Open Access Rheumatology: Research and Reviews

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Spotlight on certolizumab pegol in the treatment of axial spondyloarthritis: efficacy, safety and place in therapy

This article was published in the following Dove Press journal:
Open Access Rheumatology: Research and Reviews

Josefina Marin
María Laura Acosta Felquer
Enrique R Soriano

Rheumatology Unit, Internal Medical Serivces, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

Abstract: Certolizumab pegol (CZP) is a pegylated humanized tumor necrosis factor-α inhibitor (TNFi) approved for the treatment of ankylosing spondylitis (AS) in the USA and for AS and non-radiographic axial spondyloarthritis (nr-axSpA) in Europe and in some Latin American countries. CZP lacks Fc region, preventing complement fixation and cytotoxicity mediated by antibody; CZP does not actively cross the placenta, unlike other TNFi. RAPID-axSpA study is a Phase III trial conducted in patients with AS and nr-axSpA as double blind and placebo controlled to week 24, dose blind to week 48 and open label to week 204. Of a total of 325 patients recruited, 107 patients were assigned to placebo and 218 patients to CZP (111 to CZP 200 mg Q2W, 107 to CZP 400 mg Q4W). Improvements in axial involvement, joint involvement, enthesitis and quality of life were reported in patients treated with CZP. Safety profile was like that reported for other TNFi in axSpA patients. In this article, we summarized the pharmacology and we reviewed the efficacy and tolerability of this drug for the treatment of axSpA. Some special considerations of CZP during pregnancy are included. CZP, the latest TNFi to be approved, showed efficacy in all manifestations of AS and nr-axSpA.

Keywords: certolizumab pegol, tumor necrosis factor-α inhibitors, ankylosing spondylitis, non-radiographic axial spondyloarthritis, efficacy, safety

Introduction

Axial spondyloarthritis (axSpA) is a chronic disease, characterized by involvement of the sacroiliac (SI) joints and spine, resulting in chronic inflammatory back pain.

The estimated prevalence of axSpA is between 0.2% and 1.2% in white European populations.[1] The diagnosis is often delayed by up to 8 years, mainly because sacroiliitis, which is considered a hallmark of ankylosing spondylitis (AS), is not visible on plain radiographs in the early stages of the disease.[2,3]

For the diagnosis of AS, fulfillment of modified New York classification criteria, which requires the presence of radiographic sacroiliitis, is needed.[4] With the use of magnetic resonance imaging (MRI) allowing earlier detection of inflammation in the SI joints, it has been possible to identify patients with clinical characteristics of AS, but who do not fulfill the modified New York criteria. These patients have been classified as having non-radiographic axSpA (nr-axSpA).[5,6] New classification criteria[4–7] were developed in an attempt to improve diagnostic delay.[8,9] This new criteria allowed the inclusion of nr-axSpA in clinical studies.

It has been proposed that nr-axSpA may represent an early form of AS, as many patients progress to AS over time.[10,11] The fact that not all patients progress to AS over

Correspondence: Enrique R Soriano
Sección Reumatología, Servicio de Clínica Médica, Hospital Italiano de Buenos Aires, Instituto Universitario Escuela de Medicina, Juan D Perón 4190 (C1181ACH), Buenos Aires, Argentina
Tel + 54 11 4959 0200 (Extension 5443)
Fax +54 11 4959 0378
Email enrique.soriano@hospitalitaliano.org.ar

submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/OARRR.S116654

time, and the identification of genetic and sex differences between AS and nr-axSpA, has led some to think that they might be distinct diseases[12–14] and have led to the reluctance of FDA to approve tumor necrosis factor inhibitors (TNFis) in nr-axSpA.[15] In general, disease activity and burden of symptoms did not differ between both, and both need the same kind of treatment.[16–19]

The treatment of SpA has changed drastically since the use of biological agents such as TNFi.[20–23] Certolizumab pegol (CZP), a novel TNFi, was the last TNFi approved for the treatment of axSpA (European Commission [EMA] and AS (EMA and FDA). We will describe the current evidence for the use of CZP in the treatment of active axSpA in the following text.

Certolizumab pegol

CZP is formed by the combination of a humanized Fab fragment (50 kDa) and a 40-kDa polyethylene glycol moiety (a polymer that is not immunogenic or toxic).[24,25] Its molecular structure leads to an increase of plasma half-life of the molecule to about 2 weeks. This allows 2–4 weekly subcutaneous injections. PEGylation is also assumed to be associated with decreased inmmunogenicity.[25] The lack of Fc region prevents complement fixation and cytotoxicity mediated by antibody. CZP does not lead to apoptosis of peripheral blood monocytes or lymphocytes or neutrophil necrosis.[24,25]

CZP has been characterized as producing dose-dependent inhibition of TNF (soluble and membrane-bounded TNF) and inhibition of the production of lipopolysaccharide-induced TNF-α and IL-1β by monocytes. CZP does not induce complement or cytotoxicity mediated by antibody in vitro and induces cell death by a nonapoptotic signaling (probable by transmembrane TNF-α). It has also been shown greater drug distribution into inflamed tissues than that of infliximab (IFX) and adalimumab (ADA).[24,26]

Clinical efficacy

CZP efficacy in the treatment of both AS and nr-axSpA patients was evaluated by a randomized control trial: RAPID-axSpA trial.[27–32]

The objective of RAPID-axSpA (NCT01087762), a 4-year, Phase III randomized trial, double blind and placebo controlled to week 24, dose blind to week 48 and open label to week 204, was to study the efficacy and safety of CZP for the treatment of axSpA.[27–32]

