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REVIEW

Profile of tocilizumab and its potential in the treatment of giant cell arteritis

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Abstract: Giant cell arteritis (GCA) remains a medical emergency due to the threat of permanent sight loss. High-dose glucocorticoids (GCs) are effective in inducing remission in the majority of patients, however, relapses are common which lengthen GC therapy. GC toxicity remains a major morbidity in this group of patients, and conventional steroid-sparing therapies have not yet shown enough of a clinical benefit to change the standard of care. As the understanding of the underlying immunopathophysiology of GCA has increased, positive clinical observations have been made with the use of IL-6 receptor inhibitor therapies, such as tocilizumab (TCZ). This has led to prospective randomized control trials that have highlighted the safety and efficacy of TCZ in both new-onset and relapsing GCA.

Keywords: giant cell arteritis, temporal arteritis, Horton disease, interleukin-6, tocilizumab, treatment

Introduction

Giant cell arteritis (GCA) continues to be a disease of major concern for practicing clinicians[1] and patients[2] due to the threat of permanent sight loss and the cumulative toxicity caused by glucocorticoid (GC) therapy.[3,4] It is the commonest immunomediated primary systemic vasculitis affecting medium-to-large arteries that almost exclusively affects patients over 50 years of age[5] with an increased incidence with increasing age[6] and a striking female predominance.[7,8] The overall prevalence is estimated at ~1 in 500.[8]

Currently, the main intervention is immediate administration of high-dose GCs.[9,10] There are no randomized controlled trials (RCTs) to support or direct the use of GCs in GCA. Prior to GC therapy, between 30% and 60% of patients went blind,[11] but now the rate of visual loss is somewhere between 5% and 20%.[12–14] Typically, a standard taper of GC is prescribed to all patients according to the clinical symptoms, signs and acute-phase serological markers.[9,10] Relapses occur, lengthening the treatment, and further complications of the disease occur including aortic aneurysms[15,16] and late visual loss.[17] The morbidity associated with high cumulative doses of GC is well established,[3,18] with >85% of patients experiencing at least one side effect. Common GC-induced side effects are diabetes mellitus, osteoporosis and fractures.[4] GCA, the disease and the side effects of GCs, confers a significant health-related economic burden.[19]

Trials investigating steroid-sparing agents such as azathioprine,[20] which was shown to be effective at reducing the overall steroid dose, failed due to higher rates of discontinuation when compared to GCs. The evidence for the use of methotrexate (MTX) is

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conflicting[21–23] and on meta-analysis showed modest benefit.[24] The RCTs investigating tumor necrosis factor antagonists such as infliximab[25] and other targeted therapies such as etanercept[26] and adalimumab,[27] did not confer a significant enough benefit for a change from standard GC therapy. More recently, a trial investigating the concurrent use of abatacept with corticosteroids showed that at 12 months, 48% of those receiving abatacept and 31% of those receiving placebo were in remission (p=0.049).[28]

Interleukin (IL)-6 receptor inhibition presents a promising approach, and tocilizumab (TCZ; a recombinant, humanized anti-IL-6 receptor [IL-6R] monoclonal antibody) has undergone RCTs to show efficacy and safety for use in GCA.[29,30] This review focused on the rationale of IL-6R inhibition, and the trial profile of TCZ in rheumatoid arthritis (RA), thus demonstrating the safety signals and its recent evidence base in the treatment of GCA.

Pathogenesis of GCA

GCA is a polygenic and multifactorial disease. Genetic association studies have described several genes that are associated with a predisposition to develop GCA. The commonest being genes of the human leukocyte antigen (HLA) class I and II regions.[31,32] Carriage of *HLA-DRB1**04 allele is strongly associated with a susceptibility to GCA.[33,34] There are other genes of interest that are not part of the HLA gene, with the strongest association reported as being protein tyrosine phosphatase, non-receptor type 22 (*PTPN22*).[35] Since its early clinical descriptions by Hutchinson[36] and Horton et al,[37] there has long been speculation about the nature of the triggering event in GCA. Some authors have reported a seasonal variation in the disease,[38] whereas others have not found such an association.[39,40] Various infectious agents have been linked to the condition; previously, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae* and parvovirus B19 have been associated.[41,42] More recently, the varicella-zoster virus has been reinvestigated, with some groups implicating it as its presence was found in temporal artery biopsy specimens,[42] whereas others have not corroborated the findings.[43,44]

