Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial

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Summary

Background Giant cell arteritis is an immune-mediated disease of medium and large-sized arteries that affects mostly people older than 50 years of age. Treatment with glucocorticoids is the gold-standard and prevents severe vascular complications but is associated with substantial morbidity and mortality. Tocilizumab, a humanised monoclonal antibody against the interleukin-6 receptor, has been associated with rapid induction and maintenance of remission in patients with giant cell arteritis. We therefore aimed to study the efficacy and safety of tocilizumab in the first randomised clinical trial in patients with newly diagnosed or recurrent giant cell arteritis.

Methods In this single centre, phase 2, randomised, double-blind, placebo-controlled trial, we recruited patients aged 50 years and older from University Hospital Bern, Switzerland, who met the 1990 American College of Rheumatology criteria for giant cell arteritis. Patients with new-onset or relapsing disease were randomly assigned (2:1) to receive either tocilizumab (8 mg/kg) or placebo intravenously. 13 infusions were given in 4 week intervals until week 52. Both groups received oral prednisolone, starting at 1 mg/kg per day and tapered down to 0 mg according to a standard reduction scheme defined in the study protocol. Allocation to treatment groups was done using a central computerised randomisation procedure with a permuted block design and a block size of three, and concealed using central randomisation generated by the clinical trials unit. Patients, investigators, and study personnel were masked to treatment assignment. The primary outcome was the proportion of patients who achieved complete remission of disease at a prednisolone dose of 0·1 mg/kg per day at week 12. All analyses were intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01450137.

Results Between March 3, 2012, and Sept 9, 2014, 20 patients were randomly assigned to receive tocilizumab and prednisolone, and ten patients to receive placebo and glucocorticoid; 16 (80%) and seven (70%) patients, respectively, had new-onset giant cell arteritis. 17 (85%) of 20 patients given tocilizumab and four (40%) of ten patients given placebo reached complete remission by week 12 (risk difference 45%, 95% CI 11–79; p=0·0301). Relapse-free survival was achieved in 17 (85%) patients in the tocilizumab group and two (20%) in the placebo group by week 52 (risk difference 65%, 95% CI 36–94; p=0·0010). The mean survival-time difference to stop glucocorticoids was 12 weeks in favour of tocilizumab (95% CI 7–17; p<0·0001), leading to a cumulative prednisolone dose of 43 mg/kg in the tocilizumab group versus 110 mg/kg in the placebo group (p=0·0005) after 52 weeks. Seven (35%) patients in the tocilizumab group and five (50%) in the placebo group had serious adverse events.

Interpretation Our findings show, for the first time in a trial setting, the efficacy of tocilizumab in the induction and maintenance of remission in patients with giant cell arteritis.

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Introduction

Giant cell arteritis is characterised by a destructive, granulomatous inflammation of the walls of medium and large-sized arteries. Annual incidence varies between six and 32 cases per 100 000 people worldwide.[1–4] Glucocorticoids are the gold-standard for controlling symptoms and reducing the risk of vascular complications, such as blindness. However, necessary doses and long duration of treatment invariably lead to high morbidity and substantial mortality.[5] Neither conventional immunosuppressive drugs nor biological agents effectively induce remission,[6,7] and the extent of their steroid-sparing effect during maintenance, for instance with methotrexate, remains a matter of debate.[8,9]

Interleukin-6 induces acute phase responses and has a central role in the pathogenesis of giant cell arteritis.[10,11] Serum and tissue samples of patients with this disorder show increased concentrations of interleukin-6.[12,13] Tocilizumab, used to treat rheumatoid arthritis and juvenile rheumatoid arthritis,[14,15] is a humanised immunoglobulin G1 kappa monoclonal antibody that blocks signalling by binding to the alpha chain of the human interleukin-6 receptor.[16]

Results of several case studies have shown rapid induction and maintenance of remission of giant cell arteritis using tocilizumab.[17–20] We therefore decided to do the first randomised, placebo-controlled trial to study the efficacy and safety of induction and maintenance of

Research in context

Evidence before this study

We searched PubMed for studies published in any language between Jan 1, 1980, and Feb 18, 2016, with the terms "giant cell arteritis" and "IL-6". We included clinical trials, clinical observations, and preclinical studies, both in vitro and in vivo in animals and human beings. We also searched conference abstracts from the American College of Rheumatology and The European League Against Rheumatism from the past 5 years. Besides laboratory studies, we found 15 case series and one open-label study. ClinicalTrials.gov lists an ongoing double-blind, placebo-controlled trial of subcutaneous tocilizumab treatment for giant cell arteritis with proportion of patients in sustained remission at week 52 as the primary outcome (NCT01791153).