Patients were recruited from 83 different sites in central/Eastern and Western Europe, North America and Latin America. To be included in the study, patients need to fulfill Assessment of SpondyloArthritis international Society (ASAS) criteria for the diagnosis of SpA and to have active disease, defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4 and spinal pain ≥4 on a 0–10 Numerical Rating Scale. Intolerance or inadequate response to at least one nonsteroidal anti-inflammatory drug (NSAID) was also needed.[28] A total of 325 patients were recruited. One hundred and seven patients were assigned to placebo and 218 patients to CZP (111 to CZP 200 mg Q2W and 107 to CZP 400 mg Q4W). Of the group of patients treated with CZP, 121 had AS and 97 had nr-axSpA (Figure 1).[28] Baseline disease activity among the groups of patients and between AS and nr-axSpA patients was similar. More than half of the patients in the CZP-treated group (63% [199/315]) completed the study at week 204. The completion rates were similar between both CZP groups and between AS and nr-axSpA patients. ASAS20, ASAS40, BASDAI, Ankylosing Spondylitis Disease Activity Score, Bath Ankylosing Spondylitis Metrology Index and Bath Ankylosing Spondylitis Functional Index responses (nonresponder imputation and observed case) at week 204 are shown in Table 1.[31,32]

Ankylosing Spondylitis Disease Activity Score-ID sustained remission, and ASAS partial remission was achieved by one-third of patients with similar responses rates among AS and nr-axSpA (Table 1).[27,32]

Patient-reported outcomes

Patients-reported outcomes (PROs) are widely used measurements that allow the collection of information related to specific disease aspects, usually not scored by the physicians, directly from the patient. Among them, improvements in back pain, fatigue, sleep (Medical Outcomes Study Sleep Scale), SF-36 (both physical and mental outcomes) and Ankylosing Spondylitis Quality of Live were seen after 24 weeks of the initiation of treatment with CZP, and these results were maintained until week 204[28,31] (Table 2). Comparable improvement in total back pain, fatigue and Ankylosing Spondylitis Quality of Live was seen in AS and nr-axSpA groups.[28] Clinically relevant improvement in pain response to CZP was observed as rapid as from day 2.[30]

Peripheral arthritis and enthesitis

By week 24, similar improvements in arthritis and enthesitis were seen in both AS and nr-axSpA patients,[28] which was maintained until week 204 (Table 3).[27] Enthesitis was assessed by the MASES score. Both AS and nr-axSpA patients had a similar improvement in mean MASES score, although baseline scores were higher in nr-axSpA patients (AS: 4.7 and nr-axSpA: 5.6).[28]

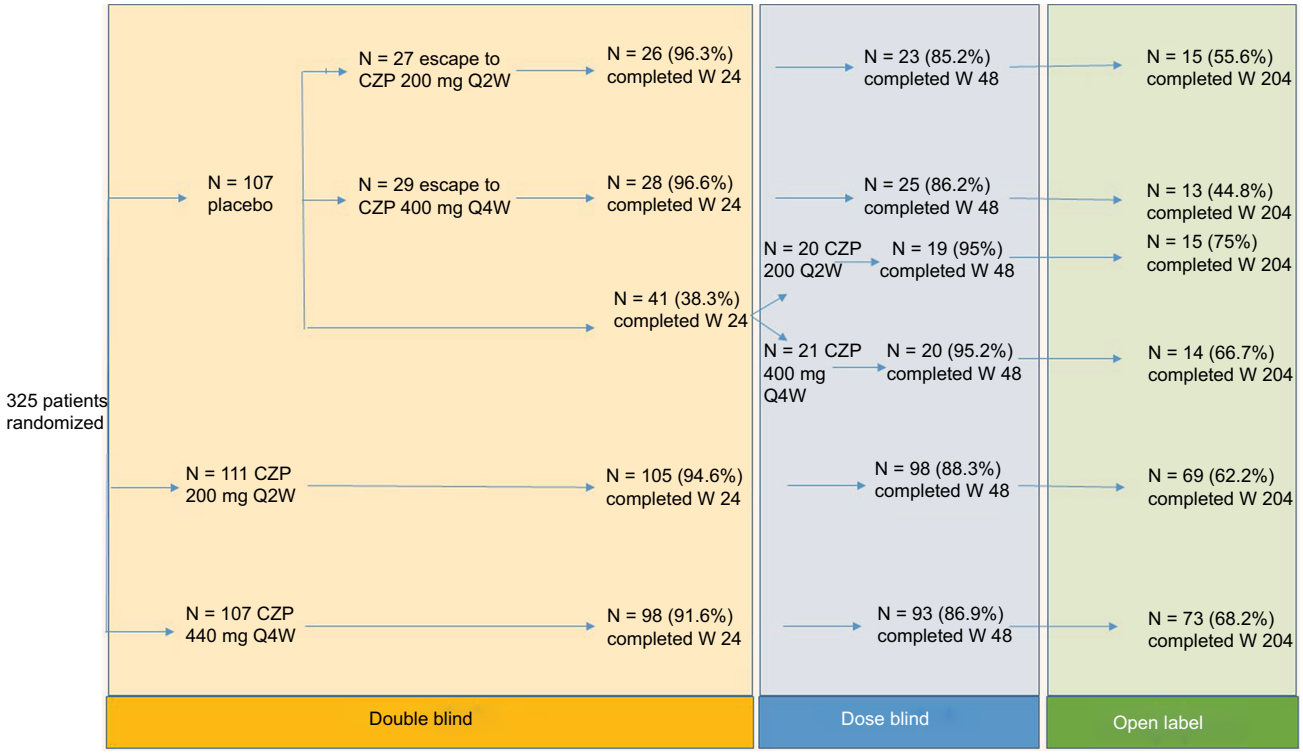

Figure 1 Chart flow of RAPID-axSpA trial[27–32] during the three different phases of the trial.
Abbreviations: CZP, certolizumab pegol; axSpA, axial spondyloarthritis.

