigned but did not receive treatment. Therefore, 49 patients were included in the intention-to-treat population.

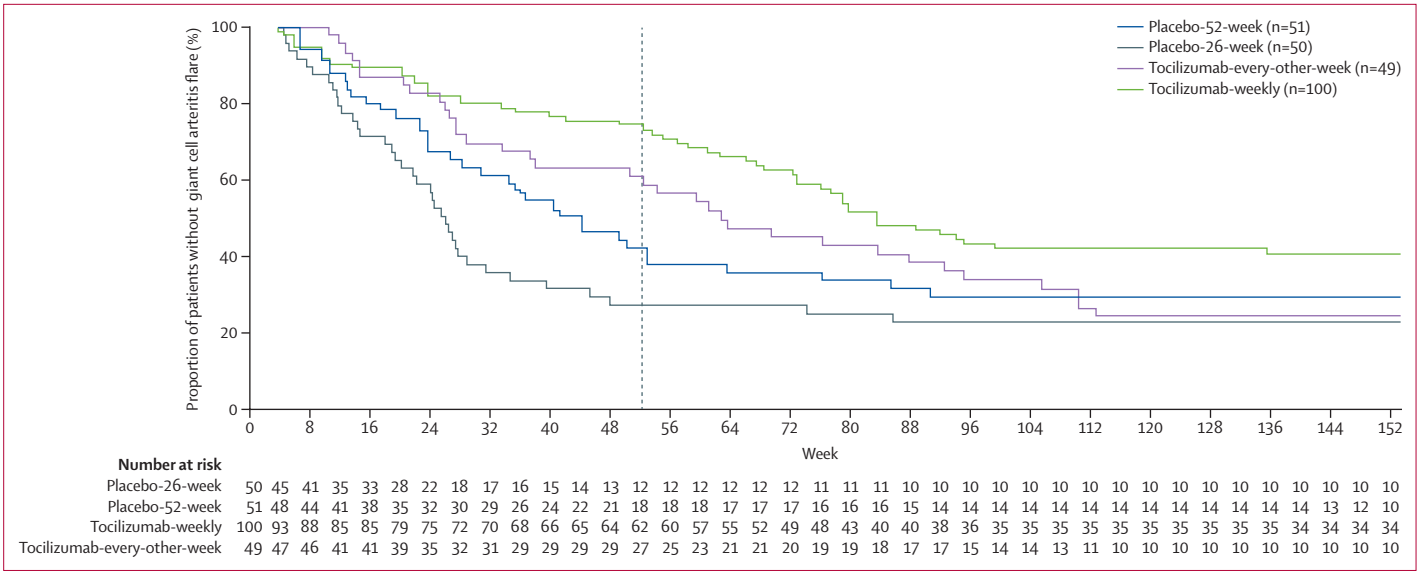

Figure 2: **Kaplan-Meier plot of time to first relapse after clinical remission according randomly assigned treatment in part one**
Patients who were never in remission were censored at day 1, and patients who withdrew were censored from the time of withdrawal. The vertical dashed line at week 52 represents the start of part two.

for of the full duration of part two of the trial. Cumulative glucocorticoid dose and maintenance of tocilizumab-free and glucocorticoid-free clinical remission were analysed according to the original treatment assignments in part one.

Patient-reported outcomes were evaluated in post-hoc analyses of subgroups of patients who maintained tocilizumab-free and glucocorticoid-free clinical remission throughout parts one and two, and in patients who achieved clinical remission in part one and were initially tocilizumab-free and glucocorticoid-free in part two. The 36-Item Short Form Health Survey (SF-36) Mental Component Summary (MCS) scores were assessed (range 0–50; higher scores represent better health-related quality of life). Serum IL-6 concentrations were measured in these subgroups using validated enzyme-linked immunosorbent assays (Quantikine, Leiden, the Netherlands). Post-hoc analyses of SF-36 MCS were done because earlier studies suggested an effect of IL-6R blockade on pain, fatigue, and mood.[19–21]