Immunopathology of GCA

GCA predominantly affects medium and large arteries of the external cranial branches of the carotid artery and the aorta. Arteries are composed of three layers, namely, the adventitia; the media, which contains smooth muscle cells; and the intima, a network of endothelial cells. Following an unknown trigger, the initial inflammatory cascade starts with a breakdown of the immune privilege in the adventitia, where vascular dendritic cells recruit and activate cluster differentiation (CD)4$^+$ naïve T cells. CD4$^+$ T cells proliferate into T helper (Th)1 cells, Th17 cells and T regulatory (Treg) cells. Th1 predominantly produces interferon (IFN)-γ and IL-2, and Th17 produces IL-17, IL-21, IL-22, IL-8 and IL-26.

Macrophages (Mo) are attracted and differentiate into a heterogeneous group of cells producing a variety of chemokines. Within the adventitia, Mo produce IL-6 and IL-1β. In the media, Mo produce metalloproteinases, which destroy the elastic lamina, and growth factors, such as platelet-derived growth factor, transforming growth factor (TGF)-β and vascular endothelial growth factor, which in turn fuel the intimal hyperplasia. In some, highly activated Mo form multinucleated giant cells. The Mo also produce reactive oxidative species, which cause injury to the smooth muscle of the media. To the injury, arterial cells (vascular smooth muscle cells, endothelial cells and fibroblasts) respond with a dysfunctional repair, which leads to media thinning, luminal occlusion and ischemia.[45,46]

Focus on IL-6

IL-6 was found to be significantly elevated in the serum of untreated GCA patients, with some patients having persistently high levels after GC treatment.[47] Furthermore, serum IL-6 levels were found to be a more sensitive marker of disease activity than erythrocyte sedimentation rate (ESR)[48] and the levels readily suppressed with GC therapy.[49]

IL-6 is a pleiotropic cytokine and was originally described as a B-cell differentiation factor.[49] It has been found to be produced by T cells, B cells, Mo, endothelial cells and fibroblasts on various stimuli.[50] IL-6 activates a receptor complex, namely, the IL-6R and the signal-transducing receptor subunit gp130.[51] IL-6R occurs as a membrane bound and a soluble form. IL-6 binds to both of these forms, which can then interact with gp130 and members of the Janus kinase (Jak) family, such as Jak1, Jak2 and tyrosine kinase 2 (Tyk2), which are associated with gp130.[52]

Among its actions, IL-6 stimulates hepatocytes to synthesize and release the acute phase reactants, C-reactive protein (CRP),[48] and it promotes the transition from acute to chronic inflammation. Of further interest, IL-6 participates in the activation of naïve T cells and differentiation into Th17 cells in the presence of TGF-β[53] and inhibits TGF-β-induced Treg cells' differentiation and function. Treg cells function to restrain excessive effector T-cell responses. IL-6 therefore has a critical role in altering the balance between Treg and Th17 cells, and its overproduction contributes to the pathogenesis of GCA and other inflammatory disorders, including RA,

pancreatitis, multiple sclerosis, systemic lupus erythematosus (SLE), Crohn's disease, asthma, multiple myeloma, colorectal cancer, breast cancer and lymphoma.

Considering the evidence of IL-6 involvement in the immunopathophysiology of GCA makes it a prime therapeutic target. Blocking IL-6 may alter or halt the differentiation of CD^+4 cells into Th-17 cells[54,55] and potentially could upregulate the generation of Treg cells.[56]