MRI outcomes

MRIs of the sacroiliac (SI) joints and spine were performed at baseline and week 12, 48 and 96.[29] For lesions on MRI in the SI joints, the Spondyloarthritis Research Consortium of Canada (SPARCC) scoring method[33] was used and for lesions in the spine the Berlin modification of Ankylosing Spondylitis spine MRI scoring system for disease activity (Berlin) was used.[34] Only patients with MRI evidence of inflammation at baseline were analyzed for MRI remission. CZP treatment of patients with axSpA significantly reduced MRI inflammation in the SI joints and spine over 12 weeks.[29] Improvements were seen and maintained through week 96 for AS and nr-axSpA patients treated with CZP.[29]

Nonradiographic axial spondyloarthritis

RAPID-axSpA is the only trial including patients with both r-axSpA and nr-axSpA with either positive C-reactive protein (CRP) or MRI (with stratified randomization for the presence of radiographic sacroiliitis),[35] and as mentioned earlier, overlapping results were observed between the two groups for most of the outcomes measured (Table 1). The improvement in disability (Bath Ankylosing Spondylitis Functional Index) was greater for patients with nr-axSpA.[35] The effect of etanercept, ADA and golimumab in patients with nr-axSpA was tested in three separate trials.[36–38] For all three drugs, responses were not statistically significant and smaller in patients with normal CRP and MRI at baseline.[35] In patients who had a positive MRI or an increased CRP (ADA and golimumab) and in patients who had both (etanercept), the effect sizes were far greater and statistically significant.[35]

In summary, for patients with nr-axSpA, there is good evidence for the efficacy of CZP, etanercept, ADA and golimumab, but their use should be restricted to patients with abnormal CRP and/or MRI.

Safety

The safety profile of these TNFi has been shown in different clinical trials performed in patients with psoriatic and rheumatoid arthritis.[39–41]

The initial RAPID axSpA trial reported that the adverse events (AEs) were mild to moderate in both CZP and placebo groups. During the 24 weeks of the study, any AE occurred in 62.6% of the placebo group and 76% of the CZP group. Serious AEs occurred in 4.7% and 3.6% of patients in the first group and second group, respectively, and serious infections occurred in 0% and 1.8% of patients in the first group and second group, respectively.[28] In the placebo group any AE, serious AEs and serious infections occurred in 74.8%, 6.5% and 0%, respectively.[28] No deaths, malignancies or tuberculosis events were observed, and no new safety signals for CZP in AS were observed compared to other indications for CZP.[28]

Table 1 Efficacy of subcutaneous certolizumab pegol in adult patients with axial spondyloarthritis in the randomized, double-blind, multicenter RAPID-axSpA trial[28]

Outcome	All patients axSpA (N = 218)					AS (N = 121)					nr-axSpA (N = 97)				
	Baseline	Week 24	Week 24	Week 204	Week 204	Baseline	Week 24	Week 24	Week 204	Week 204	Baseline	Week 24	Week 24	Week 204	Week 204
	N = 218	OC (N = 205)	Imputed	OC (N = 140)	Imputed	N = 121	OC (N = 112)	Imputed	OC (N = 80)	Imputed	N= 97	OC (N = 93)	Imputed	OC (N =60)	Imputed
ASDAS-ID, n/N (%)		66/205 (32.2)	66 (30.3)	44/140 (31.4)	70 (32.1)		33/112 (29.5)	33 (27.3)	23/80 (28.8)	39 (32.2)		33/93 (35.5)	33 (34)	21/60 (35)	31 (32)
ASDAS-MD, n/N (%)	3 (1.4)	51/205 (24.9)	54 (24.8)	41/140 (29.3)	59 (27.1)	2 (1.7)	27/112 (24/1)	29 (24)	25/80 (31.3)	33 (27.3)	1 (1)	24/93 (25.8)	25 (25.8)	16/60 (26.7)	26 (26.8)
ASAS20, n/N (%)		147/201 (73.1)	149 (68.3)	113/135 (83.7)	118 (54.1)		81/108 (75)	83 (68.6)	64/75 (85.3)	68 (56.2)		66/93 (71)	66 (68)	49/60 (81.7)	50 (51.5)
ASAS40, n/N (%)		111/201 (55.2)	113 (51.8)	91/135 (68.1)	96 (44)		62/108 (57.4)	64 (52.9)	51/75 (68)	54 (44.6)		49/93 (52.7)	49 (50.5)	41/60 (68.3)	42 (43.3)
ASAS 5/6, n/N (%)		90/199 (45.2)	92 (42.2)	72/134 (53.7)	75 (34.4)		48/108 (44.4)	48 (39.7)	40/75 (53.3)	41 (33.9)		42/91 (46.2)	44 (45.4)	32/59 (54.2)	34 (35.1)
ASAS-PR, n/N (%)		66/204 (32.4)	66 (30.3)	50/137 (36.5)	51 (23.4)		34/111 (30.6)	34 (28.1)	25/77 (32.5)	26 (21.5)		32/93 (34.4)	32 (33)	25/60 (41.7)	25 (25.8)
BASDAI ≤2 PCR normal, n/N (%)		66/205 (32.2)	66 (30.3)	46/142 (32.4)	72 (33)		33/112 (29.5)	33 (27.3)	23/81 (28.4)	38 (31.4)		33/93 (35.5)	33 (34)	23/61 (37.7)	34 (35.1)
BASDAI 50, n/N (%)		114/205 (55.6)	114 (52.3)	89/140 (63.6)	89 (40.8)		59/112 (52.7)	59 (48.8)	51/80 (63.8)	51 (42.1)		55/93 (59.1)	55 (56.7)	38/60 (63.3)	38 (39.2)
Mean (SD) ASDAS	3.8 (0.9)	2 (1)	2.1 (1.1)	1.9 (0.9)	2 (1.1)	3.9 (0.99)	2 (1)	2 (1.1)	2 (0.9)	2.1 (1.2)	3.8 (0.8)	2 (1.1)	2 (1.1)	1.8 (1)	1.9 (1)
Mean (SD) BASDAI	6.4 (1.5)	3.2 (2.2)	3.3 (2.3)	2.7 (2)	3 (2.3)	6.4 (1.5)	3.2 (2.1)	3.4 (2.2)	2.8 (1.9)	3 (2.3)	6.6 (1.5)	3.2 (2.5)	3.3 (2.5)	2.6 (2.2)	2.9 (2.3)
Mean (SD) BASFI	5.3 (2.3)	2.9 (2.5)	3 (2.5)	2.6 (2.2)	2.7 (2)	5.6 (2.3)	3.2 (2.6)	3.3 (2.6)	2.9 (2.2)	3 (2.4)	5 (2.3)	2.6 (1.5)	2.6 (1.5)	2.4 (1.2)	2.5 (1.3)
Mean (SD) BASMI-linear	3.8 (1.7)	3.2 (1.7)	3.2 (1.7)	3.1 (1.7)	3.1 (1.7)	4.2 (1.7)	3.6 (1.7)	3.6 (1.7)	3.6 (1.8)	3.6 (1.8)	3.2 (1.5)	2.6 (1.5)	2.6 (1.5)	2.4 (1.2)	2.5 (1.3)

