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CADTH COMMON DRUG REVIEW

Clinical Review Report

Tocilizumab (Actemra)

(Hoffmann-La Roche Limited)

Indication: For the treatment of giant cell arteritis (GCA) in adult patients.

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

ACE	Arthritis Consumer Experts
ACR	American College of Rheumatology
CDR	CADTH Common Drug Review
CI	confidence interval
CRP	C-reactive protein
CTA	computed tomography angiography
EQ-5D	EuroQoL 5-Dimensions questionnaire
EQ-5D-3L	EuroQoL 5-Dimensions 3-Levels questionnaire
ESR	erythrocyte sedimentation rate
FACIT-F	Functional Assessment of Chronic Illness Therapy–Fatigue
GC	glucocorticoid
GCA	giant cell arteritis
IL-6	interleukin-6
ICC	intraclass coefficient
ITT	intention-to-treat
MCID	minimal clinically important difference
MCS	mental component score
MRA	magnetic resonance angiography
PCS	physical component score
PET	positron emission tomography
PGA	Patient's Global Assessment
PMR	polymyalgia rheumatica
RA	rheumatoid arthritis
RCT	randomized controlled trial
SD	standard deviation
SF-36	Short Form (36) Health Survey
VAS	visual analogue scale

Drug	Tocilizumab (Actemra)
Indication	For the treatment of giant cell arteritis (GCA) in adult patients
Reimbursement request	As per indication
Dosage form(s)	Tocilizumab doses of 162 mg administered via subcutaneous injection weekly plus 26-week prednisone tapering
NOC date	October 27, 2017
Manufacturer	Hoffmann-La Roche Limited

Executive Summary

Introduction

Giant cell arteritis (GCA) is a systemic large-vessel vasculitis found almost exclusively in patients aged 50 years and older.1 Symptoms of GCA include headache, fatigue, jaw claudication, temporary or permanent loss of vision, scalp tenderness, aortic arch syndrome, and polymyalgia rheumatica.1 Vessel wall granulomatous inflammation mostly occurs in the aorta and the branches of the aorta and external carotid and can lead to stenoses, occlusions, or aneurysms.2 Severe, permanent vision loss, sometimes heralded by temporary vision loss, eye pain, or diplopia, can occur suddenly due to occlusion of the short posterior ciliary arteries.3 Treatment options for GCA are limited and guidelines state that therapy with prednisone or prednisolone should be initiated immediately upon suspicion of GCA, even prior to confirmation of diagnosis via a temporal artery biopsy or imaging. Symptoms typically resolve rapidly in response to corticosteroid therapy and if the patient is free of symptoms and abnormal laboratory parameters, the corticosteroid dose can be tapered gradually over the course of one to two years. The long-term use of oral corticosteroid therapy introduces a host of adverse effects and increases the risk of bone fractures, worsening of diabetes and hypertension, thrombotic events, gastrointestinal bleeding, muscle weakness from myopathy, glaucoma, and cataracts.[4,5] Emotional effects related to corticosteroid therapy include insomnia, restlessness, hypomania, and depression.[6] Given the high relapse rate and adverse effects associated with oral corticosteroid therapy, there is a need for other therapies for the treatment of GCA in patients.

Tocilizumab is an anti-human interleukin-6 (IL-6) receptor monoclonal antibody that binds to and inhibits signalling through both soluble and membrane-bound IL-6 receptors.[7] It is approved for the treatment of GCA in adults, with a recommended dose of 162 mg by subcutaneous (SC) injection once weekly. Tocilizumab is also approved in Canada for patients with polyarticular juvenile idiopathic arthritis and systemic juvenile idiopathic arthritis.

The objective of this report was to perform a systematic review of the beneficial and harmful effects of tocilizumab 162 mg/0.9 mL pre-filled syringe for SC injection for the treatment of GCA in adults.

Results and Interpretation

Included Studies

The GiACTA trial was a 52-week double-blind randomized controlled trial (RCT) that evaluated the use of tocilizumab SC versus placebo in patients with active GCA who were 50 years of age or older. All patients had a confirmed diagnosis of GCA, meaning the patient had to present with unequivocal cranial symptoms of GCA and/or symptoms of polymyalgia rheumatica, and have a positive temporal artery biopsy and/or imaging test. Patients enrolled were either newly diagnosed or had relapsing disease and were receiving treatment with 20 mg to 60 mg of prednisone daily. Study patients (N = 251) were predominantly female (70% to 78%), white (94% to 100%), and had a mean age per group that ranged from 67.8 to 69.5 years.

Patients were randomized to tocilizumab 162 mg SC weekly or every other week (both with a 26-week prednisone taper), placebo with 26-week prednisone taper, or placebo with 52-week prednisone taper. The protocol-defined prednisone taper had an open-label phase (for dosages from 60 mg/day to 20 mg/day) and a double-blind phase (for dosages less than 20 mg/day), and by either week 26 or week 52, patients would be weaned off prednisone. Patients who experienced a disease flare or could not adhere to the taper due to ongoing disease activity stopped the protocol-defined tapering schedule and could receive escape prednisone.

Flare was determined by the investigator and defined as the recurrence of signs or symptoms of GCA and/or an erythrocyte sedimentation rate (ESR) ≥ 30 mm per hour attributable to GCA. A patient could have symptoms of GCA or elevated ESR and still be considered in remission if the investigator determined these symptoms were not severe enough to be classified as a disease flare. Remission was defined as the absence of flare (as defined above) and normalization of C-reactive protein (less than 1 mg/dL). Sustained remission (the primary end point) was defined as the absence of flare following induction of remission within 12 weeks of randomization and maintained from week 12 up to week 52. The primary outcome analysis compared the proportion of patients in sustained remission at week 52 for each tocilizumab group versus the placebo plus 26-week prednisone taper group. The key secondary outcome assessed noninferiority of each tocilizumab group versus the placebo plus 52-week taper for the proportion of patients in sustained remission.

The GiACTA study was not adequately powered or of sufficient duration to evaluate longer-term GCA- and prednisone-related morbidities such as fractures and cardiovascular events, which are important to patients. Moreover, the available evidence was limited to a single RCT with a relatively small number of patients per treatment group (50 or 100).

Efficacy

Overall, 56% and 53% of patients in the tocilizumab weekly and biweekly groups (plus 26-week prednisone taper) were in sustained remission at week 52 compared with 14% and 18% of those in the placebo plus 26-week prednisone taper and the placebo plus 52-week taper groups, respectively. The proportion of patients in prednisone-free sustained remission at week 52 was statistically significantly higher for both tocilizumab regimens

compared with placebo plus 26-week taper in the intention-to-treat population, with an absolute difference of 42%; 99.5% confidence interval (CI), 18% to 66% ($P < 0.0001$) for the weekly tocilizumab regimen, and 39%; 99.5% CI, 12% to 66% ($P < 0.0001$) for the tocilizumab biweekly group.

The key secondary end point demonstrated the noninferiority and superiority of both tocilizumab regimens compared with placebo plus 52-week taper in the intention-to-treat population, with an absolute increase in proportion of patients with sustained remission of 38%; 99.5% CI, 18% to 59% ($P < 0.0001$) for the weekly regimen, and 35%; 99.5% CI, 10% to 60% ($P = 0.0002$) for the tocilizumab biweekly group. For both tocilizumab dosage groups, the lower bound of the 99.5% CI for the difference in remission rates exceeded the −22.5% noninferiority margin. Similar results were observed in the analysis of patients who completed the study and were compliant with treatment.

Sensitivity analyses for the primary outcome suggested that the findings were generally robust. Descriptive subgroup data based on disease status at baseline showed sustained remission rates among new-onset versus relapsing patients of 60% versus 53% in the weekly tocilizumab group, and 58% versus 48% for biweekly tocilizumab. The sustained remission rates in the placebo groups ranged from 7% to 22%. These data suggested no notable differences in sustained remission rate with tocilizumab versus placebo for relapsing GCA patients versus new-onset patients, although the data were limited by small sample sizes and no between-group comparisons or treatment-by-disease status interaction *P* values were reported.

The proportion of patients who received escape prednisone was 23%, 33%, 74%, and 55% in the tocilizumab weekly, tocilizumab biweekly, placebo (26-week taper) and placebo (52-week taper) groups, respectively. The median cumulative prednisone dose over the 52-week blinded treatment period (which included scheduled taper doses and all escape or commercial prednisone doses) was 1,862 mg in both tocilizumab groups, 3,296 mg in the placebo plus 26-week taper group, and 3,818 mg in the placebo plus 52-week taper group. The time-to-first-flare data suggested that flare may be delayed with weekly tocilizumab versus both placebo groups and for biweekly tocilizumab versus the placebo plus 26-week taper group, with hazard ratios ranging from 0.23 to 0.39, and 99% CIs that excluded the null. However, the cumulative prednisone dose and time to first flare were secondary outcomes that were outside the statistical testing hierarchy and should be interpreted as exploratory.

Overall, few clinically important differences were detected between tocilizumab and placebo groups on health-related quality of life based on the Short Form (36) Health Survey and Patient's Global Assessment of disease activity visual analogue scale. However, the trial was not powered for patient-reported outcomes and the instruments used may not be responsive to change in GCA patients. The results were potentially biased due to the exclusion of post-escape data as these data were not missing at random and their exclusion may have violated the assumptions of the repeated measures model, although a post hoc analysis that included post-escape data yielded similar results. All patient-reported outcomes were outside the statistical testing hierarchy and were limited by the extent of missing data.

In terms of GCA-related morbidity, there were no new cases of permanent vision loss during the study. The most common visual complication was blurred vision (tocilizumab: 8% to 20%; placebo: 16%), a symptom that can be caused by corticosteroid treatment. Most

patients in all of the groups displayed signs and symptoms of GCA during the trial, though they did not always signal a disease flare.

According to the clinical expert consulted for this review, the differences in sustained remission rate and prednisone exposure seen with tocilizumab treatment as compared with placebo (with 26-week or 52-week prednisone taper) were clinically meaningful. However, it is unclear if the reductions in prednisone doses are generalizable, as corticosteroid tapering does not follow a standardized regimen in clinical practice. Moreover it is unknown if the treatment effects will result in longer-term reductions in GCA-related morbidity (such as stroke) or corticosteroid-related morbidity (such as fractures, diabetes, cardiovascular events, and cataracts), as the trial was not powered, or of sufficient duration, to detect differences in these outcomes.

Harms

Most patients in the 52-week GiACTA study experienced one or more adverse events, including serious adverse events, which were reported in 14% to 15% of tocilizumab-treated patients, and 22% to 26% of placebo-treated patients. Infections or infestations were the most commonly reported system organ class group of adverse events (tocilizumab: 73% to 75%, placebo: 65% to 76%), of which 4% to 7% of patients in the tocilizumab groups and 4% to 12% in the placebo groups had infections that were considered serious. The frequency of withdrawals due to adverse events was similar in the tocilizumab and placebo groups with a 26-week prednisone taper (11% to 12%), whereas no patients in the placebo plus 52-week taper stopped treatment due to adverse events. Other than infection, the notable adverse events identified in this review's protocol were generally infrequent or showed a similar frequency across treatment groups. Of note, the trial duration was limited to 52 weeks, and thus does not provide information on longer-term adverse events, although the safety profile of tocilizumab is generally known, as the drug is approved in Canada for rheumatoid arthritis and juvenile idiopathic arthritis.

Potential Place in Therapy[a]

According to the clinical expert consulted for this review, the first objective of the treatment of GCA is to control the signs and symptoms of the disease and to prevent complications such as visual loss and stroke. Provided complications are not present at baseline, they hardly ever occur following initiation of oral high-dosage (60 mg/day to 80 mg/day) corticosteroids. The second objective is to taper steroids to prevent the morbidities of chronic high- and moderate-dose steroids.

The initial high corticosteroid dose is usually maintained for about one month, at which time symptoms and acute-phase reactants (ESR, C-reactive protein) normalize, and then tapered slowly to achieve a maintenance dosage of 5 mg/day to 10 mg/day at six months to a year. The tapering schedule is based on physician experience modified by patients' symptoms at each follow-up visit and supported by changes in laboratory data. There is no established protocol for steroid tapering. Most physicians would continue low-dose corticosteroids for the second year of disease and then attempt a taper to 0 mg/day. Fewer than 50% of patients can stop steroids completely and are on life-long therapy.

[a] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Chronic treatment with corticosteroids is associated with numerous morbidities and the search for an alternative treatment and/or a corticosteroid-sparing agent has been a long-standing objective. Methotrexate has not met the challenge. Tocilizumab is the first breakthrough in the treatment of GCA. The GiACTA study has shown it to be effective as a corticosteroid-sparing agent. The finding that corticosteroids can be tapered in about 50% of patients at six months is a compelling observation. The data further support the hypothesis that tocilizumab treats the fundamental disease process. Total proof of the latter, the ability to avoid corticosteroids completely, will require a separate study. Moreover, evidence that tocilizumab can reduce longer-term GCA- or corticosteroid-related morbidity is lacking.

The clinical expert indicated that the methods of diagnosing a patient with GCA may be variable across centres due to the availability and access to diagnostic tools such as magnetic resonance angiography (MRA), computed tomography angiography (CTA), or positron emission scanning (PET) scanning. Entry to the GiACTA trial required a confirmed diagnosis of GCA, obtained through temporal artery biopsy and/or imaging such as MRA/CTA or positron emission tomography (PET) scanning. In the real world, obtaining such confirmation is problematic. Access to temporal artery biopsy is not often timely and not all patients will be biopsy-positive. PET scanning is not available in most centres. MRA and CTA provide important diagnostic information, but timely access varies across Canada and making them an absolute requirement for trial entry adds substantial costs. Further, the sensitivity and specificity of imaging is not established. In addition, still to be established is the utility of imaging to confirm the definition of remission and the duration of therapy. In the absence of biopsy and imaging information, the clinician depends on the clinical presentation and the presence of elevated acute-phase reactants. Even here there is variability in presentation, including a normal ESR in about 25% of patients. Thus, physician judgment that the patient has GCA, supported as much as possible by confirmatory tests, is the current standard of care. Any reimbursement criteria that includes an absolute requirement for a confirmatory test would limit access to those in need.

A dedicated register of all Canadian patients treated with tocilizumab would be invaluable in answering important aspects of safety.

Conclusions

One trial, which evaluated the use of tocilizumab SC versus placebo in patients with active GCA, met the inclusion criteria for the systematic review. Statistically significantly more patients who received tocilizumab weekly or biweekly in combination with a 26-week prednisone tapering regimen achieved sustained remission at 52 weeks than those on placebo. Data on the cumulative prednisone dose and time to first flare also favoured tocilizumab versus placebo, although these outcomes should be interpreted as exploratory. The treatment effects observed were clinically important, but it is unclear if these benefits will result in longer-term reductions in GCA- or corticosteroid-related morbidity or mortality, which are important to patients.

Few clinically important differences between tocilizumab and placebo in health-related quality of life were detected. However, the study was not powered for these measures and the instruments used may not be responsive in patients with GCA. These analyses may also be biased due to the exclusion of data from patients who required escape prednisone therapy, and due to the extent of missing data.

Infections were the most frequently reported adverse event in all treatment groups.

The available evidence was limited to a single RCT with a relatively small number of patients per treatment group and treatment duration of 52 weeks.

Table 1: Summary of Results

	GiACTA			
Outcome	**Tocilizumab Weekly (26-week taper) N = 100**	**Tocilizumab Every 2 Weeks (26-Week Taper) N = 49**	**Placebo (26-Week Taper) N = 50**	**Placebo (52-Week Taper) N = 51**
Sustained remission at 52 weeks				
n (%)	56 (56)	26 (53)	7 (14)	9 (18)
Between-group difference, % (99.5% CI), *P* value[a]				
versus placebo (26-week taper)	42% (18 to 66), *P* < 0.0001	39% (12 to 66), *P* < 0.0001	reference	NA
versus placebo (52-week taper)	38% (18 to 59), *P* < 0.0001	35% (10 to 60), *P* = 0.0002	NA	reference
Cumulative prednisone dose, mg				
Expected dose[b] median (range)	1,337 (350 to 2,632)	1,442 (333 to 2,632)	1,337 (952 to 2,632)	2,608 (823 to 3,903)
Actual dose[c] median (range)	1,862 (630 to 6,603)	1,862 (295 to 9,913)	3,296 (932 to 9,778)	3,818 (823 to 10,698)
Difference in actual doses, *P* value versus placebo (26-week taper)	*P* < 0.0001[d]	*P* = 0.0003[d]	reference	NA
Difference in actual doses, *P* value versus placebo (52-week taper)	*P* < 0.0001[d]	*P* < 0.0001[d]	NA	reference
Time to disease flare				
n (%)	23 (23)	13 (26.5)	34 (68)	25 (49)
HR (99% CI), *P* value[e]				
versus placebo (26-week taper)	0.23 (0.11 to 0.46), *P* < 0.0001[d]	0.28 (0.12 to 0.66), *P* = 0.0001[d]	reference	NA
versus placebo (52-week taper)	0.39 (0.18 to 0.82), *P* = 0.0011[d]	0.48 (0.20 to 1.16), *P* = 0.032[d]	NA	reference
Patients with ≥ 1 SAE, n (%)	15 (15)	7 (14)	11 (22)	13 (26)
Patients who stopped treatment due to AEs, n (%)	11 (11)	6 (12)	6 (12)	0
Infections and infestations (SOC)	5 (5)	1 (2)	1 (2)	0

	GiACTA			
Outcome	**Tocilizumab Weekly (26-week taper) N = 100**	**Tocilizumab Every 2 Weeks (26-Week Taper) N = 49**	**Placebo (26-Week Taper) N = 50**	**Placebo (52-Week Taper) N = 51**
Notable harms, n (%)				
Infection or infestations (SOC)	75 (75)	36 (73)	38 (76)	33 (65)
Serious infection	7 (7)	2 (4)	2 (4)	6 (12)
Neutropenia	4 (4)	2 (4)	0	0

AE = adverse event; CI = confidence interval; HR = hazard ratio; NA = not applicable; SAE = serious adverse event; SOC = system organ class.

Note: *P* < 0.005 required for statistical significance for sustained remission at 52 weeks; *P* < 0.01 required for all other end points (*P* values are descriptive).

[a] Cochran–Mantel–Haenszel test adjusted for starting prednisone dose (≤ 30 mg/day, > 30 mg/day).