The safety population included all patients in the intention-to-treat population who received at least one dose of trial medication. Adverse event data were pooled across part one and part two and were assessed using two approaches. First, we assessed adverse events in all patients who received tocilizumab in any part of the study (ie, all events that occurred after any exposure to tocilizumab ['ever-received-tocilizumab']), and in patients assigned to the placebo groups who never received tocilizumab or who experienced adverse events occurring before starting tocilizumab ('never-received-tocilizumab'). Second, we assessed all adverse events that occurred during or within 14 days after tocilizumab treatment (ie, on-tocilizumab events) versus all other adverse events (not-on-tocilizumab events; appendix pp 13–14).

Statistical analysis

Exploratory efficacy and safety analyses were done in the intention-to-treat population, and post-hoc analyses were done in the indicated subgroups. Glucocorticoid doses (prednisone equivalents) were calculated for all conditions (giant cell arteritis and non-giant cell arteritis) and compared using the van Elteren test stratified by starting prednisone dose (≤30 mg per day *vs* >30 mg per day). Subgroup comparisons for continuous variables were based on mixed model with repeated measures analysis, with the nominal type 1 error set at 5% and no adjustment for multiple comparisons. Other comparisons were made using descriptive statistics. This trial is registered with ClinicalTrials.gov, NCT01791153.

Role of the funding source

F Hoffmann-La Roche was involved in the study design, analysis and interpretation of the data, writing of the report, and decision to submit the paper for publication. The investigators and sponsor designed the study and gathered and analysed the data. The sponsor provided study medication and participated in manuscript editing. All authors had access to the data, vouch for the fidelity of this manuscript to the protocol, and participated in writing the manuscript. JHS and JH had full access to all the data in the study and had final responsibility for the decision to submit the manuscript for publication.

Results

215 (86%) of 251 patients from part one of the trial entered part two of the trial, and 197 (92%) of 215 patients completed all 2 years of follow up. 184 (86%) of 215 patients were in clinical remission at the end of part one (week 52) regardless of whether they did or did

	Placebo-26-week	Placebo-52-week	Tocilizumab-weekly	Tocilizumab-every-other-week
In clinical remission at week 52*	33/44 (75%)	34/46 (74%)	81/85 (95%)	36/40 (90%)
Maintained clinical remission throughout part two, regardless of tocilizumab and glucocorticoid treatment†	18/33 (55%)	20/34 (59%)	38/81 (47%)	13/36 (36%)
Maintained clinical remission throughout part two and tocilizumab-free and glucocorticoid-free throughout part two‡	7/18 (39%)	10/20 (50%)	25/38 (66%)	8/13 (62%)
In clinical remission at week 52 and receiving no tocilizumab and glucocorticoid treatment at week 52*	12/44 (27%)	16/46 (35%)	59/85 (69%)	28/40 (70%)
In clinical remission at week 52, receiving no tocilizumab and glucocorticoid treatment at week 52, and maintained tocilizumab- and glucocorticoid-free clinical remission throughout part two§	7/12 (58%)	10/16 (63%)	25/59 (42%)	8/28 (29%)

Data are n/N (%). Data on patients who completed week 52 and entered part two of the trial. Clinical remission was defined as the absence of disease activity as determined by the investigator. *Percentages based on number of patients who completed week 52. †Percentages based on number of patients in clinical remission at week 52. ‡Percentages based on number of patients who maintained clinical remission throughout part two. §Percentages based on number of patients in clinical remission at week 52 and receiving no tocilizumab and glucocorticoid treatment at week 52.