Abbreviations: axSpA, axial spondyloarthritis; AS, ankylosing spondylitis; nr-axSpA, non-radiographic axial SpA; OC, observed cases; n/N, number positive/number included; ASAS, Assessment of SpondyloArthritis international Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; ASDAS, Ankylosing Spondylitis Disease Activity Score; ASAS-PR, Assessment of SpondyloArthritis international Society Partial Remission criteria; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index.

Table 2 Effect of subcutaneous certolizumab pegol on key patient-reported outcomes in the RAPID-axSpA study[30]

Patient-reported outcome	All patients (N = 218)					AS (N = 121)					nr-axSpA (N = 97)				
	Baseline	Week 24	Week 24	Week 204	Week 204	Baseline	Week 24	Week 24	Week 204	Week 204	Baseline	Week 24	Week 24	Week 204	Week 204
	N = 218	OC (N = 205)	Imputed	OC (N = 140)	Imputed	N =121	OC (N = 112)	Imputed	OC (N = 80)	Imputed	N = 97	OC (N = 93)	Imputed	OC (N = 60)	Imputed
Morning stiffness	6.6 (1.9)	2.9 (2.4)	3 (2.5)	2.5 (2)	2.7 (2.4)	6.6 (1.9)	2.9 (2.1)	3.1 (2.2)	2.5 (1.9)	2.7 (2.3)	6.6 (1.9)	3 (2.8)	3 (2.8)	2.5 (2.2)	2.6 (2.5)
Fatigue	6.8 (1.8)	3.9 (2.6)	4.1 (2.7)	3.2 (2.2)	3.6 (2.6)	6.7 (1.9)	3.9 (2.5)	4.1 (2.6)	3.3 (2.2)	3.6 (2.6)	6.9 (1.8)	3.9 (2.7)	4 (2.7)	3.1 (2.3)	3.6 (2.6)
Sleep	49 (19.2)	35.3 (20.1)	36.2 (20.2)	32.4 (17.3)	34.4 (18.6)	46.8 (19.9)	35.1 (19.3)	36.3 (19.5)	32.3 (15.9)	34.1 (17.5)	51.7 (18)	35.4 (21.2)	36.1 (21)	32.5 (19.2)	34.9 (20)
Nocturnal back pain	6.9 (2.3)	3.1 (2.6)	3.3 (2.7)	2.7 (2.4)	3 (2.7)	6.8 (2.3)	3.1 (2.4)	3.3 (2.6)	2.7 (2.3)	3.1` (2.6)	7 (2.3)	3.1 (2.9)	3.2 (2.9)	2.7 (2.6)	2.9 (2.7)
Total back pain	7 (1.9)	3.5 (2.6)	3.8 (2.7)	3 (2.4)	3.3 (2.7)	7 (2)	3.5 (2.3)	3.8 (2.5)	3.1 (2.3)	3.4 (2.7)	7 (1.8)	3.6 (2.9)	3.8 (3)	2.8 (2.5)	3.3 (2.7)
ASQoL	11.6 (4.4)	6.2 (5.5)	6.5 (5.6)	4.9 (5)	5.7 (5.4)	11.6 (4.4)	6.3 (5.3)	6.8 (5.6)	5.2 (4.9)	5.9 (5.5)	11.6 (4.4)	6.1 (5.7)	6.1 (5.7)	4.5 (5.1)	5.3 (5.3)
SF-36 PCS	32.4 (7.5)	42.1 (10)	41.8 (9.9)	44.3 (9.4)	43.5 (9.6)	31.7 (7.2)	41.3 (9.6)	40.7 (9.6)	43.7 (9.5)	42.8 (10)	33.2 (7.9)	43.2 (10.4)	43.1 (10.3)	45.1 (9.2)	44.4 (9)
SF-36 MCS	41 (12)	46.6 (11.6)	46 (11.8)	46.8 (11)	45.6 (11.5)	41.7 (11.5)	46.8 (11.1)	45.8 (11.6)	45.8 (10.7)	44.8 (11.3)	40.1 (12.6)	46.5 (12.2)	46.2 (12.1)	48.1 (11.4)	46.6 (11.6)

Note: Values are given as mean and (SD), unless stated otherwise.

Abbreviations: axSpA, axial spondyloarthritis; AS, ankylosing spondylitis; nr-axSpA, non-radiographic axial SpA; OC, observed cases; SF-36 PCS, Short Form (36) Health Survey Physical Component Summary; SF-36 MCS, Short Form (36) Health Survey Mental Component Summary.