[b] Expected cumulative dose was based on the patient's starting prednisone dose and assuming the taper was continued without error.

[c] Actual prednisone dose was based on patients' record of prednisone taken and included all escape therapy and use of commercial prednisone as well as doses received as part of the tapering process. *P* values based on van Elteren test stratified by baseline prednisone dosage (≤ 30 mg/day versus > 30 mg/day). Missing doses during the taper were assumed to be the minimum-dose tablets from that pack. Patients who received an increased dose of prednisone because they entered escape therapy were included in their originally assigned treatment group. There was no imputation of missing data.

[d] Outside the statistical testing hierarchy.

[e] Cox proportional hazards model adjusting for stratification factor of starting prednisone dose (≤ 30 mg/day, > 30 mg/day).

Source: Clinical Study Report.[8]

Introduction

Disease Prevalence and Incidence

Giant cell arteritis (GCA) is a systemic large-vessel vasculitis found almost exclusively in patients aged 50 years and older.[1] Symptoms of GCA include headache, fatigue, jaw claudication, temporary or permanent loss of vision, scalp tenderness, aortic arch syndrome, and polymyalgia rheumatica (PMR).[1] Vessel wall granulomatous inflammation mostly occurs in the aorta and the branches of the aorta and external carotid and can lead to stenoses, occlusions, or aneurysms.[2] Severe, permanent vision loss, sometimes heralded by temporary vision loss, eye pain, or diplopia, can occur suddenly due to occlusion of the short posterior ciliary arteries.[3] Severe vision loss occurs in about 15% to 30% of GCA cases.[4,9] PMR is characterized by bilateral pain and stiffness in the shoulders, and both GCA and PMR are associated with an elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level.[10] Both conditions are related to systemic inflammation and approximately 50% of GCA patients also have PMR.[6] The etiology of both of these conditions remains unknown.

Patient experiences with GCA and the glucocorticoid therapy used to treat it vary depending on how quickly and completely symptoms resolved. Some patients, such as the one providing input for this CADTH Common Drug Review (CDR), experience minimal symptoms while others have more severe symptoms lasting up to a few years. A recent qualitative study conducted using telephone interviews with UK patients identified impacts of GCA and its treatment that are important to patients.[11] Patients often did not attempt to distinguish between symptoms of GCA and symptoms of glucocorticoid therapy. Patients described fatigue as intense and continuous and it affected their ability to work, volunteer, participate in hobbies, and perform household and daily self-care tasks. These abilities were also affected by various manifestations of pain and discomfort, such as muscle pain and extreme scalp sensitivity, as well as by difficulty in sleeping. Financial burden arose from inability to work and the need to hire people to help with household tasks. Uncertainty in the severity of symptoms of pain, fatigue, and insomnia from day to day made it difficult to plan social activities and outings. Permanent vision loss leading to partial or total blindness in one or both eyes was particularly devastating and was accompanied by a sense of bereavement and vulnerability in addition to continual fear of further vision loss. Other visual symptoms included blind spots, blurred vision, and cataracts. Loss of vision affected regular activities, including driving, and led to increased dependence on others. Patients were also affected by changes in appearance due to weight gain, facial puffiness, profuse sweating, and extensive bruising. These changes led to low mood and a loss of confidence. The mood changes described in association with treatment dosage were severe, with several patients describing their own behaviour becoming intolerant, short-tempered, and irritable. These patients expressed guilt and regret over how their relationships with their partners and others suffered during treatment with high doses of medication. There were descriptions of depression as well as great frustration over symptoms and their impacts. Patients struggled to cope with the effects of GCA and treatment on their lives and some were critical of their own ability to manage these effects. Feelings of fear and uncertainty were also described with regard to potential for further vision loss or relapse, improvement in symptoms, and which symptoms were caused by GCA as opposed to treatment.[11]

Incidence estimates for GCA vary by geographic region and diagnostic criteria, with annual incidence rates highest in northern Europe (ranging from 15 to 35 per 100,000 persons over the age of 50 years)[12] and other locations with populations of northern European descent (11.2 per 100,000 person over 50 years of age and 22 per 100,000 persons over 40 years of age in the UK[13,14] and 19.8 per 100,000 persons over the age of 50 years in Olmsted county in the US[15]). In contrast, the estimated annual incidence rate in Japan is 1.47 per 100,000 persons 50 years of age and older.[16] GCA is more common in females than in males, with a female-to-male incidence ratio ranging from 1.7 to 2.6 for the aforementioned populations.[12-14,16] Availability of prevalence estimates is limited, with values in populations over the age of 50 years of 0.28% in Olmsted County, 0.11% in Skane, Sweden, and 0.04% in Germany.[17]

The manufacturer's submission included information from two Canadian studies on the epidemiology of GCA. Incidence of biopsy-proven GCA for the Saskatoon area was estimated at 9.4 per 100,000 persons over 50 years of age based on patients from a single neuro-ophthalmology clinic in Saskatoon.[18] Out of the 37 patients diagnosed with GCA, 35 were of European descent and two were of Aboriginal descent. A study in British Columbia in persons 20 years of age and older using physician billing and hospitalization databases found an annual incidence rate of 2.7 per 100,000 persons and a prevalence rate of 17.3 per 100,000 persons (0.017%).[19]

Diagnosis

Diagnosis of GCA is based on age, symptoms, ESR and CRP levels, and temporal artery biopsy or non-invasive imaging.[1,10] The 1990 American College of Rheumatology (ACR) classification scheme, developed to differentiate GCA from other forms of vasculitis, requires the presence of at least three of the following criteria for a GCA diagnosis: age of at least 50 years at disease onset, new localized headache, temporal artery tenderness or decreased pulse, elevated ESR (≥ 50 mm/hour), and abnormal artery biopsy (usually of the temporal artery).[1] Temporal artery biopsy is often used as a reference standard, although estimates of false-negative rates vary widely (1.8% to 34%) and may be caused by skip lesions, lack of temporal artery involvement, or steroid therapy prior to biopsy.[20]

Non-invasive imaging techniques have also been developed for the detection of arterial inflammation. However, methods of image acquisition and analysis or interpretation are not standardized and the studies performed to characterize diagnostic accuracy have been small (sample sizes are generally smaller than 100 patients).[10] A recent review surveyed sensitivity and specificity values for ultrasonography, magnetic resonance imaging, and ^{18}F-fluorodeoxyglucose positron emission tomography (PET).[10] The reference standard was one of the following: clinical diagnosis, temporal artery biopsy result, or fulfillment of the ACR criteria.[10] Ultrasonography using the "halo sign" in the temporal artery yielded sensitivities of 55% to 100% and specificities of 78% to 100% in 10 studies.[10] Contrast-enhanced magnetic resonance imaging of the temporal and occipital arteries had sensitivities ranging from 68% to 89% and specificities ranging from 73% to 97%.[10] The lone ^{18}F-fluorodeoxyglucose PET study meeting the inclusion criteria of the review reported a sensitivity of 77% and specificity of 66% in 69 cases.[10] Arterial signs of GCA may subside after initiation of treatment and result in lower diagnostic accuracy of the imaging tests.[21]

Standards of Therapy

While Canadian guidelines are not available, the British Society for Rheumatology and British Health Professionals in Rheumatology have developed guidelines for management of GCA[22] and the European League Against Rheumatism has developed recommendations for the management of large-vessel vasculitis.[23] Treatment options for GCA are limited and all guidelines agree that glucocorticosteroid (also known as glucocorticoid or corticosteroid) therapy with prednisone or prednisolone should be initiated immediately upon suspicion of GCA, even prior to confirmation of diagnosis via temporal artery biopsy or imaging. Biopsy or imaging may not be available in a timely manner and treatment must be initiated to reduce the risk of vision loss. The dose and route of administration vary depending on the presenting symptoms and the optimal dose regimen is unclear. The British Society for Rheumatology and British Health Professionals in Rheumatology recommend an initial dosage of 40 mg to 60 mg daily[22] while the European League Against Rheumatism recommends a starting dosage of 1 mg/kg (maximum 60 mg) daily.[23] Patients with evolving vision loss may be started on high-dose intravenous methylprednisolone therapy prior to transitioning to oral corticosteroid therapy.[22,23] Symptoms typically resolve rapidly in response to corticosteroid therapy and if the patient is free of symptoms and abnormal laboratory parameters, the corticosteroid dose can be tapered gradually over the course of one to two years. It is common for patients to experience symptom flare or relapse during or after the tapering regimen, necessitating an increase in corticosteroid dose. Depending on length of follow-up, symptom flare has been reported to occur in about 34% to 79% of patients, with most flares occurring within the first year following initial GCA diagnosis.[24-27] Estimates of percentages of patients experiencing more than one flare range from 8% to 50%, again depending on length of follow-up.[24-27] According to the clinical expert, the presence of flare is determined by symptoms and not levels of ESR or CRP.

The long-term use of oral corticosteroid therapy introduces a host of adverse effects and increases the risk of bone fractures, worsening of diabetes and hypertension, thrombotic events, gastrointestinal bleeding, muscle weakness from myopathy, glaucoma, and cataracts.[4,5] Emotional effects related to corticosteroid therapy include insomnia, restlessness, hypomania, and depression.[6] Given the high relapse rate and adverse effects associated with oral corticosteroid therapy, there is a need for other therapies for the treatment of GCA in patients. A therapy that allows the exposure of a patient to corticosteroid to be lowered would reduce harms resulting from long-term corticosteroid therapy. Methotrexate is a common steroid-sparing agent used as an adjuvant to corticosteroid, but there is limited evidence to support its efficacy in GCA.[10]

Drug

Tocilizumab is an anti-human interleukin-6 (IL-6) receptor monoclonal antibody that binds to and inhibits signalling through both soluble and membrane-bound IL-6 receptors.[7] IL-6 is a pleiotropic cytokine associated with the product of acute-phase proteins and mediation of immune response, and its serum levels have been shown to correlate with disease activity in GCA patients.[28] When given through subcutaneous (SC) injection, tocilizumab is available as a single-use, pre-filled syringe containing a single dose (162 mg) in 0.9 mL of solution.[7] The SC form of tocilizumab is reviewed in the present CDR clinical report for the treatment of GCA in adult patients. Tocilizumab is also indicated for reducing signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis.[7]

Tocilizumab is also available as intravenous injection for the treatment of signs and symptoms of active polyarticular juvenile idiopathic arthritis in patients two years of age and older who have responded inadequately to previous therapy with disease-modifying antirheumatic drugs and for the treatment of active systemic juvenile idiopathic arthritis in patients two years of age and older who have responded inadequately to previous therapy with one or more nonsteroidal anti-inflammatory drugs and systemic corticosteroids.[7]

Table 2: Key Characteristics of Tocilizumab (Actemra)

	Tocilizumab (Actemra)
Mechanism of Action	Tocilizumab binds to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), and has been shown to inhibit sIL-6R– and mIL-6R–mediated signalling through these receptors.
Indication[a]	**Treatment of giant cell arteritis in adult patients**
Route of Administration	Subcutaneous injection
Recommended Dose	For adult patients with GCA, the recommended dose of tocilizumab is 162 mg given once every week as a subcutaneous injection, in combination with a tapering course of glucocorticoids. A dose of 162 mg given once every other week as a subcutaneous injection, in combination with a tapering course of glucocorticoids, may be prescribed based on clinical considerations. Tocilizumab can be used alone following discontinuation of glucocorticoids. Dose adjustment may be needed for management of dose-related laboratory abnormalities, including elevated liver enzymes, neutropenia, and thrombocytopenia. Intravenous administration is not approved for GCA.

Serious Side Effects and Safety Issues	Contraindications:
	• Known hypersensitivity to tocilizumab or any of its components
	• Active infections
	
	Warnings and precautions:
	• Serious infections
	• Gastrointestinal perforations
	• Laboratory abnormalities:
	  ○ Elevated liver enzymes
	  ○ Low neutrophil count
	  ○ Low platelet count
	• Hyperlipidemia
	• Hypertension
	• Serious hypersensitivity reactions

GCA = giant cell arteritis; IL-6 = interleukin-6; mIL-6R = membrane-bound interleukin-6 receptor; sIL-6R = soluble interleukin-6 receptor.
[a] Health Canada indication.
Source: Actemra product monograph.[7]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of tocilizumab 162 mg/0.9 mL pre-filled syringe for SC injection for the treatment of GCA in adults.

Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase III studies were selected for inclusion based on the selection criteria presented in Table 3.

Table 3: Inclusion Criteria for the Systematic Review

Patient Population	Adults with giant cell arteritis Subgroups • Newly diagnosed GCA versus patients with relapse
Intervention	Tocilizumab 162 mg per week[a] by SC injection alone or as add-on therapy to corticosteroids
Comparators	Corticosteroids Methotrexate Placebo
Outcomes	**Key efficacy outcomes:** • Morbidity and mortality related to GCA (e.g., myocardial infarction, aortic aneurysm, stroke, vision loss) • Remission • Disease flares • Corticosteroid-sparing effects (e.g., dose, duration) • Corticosteroid-related morbidity[b] (e.g., fractures, cataracts, glaucoma, infection, glucose intolerance, cardiovascular disease) • Health-related quality of life **Other efficacy outcomes:** • Patient symptoms (e.g., fatigue, pain) **Harms outcomes:** AEs, SAEs, WDAEs, mortality, infection, neutropenia, anaphylaxis, injection-site reactions, gastrointestinal perforation, thrombocytopenia, hypertension, immunogenicity, elevated lipid parameters, elevated liver enzymes, malignancies
Study Design	Published and unpublished phase III RCTs

AE = adverse event; GCA = giant cell arteritis; RCT = randomized controlled trial; SAE = serious adverse event; SC = subcutaneous; WDAE = withdrawal due to adverse event.

[a] In accordance with the originally submitted draft product monograph. An updated version of the product monograph adds that a dose of 162 mg given once every other week as a subcutaneous injection may be prescribed based on clinical considerations.[7] Therefore, both dose regimens were considered in this report.

[b] Identified by patient groups as important to patients.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present via Ovid; Embase (1974–) via

Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Actemra (tocilizumab) and Giant Cell Arteritis.

No methodological filters were applied to limit retrieval. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on October 24, 2017. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on February 21, 2018. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters):

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4: Details of Included Studies. Excluded studies (with reasons) are presented in Appendix 3.

Results

Findings from the Literature

A total of one study was identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4: Details of Included Studies and described. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

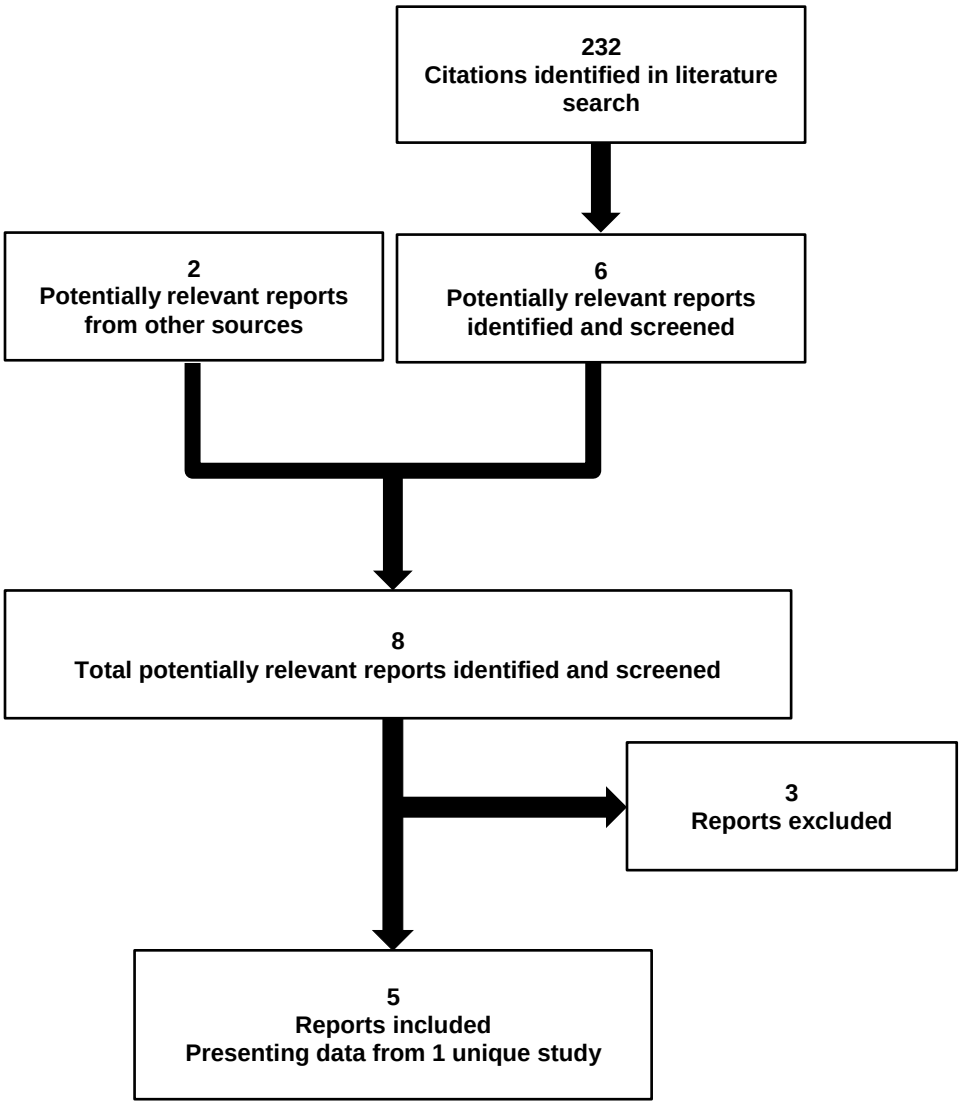


Table 4: Details of Included Studies

		GiACTA
Designs & Populations	**Study Design**	Double-blind RCT
	Locations	61 centres in Europe, 14 centres in the US and one in Canada
	Randomized (N)	251
	Inclusion Criteria	• Patients ≥ 50 years of age with active GCA within past 6 weeks and a history of elevated ESR (≥ 50 mm/hour)[a] due to GCA • At time of diagnosis patients had unequivocal cranial symptoms of GCA (new-onset localized headache, scalp tenderness, temporal artery tenderness or decreased pulsation, ischemia-related vision loss, or other mouth or jaw pain on mastication) and/or symptoms of polymyalgia rheumatica (shoulder or hip girdle pain associated with inflammatory morning stiffness) • Diagnosis confirmed by temporal artery biopsy revealing features of GCA or evidence of large-vessel vasculitis by angiography, MRA, CTA, or PET-CT • Patients were either newly diagnosed (diagnosis within 6 weeks of study baseline visit) or had relapsing disease (diagnosis more than 6 weeks ago and treatment with ≥ 40 mg/day prednisone for at least 2 weeks) • At baseline, patients were receiving 20 mg to 60 mg of prednisone daily
	Exclusion Criteria	• Recent major ischemic event or major surgery • History of transplanted organs • Previous treatment with cell-depleting therapies (e.g., alemtuzumab, anti-CD4, anti-CD5, anti-CD3, anti-CD19, or anti-CD20); alkylating agents (e.g., chlorambucil or total lymphoid irradiation); tocilizumab; tofacitinib • Recent gamma globulin or plasmapheresis therapy (past 6 months); live/attenuated vaccine (past 4 weeks); etanercept (2 weeks); infliximab, certolizumab, golimumab, abatacept or adalimumab (8 weeks); anakinra (1 week), cyclophosphamide (6 months) • Systemic corticosteroids for conditions other than GCA that may interfere with the taper • Chronic use of corticosteroids for more than 4 years or inability to withdraw therapy due to adrenal insufficiency • Received > 100 mg daily IV methylprednisolone within 6 weeks • Serious uncontrolled medical condition • History of severe allergic reactions to monoclonal antibodies or prednisone • Current liver disease; hepatitis B or C infection • History of diverticulitis or chronic ulcerative lower gastrointestinal disease • Active tuberculosis; current active or history of recurrent infections; any major infection requiring hospitalization or IV antibiotic within 4 weeks or oral antibiotics within 2 weeks of baseline • Immunodeficiency • Malignancy within past 5 years • Body weight > 150 kg • Laboratory exclusions based on several renal, hepatic, or hematologic parameters
Drugs	**Intervention**	• Tocilizumab 162 mg SC every week plus 26-week prednisone taper • Tocilizumab 162 mg SC every 2 weeks plus 26-week prednisone taper
	Comparator(s)	• Placebo SC weekly plus 26-week prednisone taper • Placebo SC weekly plus 52-week prednisone taper
Duration	**Phase**	
	Run-in	NA
	Double-blind	52 weeks (Part 1)
	Follow-up	104 weeks (Part 2 – open-label follow-up period)

