RHEUMATOLOGY

Rheumatology 2018;57:2101–2105
doi:10.1093/rheumatology/key197
Advance Access publication 12 July 2018

Concise report

Certolizumab pegol in the treatment of Takayasu arteritis

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Abstract

Objectives. Certolizumab pegol (CZP) is a PEGylated antigen-binding fragment-fragment of a humanized mAb neutralizing TNF. It lacks Fc-fragment and has a very low potential to cross the placenta. We aimed to report the efficacy and safety of CZP in a case series of patients with refractory Takayasu arteritis (TA).

Methods. Ten females of reproductive age (18–35 years) with TA were treated with CZP (at a dose of 400 mg at weeks 0, 2 and 4 and at 200 mg every 2 weeks thereafter) for a median of 10 months (range 3–28). Prior to CZP administration all patients received glucocorticoids and ± MTX, CYC, AZA, HCQ, LEF or MMF. Six patients were previously treated with other biological anti-cytokine drugs. The National Institutes of Health criteria and the Indian Takayasu Clinical Activity Score 2010 were used to define disease activity.

Results. All patients rapidly responded to treatment with CZP and were able to taper prednisone and MTX doses. Treatment with CZP resulted in a significant decrease in median serum CRP levels and normalization of Indian Takayasu Clinical Activity Score 2010 score in 9 of 10 patients. Remission of systemic vasculitis was achieved in all patients. Seven patients maintained remission for at least 4 months, while one patient developed relapse after 2 years of CZP treatment. Side effects included mild infections ($n = 5$).

Conclusion. Our case series suggests that CZP may be an effective and steroid-sparing treatment option in patients with active TA even if they did not previously respond to other TNF inhibitors or tocilizumab.

Key words: TNF inhibitors, certolizumab pegol, Takayasu arteritis

Rheumatology key messages

- Certolizumab pegol rapidly induced and maintained remission in 9 of 10 patients with refractory Takayasu arteritis.
- Certolizumab pegol had a steroid-sparing effect in patients with Takayasu arteritis.
- Certolizumab pegol could be considered in female patients with Takayasu arteritis planning pregnancy.

Introduction

Takayasu arteritis (TA) is a large-vessel, granulomatous vasculitis that affects the aorta and/or its main branches leading to stenosis, occlusion and aneurism formation [1, 2]. The disease has a prolonged chronic course and requires long-term immunosuppressive treatment. The treatment strategy in patients with TA is based on glucocorticoids usually given at the initial dose of 0.5–1 mg/kg/day for a month and tapered to the maintenance dose [3]. However, less than half of patients achieve sustained remission on prednisone monotherapy. Therefore, synthetic immunosuppressive drugs such as MTX, AZA, MMF and CYC are frequently required [3]. The effectiveness of biological DMARDs (bDMARDs), for example, TNF-α inhibitors and tocilizumab, in TA was shown in several case series and retrospective studies [4–6]. TNF plays a major role in the development of granulomatous inflammation that is typical of TA. Several studies have shown high serum TNF levels in patients with active TA and increased production of this cytokine by immune cells [7].

TA occurs predominantly in young females of reproductive age (<40 years). Prednisone and AZA are relatively safe in pregnancy. However, a significant proportion of patients with TA do not respond to monotherapy with glucocorticoids, while the efficacy of AZA in large-vessel systemic vasculitis is not established. Among TNF inhibitors, certolizumab pegol (CZP) has the

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Submitted 31 December 2017; revised version accepted 4 June 2018

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CLINICAL SCIENCE

best safety profile in pregnancy and lactation [8, 9], given a minimal transfer through the placenta due to the lack of Fc domain [10, 11]. Therefore, CZP may be a valuable agent for women of child-bearing potential with active TA who require intensification of immunosuppressive treatment. In the available literature we have found no reports of the use of CZP in patients with TA.

We evaluated the efficacy and safety of treatment with CZP in a case series of 10 young females with active TA who were refractory to standard immunosuppressive treatment.