TCZ

TCZ is a recombinant, humanized anti-IL-6R antibody that competitively inhibits binding of IL-6 to both the membrane-bound and soluble IL-6Rs.[57] It was approved in 2005 to be used in Japan as an orphan drug for Castleman disease. It was subsequently licensed for use to treat adults with moderate-to-severe active RA in Europe, Japan, USA and other countries. TCZ has been approved to be prescribed alone or in combination with disease-modifying anti-rheumatic drugs in the pediatric group older than 2 years with the systemic form of juvenile idiopathic arthritis and/or polyarticular juvenile idiopathic arthritis in both the UK and the USA.[58,59] Additionally, there have been a number of off-license indications reported in the following diseases: Crohn's disease,[60] SLE,[61] Takayasu's arteritis,[62,63] polymyalgia rheumatica (PMR)[63,64] and adult-onset Still's disease.[65]

Safety profile of TCZ

Preclinical studies, where systemic plasma steady-state concentrations of TCZ were eight to ten times greater than seen in any clinical trial, showed changes in absolute neutrophil counts likely related to incomplete granulopoiesis or peripheral sequestration and mild-to-moderate elevations of hepatic transaminases. Importantly, there was no measurable effect on electrophysiological performance, blood pressure, cardiac tissue integrity or prothrombotic activity in intravenous (IV) doses up to 50 mg/kg, and there was no detectable change in bone homeostaisis.[59]

The largest human studies highlighting the safety and efficacy of TCZ are in treating autoimmune arthritis, both IV and subcutaneous administrations, which have since been the subject of meta-analysis. In summary, the Cochrane systematic review of eight RCTs (n=3334) demonstrated a significant benefit of TCZ (8 mg/kg IV every 4 weeks) plus MTX over placebo plus MTX in achieving an American College of Rheumatology Rheumatoid Arthritis Score of disease activity of 50 (ARC50) response (38.8% versus 9.6%) in RA.[66] The drug was generally well tolerated across the trials, although a statistically significant association was reported for changes in liver enzymes, total cholesterol and triglycerides. Where treatment was commenced for dyslipidemia, the returning of serum levels to normal was noted in a number of trials.[67–69]

Notable adverse drug reactions included gastrointestinal (GI) disorders such as hemorrhage and perforation (in the AMBITION trial,[70] one case was fatal). A past history of diverticulitis is a contraindication for using TCZ, particularly if used in conjunction with nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids of MTX. The risk of infection is a major consideration,[71] and this appears to be independent of transient neutropenia[72] that has been noted in the following trials: TOWARD,[68] OPTION,[67] AMBITION,[70] RADIATE[73] and LITHE.[74] Risks of tuberculosis reactivation, malignancy and hepatitis have not been found to be significantly elevated. Patients can also have higher rates of headache and hypertension.[68] Injection site reactions have been highlighted when using TCZ subcutaneously.[75] Table 1 highlights the serious adverse events (SAEs) documented in RA trials.

Pharmacokinetic studies in human beings have not shown any differences in changes in gender, age or ethnicity, mild renal impairment or concurrent treatment with NSAIDs, MTX or corticosteroids.[59] This is an important evidence as the populations studied in RA tend to have a much younger mean age than those who will be treated for GCA (Table 1). As yet, there are no published studies on those with moderate-to-severe renal impairment or on those with hepatic impairment or pregnancy.

Experience of TCZ in GCA

Seitz et al[76] described the first case series of IV TCZ in five patients with GCA with concomitant GC use. There was a resulting rapid remission of the condition and normalization of the acute-phase reactants.

Other groups presented their series corroborating these findings.[77,78]

Villiger et al[29] published the first RCT of TCZ in GCA. It was a single-center study that enrolled 30 patients with new-onset or relapsing disease. GCA was confirmed by either a positive temporal artery biopsy or large vessel imaging, and all subjects were required to have elevated inflammatory markers (ESR, CRP) at baseline. In all, 20 participants received IV TCZ 8 mg/kg/month for 52 weeks and 10 participants received placebo. All subjects received concomitant prednisone 1 mg/kg/day with a steroid taper protocol. Those in remission by 12 weeks received an average of 7 mg/day of prednisone. In all, 85% of patients in the TCZ group achieved the primary outcome, complete