Added value of this study

This study is the first randomised, placebo-controlled trial to show the efficacy of tocilizumab in the induction and maintenance of remission in patients with giant cell arteritis.

Implications of all the available evidence

These findings are consistent with the hypothesis that interleukin-6 plays an important part in the pathogenesis of giant cell arteritis, and that inhibition of interleukin-6 might induce and maintain remission of the disease. A phase 3 study of tocilizumab in giant cell arteritis is needed to confirm these findings.

disease remission in patients with newly diagnosed or recurrent giant cell arteritis.

Methods

Study design and patients

For the **protocol** see http://www.ria.insel.ch/de/rheumatologie/forschung-research/

In this phase 2, randomised, double-blind, placebo-controlled study, we recruited patients from the University Hospital Bern, Switzerland. The protocol was approved by the local ethics committee and the study was done in accordance with the Declaration of Helsinki. Tocilizumab was provided by Roche.

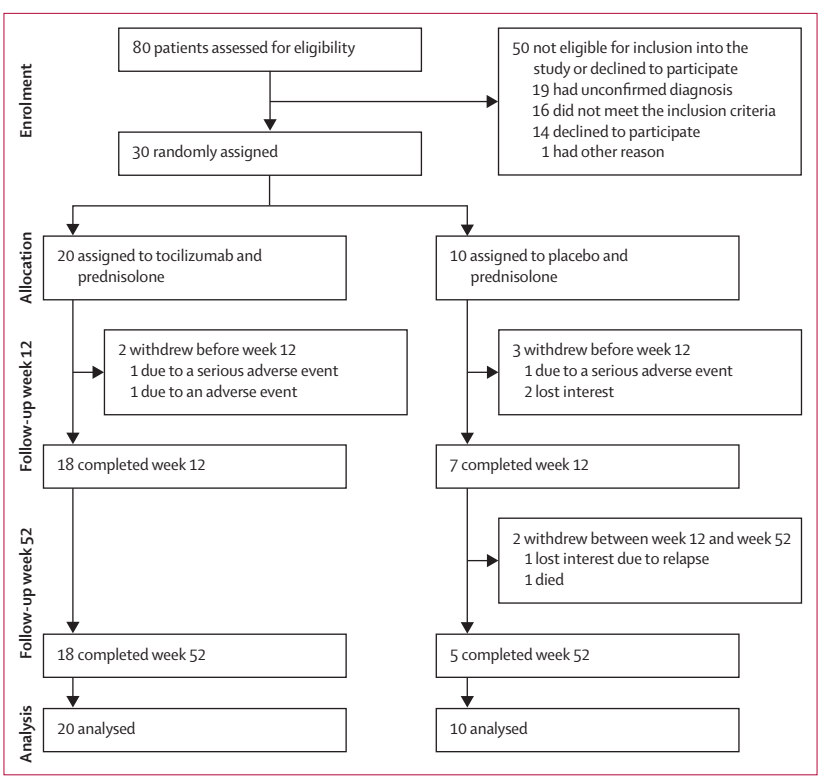

Figure 1: **Trial profile**

Patients older than 50 years of age with new-onset or relapsing giant cell arteritis who fulfilled the 1990 American College of Rheumatology criteria[21] were eligible for study participation. Giant cell arteritis had to be proven by positive temporal artery biopsy or assessed as large vessel vasculitis by MR angiography, and had to be humorally active at inclusion (erythrocyte sedimentation rate of ≥40 mm in the first hour, and C-reactive protein level of ≥20 mg/L). Patients were excluded if they had uncontrolled concomitant health problems, active infection, or any disease requiring systemic glucocorticoid treatment. Previous treatment with tocilizumab or any other biological agent was not allowed. Patients were permitted to receive prednisolone up to 1 mg/kg bodyweight for a maximum of 10 days between inclusion in the trial and the first infusion. All patients gave written informed consent before study enrolment.