Methods

Patients

We conducted a retrospective study. The decision to use CTZ was made by treating physicians in the referral centres. Ethical approval was not obtained given the retrospective design of the study. All patients gave an informed consent for use of their medical data for this study.

The diagnosis of TA was established according to the classification criteria of the ACR or Ishikawa criteria modified by Sharma *et al.* [12, 13]. CZP was administered subcutaneously at a starting dosage of 400 mg at weeks 0, 2 and 4. Subsequently, it was used at a standard dose of 200 mg every 2 weeks.

Activity of the disease was evaluated using the National Institutes of Health criteria: general signs of inflammation (fever, malaise, weight loss, etc.); elevated acute-phase inflammatory markers (ESR, CRP) in the absence of infection or malignancy; development of clinically significant vascular ischaemia (low or absent pulse loss on extremities, asymmetric blood pressure, intermittent claudication, etc.); and new arterial lesions (e.g. stenoses or aneurysms), detected with visualization methods. The activity was defined as a new onset or worsening of at least two criteria. Prior to and after the treatment with CZP, we also calculated the Indian Takayasu Clinical Activity Score (ITAS 2010) and ITAS.A with ESR that was specifically designed to assess activity of TA. ITAS 2010 contains 44 items in six blocks [14]. Clinical, laboratory and radiological features were assessed at a baseline visit, and then regularly every 3–6 months. Ultrasonography was performed every 3–6 months, while CT-angiography and MRI were done every 6–12 months. In two patients, the choice of imaging modalities was restricted due to pregnancy and lactation. PET-CT was performed in two patients only prior to CTZ administration.

Remission was defined as the absence of the disease activity as defined by the National Institutes of Health criteria and tapering of glucocorticoid dose to 10 mg daily or less. The definition of relapse included new features of active disease (by National Institutes of Health criteria and/or elevation of CRP/ESR) in patients who have previously achieved remission of vasculitis. Clinical and laboratory parameters were monitored regularly every 3–6 months. Doppler ultrasonography, CT-angiography, MR-angiography and/or PET were used to evaluate the progression of arterial lesions.

Statistical analysis

Continuous variables are presented as medians and ranges. Statistical significance was tested using non-parametric methods (Mann–Whitney *U* test or Wilcoxon test). Statistical analyses were carried out using StatSoft version 8.0 (StatSoft, Tulsa, OK, USA; 2007). Data with $P < 0.05$ were considered statistically significant.

Results

Patients

Ten patients with TA were treated with CZP (Table 1). All patients were Caucasian or Turkish females aged 18–35 years and had a long-term history of TA (3.0 to up to 23.5 years with a median of 12 years). Eight patients presented with type V arteritis affecting the entire aorta and its branches. One patient had also AS and psoriasis. In 5 of 10 patients, initial treatment was started with a delay of >2 years. Median delay in the treatment was 22 months (range 6–120).

Prior to CZP administration, all patients received glucocorticoids and MTX, CYC, AZA, HCQ, LEF or MMF. Six patients were also treated with bDMARD (infliximab in five patients, tocilizumab in two, adalimumab in two and etanercept in one). Median duration of immunosuppressive treatment prior to the first bDMARD administration was 35 months (range 14–132).

Despite intensive immunosuppression, all patients presented with general signs of inflammation and high serum CRP or ESR (Table 2). Activity of vasculitis was also shown by the imaging methods (oedema of vessel wall or progressing stenosis on ultrasound in four patients, oedema of vessel wall on MR-angiography in three patients and/or deteriorating or new arterial lesions on CT-angiogram in three patients).

