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REVIEW

Certolizumab Pegol Treatment in Patients with Axial-Spondyloarthritis-Associated Acute Anterior Uveitis: a Narrative Review

Irene E. van der Horst-Bruinsma · Philip C. Robinson · Ennio G. Favalli · Frank D. Verbraak · Mindy Kim · Thomas Kumke · Lars Bauer · Bengt Hoepken · Atul Deodhar

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ABSTRACT

Background: Acute anterior uveitis (AAU) affects up to 40% of patients with axial spondyloarthritis (axSpA). An effective treatment for patients with axSpA that reduces the risk of AAU flares while also targeting axial symptoms is therefore highly desirable. Tumor necrosis factor inhibitors (TNFis) have been shown effective for treatment of axSpA and AAU occurrence, with guidelines conditionally recommending treating patients with axSpA and associated AAU with TNFi monoclonal antibodies. To date, most available data on the impact of TNFis on AAU in axSpA are from observational, open-label studies without parallel comparator arms. However, there is a growing body of evidence describing the impact of the TNFi certolizumab pegol (CZP) on the incidence of axSpA-associated AAU.

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I. E. van der Horst-Bruinsma (✉)
Department of Rheumatology, Radboud University Medical Centre, Location 470, Nijmegen, The Netherlands
e-mail: irene.vanderhorst-bruinsma@radboudumc.nl