Randomisation and masking

Patients were randomly assigned (2:1) to receive oral glucocorticoids and either tocilizumab at 8 mg/kg bodyweight or placebo, both intravenously. Allocation to treatment groups was done using a central computerised randomisation procedure with a permuted block design and a block size of three, and concealed using central randomisation generated by the clinical trials unit. The responsible senior statistician was not involved in study conduct or monitoring. Patients, investigators, and study personnel were masked to treatment assignments during the study; we used subsequently opened sealed, opaque, sequentially numbered envelopes containing the allocation information. The site oncology nurse who prepared the study drug was not masked to this information but had no contact with patients or health professionals involved in their care.

Procedures

Patients received 13 infusions every 4 weeks until week 52. Prednisolone was started at 1 mg/kg per day and tapered weekly by 0·1 mg/kg per day until week 8, then weekly by

0·05 mg/kg, reaching 0·1 mg/kg by week 12. Thereafter, the dose was reduced every month by 1 mg per day to 0 mg. Concomitant drugs in all patients consisted of 100 mg aspirin per day, 40 mg pantoprazole per day, 1000 mg calcium per day, 800 U cholecalciferol per day, and 3 mg ibandronate intravenously every 3 months.

In cases of a minor relapse, patients received the previous dose of prednisolone plus 10 mg per day; in cases of positive clinical response within 72 h, glucocorticoid dosage was continued for 2 weeks and subsequently tapered according to protocol. In cases of a major relapse, the glucocorticoid induction scheme was reapplied to prevent unfavourable outcomes such as blindness.

Outcomes

The pre-specified primary endpoint was complete remission at week 12 without clinical signs or symptoms of giant cell arteritis, and normal erythrocyte sedimentation rate and C-reactive protein at a prednisolone dose of 0·1 mg/kg per day. Clinical and serological monitoring were done at screening and weeks 0, 2, 4, 6, 8, 10, 12, and every 4 weeks thereafter. Secondary endpoints were relapse-free survival at week 52, time to first relapse after induction of remission, and cumulative dose of prednisolone.

Relapse was defined as a re-increase of erythrocyte sedimentation rate from less than 20 mm in the first hour to 40 mm or greater, and of C-reactive protein from normal to 10 mg/L or greater, as well as at least one of the following symptoms of giant cell arteritis: new or recurrent headache or pain or tenderness of the scalp or the temporal artery; new or recurrent claudication of the tongue or masseter muscle claudication; new, recurrent, or worsening temporal artery signs and symptoms; transient cerebral ischaemia; MR angiographic abnormalities; classic polymyalgia rheumatic-like symptoms; or sustained daily recurrent fever with a temperature over 38°C for more than 1 week. Relapse was defined as major if cranial symptoms were present, whereas in all other situations relapse was regarded as minor.

Statistical analysis

We calculated that a sample size of 30 patients would yield a power of more than 80% to detect a risk difference of 60% at a conventional α level of 0·05, assuming complete remission to be 90% in the tocilizumab group and 30% in the placebo group. We expected a dropout rate of 10%. An interim analysis was not planned or done.

All randomly assigned patients were included in the intention-to-treat analysis and analysed according to the intervention they were assigned to at randomisation. Because all randomly assigned patients received study drug and crossovers did not occur, the definition of the intention-to-treat analysis corresponds to both the initial definition in the study protocol (all randomly assigned patients receiving some part of a study drug) and the definition of the safety analysis. The intention-to-treat analysis was done for all efficacy and safety parameters. The primary outcome and binary secondary outcomes were calculated as crude risk difference with corresponding 95% confidence intervals. p values were derived by Fisher's exact test. Patients who discontinued the study before or at week 10 (primary outcome) and 44 (complete remission after 52 weeks), respectively, were deemed not to be in remission. Kaplan-Meier survival curves were plotted for time-to-event endpoints and discontinuations were accounted for by censoring. We calculated restricted mean survival times at a truncation time of 52 weeks as the area under the Kaplan-Meier curves. Continuous secondary endpoints were calculated as median and corresponding interquartile range, and p values were derived by the