		GiACTA
Outcomes	**Primary End Point**	Percentage with sustained remission at 52 weeks versus placebo (26-week taper)
	Secondary End Points	• Percentage with sustained remission at 52 weeks versus placebo (52-week taper) • Time to first flare • Cumulative prednisone dose over 52 weeks • SF-36 MCS and PCS (change from baseline to 52 weeks) • Patient's Global Assessment of disease activity using VAS (change from baseline to 52 weeks)
	Other End Points	• Annualized relapse rate • Remission rate over time • Duration of glucocorticoid use • Percentage with sustained remission versus placebo (52 week taper) • SF-36 MCS and PCS (change in categories from baseline to 52 weeks) • Change in FACIT-F score • Change in EQ-5D • Duration of corticosteroid use • Harms
Notes	**Publications**	Stone 2017[29]

CTA = computed tomography angiography; CDR = CADTH Common Drug Review; CRP= C-reactive protein; EQ-5D = EuroQoL 5-Dimensions questionnaire; ESR = erythrocyte sedimentation rate; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue; GCA = giant cell arteritis; IV = intravenous; MCS = mental component summary; MRA = magnetic resonance angiography; PCS = physical component summary; PET-CT = positron emission tomography–computed tomography; SC = subcutaneous; SF-36 = Short Form (36) Health Survey; VAS = visual analogue scale.

Note: Three additional reports were included (CDR submission,[30] Health Canada Reviewers Report[31] and FDA Review[32]).

[a] If historical ESR was not available, then a history of CRP ≥ 2.45 mg/dL was accepted.

Source: Clinical Study Report.[8]

Included Studies

Description of Studies

Part 1 of the GiACTA trial was a 52-week double-blind randomized controlled trial (RCT) that evaluated the use of tocilizumab SC versus placebo in patients with active GCA who were 50 years of age or older. Patients were randomized 2:1:1:1 (using an interactive voice response system) to tocilizumab weekly or tocilizumab every other week (both with a 26-week prednisone taper), placebo with 26-week prednisone taper, or placebo with 52-week prednisone taper. Randomization was stratified according to the baseline prednisone dosage (≤ 30 mg per day versus > 30 mg/day). The primary end point was the proportion of patients in sustained remission at week 52 following induction and adhering to the protocol-defined prednisone taper regimen.

Patients were managed by two assessors: a clinical assessor who evaluated patients for signs and symptoms of GCA and managed the prednisone taper; and a laboratory assessor, who was responsible for the overall clinical management of patients outside their GCA. The clinical assessor was blinded to laboratory data, such as ESR and CRP values. The laboratory assessor was allowed to discuss ESR elevations pre-specified in the study protocol (ESR above 30 mm per hour) with the clinical assessor as required for the management of the patient, but only after the clinical assessor had completed the evaluation of the patient for signs and symptoms of GCA. All site staff were blinded to CRP levels that were analyzed in a central laboratory.

The first four patient visits occurred weekly and were followed by patient visits every four weeks up to week 52.

Part 2 of the GiACTA trial was a 104-week open-label period. Those in remission at the end of 52 weeks were followed for 104 weeks off study drug. Those not in remission had the option to receive open-label tocilizumab 162 mg SC weekly for up to 104 weeks. Patients could receive corticosteroids or methotrexate at the investigator's discretion. Data for part 2 were not available when this report was compiled.

Populations

Inclusion and Exclusion Criteria

Patients who were either newly diagnosed or had relapsing GCA were eligible for enrolment. A limit of up to 70% of patients with relapsing disease was set. A diagnosis of GCA meant the patient had to present with unequivocal cranial symptoms of and/or symptoms of PMR. The diagnosis had to be confirmed by temporal artery biopsy and/or imaging. Additional details are available in Table 4.

Patients were defined in the Clinical Study Report (page 40)[8] as follows:

- "New-onset: diagnosis of active GCA within six weeks of baseline visit (defined as the presence of clinical signs and symptoms and ESR ≥ 30 mm/hour or CRP ≥ 1 mg/dL; elevations in ESR and CRP were not required if the patient had a positive temporal artery biopsy within the six weeks prior to baseline)."
- "Relapsing: diagnosis of GCA more than six weeks before baseline visit, previous treatment with ≥ 40 mg/day prednisone (or equivalent) for at least two consecutive weeks at any time, and active GCA within six weeks of baseline visit (defined as the presence of clinical signs and symptoms and ESR ≥ 30 mm/hour or CRP ≥ 1 mg/dL; elevations in ESR and CRP were not required if the patient had a positive temporal artery biopsy within the six weeks prior to baseline). This included patients who had previously achieved remission and subsequently flared and those who had not achieved remission since the diagnosis of disease (i.e., refractory patients)."

Many of the selection criteria were designed to exclude patients susceptible to infection, such as patients previously treated with cell-depleting therapies or alkylating agents and patients who were immunodeficient. Patients with liver disease, hepatitis B or C infection, or tuberculosis were also excluded. With regard to corticosteroid use, patients receiving methylprednisolone (more than 100 mg daily) recently or systemic corticosteroids chronically for over four years (or those unable to withdraw therapy due to adrenal insufficiency) were excluded.

Baseline Characteristics

The patients enrolled in the GiACTA trial were predominantly female (70% to 78%), white (94% to 100%), and had a mean age that ranged from 67.8 to 69.5 years across treatment groups (Table 5). Approximately half the patients were newly diagnosed with GCA or were receiving more than 30 mg per day of prednisone at baseline. Between 37% and 47% of patients per treatment group had both cranial and PMR symptoms. Baseline characteristics regarding demographics, disease history, and concomitant medications were, in general, balanced among all four groups. Disease duration had similar ranges in all the groups, with the exception of the placebo with 52-week taper group, which had a maximum value of 1,789 days compared with maximum values of 2,698 to 2,856 days for the other groups. The mean and median disease durations for the placebo with 26-week taper group were

higher than in the other groups. Given the large ranges and standard deviations in disease duration, the importance of these differences is uncertain.

Table 5: Summary of Baseline Characteristics

	GiACTA			
	Tocilizumab Weekly (26-Week taper) N = 100	**Tocilizumab Every 2 Weeks (26-Week Taper) N = 50**	**Placebo (26-Week Taper) N = 50**	**Placebo (52-Week Taper) N = 51**
Mean age, years (SD)	69.5 (8.5)	69.4 (8.2)	69.3 (8.1)	67.8 (7.7)
Female, n (%)	78 (78)	35 (70)	38 (76)	37 (73)
Race, n (%)				
White	97 (97)	47 (94)	50 (100)	49 (96)
Black	1 (1)	0	0	2 (4)
Asian	0	1 (2)	0	0
Other/unknown	2 (2)	2 (4)	0	0
Body mass index, mean kg/m^2 (SD)	26.0 (4.4)	26.0 (6.2)	25.7 (4.5)	25.8 (4.1)
Newly diagnosed GCA, n (%)	47 (47)	26 (52)	23 (46)	23 (45)
Relapsing GCA, n (%)	53 (53)	24 (48)	27 (54)	28 (55)
Prednisone dose				
mg/day, mean (SD)	34.6 (13.4)	35.9 (13.8)	34.6 (13.0)	34.5 (14.2)
≤ 30 mg/day, n (%)	52 (52)	25 (50)	27 (54)	26 (51)
> 30 mg/day, n (%)	48 (48)	25 (50)	23 (46)	25 (49)
Disease duration, days				
median (range)	52 (9 to 2,856)	41.5 (13 to 2,708)	80 (12 to 2,698)	53 (8 to 1,789)
mean (SD)	307 (564)	258 (501)	365 (570)	255 (435)
Signs and symptoms, n (%)				
Cranial only	41 (41)	18 (36)	20 (40)	16 (31)
Polymyalgia rheumatic only	22 (22)	9 (18)	10 (20)	11 (22)
Both	37 (37)	23 (46)	20 (40)	24 (47)
ESR mm/h, mean (SD)	24.6 (18.7)	20.8 (18.1)	28.8 (25.4)	24.2 (18.2)
Concomitant methotrexate, n (%)	11 (11)	5 (10)	8 (16)	9 (18)

ESR = erythrocyte sedimentation rate; GCA = giant cell arteritis; SD = standard deviation.

Source: Clinical Study Report.[8]

Interventions

Identical pre-filled syringes of tocilizumab 162 mg or placebo doses were supplied in boxes of two, with syringes numbered 1 and 2. All patients were to inject the study drug weekly in the numerical order. Those randomized to tocilizumab every two weeks received one active and one placebo syringe per box. The first four doses were administered under supervision during study visits.

At the baseline study visit, all patients were receiving 20 mg to 60 mg of prednisone daily. The protocol-defined prednisone taper had an open-label phase (for dosages from 60 mg/day to 20 mg/day) and a double-blind phase (for dosages less than 20 mg/day). Patients were supplied with open-label 10 mg or 5 mg prednisone tablets for the open-label phase, and blister packs of blinded encapsulated prednisone and/or placebo tablets for the double-blind phase.

Patients were assessed at every visit to determine if the patient could adhere to the prednisone tapering schedule. If the patient experienced a disease flare or could not adhere to the taper due to ongoing disease activity, the patient stopped the protocol-defined tapering schedule and could receive escape prednisone. Patients who required escape therapy during the open-label taper period (baseline to prednisone 20 mg/day) or during the double-blind taper period (< 20 mg prednisone per day) continued to receive blinded tocilizumab or placebo injections, and study assessments for the 52 weeks. Those requiring escape therapy during the double-blind taper period received open-label prednisone of at least 20 mg daily. Ongoing escape prednisone dosing and duration was at the discretion of the investigator.

The prednisone taper regimen for the open-label phase involved daily dosages that decreased by 5 mg or 10 mg at weekly intervals for up to seven weeks of the schedule: 60 mg, 50 mg, 40 mg, 35 mg, 30 mg, 25 mg, and 20 mg per day. Patients started at one of the seven weeks in the schedule depending on their baseline dose and proceeded with the tapering such that the length of the open-label tapering phase varied between patients. In the blinded phase that followed, the 26-week prednisone taper regimen started at a daily dose of 15 mg at week 8, stayed at 12.5 mg for weeks 9 and 10, decreased weekly by 1 mg from 10 mg to 6 mg, and decreased biweekly by 1 mg from 6 mg to 0 mg. The 52-week prednisone taper regimen started at a daily dose of 17.5 mg at week 8, decreased biweekly by 2.5 mg from 17.5 mg to 12.5 mg, decreased the following week to 10 mg, and decreased in 1 mg increments every four weeks to 0 mg. Patients on both taper regimens took prednisone and/or placebo for the entire 52-week period.

Patients were allowed to receive anti-platelet therapy, lipid-lowering agents, and bisphosphonates at the discretion of the investigator. All patients were to receive calcium and vitamin D supplements. The use of methotrexate was allowed if it was started prior to screening and the dose did not increase during the double-blind period. Methotrexate doses could be reduced or therapy stopped, as appropriate. Short-term corticosteroids could be administered in addition to the study prednisone if required to manage events such as serious infection or to prevent adrenal insufficiency.

Outcomes

The primary outcome was the proportion of patients in sustained remission at week 52 following induction and adherence to the protocol-defined prednisone taper regimen. Induction of remission had to occur within 12 weeks of randomization and patients had to follow the protocol-defined prednisone taper regimen.

Flare was determined by the investigator and defined as the recurrence of signs or symptoms of GCA and/or ESR ≥ 30 mm per hour attributable to GCA. A patient could have symptoms of GCA or elevated ESR and still be considered in remission if the investigator determined these symptoms were not severe enough to be classified as a disease flare.

Remission was defined as the absence of flare (as defined above) and normalization of CRP (greater than 1 mg/dL). Sustained remission was defined as the absence of flare following induction of remission within 12 weeks of randomization and maintained from week 12 up to week 52. Patients were considered non-responders due to non-normalization of CRP if they had elevated CRP values at two consecutive study visits.

For the primary outcome analysis, the tocilizumab groups were compared with placebo plus 26-week prednisone taper, and for the key secondary outcome analysis, the tocilizumab groups were compared with placebo plus 52-week prednisone taper.

Other secondary outcomes included the time to GCA disease flare after clinical remission, the cumulative glucocorticoid dose, quality of life measured using the Short Form (36) Health Survey (SF-36), and the Patient's Global Assessment of disease activity on a visual analogue scale (VAS). Exploratory outcomes included fatigue as measured by Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) score; and EuroQoL 5-Dimensions (EQ-5D) index score. Patient-reported outcome data in the GiACTA trial was collected by providing paper-based documents to patients to complete. The instruments were translated as required in the local language. The recall period was four weeks for the SF-36. Starting at baseline, the Patient's Global Assessment, EQ-5D, and SF-36 instruments were administered every 12 weeks and at week 52, while the FACIT-Fatigue scale was administered every 24 weeks and at week 52.

SF-36 is a generic health assessment questionnaire that has been used in clinical trials to measure health-related quality of life (HRQoL). It consists of eight domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health). The SF-36 also provides two component summaries: the physical component summary (PCS) and the mental component summary (MCS). All domains and summary scores are measured on a scale of 0 to 100, with an increase in score indicating improvement in health status. In general use, a minimal clinically important difference (MCID) of 2 to 4 points for each domain or 2 to 3 points for the MCS and PCS has been reported in the literature.[33] No MCID for the SF-36 was identified in the literature for patients with GCA. However, in patients with rheumatoid arthritis (RA), an MCID of 5.1 to 7.2 for the PCS has been reported.[34] It is unclear if the SF-36 PCS and MCS are responsive to GCA- and corticosteroid therapy-related changes in HRQoL (see Appendix 5 for further details).

The Patient's Global Assessment of disease activity was measured using a VAS. Patients in the GiACTA trial were asked, "On a scale of 0-100 where would you rate the overall effect your giant cell arteritis has on you at this time?" Patients were instructed to draw a vertical mark on a horizontal line (i.e., VAS) to indicate their answer or give a verbal answer if unable to see the scale. The left end of the scale corresponded to a value of 0 and "has no effect at all" and the right end corresponded to a value of 100 and "worst possible effect." No information was found on the use of the Patient's Global Assessment on a VAS in the GCA population and reliability in the RA population was highly variable, possibly due to the lack of standardization of the instrument. Out of a range of values of 0 to 100, with higher numbers corresponding with increased disease activity, the clinical expert consulted for this review estimated an MCID of −10 for RA patients with baseline values of around 40, based on previous rheumatology studies.

The EQ-5D is a generic HRQoL instrument that may be applied to a wide range of health conditions and treatments. The first of two parts of the EQ-5D are a descriptive system that classifies respondents based on the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D index score is generated by applying a multi-attribute utility function to the descriptive system. Reported MCIDs have ranged from 0.033 to 0.074 for general use.[35] The MCID for the three-level EQ-5D among GCA patients remains unknown.

The FACIT-F scale is a questionnaire that assesses self-reported fatigue, including feelings of tiredness, listlessness, and energy, as well as fatigue's impact on daily activities and function. The FACIT-F scale includes 13 items and has a range of scores of 0 to 52, with higher scores indicating less fatigue. Information on the FACIT-F scale in GCA patients was not found, but the instrument has acceptable test-retest reliability and construct validity in the RA population. The FACIT-F scale has an estimated MCID in RA patients of 5.5.

More details on the patient-reported outcomes can be found in Appendix 5.

Statistical Analysis

The primary outcome was analyzed using a Cochran–Mantel–Haenszel test adjusted for starting prednisone dose (≤ 30 mg/day, > 30 mg/day). The analysis was based on the intention-to-treat (ITT) population. Patients who did not achieve remission within 12 weeks of baseline were classified as non-responders. From week 12 onwards, patients with a flare or who received escape therapy, who did not adhere to the prednisone taper (> 100 mg additional glucocorticoids), who withdrew from the study prior to 52 weeks, who had elevated CRP values at two consecutive study visits, or whose remission status could not be determined at week 52 were classified as non-responders in the primary analysis.