Table 1: **Remission in part two according to randomly assigned treatment in part one**

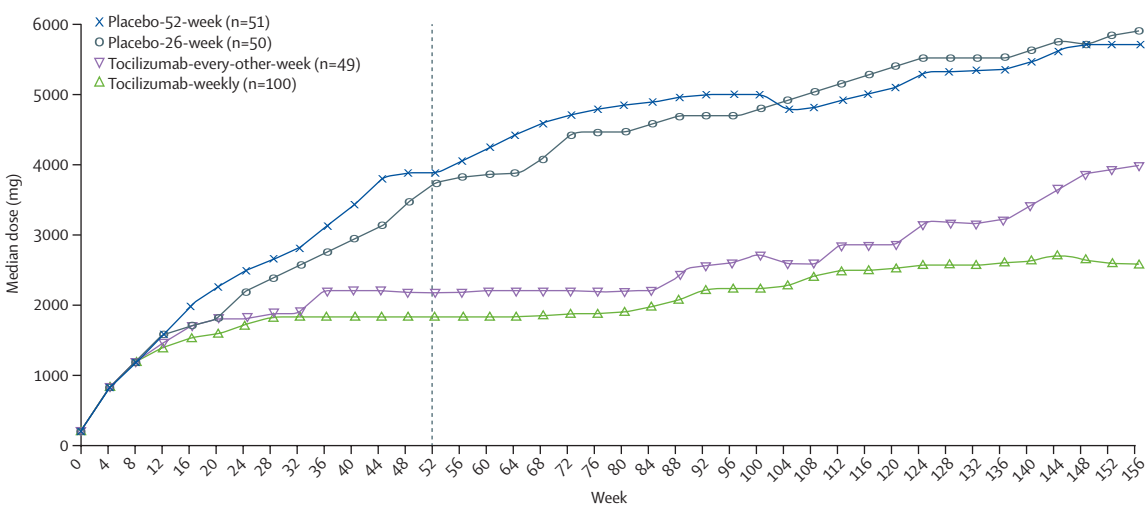

Figure 3: **Cumulative glucocorticoid dose according to randomly assigned treatment in part one until patient withdrawal or the end of follow-up**
Cumulative dose is based on actual records and includes all prednisone received (prednisone or prednisone equivalent dose, including all study medication and commercial prednisone). Patients who withdrew from the study were excluded from the summaries at subsequent visits.

not receive treatment (figure 1). Demographic and disease characteristics are summarised in the appendix (p 8).

59 (66%) of 90 patients in the original placebo groups started part two on prednisone compared with 32 (26%) of 125 patients in the original tocilizumab groups. This disparity in prednisone treatment resulted from the higher proportions of relapses in part one among the placebo groups (figure 2). Relapses in part one necessitated escape prednisone treatment, which was generally continued throughout part two. Consequently, patients from the original placebo groups received more prednisone before their first disease relapse in part two than did those from the original tocilizumab groups (median cumulative prednisone dose 935 mg [n=11] in the placebo with 26-week taper group; 826 mg [n=8] in the placebo with 52-week taper group *vs* 431 mg [n=17] in the tocilizumab once-a-week group, and 751 mg [n=5] in the tocilizumab once-every-other week group; appendix p 9).

Over the 3-year study period, the median time to first giant cell arteritis disease flare after clinical remission was 577 days in the tocilizumab once-a-week group, 428 days in the tocilizumab-every-other-week group, 162 days in the placebo with 26-week prednisone taper group, and 295 days in the placebo with 52-week prednisone taper group (figure 2).

Among the 81 patients in the original tocilizumab once-a-week group who were in clinical remission at week 52, 59 (73%) were tocilizumab-free and glucocorticoid-free at the start of part two (figure 1, table 1). 25 (42%) of these patients maintained tocilizumab-free and glucocorticoid-free clinical remission throughout part two, including 11 with relapsing giant cell arteritis and

14 with newly diagnosed giant cell arteritis at baseline. In the original tocilizumab-every-other-week group, 28 (78%) of 36 patients in clinical remission at the start of part two were tocilizumab-free and glucocorticoid free; eight (29%) of these patients maintained tocilizumab-free and glucocorticoid-free clinical remission throughout part two. Among the 67 patients in the combined placebo groups who were in clinical remission at week 52, 28 (42%) were tocilizumab-free and glucocorticoid-free at the start of part two (figure 1, table 1). 17 (61%) of these patients maintained tocilizumab-free and glucocorticoid-free remission throughout part two.