	Tocilizumab plus prednisolone (N=20)	Placebo plus prednisolone (N=10)
Women	13 (65)	8 (80)
Age (years)	71·3 (8·9)	68·8 (16·9)
BMI (kg/m²)	23·6 (3·0)	27·9 (3·7)
New-onset giant cell arteritis	16 (80)	7 (70)
Biopsy of the temporal artery		
Normal	5 (25%)	0
Abnormal	13 (65%)	8 (80%)
Not done	2 (10%)	2 (20%)
Thoracoabdominal MR angiography		
Normal	9 (45%)	2 (20%)
Abnormal	11 (55%)	6 (60%)
Not done	0	2 (20%)
Symptoms and signs of giant cell arteritis		
Fever	1 (5%)	1 (10%)
Weight loss	6 (30%)	3 (30%)
Night sweats	3 (15%)	2 (20%)
Headache	13 (65%)	5 (50%)
Scalp tenderness	9 (45%)	1 (10%)
Claudication of tongue	2 (10%)	0
Masseter muscle claudication	11 (55%)	4 (40%)
Claudication of upper limbs	4 (20%)	2 (20%)
Claudication of lower limbs	0	2 (20%)
Visual impairment	5 (25%)	2 (20%)
Blood pressure (mmHg)		
Systolic right arm	130·6 (18·0)	137·7 (16·4)
Diastolic right arm	74·3 (11·8)	77·7 (15·2)
Systolic left arm	131·3 (16·3)	136·9 (13·0)
Diastolic left arm	75·1 (11·5)	82·8 (8·5)
Erythrocyte sedimentation rate (mm/h)		
At screening	69·0 (45·5–80·0)	40·0 (27·3–68·8)
At remission	5·0 (4·3–7·8)	6·5 (3·5–12·5)
C-reactive protein (mg/L)		
At screening	25·5 (16·8–50·3)	39·0 (23·5–64·3)
At remission	0·0	0·0

Data are n (%), mean (SD), or median (IQR).

Table 1: **Baseline characteristics**

	Tocilizumab plus prednisolone (N=20)	Placebo plus prednisolone (N=10)	Risk difference (95% CI)	p value
Endpoints				
Complete remissions				
After 12 weeks	17 (85%)	4 (40%)	45% (11 to79)	0·0301
After 52 weeks	17 (85%)	2 (20%)	65% (36 to 94)	0·0010
Patients whose prednisolone dose tapered to 0 mg per day	16 (80%)	2 (20%)	60% (30 to 90)	0·0041
Cumulative prednisolone dose (mg/kg)				
After 12 weeks	34 (32 to 35)	36 (34 to 39)	..	0·0477
After 26 weeks	41 (39 to 46)	66 (52 to 75)	..	0·0015
After 52 weeks	43 (39 to 52)	110 (88 to 150)	..	0·0005
Patients with any adverse event	15 (75%)	7 (70%)	5% (–29 to 39)	1·00
Patients with a serious adverse event	7 (35%)	5 (50%)	–15% (–52 to 22)	0·46
First relapse*				
Timepoint of first relapse (weeks)	11·0	12·0 (10·1 to 17·1)	..	0·77
Prednisolone dose at first relapse (mg/kg per day)	0·11	0·10 (0·09 to 0·17)	..	0·77
Erythrocyte sedimentation rate at first relapse (mm/h)	2·00	20·0 (10·0 to 30·0)	..	0·14
C-reactive protein concentration at first relapse (mg/L)	3·00	16·0 (11·0 to 25·0)	..	0·23

Data are n (%) or median (IQR) unless stated otherwise. *One patient in the tocilizumab group and five in the placebo group had first relapse.

Table 2: **Treatment effect on primary and secondary endpoints**

Wilcoxon rank-sum test. Missing data were accounted for by carrying the last post-baseline finding forward.

To account for potential confounders, we fitted logistic regression models for the primary outcome, either crude, or adjusted for sex, age, baseline erythrocyte sedimentation rate and baseline C-reactive protein. We report odds ratios with 95% confidence intervals and corresponding p values.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. SR and LB had full access to all the data in the study and PMV had final responsibility for the decision to submit for publication.

Results

Between March 3, 2012, and Sept, 9 2014, 20 patients were randomly assigned to receive either tocilizumab and prednisolone and ten to receive placebo and prednisolone (figure 1); 16 (80%) and seven (70%) patients, respectively, had new-onset giant cell arteritis (table 1). In two patients, diagnosis was confirmed by biopsy without additional MR angiography. All patients with negative temporal artery biopsy had a positive MR angiography.

See Online for appendix

Two patients in the tocilizumab group and three patients in the placebo group withdrew from the study before week 12. Two patients of the placebo group lost interest in the study and asked to be given tocilizumab. One patient in the tocilizumab group had a major relapse before week 12 (at week 11), compared with three patients in the placebo group (at weeks 6, 10, and 12). After week 12, two additional patients in the placebo group relapsed (at weeks 17 and 20). Median prednisolone dose at first relapse was 0·11 mg/kg in the tocilizumab group and 0·10 mg/kg in the placebo group (table 2).