A tipping-point analysis was conducted to test the robustness of the primary end point. In this analysis, the tipping point was defined as the difference in the number of missing events between treatment groups that result in a change in the primary outcome conclusions. Patients who had not experienced a flare prior to early study withdrawal were analyzed as missing in the main analysis and were sequentially imputed for the tipping-point analysis. A second analysis was planned that would exclude the requirement for normalized acute-phase reactant levels (CRP and ESR) from the definition of remission (i.e., remission was defined based on signs and symptoms of GCA and not lab values). A different analysis that only excluded normalized CRP levels from the definition of remission was also reported. An exploratory analysis was planned for sustained remission at week 52, which excluded the need for adherence to prednisone taper to be classified as a responder.

The noninferiority of the tocilizumab groups versus placebo plus 52-week taper for sustained remission was defined as the key secondary outcome. Tocilizumab was noninferior to placebo if the lower bound of the 99.5% confidence interval (CI) of the difference in proportions was greater than −22.5%. This margin was selected to preserve 50% of the benefit of corticosteroids (tapered over 52 weeks). In an RCT for adalimumab, the observed response rate for corticosteroids was 71% (95% CI, 52% to 86%). Subtracting the upper limit of response rate for placebo or no treatment (7%) from the lower limit of this 95% CI (52%) results in a 45% minimum treatment effect. The 22.5% noninferiority margin is half of the 45% minimum benefit for corticosteroids. In the GiACTA study the noninferiority analyses were based on the ITT population with a supporting analysis of ITT patients who completed the study and were compliant with the study medication. Patients who did not achieve remission within 12 weeks of baseline were classified as non-responders. From week 12 onwards, patients with a flare or who received escape therapy, who did not adhere to the prednisone taper, or who withdrew from the study prior to 52 weeks, as well as those whose remission status could not be determined at week 52, were classified as non-responders in the key secondary analysis.

The primary and key secondary outcomes were tested using independent hierarchies for each tocilizumab dose regimen with a two-sided 1% significance level split evenly between

the hierarchies (Table 6). In other words, if the primary outcome was significant at a 0.5% level, the key secondary end point within the same hierarchy was then tested for noninferiority using a 99.5% CI. [redacted]

Table 6: Statistical Testing Hierarchy in GiACTA Trial

Hierarchy 1	Hierarchy 2
Primary: superiority of tocilizumab weekly plus 26-week prednisone taper versus placebo plus 26-week prednisone taper on the proportion of patients with sustained remission at week 52	Primary: superiority of tocilizumab every two weeks plus 26-week prednisone taper versus placebo plus 26-week prednisone taper on the proportion of patients with sustained remission at week 52
Key secondary: noninferiority of tocilizumab weekly plus 26-week prednisone taper versus placebo plus 52-week prednisone taper on the proportion of patients with sustained remission at week 52[a]	Key secondary: noninferiority of tocilizumab every two weeks plus 26-week prednisone taper versus placebo plus 52-week prednisone taper on the proportion of patients with sustained remission at week 52[a]

[a] Superiority of each tocilizumab group versus the placebo plus 52-week taper group was tested for superiority if noninferiority was met.

Source: Clinical Study Report.[8]

Based on 100 patients in the tocilizumab weekly group and 50 patients per group for the other treatment arms, the study had 90% power to detect a difference in the proportion of patients in sustained remission at week 52 for both tocilizumab groups versus placebo (26-week taper) at an overall alpha level of 0.01 (two-sided). Sample size calculations assumed a 40% absolute difference in remission rates, with 70% in the tocilizumab and 30% in the placebo group in sustained remission.

Time to first GCA disease flare was summarized by Kaplan–Meier curves and analyzed using a Cox proportional hazards model that included the randomization stratification variable as a covariate. Patients who withdrew from the study prior to week 52 were censored from the time of withdrawal and patients never in remission were censored from day one.

The cumulative prednisone dose over 52 weeks was analyzed using a van Elteren test stratified by the starting prednisone dose and treatment group data were presented as medians with the 95% CI for the median. Any missed doses during the taper were assumed to be the minimum-dose tablet(s) available from that pack. Patients who received prednisone as escape therapy or commercial prednisone or other corticosteroids were also included.

A number of subgroup analyses were planned for the sustained remission outcome, including those based on disease onset (new-onset, relapsing), starting prednisone dose (≤ 30 mg/day, > 30 mg/day), previous history of remission in relapsing patients, and diagnostic criteria.

The Patient's Global Assessment of disease activity was assessed on a 100 mm VAS and analyzed as the change from baseline to week 52 using a maximum likelihood-based repeated measures model. The model included treatment, baseline prednisone dose (≥ 30 mg, < 30 mg/day), visit, treatment-by-visit interaction, prednisone dose-by-visit interaction, baseline score, and baseline score-by-visit interaction. The same model was used to

analyze the change from baseline to week 52 in the SF-36 mental and physical component scores. As post-escape values were considered missing in the main analyses of Patient's Global Assessment of disease activity and SF-36 component scores, a post hoc sensitivity analysis that included the post-escape values was conducted. The change from baseline in the FACIT-F scores and EQ-5D index scores were reported descriptively, with post-escape data set to missing.

Analysis Populations

The ITT population was defined as all randomized patients who received at least one injection of study drug (tocilizumab or placebo), analyzed according to the randomized study drug.

The safety population included all randomized patients who received at least one injection of study drug and who provided at least one post-dose safety assessment. Patients were analyzed according to the actual drug received.

Patient Disposition

Of the 363 patients screened for inclusion, a total of 251 patients were randomized (69%, see Table 7). The most common reasons for failing screening were absence of a diagnosis of GCA according to protocol criteria (n = 24), no patient consent (n = 24), did not meet criteria for new-onset or relapsing GCA (n = 10), and elevated liver enzymes (n = 6).

Withdrawals from blinded treatment or from the study ranged from 10% to 18% of those randomized to placebo and 15% to 18% of patients in the tocilizumab groups. The most common reason for withdrawal was due to an adverse event (4% to 9%), except for the placebo plus 52-week prednisone taper group, which had zero such cases.

Table 7: Patient Disposition

	GiACTA			
	Tocilizumab Weekly (26-Week Taper)	**Tocilizumab Every 2 weeks (26-Week Taper)**	**Placebo (26-Week Taper)**	**Placebo (52-Week Taper)**
Screened, N	363[a]			
Randomized, N (%)	251 (69)			
	100	50	50	51
Did not received study drug, n (%)	0	1 (2)	0	0
Withdrew from blinded treatment, n (%)	18 (18)	9 (18)	9 (18)	5 (10)
Adverse event	9 (9)[b]	3 (6)[b]	3 (6)	0
Withdrew consent	5 (5)	2 (4)	2 (4)	1 (2)
Lack of efficacy	1 (1)	3 (6)	1 (2)	2 (4)
Withdrawn by physician	1 (1)	1 (2)	3 (6)	1 (2)
Nonadherence	1 (1)	0	0	0
Protocol violation	0	0	0	1 (2)
Other	1 (1)	1 (2)	0	0
Withdrew from study, n (%)	15 (15)	9 (18)	6 (12)	5 (10)
Adverse event	6 (6)	3 (6)	2 (4)	0
Withdrew consent	6 (6)	2 (4)	2 (4)	1 (2)
Lack of efficacy	1 (1)	3 (6)	2 (4)	2 (4)
Withdrawn by physician	1 (1)	0	0	1 (2)

	GiACTA			
	Tocilizumab Weekly (26-Week Taper)	Tocilizumab Every 2 weeks (26-Week Taper)	Placebo (26-Week Taper)	Placebo (52-Week Taper)
Nonadherence	1 (1)	0	0	0
Protocol violation	0	0	0	1 (2)
Other	0	1 (2)	0	0
ITT, N	100	49	50	51
Safety, N	100	49	50	51

GCA = giant cell arteritis; ITT = intention-to-treat.

[a] The most common reasons for screening failure included absence of a diagnosis of GCA according to protocol criteria (n = 24); no patient consent (n = 24), did not meet criteria for new-onset or relapsing GCA (n = 10); elevated liver enzymes (n = 6).

[b] An additional two patients were withdrawn from study treatment due to adverse events in each of the tocilizumab groups, although the investigator indicated that the patient had withdrawn for other reasons.

Source: Clinical Study Report.[8]

Exposure to Study Treatments

Compliance with blinded SC injections of tocilizumab or placebo was high for all treatment groups, with ≥ 80% of patients in each group missing no more than one dose (Table 8). Dose modifications were infrequent and the most common reason for non-compliance with study medication was the administration of less than the full amount of the pre-filled syringe.

Table 8: Exposure to Blinded Subcutaneous Study Treatments

	GiACTA			
	Tocilizumab Weekly (26-Week Taper) N = 100	Tocilizumab Every 2 Weeks (26-Week Taper) N = 49	Placebo (26-Week Taper) N = 50	Placebo (52-Week taper) N = 51
Median treatment duration, days (range)	358 (9 to 365)	358 (6 to 371)	358 (44 to 368)	358 (43 to 369)
Mean doses received / expected doses, % (SD)	97.9 (4.0)	98.7 (2.7)	98.5 (3.4)	98.0 (3.3)
Number of doses, median (range)	51.5 (2 to 53)	52 (2 to 53)	52 (7 to 53)	51 (7 to 53)
Median total cumulative dose of tocilizumab, g (range)	8.34 (0.32 to 8.59)	4.21 (0.16 to 4.37)	0	0
Missed doses, n (%)				
No missed dose	58 (58)	36 (74)	37 (74)	29 (57)
1 missed dose	24 (24)	5 (10)	6 (12)	12 (24)
2 missed doses	6 (6)	4 (8)	1 (2)	0
3 missed doses	3 (3)	2 (4)	1 (2)	4 (8)
4 missed doses	4 (4)	1 (2)	3 (6)	4 (8)
> 4 missed doses	5 (5)	1 (2)	2 (4)	2 (4)

SD = standard deviation.

Source: Clinical Study Report.[8]

Critical Appraisal

Internal Validity

Patients in the GiACTA trial were randomly allocated to treatment groups through an interactive voice response system and the randomization list was not made available to study centres, monitors, statisticians, or the project team. Blinding of patients to study treatment was maintained through the paired syringe system and blinding of patients to length of prednisone taper regimen was maintained through weekly blister packs containing prednisone capsules, placebo capsules, or a combination of the two.

Objectivity of the primary and key secondary end points depended on blinding of the clinical assessors, who were responsible for assessing signs and symptoms of GCA and managing prednisone taper or escape prednisone of patients. The clinical assessors remained blinded to the ESR levels measured at each patient visit and were alerted by laboratory assessors to ESR values above 30 mm per hour. Due to the suppressive effect of tocilizumab on acute-phase reactants,[8] ESR was more likely to be elevated in placebo patients. The clinical expert consulted for this review agreed that knowledge of ESR elevation above 30 mm per hour could sensitize a clinician to signs and symptoms of GCA when assessing a patient. If this happened more often in the placebo groups, the measured effect of tocilizumab could have been inflated. To minimize the potential bias, the clinical assessor was notified of elevated ESR levels after completing the evaluation of signs and symptoms of GCA.

In the case of laboratory anomalies that were not severe enough to warrant discontinuation of tocilizumab or placebo, the dual assessor system maintained blinding of the clinical assessor. Also, the laboratory assessor did not provide the clinical assessor with reasons for treatment discontinuation.

Patient withdrawal from the study and from blinded treatment was less than 20% and compliance with blinded treatment was high for all groups. The proportion of patients in the placebo plus 52-week taper group withdrawing from blinded treatment or the study (10%) was lower than for the other groups (12% to 18%) and none of the patients in the group withdrew due to an adverse event. Possible bias due to withdrawal was appropriately dealt with by sensitivity analyses that assumed scenarios where, of the patients who withdrew without experiencing disease flare, either all patients or only those receiving placebo were reclassified as responders.

The design of the trial ensured that patients had proven GCA and received a standard prednisone taper regimen. Definitions of flare, remission, and non-response were clearly defined and deemed appropriate by the clinical expert consulted for this review, although the expert stated that acute-phase reactants are generally not used in clinical practice to detect flares or to determine remission. The FDA stated that the sustained remission composite outcome could potentially be driven by tocilizumab's direct effect on acute-phase reactants ESR and CRP, which were two of the components of the end point. Additional sensitivity analyses were conducted by the FDA to test the robustness of the primary outcome.[32] The taper regimen and the definition of nonadherence to the taper regimen (> 100 mg of corticosteroid above the expected amount) were reasonable according to the clinical expert. However, the placebo plus 52-week taper is likely more reflective of the standard of care, and according to the FDA, was the most relevant control group.[32]

Patient dose of prednisone at baseline (> 30 or ≤ 30 mg per day) was used to stratify randomization and to adjust the analyses of all end points. The clinical expert did not identify any other known risk factors for which the analyses should have been adjusted.

All of the main analyses for the end points were pre-specified in detail. Justification for the 2:1:1:1 randomization ratio was not provided. The study had 90% power to detect a 40% absolute difference in the primary end point with a conservative significance level of 0.01. Sample size calculations were not provided for any of the other comparisons or subgroup analyses. Multiple comparisons were controlled for with conservative significance levels and a hierarchical testing scheme for the primary and key secondary outcomes. Both ITT analysis and analysis of patients adherent to study medication were performed for the key secondary end point, which was appropriate for a noninferiority test. The noninferiority margin was set at a value that preserved at least half of the beneficial effect of prednisone therapy on remission rate (−22.5% noninferiority margin). The clinical expert indicated that this margin may be larger than expected, with previous RA trials using margins of −12.5% to −15%.

The statistical tests used for the primary and secondary end points were appropriate and adjusted for baseline prednisone dose. Aside from the primary and key secondary end points, adjustments were not made for multiplicity, and *P* values were provided for descriptive purposes only. The assumption of a constant hazard ratio in the Cox proportional hazards analysis for time to disease flare may not hold if the groups were differentially affected by transition of daily prednisone dose to zero, making the hazard ratio difficult to interpret. In addition, the FDA noted that the time-to-first-flare analyses included only those patients that achieved remission by 12 weeks, which is a post-randomization variable. Thus, randomization was not preserved and the analysis is confounded by potential differences in patient and disease characteristics between patients who achieve remission and those who do not.[32] The SF-36 and Patient's Global Assessment analyses used maximum likelihood methods to handle missing data. While it is possible that disease activity and HRQoL affected patient withdrawal and patients were not necessarily missing at random, these analyses were exploratory.

The patient-reported outcomes (SF-36, Patient's Global Assessment, EQ-5D, and FACIT-F) have not been validated in patients with GCA. While there is evidence of validity of the SF-36 PCS, EQ-5D index score, and FACIT-F scale in patients with RA, these patients are typically younger than patients with GCA and experience different symptoms. As the EQ-5D and FACIT-F scores were reported descriptively and had extensive missing data at week 52, little information can be gleaned from these outcomes.

The sample size and study duration were insufficient to assess GCA-associated or corticosteroid-associated morbidities such as fractures and cardiovascular events, which are important to patients. Practically speaking, sample size is hampered by the low prevalence of GCA. Also of note, the study cannot address longer-term tocilizumab-associated harms, although the drug is approved for RA and juvenile idiopathic arthritis and safety is not expected to be substantially different in GCA. However, the average age of patients in RA studies is younger than in the GiACTA study, and the frequency of adverse events is generally higher in older patients.

External Validity

The GiACTA trial took place in many centres across Europe and North America, including one centre in Canada that enrolled two patients. The study population included both patients with a new diagnosis of GCA as well as those with disease relapse, and criteria for GCA diagnosis reflect the 1999 ACR criteria and the more recent use of non-invasive imaging. Out of the 363 patients screened, 69% were randomized, with the most common reasons for screening failure being absence of protocol-specified GCA diagnosis (21%), inability or unwillingness to provide informed consent (21%), absence of protocol-specified new or relapsing active GCA (9%), and elevated liver enzymes (5%). The study criteria excluded patients with recent major surgery, chronic corticosteroid use, active infections, and conditions that would increase susceptibility to serious infection. There was concomitant use of methotrexate in 10% to 18% of patients in each group at baseline, though the dose could not be increased during the trial.

The clinical expert consulted for this review indicated that the inclusion and exclusion criteria were reasonable and in accordance with considerations that would be made when treating GCA patients in clinical practice. The diagnostic criteria in the trials ensured that all patients had biopsy- or imaging-proven GCA. The expert stated that not all patients in Canada have timely access to temporal artery biopsy or arterial imaging. In patients with access to these tests, temporal artery biopsy will not identify all GCA patients, the sensitivity and specificity of imaging is not established, and both types of tests may decrease in sensitivity with increased time on corticosteroid therapy. Thus a broader population of patients with GCA would be potential candidates for tocilizumab therapy in clinical practice than those enrolled in the GiACTA study.

Although the ideal tapering regimen is unknown, the clinical expert consulted for this review stated that the 26-week prednisone taper regimen is shorter than that typically used in clinical practice. The 52-week taper is at the low end of duration for the typical course of corticosteroid taper,[22] and patients in the GiACTA study may have been at higher risk of relapse during corticosteroid taper than the typical GCA patient. Given that corticosteroid tapering in clinical practice does not follow a standardized protocol, it is unclear if the differences in cumulative prednisone dose in the GiACTA trial will be observed in practice. Moreover, it is unclear if reductions in prednisone dose will translate into reductions in longer-term corticosteroid-related morbidity. Additional data, for example from the second part of the GiACTA trial, will be needed to assess the safety and efficacy of continued use of tocilizumab beyond 52 weeks in patients with GCA.

The outcome measures in the GiACTA trial were relevant to patients, although the trial was not designed to assess GCA-related morbidity, which is important to patients. The patient-reported outcomes encompassed some of the impacts that patients themselves have identified,[11] including physical and mental health.

Efficacy

Only those efficacy outcomes identified in the review protocol (Table 3) are reported. See Appendix 4 for detailed efficacy data. GCA- and corticosteroid-related morbidity were included as outcomes of interest in the CDR review protocol, but the GiACTA trial was not designed to evaluate these end points. There is some discussion of these events in the harms section of this report.

GCA-Related Morbidity

There were no new reports of permanent vision loss during the study. A summary of treatment-emergent visual complications is included in Appendix 4, Table 13. Blurred vision was the most common visual complication and was reported in 8% to 20% of patients. Other GCA-related morbidity events are discussed in the notable harms section.