Table 3 Effect of subcutaneous certolizumab pegol on peripheral arthritis and enthesitis in the RAPID-axSpA study[28]

Articular manifestations, mean (SD)	All patients axSpA (N = 218)					AS (N = 121)					nr-axSpA (N = 97)				
	Baseline	Week 24	Week 24	Week 204	Week 204	Baseline	Week 24	Week 24	Week 204	Week 204	Baseline	Week 24	Week 24	Week 204	Week 204
		OC	LOCF	OC	LOCF		OC	LOCF	OC	LOCF		OC	LOCF	OC	LOCF
Swollen joint count	N = 76 Mean 4.2 SD 5.6	N = 72 Mean 1.2 SD 2.7	N = 1.5 Mean 3.2	N = 52 Mean 0.4 SD 1.1	N = 0.8 Mean 2.4	N = 42 Mean 4 SD 4.6	N = 38 Mean 1.2 SD 1.9	N = 1.7 Mean 3.1	N = 28 Mean 0.1 SD 0.4	N = 1 Mean 3	N = 34	N = 34 Mean 4.5 SD 6.8	N = 1.2 Mean 3.4	N = 24 Mean 0.7 SD 1.5	Mean 2.6 SD 2.5
Tender joint count	N = 138 Mean 6.3 SD 7.1	N = 131 Mean 3.3 SD 6.4	N = 3.6 SD 6.5	N = 89 Mena 2.4 SD 5	N = 2.9 SD 5.5	N = 74 Mean 5.9 SD 6.5	N = 69 Mean 2.7 SD 4.7	N = 3 SD 4.8	N = 48 Mean 2.1 SD 5	N = 3 SD 5.7	N = 64 Mean 6.8 SD 7.7	N = 62 Mean 4.1 SD 7.8	N = 4.3 SD 8	N = 41 Mean 2.7 SD 5.1	N = 2.8 SD 5.3
Enthesitis MASES	N = 148 Mean 5.1 SD 3.5	N = 141 Mean 2.2	N = 2.3 SD 3.5	N = 104 Mean 1.4 SD 2.5	N = 1.7 SD 3	N = 78 Mean 4.7 SD 3.4	N = 74 Mean 1.6 SD 2.7	N =1.7 SD 2.7	N = 58 Mean 1.1 SD 2.2	N = 1.3 SD 2.5	N = 70 Mean 5.6 SD 3.6	N = 67 Mean 5.6 SD 3.6	N = 2.9 SD 4.1	N = 46 Mean 1.7 SD 2.9	N = 2.1 SD 3.4
Complete resolution of enthesitis MASES = 0, n/N (%)	0	74/141 (52.5)	75 (50.7)	66/104 (63.5)	90 (60.8)	0	41/74 (55.4)	42 (53.8)	38/58 (65.5)	51 (65.4)	0	33/67 (49.3)	33 (47.1)	28/46 (60.9)	39 (55.7)
Heel enthesitis complete resolution, n/N(%)	0	32/49 (65.3)	32 (61.5)	26/35 (74.3)	37 (71.2)	0	13/23 (56.5)	13 (52)	12/17 (70.6)	17 (68)	0	19/26 (73.1)	19 (70.4)	14/18 (77.8)	20 (74.1)

Abbreviations: axSpA, axial spondyloarthritis; AS, ankylosing spondylitis; nr-axSpA, non-radiographic axial SpA; OC, observed cases; LOCF, last observation carried forward.

Sieper et al described the effects of 315 AS patients in the RAPID ax-SPA trial over 96 weeks. AEs occurred in 279 (88.6%) patients (total exposure period 486/patient years). Most of these side effects were mild (74.9%) or moderate (59.4%).[32]

They reported serious AEs in 41 patients (13.0%), which were predominantly infections and infestations (3.8%); one case of active tuberculosis was identified. Over the 96-week trial period, there were no fatalities, malignancies or drug-induced demyelinating disease. In total, 215 of the 315 patients were tested for anti-CZP antibodies at week 96, and 9 patients tested positive for the antibodies. They did not investigate the efficacy of CZP in patients who developed anti-CZP antibodies because of the small cohort of patients with positive antibodies.[32]

A boxed warning on the increased risk of serious infection and latent tuberculosis is included in the US prescribing information.[42] In the European Union (EU), CZP is contraindicated in active tuberculosis or other severe infections such as sepsis or opportunistic infections and moderate to severe heart failure (NYHA classes III/IV).[43]

Although there are no data on long-term safety of CZP in AS, data from treatment of other diseases are useful. Loftus et al collected data from five placebo-controlled trials, nine open-label studies and one dose regimen study with Crohn's disease and found an IR for serious AEs of 31.35/100 patient-years, very similar to that of placebo (24.33/100 patient-years).[44] IRs of serious infections or malignancies did not increase with long-term treatment (6.47/100 patient-years and 0.80/100 patient-years, respectively, in the all-studies group). In a comparable way, IRs of psoriasis or psoriasiform dermatitis did not increase with long-term treatment (0.93/100 patient-years and 0.09/100 patient-years, respectively, in the all-studies group).[44]

Drug survival is a surrogate of efficacy and safety in observational studies. Recently, results from a two-center cohort of AS patients treated with TNFi (ADA: n= 332, etanercept: n = 205, IFX: n = 51, golimumab: n = 40, and CZP: n = 23) in the United Kingdom have been published.[45] Median drug survival duration for first TNFi was 10.2 years, which was superior to second TNFi (5.5 years) ($P < 0.05$). No drug-specific ($P = 0.45$) differences were observed for TNFi survival, although follow-up for patients with CZP was shorter.[45]

All data show that CZP safety profile is very similar to the other TNFi that have been in the market for longer time.