Among all patients enrolled in part one of the trial, the numbers who were in sustained remission (defined as absence of flare and normalisation of C-reactive protein concentration to <1 mg/dL [from week 12 through week 52 and adherence to the prednisone taper]) at week 52 and maintained tocilizumab-free and glucocorticoid-free clinical remission throughout part two were as follows: 24 (24%) of 100 in the original tocilizumab once-a-week group, 8 (16%) of 49 in the original tocilizumab-every-other-week group, 5 (10%) of 50 in the placebo plus 26-week taper group, and 6 (12%) of 51 in the placebo plus 52-week taper group (appendix p 10).

In part one, tocilizumab treatment was associated with a reduction in median cumulative prednisone dose over 1 year.[3] This reduction was maintained through year 3 even though 57 (46%) of 125 patients from the tocilizumab groups who completed part one did not continue tocilizumab treatment in part two. The total median cumulative prednisone doses over 3 years were 2647 mg (95% CI 1987–3507) in the tocilizumab once-a-week group, 3948 mg (2352–5186) in the tocilizumab-every-other-week group, 5277 mg (3944–6685) in the placebo plus 26-week taper group, and 5323 mg (3900–6951) in the placebo plus 52-week taper group (van Elteren p≤0·0001 for tocilizumab once-a-week and p<0·05 for tocilizumab-every-other-week *vs* combined placebo groups; figure 3).

Overall treatment patterns in part two among all 184 patients who achieved clinical remission at week 52 and entered part two are summarised in the appendix (p 11). Among 89 patients who achieved clinical remission at week 52 and experienced their first relapse during part two, nine (10%) had restarted tocilizumab treatment before relapse (eight [9%] were receiving prednisone plus tocilizumab; one [1%] was receiving tocilizumab alone), 47 (53%) were receiving no treatment before relapse, and 33 (37%) were had restarted prednisone alone before relapse (appendix p 12). The mean glucocorticoid dose was 5·4 (SD 4·5) mg per day among patients receiving prednisone alone and 9·5 (13·2) mg per day among patients receiving prednisone plus tocilizumab.

Among the 89 patients who experienced at least one episode of relapse in part two, 84 (94%) received treatment (defined as newly initiated treatment received <30 days after the occurrence of relapse) for their first relapse. Of these patients, 17 were treated with tocilizumab alone, 30 with glucocorticoids alone, and 37 with tocilizumab plus glucocorticoids. Five patients were not treated within 30 days after relapse. Clinical features of these relapses are summarised in the appendix (p 12). Of the 84 patients treated for their first relapse, 80 (95%) eventually experienced clinical remission. Median time to remission among these 80 patients was 15 days (range 5–91) with tocilizumab alone (n=17), 54 days (14–117) with glucocorticoids alone (n=27), and 16 days (5–234) with tocilizumab plus glucocorticoids (n=36).

Among patients who achieved clinical remission at week 52 and maintained tocilizumab-free and glucocorticoid-free clinical remission in part two, SF-36 MCS scores diverged between treatment groups after 36 weeks, with patients originally treated with tocilizumab (n=33) showing greater improvements than patients in the original placebo groups (n=17) in a post-hoc analysis (appendix pp 4–5). Differences in the least-squares mean change between original treatment groups were 5·6 (95% CI 1·1–10·2; p=0·016) at week 52, 6·5 (0·9–12·1; p=0·023) at week 100, and 7·4 (2·9–11·9; p=0·002) at week 156. These differences exceeded the minimum clinically important difference for SF-36 MCS of 2·5,[22] even though no patient in either subgroup received tocilizumab or prednisone after week 52. There were no clear differences between the treatment groups for SF-36 PCS (data not shown).