Table 1 Safety of tocilizumab in rheumatoid arthritis studies

Trial name	Year published	Reference	Study length	Study design	Study population	Sample size	Number of arms	Arms
CHARISMA	2006	Maini et al[79]	16 weeks	Multicenter RCT	Patients with active RA and an inadequate response to MTX	359	7	TCZ 2 mg/kg TCZ 4 mg/kg TCZ 8 mg/kg TCZ 2 mg/kg+MTX TCZ 4 mg/kg+MTX TCZ 8 mg/kg+MTX MTX
SAMURAI	2005	Nishimoto et al[60]	52 weeks	Multicenter, X-ray reader-blinded RCT	Patients with active RA of <5 years duration	306	2	TCZ 8 mg/kg DMARD
OPTION	2008	Smolen et al[67]	24 weeks	Double-blind, randomized, placebo-controlled, parallel-group Phase III study	Adult patients with moderate-to-severe active RA of >6 months duration and an inadequate response to MTX	623	3	TCZ 8 mg/kg+MTX TCZ 4 mg/kg+MTX Placebo+MTX
RADIATE	2008	Emery et al[73]	24 weeks	Double-blind, randomized, placebo-controlled, parallel-group, Phase III study	Patients with RA refractory to TNF antagonist therapy	499	3	TCZ 8 mg/kg+MTX TCZ 4 mg/kg+MTX Placebo+MTX
SATORI	2008	Nishimoto et al[62]	24 weeks	Double-blind, randomized, controlled, multicenter study	Active RA patients with inadequate response to MTX	125	2	TCZ 8 mg/kg+placebo Placebo+MTX
AMBITION	2010	Jones et al[70]	24 weeks	Double-blind, double-dummy, parallel-group, randomized study	Adult patients with moderate-to-severe RA for >3 months	673	2*	MTX TCZ 8 mg/kg
LITHE	2011	Kremer et al[69]	104 weeks	Randomized, placebo-controlled, parallel-group, multicenter Phase III trial	Patients with moderate-to-severe RA and an inadequate response to MTX	1196	3	TCZ 4 mg/kg+MTX TCZ 8 mg/kg+MTX Placebo+MTX

Subgroup sample	Mean age, years	Female, %	Baseline DAS28	Primary end point	ACR20 (%)	ACR50 (%)	ACR70 (%)	DAS28 <2.6 (%)	Number of patients with SAE	Most common SAEs with TCZ
53	52.2	83	6.48	ACR20 @ 16 weeks	64	32	2		8	
54	49.3	76	6.55		63	37	6		5	
52	50.1	73	6.43		74	53	16	34	3	
52	49.2	87	6.58		31	6	14		4	
49	50.2	76	6.34		61	28	12		1	
50	50.1	78	6.47		63	41	37	17	7	
49	50.9	93	6.75		41	29	16	8	2	Infections and GI disorders
157	52.9	79.60	6.5	Radiographic progression		Mean sharp score: 2.3			12	
145	53.1	82.10	6.4			Mean sharp score: 6.1			8	
205	50.8	85	6.8	ACR20 @ 24 weeks	59.0	44	22	27	6	
213	51.4	82	6.8		48.0	31	12	13	3	
204	50.6	78	6.8		26.0	11	2	0.8	2	Infections
170	53.9	84	6.79	ACR20 @ 24 weeks	50.0	28.8	12.4	30.10	11	
161	50.9	81	6.78		30.4	16.8	5.0	7.60	12	
158	53.4	79	6.8		10.1	3.8	1.3	1.60	18	Infections, GI symptoms, rash and headache
61	52.6	90.10	6.1	ACR20 @ 24 weeks	80.3	49.2	29.5	43	4	
64	50.8	75	6.2		25.0	10.9	6.3	1.60	3.00	Most commonly nasopharyngitis
284	50	79	6.8	ACR20 @ 24 weeks	69.9	44.1	28	33.6	11	
286	50.7	83	6.8		52.5	33.5	15.1	12.1	8	Infections and GI disorders
399	51.4	84	6.5	Genant-modified total sharp score						
398	53.4	82	6.6	AUC for change in HAQ-DI	54.5	38.9	22.4	64.7		
392	51.3	83	6.5		29.3	19.8	12.2	52.9		Infections, hypertension and increased transaminase levels

(*Continued*)

Table 1 (*Continued*)