Pregnancy

Drugs used to treat women at fertile age, commonly affected with rheumatic diseases, may alter fertility and increase the

risk of miscarriages and congenital abnormalities. On the other side, disease activity could be an independent risk factor for adverse pregnancy outcomes.[46–48]

Concerns related to the safety of biologics during pregnancy existed until few years ago when data from many studies suggested that pregnant women with inflammatory bowel disease or inflammatory arthritis receiving TNF inhibitors was not associated with adverse pregnancy outcomes or any increase in teratogenicity.[49–53]

CZP differs from other TNF blockers in that it has no Fc region and is not actively transported through the placenta, and as expected, concentrations in the fetus would be lower.[54]

In a study performed in 2013, authors measured the serum and cord concentrations of drugs in the mother, infant and cord blood.[55] They included 31 pregnant women with inflammatory bowel disease receiving IFX (n=11), ADA (n=10) and CZP (n=10). Drug concentrations in infants at birth and cord were compared with those of the mother. IFX and ADA concentrations were higher in infants at birth and their cords than in their mothers. The median level of IFX and ADA in the cord was 160% and 153% higher than that of the mother, respectively. By contrast, the median level of CZP in the cord was 3.9% higher than that of the mother. They detected IFX and ADA in the infants for as long as 6 months, while CZP in the infant plasma and cord was undetectable. No congenital malformations or adverse pregnancy outcomes were reported.[24,55]

An analysis of 253 pregnancies with known outcomes from a total of 625 pregnancies from UCB Pharma global safety database was published.[56] Only one-third of pregnancies continued the treatment through second or third trimester, while most of women were exposed during the first trimester. Most of the women had Crohn's disease. In total, 75.5% pregnancies resulted in live births. Ten percent of women had elective terminations, and spontaneous miscarriages were reported in 14% of patients.[56] Three congenital malformations were reported after maternal exposure, which is comparable to that of the general population.[56]

The 2016 "EULAR recommendations for use of antirheumatic drugs during pregnancy and lactation" recommended discontinuing monoclonal antibodies IFX, ADA and golimumab around gestational week 20. Etanercept (a fusion protein) may be continued until week 30–32, and CZP has minimal transplacental passage for use throughout pregnancy but needs confirmation from prospective studies.[51]

Administration and doses

In the United States, CZP has been approved by FDA only for the treatment of adult patients with active AS.[42]

In the EU, subcutaneous CZP has been approved for the treatment of patients with severe active AS who have had an inadequate response to or are intolerant to NSAIDs and adults with severe active axSpA without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and/or MRI who have had an inadequate response to or are intolerant to NSAIDs.[43]

The recommended doses and administration schedules are 400 mg (given as 2 subcutaneous injections of 200 mg each) initially and at weeks 2 and 4, followed by 200 mg every other week or 400 mg every 4 weeks.

The purpose of indicating LD is to achieve high concentrations of the drug during early stages of treatment, which accelerates drug response and reduces the production of drug antibodies.[24]

Place in therapy

TNFis are recommended in all international and local guidelines after NSAID failure in AS and nr-axSpA.[57,58] CZP, a new TNFi, is placed at that same level, although some concerns due to less long-term and real-life date might be raised. CZP demonstrated efficacy not only in axial involvement but also in peripheral arthritis and enthesitis and hence should be considered in patients with more than one involvement. Because of its advantages related to low cross-placental and breast milk transfer, CZP may be considered as the TNFi of choice in female patients considering pregnancy and of course in pregnant patients. As always, risks and benefits of therapy should be discussed with the patient taking into account neonatal risks and the risk of disease flare. Also, the course of a pregnancy with a very active disease might have far more consequences to neonatal development. In general, it is not recommended to switch to CZP if a pregnant patient is doing well on other TNFi. Having other options for the treatment of these patients, is there any advantage to use CZP? Some CZP features, apart from placental and breast milk transfer, that make CZP in some way different to other TNFi might be considered at the time of offering the patient a new treatment: a fortnightly or monthly subcutaneous drug regime due to a long half-life; quick and long-lasting efficacy and low generation of anti-TNFi (anti-ADA) antibodies after a loading dose; and proven good distribution into inflamed tissues due to PEGylation. On the other hand, up to now, in spite of these differences, CZP safety profile looks similar to other TNFi.

Conclusion

CZP, the newest original TNFi, has shown very good efficacy and has sustained on the long term in several manifestations of axSpA, including peripheral disease, enthesitis and PROs.

CZP is a new TNFi with a novel composition that is gaining experience around the world and performing according to expectations.

Disclosure

ERS participated in advisory boards, gave conferences or received grants from Abbvie, Bristol-Myers Squibb, Genzyme, GlaxoSmithKline, Janssen, Lilly, Novartis, Pfizer, Roche, Sandoz and UCB. MLAF and JM gave conferences for Novartis. The authors report no other conflicts of interest in this work.