All relapsed patients had typical clinical signs and symptoms of giant cell arteritis, in most cases reflecting initial presentation of the disease. Because the treating physicians knew that tocilizumab suppresses C-reactive protein and erythrocyte sedimentation rate, the acute phase was not fully taken into consideration to avoid missing relapse in patients in the tocilizumab group. The five relapsing patients in the placebo group had 13 relapses; six were deemed to be major, and seven to be minor.

After 12 weeks, 17 (85%) patients in the tocilizumab group and four patients (40%) in the placebo group were still in complete remission, yielding a risk difference of 45% (95% CI 11–79). Adjustment for potential confounders (ie, age, sex, baseline erythrocyte sedimentation rate, and baseline C-reactive protein) had no major effect on the result (appendix p 1). After 52 weeks, we recorded relapse-free survival in 17 (85%) of 20 patients in the tocilizumab group versus two (20%) of ten patients in the placebo group, resulting in an increase of 25 weeks (95% CI 11–39; p=0·0005) of relapse-free survival within the 52 weeks of follow-up of patients in the tocilizumab group (figure 2A).

In 16 (80%) patients in the tocilizumab group, prednisolone was tapered to 0 mg per day at the end of the trial, compared with two (20%) patients in the placebo group (risk difference 60%, 95% CI 30–90). The mean follow-up time to stop prednisolone was 38 weeks (95% CI 35–42) in the tocilizumab group versus 50 weeks (46–54) in the placebo group, leading to a

difference of 12 weeks (7–17; p<0·0001; figure 2B). The cumulative prednisolone dose was lower after 12 weeks (34 mg/kg [IQR 32–35] in the tocilizumab group *vs* 36 mg/kg [34–39] in the placebo group; p=0·0477). After 26 weeks and at the end of the trial, the cumulative weight-adapted prednisolone dose was significantly higher in the placebo group (at week 26, 41 mg/kg [39–46] *vs* 66 mg/kg [52–75], respectively; p=0·0015); and at week 52, 43 mg/kg [39–52] *vs* 110 mg/kg [88–150]; p=0·0005; table 2).

The change in C-reactive protein concentrations document the expected effect of tocilizumab on the acute phase response. C-reactive protein increased in the placebo group during the rapid glucocorticoid reduction (weeks 12 to 24; appendix p2). Notably, C-reactive protein was increased in five situations in the tocilizumab group during combination therapy but never during the phase of tocilizumab monotherapy.

26 adverse events were recorded in 15 patients (75%) in the tocilizumab group compared with 23 recorded in seven (70%) patients in the placebo group (table 3). We recorded no infusion-related adverse events. Seven serious adverse events occurred in seven patients in the tocilizumab group versus ten in five patients given placebo (appendix p3). Three cardiovascular serious adverse events were noted in the placebo group: one patient experienced a syncope and another underwent percutaneous coronary intervention for coronary artery disease and finally suffered a lethal myocardial infarction. One patient in the tocilizumab group had severe headache with tinnitus leading to admittance to hospital, the symptoms were not judged to be caused by giant cell arteritis. Three gastrointestinal complications occurred in the tocilizumab group: one patient not taking prescribed pantoprazole developed a prepyloric ulcer perforation, a second suffered hepatopathy due to an undefined viral infection, and a third underwent gastrointestinal endoscopy due to gastrointestinal bleeding 12 days after start of treatment. One patient in the placebo group with previously undiagnosed diverticulosis had a sigmoid perforation. Glucocorticoid-related problems were severe psychosis in one of the patients in the tocilizumab group and immobilising steroid-induced myopathy and hyperglycaemia in two patients given placebo. One placebo patient had two episodes of severe and immobilising back pain, while another had to be admitted to hospital twice for lumbar fractures and vertebroplasty. One eye infection due to *Moraxella catarrhalis* and herpes led to inpatient treatment in a patient in the tocilizumab group. A case of Stevens-Johnson syndrome developed in another tocilizumab patient 3 days after the third infusion, the causal relationship could not be determined as multiple drugs had been started within the possible timeframe.

The appendix shows laboratory values recorded outside the normal range during baseline and follow-up in the two groups (appendix p4). We noted no difference in concentrations of thrombocytes or transaminases. Cholesterol concentrations were high in both groups. Nine episodes of neutropenia happened in four patients in the tocilizumab group versus none in the placebo group. 15 episodes of leucopenia occurred in six patients in the tocilizumab group compared with only one in the placebo group.