Of those who achieved clinical remission at week 52 and maintained tocilizumab-free and glucocorticoid-free

	Never-received-tocilizumab n=101	Ever-received-tocilizumab n=199
Total patient-years at risk*	193·8	492·7
Total adverse events	1233; 636·3 (601·3–672·9)	2652; 538·3 (518·0–559·2)
Serious adverse events	45; 23·2 (17·0–31·1)	125; 25·4 (21·1–30·2)
Death	0	4†
Infections	236; 121·8 (106·8–138·4)	592; 120·2 (110·7–130·2)
Serious infections	9; 4·6 (2·1–8·8)	17; 3·5 (2·0–5·5)
Malignancy	4; 2·1 (0·6–5·3)	9; 1·8 (0·8–3·5)
Stroke	3; 1·6 (0·3–4·5)	8; 1·6 (0·7–3·2)
Myocardial infarction	0	3; 0·6 (0·1–1·8)
Gastrointestinal perforation	0	1; 0·2 (0·0–1·1)

Data are number of events; rate per 100 patient-years (95% CI). *The ever-received-tocilizumab subgroup exposure time includes all the time after the first dose of tocilizumab was received for patients who had ever received any tocilizumab. Patients who started tocilizumab in part one or who switched from placebo in part one to tocilizumab in part two contributed to the exposure time for the ever-received-tocilizumab subgroup. The never-received-tocilizumab subgroup exposure time includes all the time during the study for patients who never received tocilizumab during the study or any time before the first dose of tocilizumab if patients switched from placebo in part one to tocilizumab in part two. Patients who started placebo in part one and were not receiving tocilizumab in part two or who switched from placebo in part one to tocilizumab in part two contributed to the exposure time of the never-received-tocilizumab subgroup. †Two patients were assigned to placebo-26-week during part one, one patient to tocilizumab-weekly, and one patient to tocilizumab-every-other-week. Causes of death included aortic dissection (n=1), aortic aneurysm rupture (n=1), acute myocardial infarction (n=1), and small cell lung cancer metastatic disease (n=1); no deaths were considered related to tocilizumab. Adverse events reported during part one and part two were assessed in the ever-received-tocilizumab group if they occurred after the first dose of tocilizumab or in the never-received-tocilizumab group if the event occurred before the first dose of tocilizumab or if the patient never received any tocilizumab.

Table 2: **Safety summary based on exposure to tocilizumab at any point during the study (part one and part two)**

clinical remission in part two, mean serum IL-6 concentration in 17 patients in the original placebo groups remained low throughout the 3-year study period, but in the tocilizumab groups, IL-6 concentrations increased after the initiation of tocilizumab treatment at the beginning of part one of the trial. Concentrations remained high until week 52, when tocilizumab treatment was stopped, and then decreased to a level similar to that in the placebo groups (appendix p 6).

During the 3-year study, 199 patients contributed to exposure time for the ever-received-tocilizumab subgroup, and 101 patients contributed to exposure time for the never-received-tocilizumab subgroup (table 2). Time at risk was 193·8 patient-years for the never-received-tocilizumab group and 492·7 patient-years for the ever-received-tocilizumab group. The adverse event rate was 636 events per 100 patient-years (95% CI 601–673) in the never-received-tocilizumab group and 538 events per 100 patient-years (518–559) in the ever-received-tocilizumab group. No patients experienced vision loss, and there were only two reports of visual symptoms (blurred vision and diplopia in one patient each) among patients who experienced giant cell arteritis flare in part two. Overall, no differences in adverse event rates between groups and no new or unexpected safety signals were observed (adverse events are shown in appendix [pp 13–14] for the receiving-tocilizumab and not-receiving-tocilizumab groups).