References

1. Sieper J, Rudwaleit M, Khan MA, Braun J. Concepts and epidemiology of spondyloarthritis. *Best Pract Res Clin Rheumatol*. 2006;20(3):401–417.
2. Sykes MP, Doll H, Sengupta R, Gaffney K. Delay to diagnosis in axial spondyloarthritis: are we improving in the UK? *Rheumatology (Oxford)*. 2015;54(12):2283–2284.
3. Feldtkeller E, Khan MA, van der Heijde D, van der Linden S, Braun J. Age at disease onset and diagnosis delay in HLA-B27 negative vs. positive patients with ankylosing spondylitis. *Rheumatol Int*. 2003;23(2):61–66.
4. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum*. 1984;27(4):361–368.
5. Baraliakos X, Braun J. Non-radiographic axial spondyloarthritis and ankylosing spondylitis: what are the similarities and differences? *RMD Open*. 2015;1(Suppl 1):e000053.
6. Kiltz U, Baraliakos X, Karakostas P, et al. The degree of spinal inflammation is similar in patients with axial spondyloarthritis who report high or low levels of disease activity: a cohort study. *Ann Rheum Dis*. 2012;71(7):1207–1211.
7. Rudwaleit M, van der Heijde D, Landewe R, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis*. 2009;68(6):777–783.
8. Deodhar A, Mittal M, Reilly P, et al. Ankylosing spondylitis diagnosis in US patients with back pain: identifying providers involved and factors associated with rheumatology referral delay. *Clin Rheumatol*. 2016;35(7):1769–1776.
9. Salvadorini G, Bandinelli F, Delle Sedie A, et al. Ankylosing spondylitis: how diagnostic and therapeutic delay have changed over the last six decades. *Clin Exp Rheumatol*. 2012;30(4):561–565.
10. Poddubnyy D, Rudwaleit M, Haibel H, et al. Rates and predictors of radiographic sacroiliitis progression over 2 years in patients with axial spondyloarthritis. *Ann Rheum Dis*. 2011;70(8):1369–1374.
11. Sampaio-Barros PD, Bertolo MB, Kraemer MH, Marques-Neto JF, Samara AM. Undifferentiated spondyloarthropathies: a 2-year follow-up study. *Clin Rheumatol*. 2001;20(3):201–206.
12. Ortega Castro R, Font Ugalde P, Castro Villegas MC, et al. Different clinical expression of patients with ankylosing spondylitis according to gender in relation to time since onset of disease. Data from REGISPONSER. *Reumatol Clin*. 2013;9(4):221–225. Spanish [with English abstract].
13. Tournadre A, Pereira B, Lhoste A, et al. Differences between women and men with recent-onset axial spondyloarthritis: results from a prospective multicenter French cohort. *Arthritis Care Res (Hoboken)*. 2013;65(9):1482–1489.
14. Wallis D, Inman RD. Recognition of preclinical and early disease in axial spondyloarthritis. *Rheum Dis Clin North Am*. 2014;40(4):685–697.
15. Deodhar A, Reveille JD, van den Bosch F, et al. The concept of axial spondyloarthritis: joint statement of the spondyloarthritis research and treatment network and the Assessment of SpondyloArthritis International Society in response to the US Food and Drug Administration's comments and concerns. *Arthritis Rheumatol*. 2014;66(10):2649–2656.
16. Rumyantseva DG, Dubinina TV, Demina AB, et al. [Ankylosing spondylitis and non-radiographic axial spondyloarthritis: two stages of disease?]. *Ter Arkh*. 2017;89(5):33–37. Russian [with English abstract].
17. de Winter JJ, van Mens LJ, van der Heijde D, Landewe R, Baeten DL. Prevalence of peripheral and extra-articular disease in ankylosing spondylitis versus non-radiographic axial spondyloarthritis: a meta-analysis. *Arthritis Res Ther*. 2016;18:196.
18. Wallman JK, Kapetanovic MC, Petersson IF, Geborek P, Kristensen LE. Comparison of non-radiographic axial spondyloarthritis and ankylosing spondylitis patients—baseline characteristics, treatment adherence, and development of clinical variables during three years of anti-TNF therapy in clinical practice. *Arthritis Res Ther*. 2015;17:378.
19. Song IH, Weiss A, Hermann KG, et al. Similar response rates in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis after 1 year of treatment with etanercept: results from the ESTHER trial. *Ann Rheum Dis*. 2013;72(6):823–825.
20. Song IH, Hermann KG, Haibel H, et al. Consistently good clinical response in patients with early axial spondyloarthritis after 3 years of continuous treatment with etanercept: longterm data of the ESTHER trial. *J Rheumatol*. 2014;41(10):2034–2040.
21. Rudwaleit M, Claudepierre P, Wordsworth P, et al. Effectiveness, safety, and predictors of good clinical response in 1250 patients treated with adalimumab for active ankylosing spondylitis. *J Rheumatol*. 2009;36(4):801–808.
22. Rudwaleit M, Schwarzlose S, Hilgert ES, Listing J, Braun J, Sieper J. MRI in predicting a major clinical response to anti-tumour necrosis factor treatment in ankylosing spondylitis. *Ann Rheum Dis*. 2008;67(9):1276–1281.
23. Rudwaleit M, Listing J, Brandt J, Braun J, Sieper J. Prediction of a major clinical response (BASDAI 50) to tumour necrosis factor alpha blockers in ankylosing spondylitis. *Ann Rheum Dis*. 2004;63(6):665–670.
24. Acosta-Felquer ML, Rosa J, Soriano ER. An evidence-based review of certolizumab pegol in the treatment of active psoriatic arthritis: place in therapy. *Open Access Rheumatol*. 2016;8:37–44.
25. Goel N, Stephens S. Certolizumab pegol. *MAbs*. 2010;2(2):137–147.
26. Nesbitt A, Fossati G, Bergin M, et al. Mechanism of action of certolizumab pegol (CDP870): in vitro comparison with other anti-tumor necrosis factor alpha agents. *Inflamm Bowel Dis*. 2007;13(11):1323–1332.
27. van der Heijde D, Dougados M, Landewe R, et al. Sustained efficacy, safety and patient-reported outcomes of certolizumab pegol in axial spondyloarthritis: 4-year outcomes from RAPID-axSpA. *Rheumatology (Oxford)*. 2017;56(9):1498–1509.
28. Landewé R, Braun J, Deodhar A, et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled Phase 3 study. *Ann Rheum Dis*. 2014;73(1):39–47.
29. Braun J, Baraliakos X, Hermann KG, et al. Effect of certolizumab pegol over 96 weeks of treatment on inflammation of the spine and sacroiliac joints, as measured by MRI, and the association between clinical and MRI outcomes in patients with axial spondyloarthritis. *RMD Open*. 2017;3(1):e000430.
30. Sieper J, Kivitz A, van Tubergen A, et al. Impact of certolizumab pegol on patient-reported outcomes in patients with axial spondyloarthritis. *Arthritis Care Res (Hoboken)*. 2015;67(10):1475–1480.
31. Sieper J, Kivitz A, van Tubergen A, et al. Long-term maintenance of improvements in patient-reported outcomes with certolizumab pegol in patients with axial spondyloarthritis, including ankylosing spondylitis and non-radiographic axial spondyloarthritis: 96-week results of the RAPID-axSpA Study. *Value Health*. 2014;17(7):A385–A386.