Sustained Remission From GCA

Overall, 56% and 53% of patients in the tocilizumab weekly and biweekly groups (plus 26-week prednisone taper) were in sustained remission at week 52, compared with 14% and 18% of those in the placebo plus 26-week prednisone taper and the placebo plus 52-week taper groups, respectively (Table 9).

The proportion of patients with sustained remission from week 12 to 52 was statistically significantly higher for both tocilizumab regimens compared with placebo plus 26-week taper in the ITT population, with an absolute between-group difference of 42%; 99.5% CI, 18% to 66% ($P < 0.0001$) for the weekly tocilizumab regimen, and 39%; 99.5% CI, 12% to 66% ($P < 0.0001$) for the tocilizumab biweekly group. The planned sensitivity analyses, in which truly missing values were reclassified as responders and the requirement for normalized CRP was removed from the remission definition, both demonstrated that the primary end point was robust to these potential sources of bias.

The key secondary end point demonstrated the noninferiority and superiority of both tocilizumab regimens compared with placebo plus 52-week taper in the ITT population, with an absolute increase in proportion of patients with sustained remission of 38%; 99.5% CI, 18% to 59% ($P < 0.0001$) for the weekly regimen, and 35%; 99.5% CI, 10% to 60% ($P = 0.0002$) for the tocilizumab biweekly group (Table 9). For both tocilizumab dosage groups, the lower bound of the 99.5% CI for the difference in remission rates exceeded the −22.5% noninferiority margin.

Two additional sensitivity analyses were conducted for the primary and key secondary end points. The first was conducted for the key secondary end point in patients who completed the study and were compliant with study medication, which made up about half of the patients in each group. In this population, both tocilizumab groups were noninferior to the placebo plus 52-week taper group. Second, a post hoc sensitivity analysis showed that both the primary and the key secondary end points were robust to the removal of adherence to prednisone taper from the remission definition. Detailed information on the sensitivity analyses can be found in Appendix 4, Table 14.

Descriptive subgroup data based on disease status at baseline showed sustained remission among rates for new-onset versus relapsing patients of 60% versus 53% in the weekly tocilizumab group and 58% versus 48% for biweekly tocilizumab (Appendix 4, Table 16).The sustained remission rates in the placebo groups ranged from 7% to 22%. No between-group comparisons or treatment-by-disease status interaction *P* values were reported.

A breakdown of the reasons for non-response for the primary composite outcome of sustained remission is provided in Appendix 4, Table 15. By the twelfth week, 17% and 18% of the tocilizumab weekly and biweekly groups, and 58% and 51% of patients in the placebo plus 26-week taper and prednisone plus 52-week taper groups, respectively, had failed to achieve remission. The proportion of patients who received escape prednisone was 23%, 33%, 74%, and 55% in the tocilizumab weekly, tocilizumab biweekly, placebo

(26-week taper), and placebo (52-week taper) groups, respectively. In patients who experienced a flare, it is apparent that few patients experienced elevated ESR (with or without symptoms of GCA) in the weekly and biweekly tocilizumab groups (1% and 6%), while nearly half of the patients in the placebo groups showed elevated ESR (41% to 50%). In the tocilizumab weekly and biweekly groups, 25% and 19% had a flare defined by signs and symptoms of GCA only, compared with 22% and 16% in the placebo plus 26-week taper and placebo plus 52-week taper groups, respectively.

Cumulative Prednisone Dose

Testing for the cumulative prednisone dose was outside of the statistical testing hierarchy and was not controlled for type I error. The ITT population was analyzed unless otherwise indicated.

As per the study protocol, the median expected cumulative prednisone dose (which was based on the patient's starting prednisone doses and scheduled taper doses) was similar (1,337 mg to 1,442 mg) in the tocilizumab and placebo groups with the 26-week prednisone taper, and higher in the placebo plus 52-week taper group (2,608 mg) (Table 9). The median actual cumulative prednisone dose over the 52-week blinded treatment period (which included scheduled taper doses and all escape or commercial prednisone doses) was 1,862 mg in both tocilizumab groups, 3,296 mg in the placebo plus 26-week taper group, and 3,818 mg in the placebo plus 52-week taper group. The median cumulative prednisone dose was lower in both tocilizumab groups compared with both placebo groups ($P < 0.0001$ for all comparisons). The median cumulative prednisone dose over time curves for the 26-week taper groups remain similar until the end of the taper period (weeks 21 to 27), at which point the curve for the weekly tocilizumab group plateaus and the curve for the placebo group continues to rise (Figure 2).

Table 9: Key Efficacy Outcomes

	GiACTA			
Outcome	**Tocilizumab Weekly (26-Week Taper) N = 100**	**Tocilizumab Every 2 Weeks (26-Week Taper) N = 49**	**Placebo (26-Week Taper) N = 50**	**Placebo (52-Week Taper) N = 51**
Sustained remission at 52 weeks				
n (%)	56 (56)	26 (53)	7 (14)	9 (18)
Between-group difference, % (99.5% CI), *P* value[a]				
versus placebo (26-week taper)	42% (18 to 66), $P < 0.0001$	39% (12 to 66), $P < 0.0001$	reference	NA
versus placebo (52-week taper)	38% (18, 59), $P < 0.0001$[b]	35% (10, 60), $P = 0.0002$[b]	NA	reference
Cumulative prednisone dose, mg				
Expected dose[c] median (range)	1,337 (350 to 2,632)	1,442 (333 to 2,632)	1,337 (952 to 2,632)	2,608 (823 to 3,903)
Actual dose[d] median (range)	1,862 (630 to 6,603)	1,862 (295 to 9,913)	3,296 (932 to 9,778)	3,818 (823 to 10,698)
Difference in actual doses,	$P < 0.0001$[e]	$P = 0.0003$[e]	reference	NA

	GiACTA			
P value versus placebo (26-week taper)				
Difference in actual doses, *P* value versus placebo (52-week taper)	*P* < 0.0001[e]	*P* < 0.0001[e]	NA	reference
Time to disease flare				
n (%)	23 (23)	13 (26.5)	34 (68)	25 (49)
HR (99% CI), *P* value[f]				
versus placebo (26-week taper)	0.23 (0.11 to 0.46), *P* < 0.0001[e]	0.28 (0.12 to 0.66), *P* = 0.0001[e]	reference	NA
versus placebo (52-week taper)	0.39 (0.18 to 0.82), *P* = 0.0011[e]	0.48 (0.20 to 1.16), *P* = 0.032[e]	NA	reference

CI = confidence interval; HR = hazard ratio; NA = not applicable.

Note: *P* < 0.005 required for statistical significance for sustained remission at 52 weeks; *P* < 0.01 required for all other end points (*P* values are descriptive).

[a] Cochran–Mantel–Haenszel test adjusted for starting prednisone dose (≤ 30 mg/day, >30 mg/day).

[b] *P* value for superiority. Both doses met the noninferiority criteria as the lower bounds of the 99.5% CI were greater than –22%.

[c] Expected cumulative dose was based on the patient's starting prednisone dose and assuming the taper was continued without error.

[d] Actual prednisone dose was based on patients' record of prednisone taken and included all escape therapy and use of commercial prednisone as well as doses received as part of the tapering process. *P* values based on van Elteren test stratified by baseline prednisone dose (≤ 30 mg/day versus > 30 mg/day). Missing doses during the taper were assumed to be the minimum-dose tablets from that pack. Patients who received an increased dose of prednisone because they entered escape therapy were included in their originally assigned treatment group. There was no imputation of missing data.

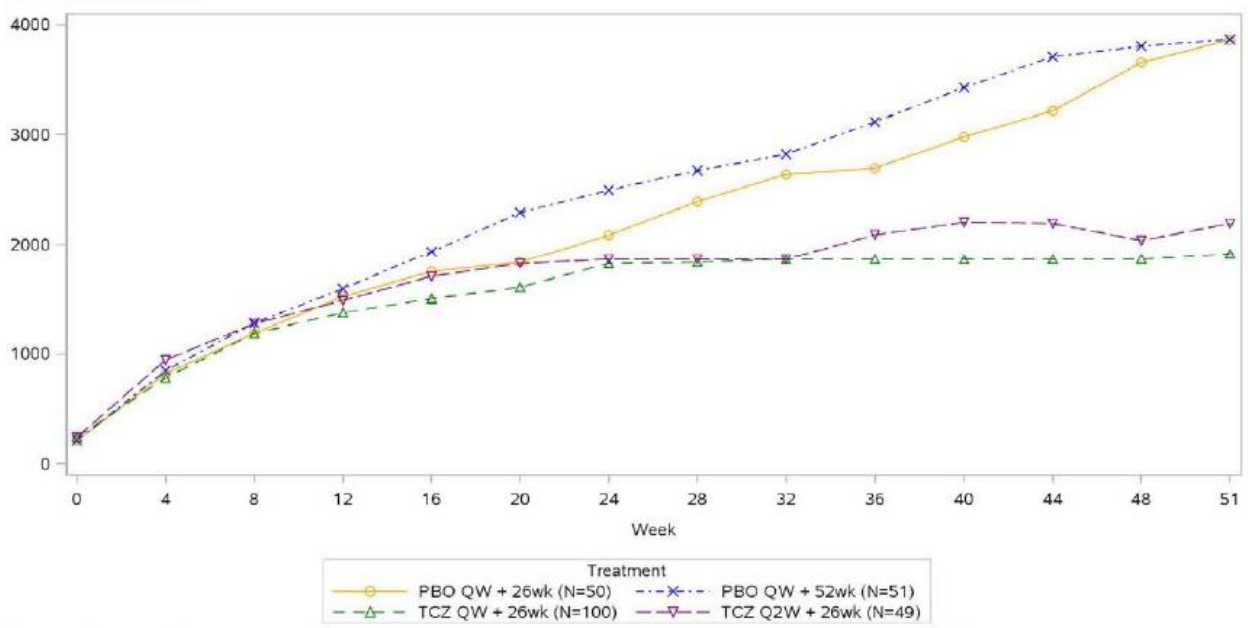
[e] Outside the statistical testing hierarchy.

[f] Cox proportional hazards model adjusting for stratification factor of starting prednisone dose (≤ 30 mg/day, > 30 mg/day).

Source: Clinical Study Report.[8]

Subgroup data for new-onset GCA patients and relapsing patients were reported descriptively and are listed in Appendix 4, Table 16. Among those in the weekly and biweekly tocilizumab groups, the new-onset patients had a higher median cumulative prednisone dose (1,942 mg and 2,202 mg) than the relapsing patients (1,385 mg and 1,568 mg). The median cumulative prednisone dose was similar in new-onset and relapsing patients in the placebo 52-week taper group (3,818 mg and 3,786 mg, respectively), and was lower in the new-onset patients (3,068 mg) versus relapsing (3,860 mg) patients in the placebo plus 26-week taper group.

Figure 2: Median Cumulative Prednisone Dose by Visit and Treatment Group to Week 52 (ITT)



For any records of missed tablets from the protocol-defined prednisone taper, the missed tablet(s) will be assumed to be the minimum dose tablet(s) available from that pack.
Patients who received increased prednisone due to entering escape therapy will be included in their original treatment group.
Patients who withdraw are excluded from the summaries for subsequent visits.
Prednisone records are reported up to study day 364. Week 0 to Week 51 includes the 52 weeks of Part 1 prednisone exposure.

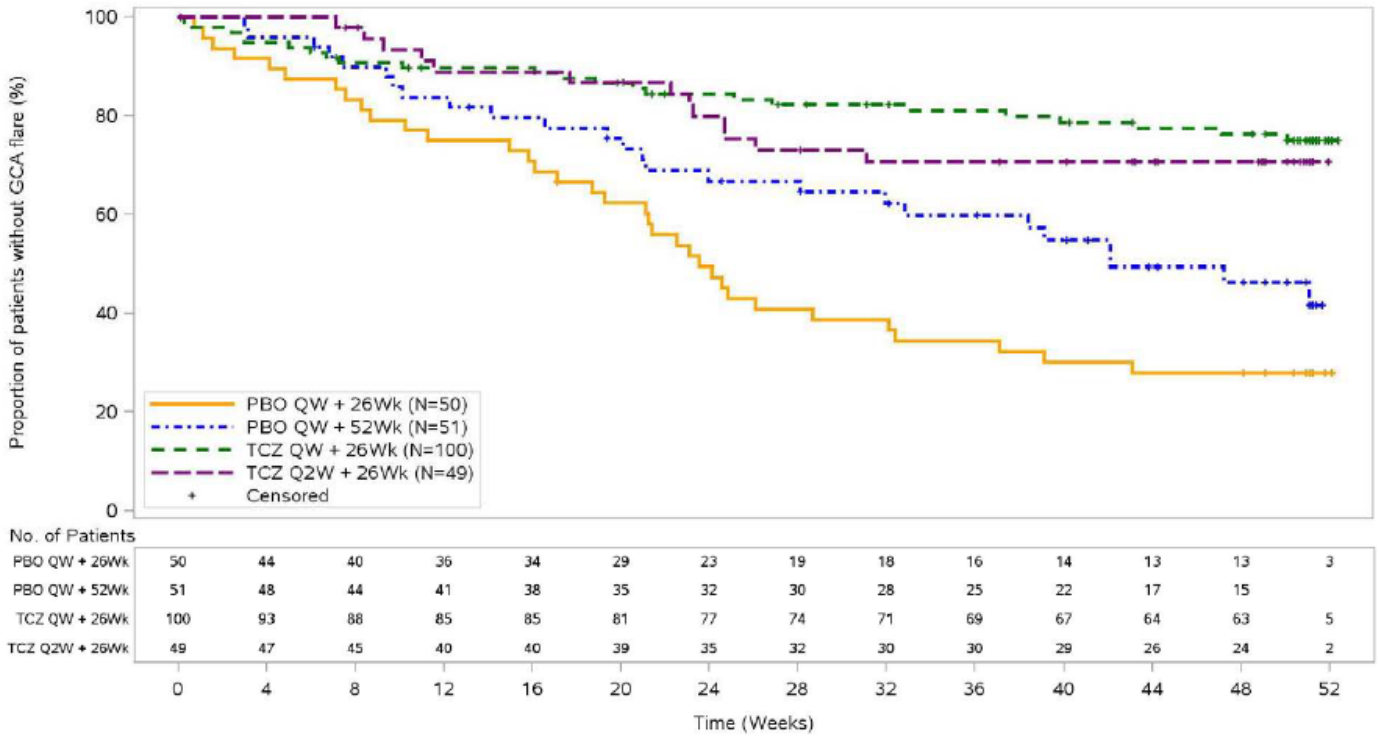
ITT = intention-to-treat; PBO = placebo; QW = weekly; Q2W = every other week; TCZ = tocilizumab; wk = week.

Source: Clinical Study Report.[8]

Time to GCA Flare

The Kaplan–Meier plot of the time to GCA flare is shown in Figure 3. The median time to disease flare was 165 days in the placebo plus 26-week taper group, 295 days in the placebo plus 52-week taper group, and was not estimable in either tocilizumab group. The hazard ratio for tocilizumab weekly versus placebo plus 26-week taper was 0.23; 99% CI, 0.11 to 0.46, and versus placebo plus 52-week taper was 0.39; 99% CI, 0.18 to 0.82 (Table 9). The hazard ratio for tocilizumab biweekly versus placebo plus 26-week taper was 0.28; 99% CI, 0.12 to 0.66, and versus placebo plus 52-week taper was 0.48; 99% CI, 0.20 to 1.16 (Table 9). While the
Kaplan–Meier plot shows a steady decrease in flare-free patients for the weekly tocilizumab and placebo plus 52-week taper groups, the curves for the biweekly tocilizumab and placebo plus 26-week taper groups decrease at a relatively greater rate around the 21- to 27-week period, which corresponds with prednisone taper to 0 mg in both groups. Similar point estimates were observed for most of the comparisons in the subgroup analysis of new GCA patients and relapsing patients, although the CIs were wider (Appendix 4, Table 16). Of note, this outcome was outside the statistical testing hierarchy.

Figure 3: Kaplan−Meier Plot of Time to First GCA Disease Flare (ITT)



ITT = intention-to-treat; PBO = placebo; QW = weekly; Q2W = every other week; TCZ = tocilizumab; Wk = week.

For time-to-flare analysis, those patients who were never in remission were censored at day one and those who withdrew prior to week 52 were censored on the day of withdrawal.

Source: Clinical Study Report.[8]

Health-Related Quality of Life

All patient-reported outcomes were outside the statistical testing hierarchy and post-escape data were set to missing. At 52 weeks, data from 69% to 94% of patients were reported for the Patient's Global Assessment of disease activity and SF-36 PCS and MCS.

At baseline the Patient's Global Assessment of disease activity mean scores were 43.6, 46.7, 35.7, and 47.8 in the tocilizumab weekly, tocilizumab biweekly, placebo plus 26-week taper, and placebo plus 52-week taper groups, respectively. Mean scores decreased in all groups from baseline to week 52, with changes of −19.0 and −25.3 in the tocilizumab groups and −3.4 and −7.2 in the placebo groups (Table 10). No statistically significant differences were noted between tocilizumab weekly and either placebo group. The mean differences between tocilizumab biweekly and the placebo groups ranged from −18.2 to −21.9, with 99% CI that excluded the null. The differences observed exceeded the 10-point difference that the clinical expert thought was clinically relevant.

The mean baseline SF-36 scores ranged from 40.5 to 47.7 for the MCS and from 40.6 to 43.1 for the PCS across the treatment groups (Table 10). The change from baseline to week 52 in the SF-36 MCS scores was 7.3, 6.1, 6.7, and 2.8, and the change in PCS scores was 4.1, 2.8, −0.3, and −1.5 in the tocilizumab weekly, tocilizumab biweekly, placebo plus 26-week taper, and placebo plus 52-week taper groups, respectively. No

statistically significant differences between tocilizumab and placebo were detected for either component score, with one exception. The mean difference between tocilizumab weekly and the placebo plus 26-week taper group was 5.6; 99% CI, 0.9 to 10.3, and exceeded the lower value of the MCID reported in the literature for patients with RA (5.1 and 7.2). No MCID for patients with GCA was identified in the literature for either the SF-36 or the Patient's Global Assessment instruments.

Post hoc sensitivity analyses were conducted using all observed data for the Patient's Global Assessment and the SF-36 PCS and MCS, and the same trends were generally observed as for the main analyses (Appendix 4, Table 17).