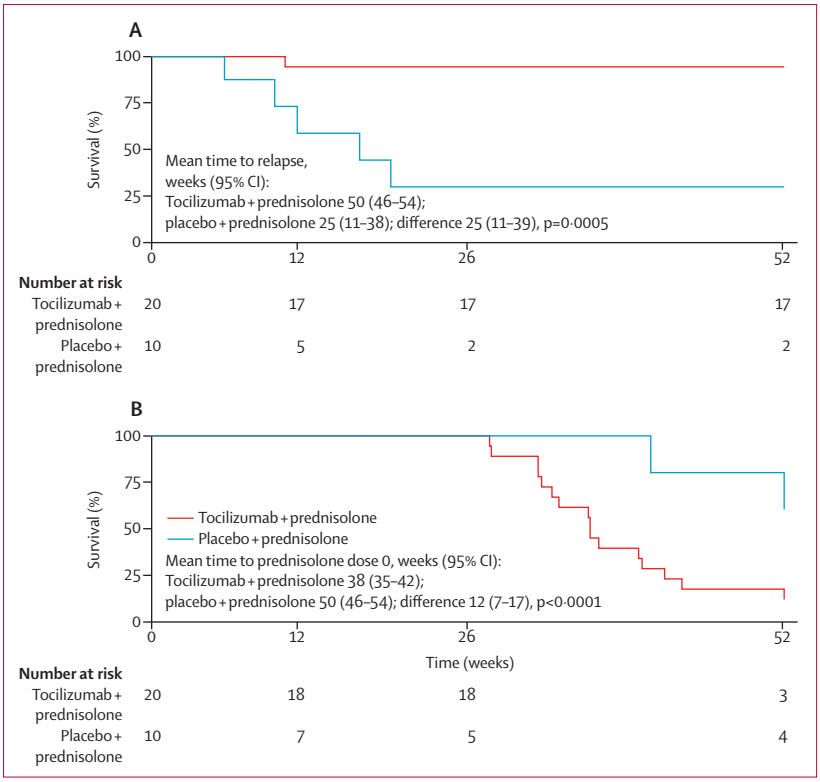

Figure 2: **Kaplan-Meier curve for relapse-free survival through to week 52 (A) and the time to taper down prednisolone to 0 mg per day (B)**

	Tocilizumab plus prednisolone (N=20)	Placebo plus prednisolone (N=10)
Number of adverse events	26 (15 patients)	23 (7 patients)
Serious adverse events	7 (7 patients)	10 (5 patients)
Cardiovascular disease	1	5 (1 cardiovascular-related death)
Gastrointestinal disease	4	1
Osteoporotic fracture	1	3
Musculoskeletal disease	5	8
Glucocorticoid-related hyperglycaemia and myopathia	3	3
Infectious disease	10	1
Skin disease	1	2
Cystic lesion mamma	1	0

The list of serious adverse events is shown in the appendix.

Table 3: **Adverse events**

Discussion

This is the first randomised controlled trial of tocilizumab in patients with giant cell arteritis, and our findings show the drug's effectiveness in inducing remission and preventing relapse. Glucocorticoids could be rapidly tapered and discontinued by 36 weeks after the initiation of tocilizumab treatment. As a consequence, the cumulative prednisolone doses were reduced. Our data corroborate the findings of several recent publications regarding the clinically important therapeutic value of tocilizumab in patients with giant cell arteritis.[19,22]

We decided to reduce prednisolone very rapidly and according to bodyweight. Patients without relapse received around 7 mg per day of prednisolone by week 12. There are several arguments favouring this protocol; some patients with giant cell arteritis respond to rather low doses of glucocorticoid, thus they would not benefit from tocilizumab, but they would be at risk of side-effects associated with combined glucocorticoids and tocilizumab.[23] The two randomised controlled trials[6,7] assessing tumour necrosis factor inhibition in giant cell arteritis used slower reduction schemes; both reported no benefit of the biological agent but an increase in side-effects. In the infliximab study,[6] glucocorticoids were tapered to 10 mg per day by month 4, whereas in the adalimumab study,[7] patients received 0·3 mg/kg bodyweight of prednisone by week 12. A small therapeutic benefit of tumour necrosis factor inhibition might have been disguised by the conservative glucocorticoid tapering scheme. Therefore, the glucocorticoid tapering regimen in the present study was designed so as to not disguise the treatment benefit of tocilizumab.