Efficacy of CZP

Duration of treatment with CZP ranged from 3 to 28 months (median 10 months). At the end of follow-up, 9 out of 10 patients continued CZP injections. All patients responded to CZP administration and were able to taper prednisone and MTX doses or discontinue glucocorticoids (Table 1). Treatment with CZP resulted in a significant decrease in median serum CRP and ESR levels and normalization of ITAS 2010 score in 9 of 10 patients. Remission of systemic vasculitis was achieved in all patients at a median of 4 months (3–8). Seven patients maintained remission for at least 4 months and up to 2 years. There were no signs of progression of arterial lesions in these patients. One patient was in remission after 3 months of treatment but relapsed after 2 years with a new-onset arterial stenosis. CZP was switched to tocilizumab. We did not evaluate the stability of remission in two patients due to the short duration of follow-up (3 months). No progression of stenosis was observed on imaging after treatment with CZP, although not all patients could be

Table 1 Baseline characteristics and response to certolizumab pegol in 10 females with refractory Takayasu arteritis

No.	Age, years	Type of TA	Disease duration, months	Duration of CZP treatment, months	DMARDs prior to CZP	bDMARDs prior to CZP	Imaging	GC dose, mg/day (before/after CZP)	CZP efficacy
1	18	III	42	6	MTX, CP	–	US	20/10	Remission
2	35	V	162	24	MTX, CP, HCQ, LEF, MMF	INF, TCZ	US, MRA, PET-CT	15/2.5	Remission
3	31	V	154	22	MTX, CYC	–	US, CTA	25/5→20	Remission/relapse
4	35	I	40	12	MTX, LEF	–	MRA, US	30/7.5	Remission
5	35	V	282	24	MTX, MMF	INF	MRA, CTA, US	10/0	Remission
6	21	V	170	8	MTX, CYC, MMF	INF	US, CTA	20/10	Remission
7	31	V	81	3	AZA, LEF	TCZ, INF	–	20/2.5	Remission
8	25	V	127	3	MTX, AZA, LEF	ADA	CTA	20/10	Remission
9	32	V	132	8	MTX, AZA, LEF	–	–	10/5	Remission
10	33	V	204	28	MTX, LEF	INF, ADA, ETA	PET-CT	10/2.5	Remission

In patients 7 and 9 imaging methods were not used due to pregnancy or lactation. CZP: certolizumab pegol; bDMARDs: biological DMARDs; INF: infliximab; TCZ: tocilizumab; GC: glucocorticoids; ADA: adalimumab; ETA: etanercept; MRA: MR-angiography; CTA: CT-angiography.

Table 2 Treatment outcomes in our cohort of 10 patients

Parameters	Before CZP	After CZP
Disease activity (defined by NIH), *n* (%)	10 (100)	1 (10)
Sustained remission, *n* (%)	–	7/8 (87.5)
Relapse, *n* (%)	–	1 (10)
ITAS 2010 score	3 (1–6)	0 (0–2)
ITAS.A with ESR score	5 (2–9)	0 (0–1)
GC dose (prednisone), mg/day	20 (10–30)	6.25 (0–20)**
MTX dose, mg/week	20 (15–25)	10 (0–20)*
ESR, mm/h	40 (10–115)	15 (5–33)*
CRP, mg/l	27.4 (18.2–44.0)	2 (0–4.5)**

Data are expressed as median (range), unless otherwise stated. *$P < 0.05$ (*vs* baseline); **$P < 0.01$. Sustained remission was evaluated in eight patients with a prolonged follow-up. CZP: certolizumab pegol; NIH: National Institutes of Health; GC: glucocorticoids; ITAS 2010: Indian Takayasu Clinical Activity Score; ITAS.A: ITAS-acute-phase reactants.

examined properly with the use of CT-angiography or MRI due to patient's refusal, technical issues, or pregnancy and lactation.

Safety of CZP

In general, CZP was well tolerated. One patient had uncomplicated pregnancy and delivered a healthy child during treatment with CZP. There were no allergic or injection reactions. Two patients developed mild herpes labialis that did not require antiviral treatment. One patient presented with community-acquired pneumonia that was effectively treated with oral amoxycillin/clavulanate. There were also mild tonsillitis treated with amoxicillin/clavulinic acid and a urinary tract infection treated with fosfomycin in a single patient. One patient developed a post-operative abscess that was probably not related to CZP due to the short duration of therapy, which was discontinued 1 month prior to surgery.