Discussion

1 year of tocilizumab treatment received during part one of this 3-year trial resulted in prolonged benefits for sustained giant cell arteritis control and glucocorticoid sparing. Withdrawal of tocilizumab did not lead to immediate relapses for most patients. In fact, 42% of patients who achieved prednisone-free remission with tocilizumab once-a-week treatment in part one and who started part two while receiving no treatment maintained tocilizumab-free and glucocorticoid-free remission for another 2 years. Sustained tocilizumab-free and glucocorticoid-free remission was observed after treatment with 1 year of tocilizumab in patients with newly diagnosed disease and in those with relapsing disease at baseline. Patients' cumulative prednisone doses over 3 years were largely dictated by their original treatment assignment; those randomly assigned to placebo with a 52-week prednisone taper received more than twice the amount of cumulative prednisone as those randomly assigned to once-a-week tocilizumab.

Attempts to discontinue prednisone in the placebo groups in part one provide context for the long-term effect of 1 year of tocilizumab once-a-week treatment. In patients receiving placebo plus prednisone in part one, discontinuation of prednisone rapidly led to flares: 58% experienced relapses, nearly all of which occurred before prednisone was discontinued entirely. The median prednisone dose at relapse in the combined placebo-plus-prednisone groups was 5·0 mg per day.[16] 25 (42%) of 59 patients who were successfully treated with tocilizumab once-a-week and who were in tocilizumab-free and glucocorticoid-free remission after 1 year were able to maintain tocilizumab-free and glucocorticoid-free remission for another 2 years, which is promising and consistent with earlier observations.[4] Furthermore, among the 28 patients from the original placebo groups who achieved clinical remission and were receiving no treatment at week 52, 17 (61%) maintained tocilizumab-free and glucocorticoid-free remission throughout part two. Therefore, data from both the tocilizumab groups and the placebo-plus-prednisone groups indicate that some patients, regardless of the remission induction regimen they receive, can continue to do well long-term even without ongoing immunosuppressive treatment.

This 3-year analysis confirms advantages of once-a-week dosing with tocilizumab versus every other week dosing. More patients treated with tocilizumab once-a-week for 52 weeks in part one maintained tocilizumab-free and glucocorticoid-free remission for another 2 years than did those who received tocilizumab-every-other-week dosing (8 of 36 [22%] *vs* 25 of 81 [31%]). More patients originally randomly assigned to tocilizumab once-a-week also achieved rapid disease control and maintained tocilizumab-free and glucocorticoid-free remission, requiring approximately 33% less glucocorticoid therapy over 3 years than did those originally randomly assigned to tocilizumab-every-other-week.

Our trial provides some evidence that it is possible for patients with giant cell arteritis who experience relapse to regain disease remission when receiving tocilizumab treatment alone. Tocilizumab alone compared favourably to treatment with glucocorticoids alone for the management of relapse in part two. After treatment for relapse in our study, the median time to remission was 15–16 days for patients receiving tocilizumab with or without glucocorticoids and 54 days for patients receiving glucocorticoids alone. This timing disparity likely reflected differences in the precise timing of recording remission, given that remission was based solely on each investigator's judgement. Patients treated for relapse with tocilizumab might have been followed up more frequently than those treated with glucocorticoids and therefore were more likely to have been deemed in remission sooner. Furthermore, glucocorticoid treatment for relapse might have been started at low doses and gradually increased, potentially delaying time to remission. Because of the risk for permanent vision loss from periods of disease activity, we urge caution in the use of tocilizumab treatment alone without more data. We cannot exclude the possibility that this finding was confounded by investigators' perceptions of relapse severity.