Trial name	Year published	Reference	Study length	Study design	Study population	Sample size	Number of arms	Arms
ROSE	2012	Yazici et al[80]	24 weeks	Double-blind, randomized, placebo-controlled, parallel-group, multicenter, Phase IIIb clinical trial	RA patients with inadequate response to DMARD	619	2	TCZ 8 mg/kg+DMARD Placebo+DMARD
ACT-STAR	2013	Weinblatt et al[81]	24 weeks	Multicenter, open-label, Phase IIIb study	Patients with moderate-to-severe RA and an inadequate response to biologics/DMARDs	886	3	TCZ 8 mg/kg TCZ 4/8 mg/kg +DMARD TCZ 8 mg/kg+DMARD
ACT-RAY	2014	Dougados et al[82]	52 weeks	Double-blind, randomized, placebo-controlled, Phase IIIb clinical trial	Adults with active RA despite MTX	556	2	TCZ 8 mg/kg+MTX (add-on) TCZ 8 mg/kg (switch)
FUNCTION	2015	Burmester et al[83]	24 weeks to primary end point 52 weeks	Double-blind, double-dummy, parallel-group, Phase III study	Patients with early RA (MTX naïve)	1162	4	TCZ 4 mg/kg+MTX TCZ 8 mg/kg+MTX TCZ+placebo Placebo+MTX TCZ 4 mg/kg+MTX TCZ 8 mg/kg+MTX TCZ+placebo Placebo+MTX
SURPRISE	2016	Kaneko et al[84]	24 weeks to primary end point 52 weeks total	Prospective, randomized, controlled study	Patients with moderate-to-severe RA and an inadequate response to MTX	223	2	TCZ 8 mg/kg+MTX (add-on) TCZ 8 mg/kg (switch) TCZ 8 mg/kg+MTX (add-on) TCZ 8 mg/kg (switch)

Abbreviations: ACR, American College of Rheumatology Rheumatoid Arthritis Score of disease activity; AUC, area under the curve; DAS, Disease Activity Score; DMARD, disease-modifying anti-rheumatic drug; GI, gastrointestinal; HAQ-DI, Health Assessment Questionnaire Disability Index; MTX, methotrexate; RA, rheumatoid arthritis; RCT, randomized controlled trial; SAE, serious adverse event; TCZ, tocilizumab; TNF, tumor necrosis factor.

remission by week 12, versus only 40% of patients in the control group, p=0.03. In addition, relapse-free survival at 52 weeks was observed in both groups (85% TCZ versus 20% placebo, p=0.001).[29]

The cumulative GC dose at 52 weeks (43 mg/kg versus 110 mg/kg, p=0.0005) was significantly better in the TCZ treatment group. SAEs occurred with equal frequencies between groups. On detailed examination, seven subjects

Subgroup sample	Mean age, years	Female, %	Baseline DAS28	Primary end point	ACR20 (%)	ACR50 (%)	ACR70 (%)	DAS28 <2.6 (%)	Number of patients with SAE	Most common SAEs with TCZ
409	55.2	79.5	8.62	ACR50 @ 24 weeks		30.1				
205	55.8	83.9	8.52			11.2	See study	See study		
138	53.5	79.7	6.01	Safety and tolerability of TCZ	46	21.2	5.8	19.80	8	
364	55.6	75	5.66		42.3	21.4	6.5	20.60	29	
381	54	77.7	5.54		48.7	22.8	8.2	25.20	32	Infections
277	53	81.9	6.33	DAS28 remission	70.8	55.4	31.4	45.5	22	
276	53.6	78.6	6.36		69.2	50.2	31.2	36.6	27	
288	51.2	79	6.7	DAS28 remission @ 24 weeks				31.90	29	
290	49.5	79	6.7					44.80	31	
292	49.9	75	6.7					38.70	25	
287	49.6	80	6.6					15%	24	
				DAS28 remission @ 52 weeks				34		
								49		
								39.40		
								19.50		Most commonly infections
115	55.8	87	5.1	DAS28 remission @ 24 weeks	74.8	54.8	33	69.6	16	
111	56.3	86.5	5.3		69.4	54.1	34.3	55	9	
				DAS28 remission @ 52 weeks	73.9	62.6	47	72.2		
					77.5	63.1	44.1	70.3		Infections and GI disorders

in the TCZ arm experienced SAEs, as documented by the investigators. These included three GI complications, one severe infection, one Stevens–Johnson syndrome, one tinnitus and one GC-induced psychosis.[29]