EQ-5D index scores were reported descriptively, with no between-group comparisons, and data at week 52 were available for 22% to 60% of patients for this exploratory outcome. The mean EQ-5D index scores at baseline were 0.74 in the tocilizumab and placebo plus 26-week taper groups, and 0.66 in the placebo plus 52-week taper group. The mean change from baseline to week 52 were reported as 0.10, 0.05, 0.07, and −0.02 in the tocilizumab weekly, tocilizumab biweekly, placebo plus 26-week taper, and placebo plus 52-week taper groups, respectively (Table 10).

Table 10: Patient-Reported Outcomes

	GiACTA			
Outcome	**Tocilizumab Weekly (26-Week Taper) N = 100**	**Tocilizumab Every 2 Weeks (26-Week Taper) N = 49**	**Placebo (26-Week Taper) N = 50**	**Placebo (52-Week Taper) N = 51**
Patient's Global Assessment of disease activity (VAS)[a]				
Baseline	N = 100	N = 49	N = 49	N = 51
Mean (SD)	43.6 (25.7)	46.7 (25.6)	35.7 (28.2)	47.8 (27.8)
Week 52	N = 88	N = 46	N = 34	N = 42
LSM change from baseline (SE)	−19.0 (NR)	−25.3 (NR)	−3.4 (NR)	−7.2 (NR)
Mean difference versus placebo + 26-week taper, (99% CI)	−15.6 (−34.3 to 3.1) *P* = 0.031	−21.9 (−42.4 to −1.4) *P* = 0.0059	reference	NA
Mean difference versus placebo + 52-week taper, (99% CI)	−11.8 (−27.2 to 3.6) *P* = 0.048	−18.2 (−35.8 to −0.5) *P* = 0.0081	NA	reference
SF-36 Mental Component Score[a]				
Baseline	N = 97	N = 49	N = 48	N = 49
Mean (SD)	42.8 (12.4)	47.7 (12.6)	42.7 (12.1)	40.5 (13.7)
Week 52	N = 85	N = 46	N = 33	N = 41
LSM change from baseline (SE)	7.3 (NR)	6.1 (NR)	6.7 (NR)	2.8 (NR)
Mean difference versus placebo + 26-week taper, (99% CI)	0.6 (−5.9 to 7.1) *P* = 0.81	−0.6 (−7.6 to 6.5) *P* = 0.84	reference	NA
Mean difference versus placebo + 52-week taper, (99% CI)	4.4 (−0.7 to 9.6) *P* = 0.025	3.3 (−2.6 to 9.1) *P* = 0.15	NA	reference
SF-36 Physical Component Score[a]				
Baseline	N = 97	N = 49	N = 48	N = 49
Mean (SD)	43.1 (9.4)	40.6 (8.0)	42.7 (10.9)	41.1 (10.0)
Week 52	N = 85	N = 46	N = 33	N = 41
LSM change from baseline (SE)	4.1 (NR)	2.8 (NR)	−0.3 (NR)	−1.5 (NR)

Outcome	GiACTA			
	Tocilizumab Weekly (26-Week Taper) N = 100	Tocilizumab Every 2 Weeks (26-Week Taper) N = 49	Placebo (26-Week Taper) N = 50	Placebo (52-Week Taper) N = 51
Mean difference versus placebo + 26-week taper, (99% CI)	4.4 (−1.6 to 10.3) *P* = 0.057	3.0 (−3.4 to 9.5) *P* = 0.22	reference	NA
Mean difference versus placebo + 52-week taper, (99% CI)	5.6 (0.9 to 10.3) *P* = 0.0024	4.3 (−1.1 to 9.6) *P* = 0.041	NA	reference
FACIT-F Score[b]				
Baseline	N = 99	N = 49	N = 50	N = 49
Mean (SD)	36.1 (11.1)	36.3 (11.5)	35.0 (12.8)	31.4 (13.6)
Week 52	N = 59	N = 26	N = 11	N = 17
Mean change from baseline (SD)	5.6 (10.1)	1.8 (8.8)	0.3 (10.7)	−1.6 (6.8)
EQ-5D Index Score[b]				
Baseline	N = 99	N = 49	N = 50	N = 49
Week 52	N = 60	N = 26	N = 11	N = 17
Mean change from baseline (SD)	0.10 (0.20)	0.05 (0.22)	0.07 (0.29)	−0.02 (0.16)

CI = confidence interval; EQ-5D = EuroQoL 5-Dimensions questionnaire; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue; GCA = giant cell arteritis; LSM = least squares mean; NA = not applicable; NR = not reported; SD = standard deviation; SE = standard error; SF-36 = Short Form (36) Health Survey; VAS = visual analogue scale.

[a] Repeated measures model including covariates for treatment, starting prednisone dose (≥ 30 mg or <3 0 mg/day), visit, treatment-by-visit interaction, starting dose-by-visit interaction, baseline score, and baseline score-by-visit interaction. No imputation of missing data. Post-escape data set to missing.

[b] Exploratory outcome. No imputation for missing data. Post-escape scores set to missing. No between-group comparisons reported.

Source: Clinical Study Report.[8]

Disease Symptoms

Fatigue was measured as an exploratory outcome using the FACIT-F instrument. The mean baseline scores were 36.1 and 36.3 points in the tocilizumab groups and 35.0 and 31.4 points in the placebo groups (Table 10). The mean change from baseline to week 52 was 5.6, 1.8, 0.3 and −1.6 points in the tocilizumab weekly, tocilizumab biweekly, placebo (26-week taper), and placebo (52-week taper) groups, respectively. Of note, FACIT-F data at week 52 were reported for 22% to 59% of patients per treatment groups and no between-group comparisons were reported.

Most patients in all of the groups displayed signs and symptoms of GCA during the trial, though they did not always signal a disease flare. Information on signs and symptoms of GCA throughout the study and during flare is provided in Appendix 4, Table 18 and Table 19.

Harms

Only those harms identified in the review protocol (see Table 3) are reported below.

Adverse Events

Most patients experienced one or more adverse events during the 52-week study period (92% to 98%), and according to system organ class, infections and infestations were the most frequently reported adverse events (65% to 75%). Headache (20% to 32%), nasopharyngitis (18% to 29%), peripheral edema (12% to 25%) and arthralgia (13% to 22%) were the most frequently reported individual events (Table 11).

Serious Adverse Events

Serious adverse events were reported in 15%, 14%, 22%, and 26% of patients in the tocilizumab weekly, tocilizumab biweekly, placebo plus 26-week taper, and placebo plus 52-week taper groups, respectively (Table 11). Two patients in the placebo plus 52-week taper group experienced serious gastroenteritis, or herpes zoster, and two patients in the tocilizumab week group had a hypertensive crisis. All other serious adverse events that occurred were reported in one patient per treatment group.

Withdrawals Due to Adverse Events

In total, 11%, 12%, 12%, and 0% of patients in the tocilizumab weekly, tocilizumab biweekly, placebo plus 26-week taper, and placebo plus 52-week taper groups, respectively, had an adverse event that led to discontinuation of tocilizumab, placebo, or prednisone. Infections were the most common reason for drug discontinuation in the tocilizumab weekly group (Table 11).

Mortality

No deaths were reported during the 52-week study period.

Notable Harms

Infections and infestations system organ class were reported in 75%, 73%, 76%, and 65% of patients, and serious infections were reported in 7%, 4%, 4%, and 12% of patients in the tocilizumab weekly, tocilizumab biweekly, placebo plus 26-week taper, and placebo plus 52-week taper groups, respectively (Table 12).

Injection-site reactions were reported in 6% to 14% of those who received tocilizumab injections, and 2% to 10% of those who received placebo.

Neutropenia was reported in 4% of patients in the tocilizumab groups and no patients in the placebo groups. Markedly low neutrophil count (< 1.5×10^9/L and a ≥ 20% change from baseline) was reported in 21% and 16% of patients who received tocilizumab and 2% of those who received placebo.

Overall, 50% to 61% of tocilizumab-treated patients and 49% to 62% of placebo-treated patients had an adverse event that was considered by the investigator to be related to corticosteroids. The most common events included nasopharyngitis, bronchitis and upper respiratory tract infection, alopecia, anxiety, insomnia, and peripheral edema. Other notable harms were reported infrequently.

Table 11: Harms

	GiACTA			
Outcome	**Tocilizumab Weekly (26-Week Taper) N = 100**	**Tocilizumab Every 2 Weeks (26-Week Taper) N = 49**	**Placebo (26-Week Taper) N = 50**	**Placebo (52-Week Taper) N = 51**
Patients with ≥ 1 AE, n (%)	98 (98)	47 (96)	48 (96)	47 (92)
Most common AEs (> 10% in any treatment group), n (%)				
Headache	27 (27)	10 (20)	16 (32)	12 (24)
Nasopharyngitis	29 (29)	12 (25)	9 (18)	13 (26)

	GiACTA			
Outcome	**Tocilizumab Weekly (26-Week Taper) N = 100**	**Tocilizumab Every 2 Weeks (26-Week Taper) N = 49**	**Placebo (26-Week Taper) N = 50**	**Placebo (52-Week Taper) N = 51**
Edema peripheral	16 (16)	12 (25)	8 (16)	6 (12)
Arthralgia	13 (13)	8 (16)	11 (22)	8 (16)
Back pain	14 (14)	7 (14)	7 (14)	10 (20)
Dizziness	6 (6)	10 (20)	6 (12)	8 (16)
Diarrhea	12 (12)	3 (6)	8 (16)	5 (10)
Upper respiratory tract infection	10 (10)	6 (12)	5 (10)	7 (14)
Hypertension	12 (12)	6 (12)	4 (8)	4 (8)
Musculoskeletal pain	12 (12)	6 (12)	5 (10)	2 (4)
Fatigue	8 (8)	5 (10)	8 (16)	3 (6)
Oropharyngeal pain	7 (7)	4 (8)	5 (10)	8 (16)
Pain in extremity	8 (8)	5 (10)	5 (10)	5 (10)
Bronchitis	8 (8)	4 (8)	5 (10)	5 (10)
Alopecia	5 (5)	7 (14)	3 (6)	5 (10)
Muscle spasms	4 (4)	6 (12)	6 (12)	4 (8)
Urinary tract infection	10 (10)	4 (8)	2 (4)	4 (8)
Cough	6 (6)	3 (6)	7 (14)	3 (6)
Nausea	8 (8)	2 (4)	5 (10)	4 (8)
Rash	7 (7)	5 (10)	4 (8)	2 (4)
Paresthesia	4 (4)	2 (4)	5 (10)	4 (8)
Oral herpes	4 (4)	5 (10)	3 (6)	2 (4)
Asthenia	5 (5)	3 (6)	5 (10)	0
Anxiety	3 (3)	1 (2)	6 (12)	1 (2)
Patients with ≥ 1 AE related to study treatment, n (%)	68 (68)	36 (74)	32 (64)	27 (53)
Patients with ≥ 1 SAE, n (%)	15 (15)	7 (14)	11 (22)	13 (26)
Most common SAEs (reported in more than 1 patient in any treatment group), n (%)				
Gastroenteritis	1 (1)	0	0	2 (4)
Herpes zoster	1 (1)	0	0	2 (4)
Hypertensive crisis	2 (1)	0	0	0
Patients with ≥ 1 SAE related to study treatment, n (%)	6 (6)	2 (4)	7 (14)	6 (12)
Deaths, n (%)	0	0	0	0
Patients who withdrew from study due to AEs, n (%)	6 (6)	3 (6)	2 (4)	0
Patients who stopped treatment due to AEs, n (%)	11 (11)	6 (12)	6 (12)	0
Infections and infestations (SOC)	5 (5)	1 (2)	1 (2)	0

AE = adverse event; SAE = serious adverse event; SOC = system organ class.

Source: Clinical Study Report.[8]

Table 12: Notable Harms

	GiACTA			
Outcome	**Tocilizumab Weekly (26-Week Taper) N = 100**	**Tocilizumab Every 2 Weeks (26-Week Taper) N = 49**	**Placebo (26-Week Taper) N = 50**	**Placebo (52-Week Taper) N = 51**
Notable harms, n (%)				
Infection or infestations (SOC)	75 (75)	36 (73)	38 (76)	33 (65)
Serious infection	7 (7)	2 (4)	2 (4)	6 (12)
Malignancy	1 (1)	0	1 (2)	1 (2)
Injection site reaction	6 (6)	7 (14)	5 (10)	1 (2)
Anaphylactic reaction[a]	0	0	0	0
Hypersensitivity reaction	11 (11)	6 (12)	6 (12)	3 (6)
Corticosteroid-related adverse events[b]	50 (50)	30 (61)	31 (62)	25 (49)
Myocardial infarction	0	0	0	0
Aortic aneurysm	NR	NR	NR	NR
Stroke	0	1 (2)	0	0
Transient ischemic attack	0	0	0	1 (2)
Gastrointestinal perforation	0	0	0	0
Neutropenia	4 (4)	2 (4)	0	0
Thrombocytopenia	0	2(4)	0	0
Treatment-induced anti-drug antibodies	1 (1), N = 95	3 (7), N = 46	1 (2), N = 49	1 (2), N = 47
Hyperlipidemia	1 (1)	0	0	0
Alanine aminotransferase increased	5 (5)	2 (4)	2 (4)	0
Aspartate aminotransferase increased	4 (4)	1 (2)	1 (2)	0
Hepatic enzyme increased	4 (4)	0	0	2 (4)

NR = not reported; SOC = system organ class.

[a] Identified by the Anaphylactic Reaction Standardized MedDRA query – narrow and occurring immediately after or within 24 hours of an injection of tocilizumab.

[b] Considered by the investigator to be related to corticosteroids.

Source: Clinical Study Report.[8]

Discussion

Summary of Available Evidence

The systematic review identified one randomized clinical trial meeting the criteria of the CDR review protocol. The GiACTA trial was a study in GCA patients on prednisone therapy comparing rates of GCA remission and exposure to prednisone between patients taking tocilizumab weekly or biweekly alongside a 26-week prednisone taper regimen and patients taking placebo alongside a 26- or 52-week prednisone taper regimen. The length of the blinded treatment phase was 52 weeks. The total number of patients was 250 and the study included both patients with new-onset GCA and those with relapsing GCA. Data from the second part of the GiACTA trial, a two-year open-label extension study, was not available at the time of this review.

Interpretation of Results

Efficacy

The GiACTA trial showed statistically significantly higher rates of sustained remission at 52 weeks in both the weekly and biweekly tocilizumab groups when compared with the placebo plus 26-week prednisone taper group (mean differences of 42% and 39%). For the comparison with the placebo plus 52-week prednisone taper group, which more closely resembles corticosteroid tapering in clinical practice, noninferiority and subsequently superiority of the weekly and biweekly tocilizumab groups were demonstrated (mean differences of 38% and 35%, respectively). Sensitivity analyses demonstrated the robustness of the results in general. However, *P* values for comparisons between the biweekly tocilizumab and placebo plus 52-week taper groups were non-significant when the requirement for CRP normalization was excluded and when study completers compliant with study treatment were analyzed. The FDA also conducted a number of sensitivity analyses that were supportive of the primary analysis.[32] Subgroup analyses suggested no notable differences in sustained remission rate with tocilizumab over placebo for relapsing GCA patients versus new-onset patients, though the results were exploratory and limited by small sample sizes.

Other outcomes tested included the cumulative prednisone dose and time to first GCA flare. Lower cumulative prednisone doses were seen in both tocilizumab groups (median 1,862 mg) compared with the placebo groups (3,296 mg and 3,818 mg). Furthermore, comparisons with the 52-week taper group are difficult to interpret due to the higher expected cumulative dose in that group, which was protocol-driven. It is unclear if reductions in prednisone doses are generalizable, as corticosteroid tapering does not follow a standardized regimen in clinical practice. The time-to-first-flare data suggested that flare may be delayed with weekly tocilizumab versus both placebo groups and for biweekly tocilizumab versus the placebo plus 26-week taper group, with hazard ratios ranging from 0.23 to 0.39, and 99% CIs that excluded the null. Median time to first flare for tocilizumab and placebo groups could not be compared as fewer than half of the patients in both tocilizumab groups had experienced a flare by week 52 (23% and 26.5%). This outcome was also outside of the statistical testing hierarchy.

In terms of GCA-related morbidity, there were no new cases of permanent vision loss during the study. The most common visual complication was blurred vision (tocilizumab: 8% to 20%, placebo: 16%), a symptom that can be caused by corticosteroid treatment. Most patients in all of the groups displayed signs and symptoms of GCA during the trial, though they did not always signal a disease flare. When examining the numbers of patients with elevated ESR, it is apparent that few patients on tocilizumab who had a flare experienced elevated ESR (1% and 6% of the weekly and biweekly groups) while nearly half of those in the placebo groups had a flare that was accompanied by elevated ESR (41% to 50%). This difference may be explained in part by the effects of tocilizumab, which is known to suppress acute-phase reactants. The GiACTA trial publication indicated that exclusion of seven flares in the placebo groups associated with ESR elevation alone did not affect the trial conclusions.[29]

According to the clinical expert, the differences in sustained remission rate, prednisone exposure, and time to first GCA flare observed with tocilizumab treatment were clinically meaningful. However, it is not known if these treatment effects will result in longer-term reductions in GCA-related morbidity (such as stroke) or corticosteroid-related morbidity (such as fractures, diabetes, cardiovascular events, and cataracts), as the trial was not powered to detect differences in these outcomes.

Overall, few clinically important differences were detected between tocilizumab and placebo groups on HRQoL based on the SF-36 and Patient's Global Assessment. However, the trial was not powered for patient-reported outcomes and the instruments used may not be responsive to change in GCA patients. The results were potentially biased due to the exclusion of post-escape data as these data were not missing at random and their exclusion may have violated the assumptions of the repeated measures model, although a post hoc analysis that included post-escape data yielded similar results.[8] The EQ-5D and FACIT-F data were of limited value as the data were reported descriptively with no between-group comparisons. All patient-reported outcomes were outside the statistical testing hierarchy and were limited by the extent of missing data.

There are some limitations in the GiACTA trial. The study was not adequately powered or of sufficient duration to evaluate longer-term GCA- and prednisone-related morbidities, which are important to patients. Moreover, the available evidence was limited to a single RCT with a relatively small number of patients per treatment group (50 or 100).