Successful treatment with tocilizumab had an effect on the SF-36 MCS, extending earlier findings on patient-reported outcomes.[23] In part one, compared with patients receiving prednisone alone, patients with giant cell arteritis receiving tocilizumab once-a-week reported

improvements in SF-36 MCS and Physical Component Summary scores and Functional Assessment of Chronic Illness Therapy–Fatigue scores that were significant and clinically meaningful.[23] In the current analysis of patients who maintained tocilizumab-free and glucocorticoid-free remission in part two, those originally randomly assigned to receive tocilizumab had higher SF-36 MCS scores than those originally randomly assigned to receive prednisone. The observed between-group differences in SF-36 MCS scores in these patients exceeded the minimum clinically important difference by a factor of more than two, even though neither group received tocilizumab or glucocorticoids during part two. These results add to the growing body of research indicating that IL-6 is an important mediator of pain, fatigue, and mood.[19–21]

The design of part two of this trial has strengths and weaknesses. The major strength is that it permitted insight into the duration of tocilizumab-free and glucocorticoid-free remission induced by 1 year of tocilizumab once-a-week therapy. Other strengths are the realisation that it can be possible to restore remission with regimens that include tocilizumab, and the observation that only 10% of first relapses in part two occurred in patients receiving tocilizumab. Weaknesses are that data are limited on the safety and efficacy of continuing tocilizumab for longer than 1 year for most patients, and that changes in treatment during part two are unknown because they were left to the discretion of the treating physician.

In conclusion, randomisation to tocilizumab plus prednisone from the outset of therapy had an effect on treatment course and cumulative glucocorticoid use for 3 years. Giant cell arteritis remains a chronic disease that entails ongoing management and careful vigilance for disease relapse, but continuous indefinite treatment with immunosuppressive drugs is not required for all patients.

Contributors

All authors were involved in careful revision of the manuscript for important intellectual content, approved the version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated or resolved. JHS contributed to study design and conceptualisation, data acquisition, interpretation of data, verification of data, and writing the manuscript. JH contributed to the data analysis, interpretation, and verification of data. MA contributed to data interpretation and writing and important input to the manuscript. DB contributed to patient recruitment and collection, analysis, and interpretation of data. EB contributed to data interpretation and carefully revising the manuscript. MCC contributed to the study design, data collection, data interpretation, writing, and literature review. BD contributed to data interpretation and writing the manuscript. JR contributed to data acquisition, analysis, and interpretation of data and carefully revising the manuscript. CS contributed to study conception and design, data collection and interpretation, and carefully revising the manuscript. RS contributed to study design, data collection, analysis and interpretation of data, and writing the manuscript. SHU contributed to acquisition, analysis, and interpretation of data and writing the manuscript. MB contributed to acquisition, analysis, or interpretation of data, verification of data, and carefully revising the manuscript.

Declaration of interests

The GiACTA trial is supported by Roche and Genentech. JHS has received research grants and consulted for Roche and Genentech and Chugai on vasculitis, IgG4-related disease, Covid-19, and glucocorticoid toxicity, outside the submitted work. JH is an employee of Genentech. MA has received study site support from Roche for the GiACTA study site; and personal fees from Roche outside the submitted work. DB has received consulting and travel fees from Roche outside the submitted work. EB has received personal fees paid to her institution from Roche outside the submitted work. MCC received personal fees from Roche for the GiACTA trial; consulting fees from GlaxoSmithKline, Janssen, and AbbVie; a research grant from Kiniksa; and lecture fees from Vifor outside the submitted work. BD has received grants and personal fees from Roche, Chugai, and Sanofi Aventis; and personal fees from GlaxoSmithKline during the conduct of the study. JR has received consultancy or speaker fees from Roche, AbbVie, Biogen, Bristol Myers Squibb, Chugai, GlaxoSmithKline, Janssen, Lilly, Merck Sharp & Dohme, Novartis, Sobi, and UCB. RS has received research funding from Roche and Genentech for the work under consideration; and research funding and consultancy fees from Roche and Genentech outside the submitted work. SHU has received grants and/or personal fees from Genentech, Janssen, Sanofi, and Kiniksa outside the submitted work. MB is an employee of Genentech and has a patent issued for subcutaneously administered anti-IL-6 receptor antibody. CS has no competing interests.

Data sharing

Qualified researchers may request access to individual deidentified patient level data and study documents (protocol and statistical analysis plan) through the clinical study data request platform (https://vivli.org/) upon publication. Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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