32. Sieper J, Landewe R, Rudwaleit M, et al. Effect of certolizumab pegol over ninety-six weeks in patients with axial spondyloarthritis: results from a phase III randomized trial. *Arthritis Rheumatol*. 2015;67(3):668–677.
33. Maksymowych WP, Inman RD, Salonen D, et al. Spondyloarthritis research Consortium of Canada magnetic resonance imaging index for assessment of sacroiliac joint inflammation in ankylosing spondylitis. *Arthritis Rheum*. 2005;53(5):703–709.
34. Lukas C, Braun J, van der Heijde D, et al. Scoring inflammatory activity of the spine by magnetic resonance imaging in ankylosing spondylitis: a multireader experiment. *J Rheumatol*. 2007;34(4):862–870.
35. Sepriano A, Regel A, van der Heijde D, et al. Efficacy and safety of biological and targeted-synthetic DMARDs: a systematic literature review informing the 2016 update of the ASAS/EULAR recommendations for the management of axial spondyloarthritis. *RMD Open*. 2017;3(1):e000396.
36. Dougados M, van der Heijde D, Sieper J, et al. Symptomatic efficacy of etanercept and its effects on objective signs of inflammation in early nonradiographic axial spondyloarthritis: a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheumatol*. 2014;66(8):2091–2102.
37. Sieper J, van der Heijde D, Dougados M, et al. Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). *Ann Rheum Dis*. 2013;72(6):815–822.
38. Sieper J, van der Heijde D, Dougados M, et al. A randomized, double-blind, placebo-controlled, sixteen-week study of subcutaneous golimumab in patients with active nonradiographic axial spondyloarthritis. *Arthritis Rheumatol*. 2015;67(10):2702–2712.
39. Kameda H, Nishida K, Nannki T, Watanabe A, Oshima Y, Momohara S. Safety and effectiveness of certolizumab pegol in patients with rheumatoid arthritis: interim analysis of post-marketing surveillance. *Nihon Rinsho Meneki Gakkai Kaishi*. 2017;40(3):196–205. Japanese [with English abstract].
40. Zhou Q, Zhou Y, Chen H, Wang Z, Tang Z, Liu J. The efficacy and safety of certolizumab pegol (CZP) in the treatment of active rheumatoid arthritis (RA): a meta-analysis from nine randomized controlled trials. *Int J Clin Exp Med*. 2014;7(11):3870–3880.
41. Ferrante M, Vermeire S, Rutgeerts PJ. Drug safety evaluation of certolizumab pegol. *Expert Opin Drug Saf*. 2014;13(2):255–266.
42. Cimzia® (certolizumab pegol) [prescribing information]. Brussels: UCB Inc; 2013. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125160s215lbl.pdf. Accessed November 18, 2017.
43. European Medicines Agency. Cimzia (certolizumab pegol): summary of product characteristics. London: European Medicines Agency; 2014. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001037/WC500069763.pdf. Accessed November 18, 2017.
44. Loftus EV Jr, Colombel JF, Schreiber S, et al. Safety of long-term treatment with certolizumab pegol in patients with Crohn's disease, based on a pooled analysis of data from clinical trials. *Clin Gastroenterol Hepatol*. 2016;14(12):1753–1762.
45. Yahya F, Gaffney K, Hamilton L, et al. Tumour necrosis factor inhibitor survival and predictors of response in axial spondyloarthritis-findings from a United Kingdom cohort. *Rheumatology (Oxford)*. 2018;57:619–624.
46. Elliott AB, Chakravarty EF. Immunosuppressive medications during pregnancy and lactation in women with autoimmune diseases. *Womens Health (Lond)*. 2010;6(3):431–440.
47. Ostensen M, Brucato A, Carp H, et al. Pregnancy and reproduction in autoimmune rheumatic diseases. *Rheumatology (Oxford)*. 2011;50(4):657–664.
48. Levy RA, de Jesus GR, de Jesus NR, Klumb EM. Critical review of the current recommendations for the treatment of systemic inflammatory rheumatic diseases during pregnancy and lactation. *Autoimmun Rev*. 2016;15(10):955–963.
49. Calligaro A, Hoxha A, Ruffatti A, Punzi L. Are biological drugs safe in pregnancy? *Reumatismo*. 2015;66(4):304–317.
50. Bazzani C, Scrivo R, Andreoli L, et al. Prospectively-followed pregnancies in patients with inflammatory arthritis taking biological drugs: an Italian multicentre study. *Clin Exp Rheumatol*. 2015;33(5):688–693.
51. Götestam Skorpen C, Hoeltzenbein M, Tincani A, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann Rheum Dis*. 2016;75(5):795–810.
52. Weber-Schoendorfer C, Oppermann M, Wacker E, et al. Pregnancy outcome after TNF-α inhibitor therapy during the first trimester: a prospective multicentre cohort study. *Br J Clin Pharmacol*. 2015;80(4):727–739.
53. Bröms G, Granath F, Ekbom A, et al. Low risk of birth defects for infants whose mothers are treated with anti-tumor necrosis factor agents during pregnancy. *Clin Gastroenterol Hepatol*. 2016;14(2):234.e1–e5–241.e1–e5.
54. Porter C, Armstrong-Fisher S, Kopotsha T, et al. Certolizumab pegol does not bind the neonatal Fc receptor (FcRn): consequences for FcRn-mediated in vitro transcytosis and ex vivo human placental transfer. *J Reprod Immunol*. 2016;116:7–12.
55. Mahadevan U, Wolf DC, Dubinsky M, et al. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2013;11(3):286–292; quiz e24.
56. Clowse ME, Wolf DC, Förger F, et al. Pregnancy outcomes in subjects exposed to certolizumab pegol. *J Rheumatol*. 2015;42(12):2270–2278.
57. Ward MM, Deodhar A, Akl EA, et al. American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network 2015 recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. *Arthritis Rheumatol*. 2016;68(2):282–298.
58. van der Heijde D, Ramiro S, Landewe R, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. *Ann Rheum Dis*. 2017;76(6):978–991.