Discussion

In the previous case series, more than 120 patients with active TA were treated with TNF inhibitors, mainly with infliximab. The indications for biologic therapy included ineffective standard treatment, intolerable side effects of glucocorticoids and immunosuppressive medications, frequent exacerbations and development of steroid dependence. TNF inhibition was effective and resulted in remission in up to 90% of patients [4, 5, 15–17]. However, randomized controlled trials of TNF inhibitors in patients with TA are still lacking [18].

Our data suggest that CZP may be as effective as other TNF inhibitors in patients with active TA. However, we reported a small case series, and larger studies are apparently needed. Imaging modalities in several patients were limited due to unavailability or pregnancy/lactation. We administered CZP to 10 females with high activity of TA despite intensive treatment with glucorticoids in combination with other immunosuppressive medications, including TNF inhibitors and tocilizumab. All patients rapidly responded to CZP, were able to taper glucocorticoids and methotrexate doses and achieved remission within a few months after initiation of the new treatment. However, 1 of 10 patients did not maintain remission and developed relapse at 2 years. CZP had a favourable safety profile.

Infectious complications were usually mild and resolved rapidly with or without treatment and did not necessitate cessation of CZP.

The majority of patients with TA are young females of reproductive age. The disease has a progressive course and usually requires prolonged or life-long immunosuppressive treatment. Therefore, rheumatologists can face a challenge in choosing a safe management strategy in young females with TA who want to bear a child. TNF inhibitors are widely used in patients of reproductive age. However, there is still a lack of evidence on their safety in pregnancy. According to the British Society for Rheumatology/British Health Professionals in Rheumatology guidelines and EULAR 2016 points to consider, infliximab and adalimumab should be stopped at weeks 16–20 of pregnancy when they start to cross the placenta [8, 19].

Immunoglobulins are Y-shaped molecules containing two antigen-binding fragments (Fab) and Fc fragment. Transplacental transfer of immunoglobulins from mother to fetus occurs via binding of Fc fragment to Fc receptor in the placental syncytiotrophoblast. CZP is a PEGylated Fab-fragment of a humanized mAb neutralizing TNF. It lacks Fc fragment and has a very low potential to cross the placenta [11, 19]. In the Mahadevan *et al.* study, concentrations of adalimumab and infliximab, but not CZP, were higher in infants at birth and their cords than in their mothers. Moreover, infliximab and adalimumab could be detected in the infants for as long as 6 months. The median level of CZP in the cord was $<4\%$ ($<2\,\mu g/ml$) of that of the mother [20]. Lack of placental transfer of CZP during pregnancy was recently confirmed in a multicentre pharmacokinetic study with a highly sensitive assay [11]. Moreover, CZP absorption by infants via breast milk was unlikely due to its low oral bioavailability and Fc-free molecular structure [9]. In our cohort, one patient was successfully and safely treated with CZP during pregnancy (from weeks 18 to 39). CZP was stopped 1 week prior to the delivery and was readministered 4 weeks after delivery and during lactation. Another patient received CZP during lactation. One patient is currently planning pregnancy.

Another possible advantage of CZP over other TNF inhibitors is its higher potential to penetrate into the inflamed tissues. In DBA/1 mice with CIA the ratio of penetration of CZP into inflamed arthritic paws compared with normal tissue was greater than that observed with adalimumab and infliximab. Also, the duration of exposure in the inflamed tissue was more prolonged with CZP [21]. Unlike infliximab and adalimumab, CZP is a monovalent, pegylated Fab′ and does not cross-link antigens to form large supramolecular complexes. This binding characteristic of CZP may explain its better tissue penetration [22].

In summary, our case series supports the administration of CZP to patients with active TA, even if they did not respond to other TNF inhibitors or tocilizumab. Lack of placental transfer from mother to infant makes CZP particularly promising for treating TA in young women of child-bearing potential. Previous pharmacokinetic studies suggest that treatment with CZP may be continued during pregnancy and lactation, when considered necessary.

Funding: No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

Disclosure statement: The authors have declared no conflicts of interest.

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