The largest RCT in GCA to date is the GiACTA trial.[30] This is a multicenter RCT where 251 GCA patients were enrolled to assess the efficacy and safety of TCZ in GCA. It is also the first RCT to compare different doses and durations of GC therapy in a masked trial. At baseline, patients with active GCA (new or relapsing) with either a positive temporal artery biopsy or proof of large vessel disease and with associated elevation in acute-phase reactants were eligible for enrollment (Box 1).[85]

Box 1 Enrollment criteria adapted from baseline characteristics of GiACTA

GiACTA eligibility criteria:

✓ ≥50 years of age

✓ History of ESR ≥50 mm/h or CRP ≥2.45 mg/dL if ESR was unavailable

Active disease: signs and symptoms of GCA and ESR ≥30 mm/h or CRP ≥1 mg/dL within 6 weeks of baseline

At least one of the following:

✓ Unequivocal cranial symptoms of GCA (new-onset localized headache, scalp or temporal artery tenderness, ischemia-related vision loss or otherwise unexplained mouth or jaw pain on mastication)

✓ Unequivocal symptoms of PMR (shoulder and/or hip girdle pain associated with inflammatory stiffness)

And at least one of the following:

✓ TAB revealing features of GCA

✓ Evidence of large-vessel vasculitis (angiography or imaging study such as MRA, CTA or PET-CT)

Abbreviations: CRP, C-reactive protein; CTA, computerized tomography angiography; ESR, erythrocyte sedimentation rate; GCA, giant cell arteritis; MRA, magnetic resonance angiography; PET-CT, positron emission tomography - computerized tomography; PMR, polymyalgia rheumatica; TAB, temporal artery biopsy.

Patients were allowed to be on stable doses of MTX with a reduction or discontinuation allowed within the study protocol. Initiation of MTX or increase in dose was not permitted. Prior use of IV methylprednisolone was not allowed. At baseline, open-label prednisone between 20 and 60 mg/day was allowed at the investigator discretion and according to the disease activity. The dose of prednisone at <20 mg/day during the GC taper was masked to the investigators and subjects. As TCZ has a profound effect on the acute-phase reactants and other liver enzymes, the study required there to be two investigators/assessors: one masked to all the biochemical results and the other to assess the results.[85]

They were randomized to one of four treatment arms. The arms were:

1. PBO+26, the short-course 26-week prednisone taper and placebo (50 patients);
2. PBO+52, the long-course 52-week prednisone taper and placebo (51 patients);
3. TCZ QW, weekly subcutaneous TCZ 162 mg and 26-week course of prednisone (100 patients); and
4. TCZ Q_2W, every other week subcutaneous TCZ 162 mg+26-week course of prednisone (49 patients).

There were several key definitions set for the GiACTA trial Table 2).[30]

Escape prednisone was allowed; however, if the cumulative dose was >100 mg, the subject would be classed as not in remission or a nonresponder. The primary end points included sustained remission, with testing of superior TCZ QW compared to PBO+26 and non-inferior TCZ QW compared to PBO-52. The secondary end points were the time to first flare, the cumulative prednisone dose and quality of life measures.

The results of the GiACTA showed that the proportion of patients achieving sustained remission at 52 weeks while adhering to the prednisone taper was achieved significantly more frequently in both TCZ arms (56% of weekly TCZ group and 53% of the every-other-week TCZ group) as compared with the 26-week prednisone placebo group (14%, $p<0.0001$) and with the 52-week prednisone placebo group (17%, $p<0.0001$ TCZ QW and $p=0.002$ TCZ Q_2W).[30] The GiACTA also provided a unique insight into the natural history of GCA as at 12 months, and 14% of the 26-week placebo arm stayed in remission.[30] This is early evidence that in a small portion of patients, less treatment is required to induce remission; more research in this area would be helpful. Biomarkers of disease activity and clinical activity rating scores are sought in GCA to help to guide treatment decisions in the future.[30]