It might be argued that patients have a higher risk of relapse when glucocorticoids are tapered rapidly. However, in any setting, patients in the placebo group are at a higher risk of disease activity or relapse. To reach statistical significance the cumulative risk will be the same. Reducing the individual risk will invariably increase the number of individuals to be studied. Our protocol yielded meaningful results despite enrolling only 30 patients.

The fact that we recorded no relapse in the tocilizumab group after discontinuation of prednisolone strongly argues for a decisive role of interleukin-6 in the pathogenesis of giant cell arteritis. This is in sharp contrast to the absence of effect of tumour necrosis factor inhibition using infliximab or adalimumab.[6,7] Nevertheless, it remains to be seen whether giant cell arteritis can be extinguished using tocilizumab or whether prolonged treatment is necessary beyond 12 months.

Because of the blunting effect of tocilizumab on the acute phase response of the liver, none of the conventional laboratory parameters used to quantify systemic inflammation are reliable. Therefore, neither C-reactive protein nor erythrocyte sedimentation rate can be used to define relapse. However, because C-reactive protein remains an important parameter for purposes such as identifying severe infection, we decided not to mask clinicians to these data. The courses of C-reactive protein concentrations in the two groups of treatment document the clinical value of C-reactive protein in the identification of infections.

It has been argued that knowledge of the acute phase reactants will unblind the clinicians and affect their subsequent assessment of the patients. Analysis of our data showed that clinicians defined relapse mainly on signs and symptoms, and that they did not fully respect the values of C-reactive protein and erythrocyte sedimentation rate because they did not want to miss relapse in the patients given tocilizumab. In fact, a small increase of the acute phase reactants rather suggested treatment with tocilizumab than treatment with placebo. Thus physicians remained masked throughout the study.

The type and frequency of tocilizumab side-effects have been well characterised by large clinical studies of rheumatoid arthritis and by multinational patient registries. There has been concern about gastrointestinal tract side-effects, particularly diverticulitis with perforation.[24,25] Despite broad exclusion criteria in this study, a perforated gastric ulcer occurred in the tocilizumab group and a perforated diverticulum was reported in the placebo group. This finding highlights the increased risk of perforation not only under tocilizumab treatment but also under high glucocorticoid doses.[24,26] Whether the higher rate of infections in the tocilizumab group can be attributed to the biological agent or to the combination of tocilizumab and glucocorticoids remains unknown. The fact that all but two occurred during the phase of combination therapy implies a contribution of glucocorticoids. One woman in the placebo group repeatedly had vertebral fractures and frequent relapses of giant cell arteritis, and one patient developed steroid-induced psychosis during the first 8 weeks of the study.

Although high systemic inflammation is typical of giant cell arteritis, we chose a conventional dosing scheme of 8 mg/kg bodyweight every 4 weeks for tocilizumab. One patient in the tocilizumab group had one relapse. This patient's characteristics and the fact that the relapse occurred rather early argues for more intense treatment in severely ill patients. Further studies will have to establish whether tocilizumab should be dosed according to the level of inflammation during the initial treatment phase. In line with this consideration, researchers should study whether doses can be reduced stepwise after patients reach lasting remission.

In summary, our findings show that tocilizumab efficiently induces and maintains remissions of giant cell arteritis (normal erythrocyte sedimentation rate and C-reactive protein and absence of signs and symptoms) after 12 weeks at a prednisolone dose of 0·1 mg/kg per day. Serious adverse events were numerically equal in the tocilizumab and placebo groups with a preponderance of

gastrointestinal serious adverse events in the tocilizumab group and with cardiovascular and metabolic complications in the placebo group.

Contributors

PMV initiated the study and wrote the first draft of the protocol. SR was responsible for the clinical study design and the methodology. PMV, SA, SK, FW, DD, MS, and SR developed and finalised the protocol. SA, SK, FW, and DD were the treating physicians of the patients and were responsible for data acquisition. MS was responsible for the amendments and coordinated the administrative work (correspondence with the local ethical committee, safety reporting to the approving official authority of Swissmedic before and during the study). VF and LB did the statistical analysis. PMV, SA, and SR interpreted the results and wrote the report.

Declaration of interests

We declare no competing interests.

Acknowledgments

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