In terms of generalizing the GiACTA trial results to the GCA patient population in Canada, candidates for tocilizumab in clinical practice may be broader than those included in the trial, which required objective confirmation of GCA diagnosis. In Canada, confirmatory diagnostic tests, such as temporal artery biopsy or newer imaging technologies, may not be available or may not show positive results in all patients who were diagnosed with GCA based on clinical history, signs, and symptoms.[20] Moreover, there is potential for indication creep if clinicians use tocilizumab to treat those with PMR, a condition that often presents in those with GCA. Tocilizumab is not approved for the treatment of PMR.

Harms

Most patients in the 52-week GiACTA study experienced one or more adverse events, including serious adverse events, which were reported in 14% to 15% of tocilizumab-treated patients, and 22% to 26% of placebo-treated patients. Infections or infestations of the system organ class were the most commonly reported adverse events (tocilizumab: 73% to 75%, placebo: 65% to 76%), of which 4% to 7% of patients in the tocilizumab

groups and 4% to 12% of those in the placebo groups had infections that were considered serious. The frequency of withdrawals due to adverse events in the tocilizumab and placebo groups with a 26-week prednisone taper (11% to 12%) was similar, whereas no patients in the placebo plus 52-week taper stopped treatment due to adverse events. Other than infection, the notable adverse events identified in this review's protocol were generally infrequent or showed a similar frequency across treatment groups. Of note, the trial duration was limited to 52 weeks, and thus does not provide information on longer-term adverse events. While the safety profile of tocilizumab is generally known as the drug is approved in Canada for RA and juvenile idiopathic arthritis, GCA patients on average are older than RA patients and the frequency of some adverse events, such as infection, may be higher among older adults[7,31].

Potential Place in Therapy[b]

According to the clinical expert consulted for this review, the first objective of the treatment of GCA is to control the signs and symptoms of the disease and to prevent complications such as visual loss and stroke. Provided complications are not present at baseline, they hardly ever occur following initiation of oral high-dosage (60 mg/day to 80 mg/day) corticosteroids. The second objective is to taper steroids to prevent the morbidities of chronic high- and moderate-dose steroids.

The initial high corticosteroid dose is usually maintained for about one month, at which time symptoms and acute-phase reactants (ESR, CRP) normalize, and then tapered slowly to achieve a maintenance dosage of 5 mg/day to 10 mg/day at six months to a year. The tapering schedule is based on physician experience modified by patients' symptoms at each follow-up visit and supported by changes in laboratory data. There is no established protocol for steroid tapering. Most physicians would continue low-dose corticosteroids for the second year of disease and then attempt a taper to 0 mg/day. Fewer than 50% of patients can stop steroids completely and are on life-long therapy.

Chronic treatment with corticosteroids is associated with numerous morbidities and the search for an alternative treatment and/or a corticosteroid-sparing agent has been a long-standing objective. Methotrexate has not met the challenge. Tocilizumab is the first breakthrough in the treatment of GCA. The GiACTA study has shown it to be effective as a corticosteroid-sparing agent. The finding that corticosteroids can be tapered in about 50% of patients at six months is a compelling observation. The data further support the hypothesis that tocilizumab treats the fundamental disease process. Total proof of the latter, the ability to avoid corticosteroids completely, will require a separate study. Moreover, evidence that tocilizumab can reduce longer-term GCA- or corticosteroid-related morbidity is lacking.

The clinical expert indicated that the methods of diagnosing a patient with GCA may be variable across centres due to the availability and access to diagnostic tools such as magnetic resonance angiography (MRA), computed tomography angiography (CTA), or PET scanning. Entry to the GiACTA trial required a confirmed diagnosis of GCA, obtained through temporal artery biopsy and/or imaging such as MRA/CTA or PET scanning. In the real world, obtaining such confirmation is problematic. Access to temporal artery biopsy is not often timely and not all patients will be biopsy-positive. PET scanning is not available in most centers. MRA and CTA provide important diagnostic information, but timely access varies across Canada, and making them absolutely required for trial entry adds substantial

[b] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

costs. Further, the sensitivity and specificity of imaging is not established. In addition, still to be established is the utility of imaging to confirm the definition of remission and the duration of therapy. In the absence of biopsy and imaging information, the clinician depends on the clinical presentation and the presence of elevated acute-phase reactants. Even here there is variability in presentation, including a normal ESR in about 25% of patients. Thus, physician judgment that the patient has GCA, supported as much as possible by confirmatory tests, is the current standard of care. Any reimbursement criteria that includes an absolute requirement for a confirmatory test would limit access to those in need.

A dedicated register of all Canadian patients treated with tocilizumab would be invaluable in answering important aspects of safety.

Conclusions

One trial, which evaluated the use of tocilizumab SC versus placebo in patients with active GCA, met the inclusion criteria for the systematic review. Statistically significantly more patients who received tocilizumab weekly or biweekly in combination with a 26- week prednisone tapering regimen achieved sustained remission at 52 weeks than those on placebo. Data on the cumulative prednisone dose and time to first flare also favoured tocilizumab versus placebo, although these outcomes should be interpreted as exploratory. The treatment effects observed were clinically important, but it is unclear if these benefits will result in longer-term reductions in GCA- or corticosteroid-related morbidity or mortality, which are important to patients.

Few clinically important differences in HRQoL were detected between tocilizumab and placebo. However, the study was not powered for these measures and the instruments used may not be responsive in patients with GCA. These analyses may also be biased due to the exclusion of data from patients who required escape prednisone therapy, and due to the extent of missing data.

Infections were the most frequently reported adverse event in all treatment groups.

The available evidence was limited to a single RCT with a relatively small number of patients per treatment group and treatment duration of 52 weeks.

Appendix 1: Patient Input Summary

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group Supplying Input

One submission was received from Arthritis Consumer Experts (ACE), a national, patient-led organization providing information and educational support to people with arthritis and their families and caregivers, rheumatologists, and other health professionals, elected officials, and senior government bureaucrats. Their organizational objectives are to inform and educate people with arthritis; provide reader-friendly, evidence-based information; and provide research decision-making training to people with arthritis. Within the last 12 months, ACE received grants-in-aid or research funding from: Amgen Canada, Arthritis Research Canada, AstraZeneca Canada, Canadian Biosimilars Forum, Canadian Institutes of Health Research, Celgene, Eli Lily Canada, Hoffmann-La Roche Canada Ltd., Merck Canada, Novartis, Pfizer Canada, Sandoz Canada, Sanofi Canada, St. Paul's Hospital in Vancouver, UCB Canada, and the University of British Columbia. The submission was prepared solely by ACE staff without advice or influence from outside individuals or groups.

2. Condition-Related Information

For this submission, one patient with giant cell arteritis (GCA) was interviewed and ACE provided information based on its day-to-day interactions with arthritis patients, its work with clinical researchers, and discussions with consumers and scientific members of the ACE Advisory Board.

The interviewed patient has been living with GCA for two years and is on medication for GCA. While the medication took longer to work than the patient had expected, the patient is able to go to the gym five days a week and do a lot of walking. There are no impacts on daily life or quality of life mentioned for the patient or her family as she is able to perform all of her daily activities.

3. Current Therapy-Related Information

The patient started on 75 mg (assumed to be 75 mg/day) of prednisone in March 2015 and is currently on 3 mg of prednisone. She has also been taking 10 mg of methotrexate since April 2017. While these medications work for the patient, she has experienced side effects that include insatiable appetite, face puffiness, and insomnia. ACE itself notes that long-term prednisone therapy increases the risk of cardiovascular disease, hypertension, and osteoporosis. Currently, the patient does not have difficulty accessing prednisone or methotrexate.

4. Expectations About the Drug Being Reviewed

The interviewed patient had no experience with tocilizumab. ACE views tocilizumab favourably, given the risks associated with long-term prednisone therapy, scientific data on tocilizumab in GCA, and the interviewed patient.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present Embase 1974 to present
Date of Search:	October 24, 2017
Alerts:	Weekly search updates until February 21, 2018
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.rn	CAS registry number
.nm	Name of substance word
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY
(actemra* or roactemra* or atlizumab* or tcz or tocilizumab* or R1569 or R 1569 or I032V2H011).ti,ab,hw,rn,ot,nm,rn,kf.
375823-41-9.rn.
1 or 2
use ppez
*tocilizumab/
(actemra* or roactemra* or atlizumab* or tcz or tocilizumab* or R1569 or R 1569 or I032V2H011).ti,ab,kw.
5 or 6
use oemezd
or 8
(arteritis or (horton* adj2 disease) or arteritides or arteriitides or aortitis or vasculitides or vasculitis).ti,ab,kw.
giant cell arteritis/
10 or 11

MULTI-DATABASE STRATEGY
9 and 12
remove duplicates from 13
conference abstract.pt.
14 not 15

OTHER DATABASES		
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.	

Grey Literature

Dates for Search:	November 2017
Keywords:	Tocilizumab AND Giant cell arteritis
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

Appendix 3: Excluded Studies

Reference	Reason for Exclusion
Villiger PM, Adler S, Kuchen S, Wermelinger F, Dan D, Fiege V, et al. Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial. The Lancet. 2016;387(10031):1921-7[36]	Phase II study; irrelevant intervention (tocilizumab IV)
Unizony SH, Dasgupta B, Fisheleva E, Rowell L, Schett G, Spiera R, et al. Design of the Tocilizumab in Giant Cell Arteritis Trial. International Journal of Rheumatology. 2013;2013:10[37]	Trial design only
Tuckwell K, Collinson N, Dimonaco S, Klearman M, Blockmans D, Brouwer E, et al. Newly diagnosed vs. relapsing giant cell arteritis: Baseline data from the GiACTA trial. Semin Arthritis Rheum. 2017 Apr;46(5):657-664[38]	Baseline data only

Appendix 4: Detailed Outcome Data

Table 13: Visual Complications During the Study

	GiACTA			
Outcome	**Tocilizumab Weekly (26-Week Taper) N = 100**	**Tocilizumab Every 2 Weeks (26-Week Taper) N = 49**	**Placebo (26-Week Taper) N = 50**	**Placebo (52-Week Taper) N = 51**
Visual Complications,[a] n (%)				
Amaurosis fugax[b]	2 (2)[c]	0	1 (2)	0
Blurred vision	8 (8)	10 (20)	8 (16)	8 (16)
Diplopia	0	0	2 (4)	2 (4)
Ischemic optic neuropathy	1 (1)[b]	1 (2)	0	0
Unilateral blindness	1 (1)[b]	0	0	0
Bilateral blindness	0	0	0	0

[a] Excludes events ongoing since baseline.

[b] Amaurosis fugax is denned as transient monocular visual loss attributed to ischemia or vascular insufficiency.

[c] One patient had amaurosis fugax, ischemic optic neuropathy, and unilateral blindness at baseline. Amaurosis fugax was again present at week 3 and ischemic optic neuropathy and unilateral blindness were reported at the week 4 visit. All these symptoms resolve by the following visit.

Source: Clinical Study Report.[8]

Table 14: Sensitivity Analyses for Sustained Remission at 52 Weeks

	GiACTA			
Sustained Remission at 52 Weeks, Sensitivity Analysis	**Tocilizumab Weekly (26-Week Taper) N = 100**	**Tocilizumab Every 2 Weeks (26-Week Taper) N = 49**	**Placebo (26-Week Taper) N = 50**	**Placebo (52-Week Taper) N = 51**
Excluding requirement for normalized CRP				
n (%)	59 (59)	27 (55)	10 (20)	17 (33)
Between-group difference, % (99.5% CI), *P* value[a]				
versus placebo (26-week taper)	39 (15 to 63), *P* < 0.0001	35 (8 to 62), *P* = 0.0004	reference	NA
versus placebo (52-week taper)	26 (3 to 49), *P* = 0.0030	22 (−5, 49), *P* = 0.029	NA	reference
Excluding requirement for adherence to prednisone taper regimen[b]				
n (%)	59 (59)	26 (53)	7 (14)	9 (18)
Between-group difference, % (99.5% CI), *P* value[a]				
versus placebo (26-week taper)	45 (21 to 69), *P* < 0.0001	39 (12 to 66), *P* < 0.0001	reference	NA
versus placebo (52-week taper)	41 (21 to 62), *P* < 0.0001	35 (10 to 60), *P* = 0.0002	NA	reference
Completers compliant with study treatment	**N = 45**	**N = 24**	**N = 27**	**N = 23**
n (%)	29 (64)	15 (63)	4 (15)	6 (26)
Between-group difference, %, (99.5% CI), *P* value[a]				

	GiACTA			
Sustained Remission at 52 Weeks, Sensitivity Analysis	**Tocilizumab Weekly (26-Week Taper) N = 100**	**Tocilizumab Every 2 Weeks (26-Week Taper) N = 49**	**Placebo (26-Week Taper) N = 50**	**Placebo (52-Week Taper) N = 51**
versus placebo (26-week taper)[c]	50 (16 to 84), *P* < 0.0001	48 (10 to 86), *P* = 0.0005	reference	NA
versus placebo (52-week taper)	38 (6 to 71), *P* = 0.0035	36 (−1, 74), *P* = 0.013	NA	reference

CI = confidence interval; CRP = C-reactive protein; NA = not applicable.

Note: *P* < 0.005 required for statistical significance. All analyses were outside the statistical testing hierarchy and should be interpreted as exploratory.

[a] Cochran–Mantel–Haenszel test adjusted for starting prednisone dose (≤ 30 mg/day, >30 mg/day).

[b] Patients who received > 100 mg of additional prednisone from week 12 on were classified as nonadherent to the prednisone taper.

[c] Post hoc analysis.

Source: Clinical Study Report.[8]

Table 15: Summary of Reasons for Not Achieving Sustained Remission at 52 Weeks

	GiACTA			
Reason for Non-Response, n (%)[a]	**Tocilizumab Weekly (26-Week Taper) N = 100**	**Tocilizumab Every 2 Weeks (26-Week Taper) N = 49**	**Placebo (26-Week Taper) N = 50**	**Placebo (52-Week Taper) N = 51**
Received escape therapy	23 (23)	16 (33)	37 (74)	28 (55)
First flare				
of any type	27 (27)	17 (35)	36 (72)	29 (57)
with SnS and ESR elevation	0	3 (6)	19 (38)	19 (37)
with SnS only	25 (25)	14 (29)	11 (22)	8 (16)
with ESR elevation only	1 (1)	0	6 (12)	2 (4)
Withdrawal from study prior to week 52	15 (15)	8 (16)	6 (12)	5 (10)
Elevated CRP without flare	5 (5)	3 (6)	26 (52)	31 (61)
Received additional prednisone, including escape	26 (26)	16 (33)	36 (72)	27 (53)

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; SnS = signs and symptoms.

[a] The number of patients who achieved remission by 12 weeks and thus were eligible for sustained remission were as follows: tocilizumab weekly 83 (83%); tocilizumab biweekly 40 (82%); placebo plus 26-week taper 21 (42%); placebo plus 52-week taper 25 (49%).

Source: Clinical Study Report.[8]

Table 16: Subgroup Data for Key Efficacy Outcomes

	GiACTA			
Outcome / Subgroup	**Tocilizumab Weekly (26-Week taper) N = 100**	**Tocilizumab Every 2 Weeks (26-Week Taper) N = 49**	**Placebo (26-Week Taper) N = 50**	**Placebo (52-Week Taper) N = 51**
Sustained remission at 52 weeks				
New-onset patients, n/N (%)	28/47 (60)	15/26 (58)	5/23 (22)	5/23 (22)
Relapsing patients, n/N (%)	28/53 (53)	11/23 (48)	2/27 (7)	4/28 (14)
Actual cumulative prednisone dose,[a] in mg,				

Outcome / Subgroup	GiACTA			
	Tocilizumab Weekly (26-Week taper) N = 100	Tocilizumab Every 2 Weeks (26-Week Taper) N = 49	Placebo (26-Week Taper) N = 50	Placebo (52-Week Taper) N = 51
median (range)				
New-onset patients	1,942 (630 to 6,602.5)	2,202 (982 to 9,912.5)	3,068 (1,125 to 9,777.5)	3,817.5 (2,017.5, to 10,275)
Relapsing patients	1,385 (658 to 5,912)	1,568 (295 to 8,410)	3,860.5 (932 to 8,043.5)	3,785.5 (822.5 to 10,697.5)
Time to disease flare[b]				
New-onset patients				
HR (99% CI) versus placebo (26-week taper)	0.25 (0.09 to 0.70) *P* = 0.0005	0.20 (0.05 to 0.76) *P* = 0.0019	reference	NA
HR (99% CI) versus placebo (52-week taper)	0.44 (0.14 to 1.32) *P* = 0.054	0.35 (0.09 to 1.42) *P* = 0.055	NA	reference
Relapsing patients				
HR (99% CI) versus placebo (26-week taper)	0.23 (0.09 to 0.61) *P* = 0.0001	0.42 (0.14 to 1.28) *P* = 0.046	reference	NA
HR (99% CI) versus placebo (52-week taper)	0.36 (0.13 to 1.00) *P* = 0.010	0.67 (0.21 to 2.10) *P* = 0.37	NA	reference

CI = confidence interval; HR = hazard ratio.

Note: *P* < 0.01 required for statistical significance. All analyses were outside the statistical testing hierarchy and should be interpreted as exploratory.

[a] Actual prednisone dose was based on patients' record of prednisone taken and included all escape therapy and use of commercial prednisone as well as doses received as part of the tapering process. Missing doses during the taper were assumed to be the minimum-dose tablets from that pack. Patients who received an increased dose of prednisone because they entered escape therapy were included in their originally assigned treatment group. There was no imputation of missing data.

[b] Cox proportional hazards model adjusting for stratification factor of starting prednisone dose (≤ 30 mg/day, > 30 mg/day).