The time to first flare showed a clear differentiation between TCZ arms and prednisone-only groups with the time to first flare being significantly longer for TCZ groups. TCZ showed a significant steroid sparing effect with patients in both TCZ-treatment groups being exposed to significantly less prednisone over time, which included escape prednisone. The median cumulative dose of prednisone was 1862 mg in each TCZ group versus 3817.5 mg in 52-week placebo arm. With a fair spread of new-onset and relapsing GCA patients between all four treatment arms, further analysis reported that the results held significant for both types of patients who entered the trial.[30] Of note, there were more relapses occurring during tapering doses between 5 and 0 mg, particularly in the 2-week TCZ and 26-week placebo arms of the trial. It may be for some that there is a requirement for a long-term maintenance dose of prednisone between 2.5 and 5 mg daily.

The percentage of adverse events (AEs) across all four trial arms was similar, with infections being the commonest AEs. There were a higher number of SAEs in the prednisone and placebo arms of the trial compared to those of the TCZ arms. Overall withdrawals were higher in the TCZ arms at TCZ QW (6%) and TCZ Q_2W (4%) compared to PBO+26 (4%) and PBO+52 (2%).[30]

Table 2 GiACTA trial definitions adapted from Stone et al[30]

Trial parameter	Trial definition
Flare	The recurrence of signs or symptoms of GCA and/or ESR (≥30 mm/h) which was attributable to GCA as determined by the investigator and necessitating an increase in the prednisone dose
Remission	The absence of flare and normalization of CRP (<1 mg/dL). A single CRP elevation (≥1 mg/dL) was not considered an absence of remission unless CRP remained elevated (≥1 mg/dL) at the next study visit. Remission should also occur within 12 weeks of randomization
Sustained remission	The absence of flare following induction of remission that was maintained up to the 52-week time point

Abbreviations: GCA, giant cell arteritis; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

The GiACTA study is the largest to date in the field of GCA and will likely encourage a review of the accepted ACR 1990 criteria for the diagnosis of GCA. More than one-third of patients were enrolled based on findings of large-vessel imaging studies (magnetic resonance angiography, computerized tomography angiography or positron emission tomography - computerized tomography) alone; 37% of patients had positive imaging studies with either no temporal artery biopsy (TAB) or negative TAB. Only 10% of patients had both positive TAB and positive imaging study findings.[85]

Presently, there are a few limitations to the therapeutic use of monoclonal antibodies in GCA. The on-the-face high cost of the therapy compared to conventional GC treatment is likely to cause funding bodies to question switching therapies. However, this will be mitigated by the cost of ongoing risk of relapse and the significant burden of short-term increased infection rate in GCA[86] and long-term side effects from GC toxicity.[3] Treatment with TCZ is currently IV or subcutaneous, which is an invasive route of administration. Like GCs, TCZ has the potential for SAEs, as evidenced in the RCTs of RA.[66] IL-6 inhibition is one targeted treatment in a disease with multiple immunological facets, and one case, treated with TCZ, reported persistent vasculitis of medium-sized and large vessels on autopsy.[63] There are other biologic agents that are being trialed in GCA, in addition to anti-IL-6-directed therapies, and emerging reports describing the use of biologics that inhibit T cells; cytokines IL-1, IL-12 and IL-23; and B cells in patients with relapsing disease.

There are a number of factors that remain unanswered, such as the role of TCZ in immediate emergency treatment in sight-threatening disease, and yet to be determined is how to maintain long-term sustained remission.[87] The evidence for using TCZ to initiate remission of GCA is strong,[29,30]and follow-up studies will help guide the field's next steps.

Disclosure

SPM has received honoraria for service on advisory boards for Roche and represented the Royal College of Ophthalmologists at the National Institute for Health and Clinical Excellence. JH has no disclosures to report. BD has received honoraria for lectures and served on advisory boards for the National Institute for Health and Clinical Excellence, Roche, Munidpharma, Napp, Merck, and GSK, and has received grant support from the European League Against Rheumatism, American College of Rheumatology, Health Technology Assessment UK, and Research for Patient Benefit UK. The authors report no other conflicts of interest in this work.

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