Source: Clinical Study Report.[8]

Table 17: Post Hoc Sensitivity Analyses for Patient-Reported Outcomes With Post-Escape Data Included

Outcome	GiACTA			
	Tocilizumab Weekly (26-Week Taper) N = 100	Tocilizumab Every 2 Weeks (26-Week Taper) N = 49	Placebo (26-Week Taper) N = 50	Placebo (52-Week Taper) N = 51
Patient's Global Assessment of disease activity (VAS)[a]				
Week 52, N	97	49	48	51
LSM change from baseline (SE)	−17.3 (NR)	−23.2 (NR)	−8.6 (NR)	−6.3 (NR)
Mean difference versus placebo + 26-week taper, (99% CI)	−8.7 (−21.1 to 3.6) *P* = 0.067	−14.6 (−29.0 to −0.2) *P* = 0.0091	reference	NA
Mean difference versus placebo + 52-week taper, (99% CI)	−11.0 (−23.4 to 1.4) *P* = 0.022	−16.9 (−31.3 to −2.4) *P* = 0.0027	NA	reference
SF-36 Mental Component Score[a]				

Outcome	GiACTA			
	Tocilizumab Weekly (26-Week Taper) N = 100	Tocilizumab Every 2 Weeks (26-Week Taper) N = 49	Placebo (26-Week Taper) N = 50	Placebo (52-Week Taper) N = 51
Week 52, N	94	49	47	49
LSM change from baseline (SE)	7.9 (NR)	6.6 (NR)	5.8 (NR)	2.8 (NR)
Mean difference versus placebo + 26-week taper, (99% CI)	2.1 (−2.2 to 6.4) *P* = 0.20	0.8 (−4.2 to 5.8) *P* = 0.68	reference	NA
Mean difference versus placebo + 52-week taper, (99% CI)	5.1 (0.8 to 9.4) *P* = 0.0022	3.8 (−1.2 to 8.8) *P* = 0.051	NA	reference
SF-36 Physical Component Score[a]				
Week 52, N	94	49	47	49
LSM change from baseline (SE)	4.1 (NR)	3.0 (NR)	−0.6 (NR)	−1.0 (NR)
Mean difference versus placebo + 26-week taper, (99% CI)	4.6 (0.9 to 8.4) *P* = 0.0016	3.6 (−0.8 to 7.9) *P* = 0.034	reference	NA
Mean difference versus placebo + 52-week taper, (99% CI)	5.1 (1.3 to 8.8) *P* < 0.001	4.0 (−0.3 to 8.4) *P* = 0.016	NA	reference

CI = confidence interval; LSM = least squares mean; NA = not applicable; NR = not reported; SD = standard deviation; SE = standard error; SF-36 = Short Form (36) Health Survey; VAS = visual analogue scale.

Note: *P* < 0.01 required for statistical significance. All analyses were outside the statistical testing hierarchy and should be interpreted as exploratory.

[a] Repeated measures model including covariates for treatment, starting prednisone dose (≥ 30 mg or < 30 mg/day), visit, treatment-by-visit interaction, starting dose-by-visit interaction, baseline score, and baseline score-by-visit interaction. No imputation of missing data.

Source: Clinical Study Report.[8]

Table 18: Summary of Signs and Symptoms at Any Time

Outcome	GiACTA			
	Tocilizumab Weekly (26-Week Taper) N = 100	Tocilizumab Every 2 Weeks (26-Week Taper) N = 49	Placebo (26-Week Taper) N = 50	Placebo (52-Week Taper) N = 51
Patients with ESR ≥ 30 mm/h attributable to GCA, n (%)	6 (6)	7 (14)	30 (60)	29 (57)
Patients with signs and symptoms of GCA, n (%)	71 (71)	41 (84)	46 (92)	44 (86)
Fever (≥ 38 °C or 100.4 °F)	2 (2)	1 (2)	6 (12)	3 (6)
Signs or symptoms of GCA	58 (58)	27 (55)	35 (70)	33 (65)
Symptoms of PMR	33 (33)	24 (49)	30 (60)	32 (63)
Unilateral blindness	1 (1)	1 (2)	1 (2)	1 (2)
Bilateral blindness	0	1 (2)	0	0
Ischemic optic neuropathy	1 (1)	2 (4)	0	0
Amaurosis fugax	2 (2)	1 (2)	1 (2)	0
Blurred vision	11 (11)	10 (20)	9 (18)	12 (24)
Diplopia	0	0	2 (4)	2 (4)
Other	20 (20)	14 (29)	24 (48)	21 (41)

ESR = erythrocyte sedimentation rate; GCA = giant cell arteritis; PMR = polymyalgia rheumatica.

Note; Patients can have multiple signs and symptoms. Signs or symptoms of GCA include: new-onset localized headache, scalp tenderness, temporal artery tenderness or decreased pulsation, ischemia-related vision loss, or otherwise unexplained mouth of jaw pain upon mastication.

Source: Clinical Study Report.[8]

Table 19: Summary of Signs and Symptoms of Flares

	GiACTA			
Outcome	**Tocilizumab Weekly (26-Week Taper) N = 100**	**Tocilizumab Every 2 Weeks (26-Week Taper) N = 49**	**Placebo (26-Week Taper) N = 50**	**Placebo (52-Week Taper) N = 51**
Flare patients, n (%)	27 (27)	17 (35)	36 (72)	29 (57)
Flare patients with ESR ≥ 30 mm/h attributable to GCA, n (% of flare patients)	1 (4)	3 (18)	27 (75)	21 (72)
Flare patients with signs and symptoms of GCA, n (% of flare patients)	25 (93)	17 (100)	32 (89)	29 (100)
Fever (≥ 38 °C or 100.4 °F)	1 (4)	0	2 (6)	1 (3)
Signs or symptoms of GCA	18 (67)	13 (77)	25 (69)	20 (69)
Symptoms of PMR	17 (63)	9 (53)	20 (56)	16 (55)
Unilateral blindness	0	0	1 (3)	0
Bilateral blindness	0	1 (6)	0	0
Ischemic optic neuropathy	0	1 (6)	0	0
Amaurosis fugax	0	0	1 (3)	0
Blurred vision	0	1 (6)	2 (6)	4 (14)
Diplopia	0	0	1 (3)	1 (3)
Other	7 (26)	4 (24)	14 (39)	15 (52)

ESR = erythrocyte sedimentation rate; GCA = giant cell arteritis; PMR = polymyalgia rheumatica.

Note: Patients can have multiple signs and symptoms at the time of flare. Signs or symptoms of GCA include: new-onset localized headache, scalp tenderness, temporal artery tenderness or decreased pulsation, ischemia-related vision loss, or otherwise unexplained mouth of jaw pain upon mastication. Percentages for flare categories are calculated based on number of patients who flare.

Source: Clinical Study Report.[8]

Appendix 5: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- Short Form (36) Health Survey (SF-36) physical component summary (PCS) and mental component summary (MCS)
- EuroQoL 5-Dimensions 3-Levels questionnaire (EQ-5D-3L)
- Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F)
- Patient's Global Assessment (PGA) of disease activity on visual analogue scale (VAS)

Findings

While information on reliability, validity, and minimal clinically important differences (MCIDs) for the above outcome measures is limited for giant cell arteritis (GCA) patients, it is readily available for the rheumatoid arthritis (RA) population. Information on the outcome measures is reported here for the RA population to supplement the limited available information in GCA patients. Patients with RA experience different symptoms from, and are generally younger than, patients with GCA, and these differences should be kept in mind when interpreting the results.

Short Form (36) Health Survey Physical Component Summary and Mental Component Summary

SF-36 is a generic health assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on health-related quality of life (HRQoL). As its name suggests, the questionnaire is made up of 36 items, with three to six response options for each item.[39] The SF-36 consists of eight domains: physical functioning (10 items), role physical (four items), bodily pain (two items), general health (five items), vitality (four items), social functioning (two items), role emotional (three items), and mental health (five items).[39] There is also one item on change in general health over the past 12 months.[39] SF-36 also provides two component summaries: the PCS and the MCS, which are created by aggregating the domains. The PCS, MCS, and individual domains are each measured on a scale of 0 to 100, with an increase in score indicating improvement in health status. Factor weights used to calculate summary scores are derived from a US-based general population sample, with country-specific weights also available for other countries (not including Canada).[39]

The SF-36 may not be responsive to GCA- and glucocorticoid (GC) therapy-related changes in HRQoL. In a trial of 20 GCA patients with the SF-36 administered four to five weeks and one year after the start of GC therapy, none of the eight domains of the SF-36 showed statistically significant differences between patients with and without GCA-related visual loss at either time point.[40] In addition, none of the domain scores showed statistically significant differences between the two time points. The PCS and MCS were not used in this trial.[40] In 30 GCA patients no longer treated with GC therapy or on a daily dosage less than or equal to 5 mg of GC for at least three months and 60 recently discharged age- and gender-matched matched control patients, PCS score, and MCS score did not statistically significantly differ between groups.[41] In the 30 GCA patients, PCS and MCS scores were not associated with duration of GC therapy (in those no longer on GC), presence of GCA-

or GC-related complications, or whether patients thought their condition was better after stopping GC therapy.[41] The PCS score was significantly lower in patients with walking difficulties (45.33 versus 51.57, *P* = 0.034) and MCS scores were significantly lower in patients who had fallen at least three times (40.25 versus 50.76, *P* = 0.046).[41] Most of those with walking difficulties attributed them to balance disorders and pain as opposed to muscle weakness expected with GC therapy.[41]

The SF-36 has been more extensively studied in the RA population. In a sample of 223 RA patients with mean age of 56 (standard deviation [SD] = 14) years and spanning all functional classes, test-retest reliability within two weeks was found to be acceptable (> 0.7[42]) for the PCS score (intraclass correlation coefficient [ICC] of 0.80) but not the MCS score (ICC = 0.58).[43] Convergent validity was demonstrated through correlations with measures of disease activity and quality of life, without hypotheses on the expected strengths of correlation.[43] All correlations were statistically significant, with the Spearman rank correlation coefficient (rho) for comparisons of PCS score with disease activity and joint tenderness and swelling ranging from −0.45 to −0.62 and correlation coefficients of MCS score with the same ranging from −0.36 to −0.55 (*P* < 0.0001 for all).[43] Correlation coefficients for associations of PCS with the Health Assessment Questionnaire, visual analogue scale for pain, and Hospital Anxiety and Depression scale ranged from −0.67 to −0.77 and correlation coefficients for associations of MCS with the same ranged from −0.59 to −0.81 (*P* < 0.0001 for all).[43]

In a sample of 243 adult patients (mean age of 51 years with SD = 14) with active RA and receiving an escalation in antirheumatic treatment, effect size was estimated for baseline and post-treatment scores.[34] Only the PCS score had acceptable (≥ 0.5 effect size[44]) responsiveness.[34] Using a patient-reported seven-point scale on disease improvement as anchor and receiver operator characteristic curve analysis, the minimal clinically important difference (MCID) required for 80% specificity in detecting a change in PCS score was 7.2 points (95% CI, 4.6 to 8.0).[34] When both sensitivity and specificity were optimized, the MCID was 5.1 points (95% CI, 2.2 to 10.7).[34] In general use of SF-36, a change of 2 to 4 points in each domain and 2 to 3 points in each component summary indicates a clinically meaningful improvement as determined by the patient.[33]

EuroQoL 5-Dimensions 3-Levels Single-Index Utility Score

The EQ-5D-3L is a generic HRQoL instrument that may be applied to a wide range of health conditions and treatments.[45,46] The first of two parts of the EQ-5D is a descriptive system that classifies respondents (aged ≥ 12 years) based on the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D-3L has three possible levels — 1, 2, or 3 — for each domain, representing “no problems,” “some problems,” and “extreme problems,” respectively. Respondents are asked to choose the level that reflects their health state for each of the five dimensions, corresponding with 243 different health states. A scoring function can be used to assign a single-index utility score to self-reported health states from a set of population-based preference weights.[45,46] The EQ-5D-3L index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score for the three-level version (corresponding to severe problems on all five attributes) varies depending on the utility function that is applied to the descriptive system (e.g., 0.59 for the UK algorithm and −0.109 for the US algorithm). Scores less than 0 represent health

states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively.

Studies assessing the use of the EQ-5D-3L index score in GCA patients were not found and information from RA patients is described instead. In a sample of 233 patients representing all functional classes of RA in the UK with a mean age of 56 years (SD = 14), convergent validity was shown through significant correlations with other instruments.[47] There were no hypotheses on strengths of correlation. The EQ-5D-3L index score was associated with disease severity and activity (rho ranging from −0.74 to −0.43), the Health Assessment Questionnaire (rho = −0.78), and the Hospital Anxiety and Depression scale (rho = −0.56) with *P* values of less than 0.001 for all comparisons.[47] Acceptable (> 0.7[42]) test-retest reliability of the EQ-5D-3L index was demonstrated using the ICC with values of 0.73 (95% CI, 0.63 to 0.83) over a three-month period and 0.78 (95% CI, 0.60 to 0.96) over a two-week period.[47] In patients with any degree of improvement over a three-month period, the mean change in the index score was 0.22, with a corresponding standardized response mean of 0.70.[47]

In a Canadian study of 313 RA patients with a mean age of 62 years (SD = 26) who self-reported disease severity and control on five-point Likert scale ("very mild" to "very severe" and "very well controlled" to "not controlled at all"), the EQ-5D-3L index score was significantly associated with self-reported severity and control (rho = 0.45 and 0.50, respectively; *P* < 0.0001 for both).[48] There were no hypotheses on strengths of correlation.[48] A mean change in score of 0.05 was estimated for an effect size of 0.2,[48] which is considered minimal and may not be clinically significant.[44] In general use, the reported MCIDs for the index score have ranged from 0.033 to 0.074.[35]

Functional Assessment of Chronic Illness Therapy–Fatigue

The FACIT-F scale is a questionnaire that assesses self-reported fatigue, including feelings of tiredness, listlessness, and energy, as well as fatigue's impact on daily activities and function. The FACIT-F scale has a seven-day recall period and includes 13 items scored using a five-point Likert scale.[49] Each item is a statement related to the patient's experience with fatigue, and possible options for level of agreement range from "not at all" to "very much."[49] The individual items are scored from 0 to 4, multiplied by 13, and divided by the number of items answered to give a total score from 0 to 52.[49] Higher scores indicate less fatigue.[49]

The items in FACIT-F were developed through input from clinicians and anemic oncology patients.[49] Although no information on the validity of the scale or its MCID in GCA patients was found, information was available in RA patients. In a sample of 636 RA patients with a mean age of 56 years (range 21 to 86 years) evaluated at three different time points, the scale demonstrated acceptable (≥ 0.7[42]) internal consistency (Cronbach's alpha = 0.86 to 0.87) and correlations with two other measures of fatigue, the SF-36 vitality domain (rho of 0.73 to 0.84, *P* < 0.001) and Multidimensional Assessment of Fatigue (rho of 0.84 to −0.88, *P* < 0.001).[50] Hypotheses on the strengths of correlation were not stated and test-retest reliability was not measured.[50] In a separate sample of 271 RA patients, the distribution-based MCID corresponding to an effect size of 0.5 was found to be 5.5 points.[50]

Patient's Global Assessment of Disease Activity on a Visual Analogue Scale

The PGA of disease activity on a VAS involves asking patients how active their disease is or how their disease is affecting them. The patients then draw a mark on a horizontal line

(often 10 cm in length with anchor wordings on both ends) to indicate where they lie on a scale of no activity or effect to maximum activity or effect.[51]

Information on assessment of the PGA of disease activity on a VAS in GCA patients was not found, though it has been used in RA patients. Test-retest reliability may be acceptable (≥ 0.7)[42] in the RA population, with an ICC of 0.70 found in a sample of 122 patients and ICCs of 0.44 and 0.75 found in samples of 22 and 24 patients.[52] In RA patients, pain is the main contributor to PGA of disease activity[51] and these results may not apply to the GCA population. The patient- and physician-assessed versions of Global Assessment of disease activity do not correlate well with each other and PGA of disease activity may be influenced by participation in support groups and patient education.[52] Reproducibility of the measure across studies suffers from lack of standardization in the wording of the question, instructions, and anchors.[52] The clinical expert consulted for this review estimated an MCID of −10 for RA patients with baseline values of around 40 based on previous studies.

Table 20: Validity and MCID of Outcome Measures

Instrument	Type	Evidence of Validity	MCID	References
SF-36 PCS and MCS	SF-36 is a generic health assessment questionnaire used to assess HRQoL in chronic disease. There are 36 items in eight domains, with three to six response options per item. Factor weights are used to generate PCS and MCS scores.	Limited evidence in GCA patients Yes, in RA patients	2 to 3 points in general use 5.1 and 7.2 points for PCS in RA patients	Jobard 2017,[41] Ruta 1998,[43] Ward 2014,[34] Ware 2007[33]
EQ-5D-3L single index utility score	EQ-5D-3L is a general, non–disease-specific, HRQoL questionnaire. There are five dimensions, with three response levels per dimension and a scoring algorithm is used to generate a single index utility score.	Yes, in RA patients	GCA or RA: unknown General use: 0.033 to 0.074 for index score	Hurst 1997,[47] Marra 2005,[48] Sinnot 2007[35]
FACIT-F	The FACIT-F scale is made up of 13 statements pertaining to fatigue, with patient agreement with each statement rated on a five-point Likert scale.	Yes, in RA patients	5.5 points in RA patients	Cella 2005[50]
PGA of disease activity on a VAS	The PGA of disease activity asks a patient to indicate how much their disease is affecting them by marking a VAS (horizontal line) to yield a value from 0 to 100.	Limited evidence in RA patients	Unknown	Anderson 2011[52]

EQ-5D-3L = EuroQoL 5-Dimensions 3-Level questionnaire; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue; GCA = giant cell arteritis; HRQoL = health-related quality of life; MCID = minimal clinically important difference; MCS = mental component summary; PCS = physical component summary; PGA = Patient's Global Assessment; RA = rheumatoid arthritis; SF-36 = Short Form (36) Health Survey; VAS = visual analogue scale.

Conclusion

Information on reliability, validity, and MCIDs for patient-reported outcome measures is generally unavailable for the GCA populations, with the exception of SF-36 data. None of the eight individual domains of the SF-36 differentiate between patients with and without GCA-related visual loss and there is no definitive evidence that the PCS and MCS scores of the SF-36 are responsive to GCA- and glucocorticoid therapy-related changes in HRQoL.

While there has been more extensive validation of these outcome measures in the RA population, it should be noted that RA patients experience different symptoms from, and are generally younger than, GCA patients. In RA patients, the SF-36 PCS score and the EQ-5D-3L index score have acceptable test-retest reliability, significant associations with related measures, and estimated MCIDs of approximately 5.1 to 7.2 points for the SF-36 PCS. The SF-35 MCS score has significant associations with related measures, but does not have acceptable test-retest reliability. The FACIT-Fatigue scale has acceptable internal consistency reliability, acceptable convergent validity when compared with other measures of fatigue, and an estimated MCID of 5.5 in RA patients. The PGA of disease activity on a VAS has a wide range of test-retest reliability estimates in RA patients (ICCs of 0.44 to 0.75), as least in part due to the lack of standardization in the wording of the question, instructions, and anchors. No estimate of the MCID was found for this outcome measure.

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