P. C. Robinson
School of Clinical Medicine, University of Queensland, Brisbane, QLD, Australia

E. G. Favalli
Department of Rheumatology, ASST Gaetano Pini-CTO Institute, Milan, Italy

E. G. Favalli
Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milan, Italy

F. D. Verbraak
Department of Ophthalmology, Amsterdam University Medical Center, Amsterdam, The Netherlands

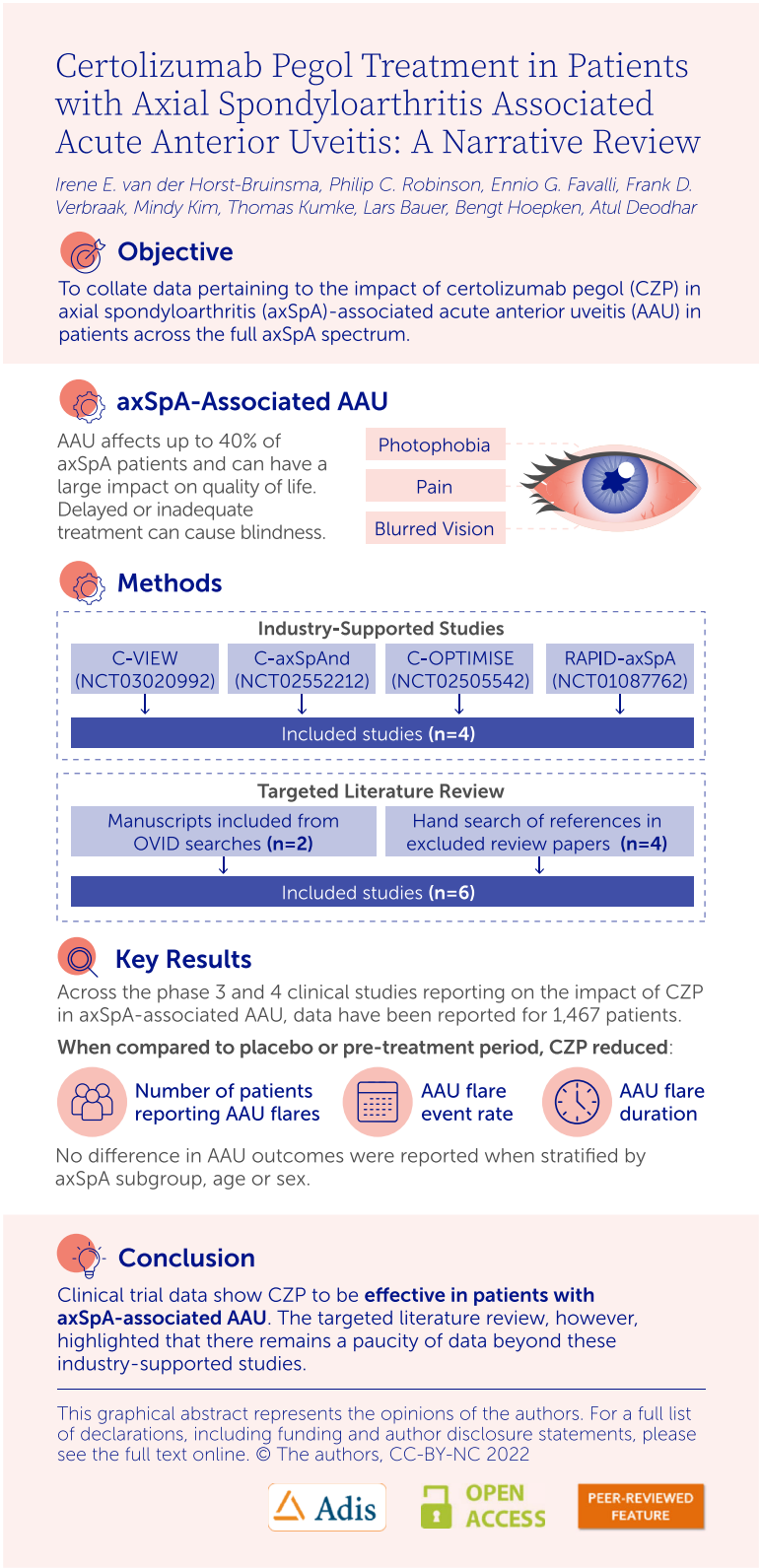
M. Kim
UCB Pharma, Smyrna, GA, USA

T. Kumke · L. Bauer · B. Hoepken
UCB Pharma, Monheim am Rhein, Germany

A. Deodhar
Oregon Health & Science University, Portland, OR, USA

Objective: Our objective was to collate data pertaining to the impact of CZP in axSpA-associated AAU in patients across the full axSpA spectrum.
Methods: Data were obtained from four industry-supported phase 3 and 4 clinical trials (C-VIEW, C-axSpAnd, C-OPTIMISE, and RAPID-axSpA). To supplement these data, a targeted literature review was performed through searches of MEDLINE, Embase, and reference lists.
Results: Available data from 1467 patients from the C-VIEW, C-axSpAnd, C-OPTIMISE, and RAPID-axSpA trials show CZP to be effective in AAU in patients across the full axSpA spectrum, reducing AAU flares when compared with placebo or pretreatment period. No differences in AAU outcomes were reported when stratified by axSpA subgroup age or sex. The targeted literature review identified six further studies of CZP in spondyloarthritis-associated AAU, only one of which was specific to axSpA.
Conclusion: CZP was effective in reducing AAU incidence in clinical trials with patients with axSpA. The targeted literature review, however, highlighted that there remains a paucity of data beyond these trials. Data from comparative studies would further enhance the body of evidence on the effects of CZP in patients with axSpA who develop AAU.

Graphical abstract:



Keywords: Axial spondyloarthritis; Certolizumab pegol; Extramusculoskeletal manifestations; TNF inhibitor; Uveitis

Key Summary Points

Acute anterior uveitis (AAU) affects up to 40% of patients with axial spondyloarthritis (axSpA).

This study collates data pertaining to the impact of the tumor necrosis factor inhibitor certolizumab pegol (CZP) in axSpA-associated AAU in patients across the full axSpA spectrum.

CZP was effective in reducing AAU incidence in studies with axSpA patients, reducing AAU flares when compared with placebo or pretreatment period.

No differences in AAU outcomes were reported when stratified by axSpA subgroup, age, or sex.

Outside of industry-supported clinical trials, however, there remains a paucity of data regarding the effectiveness of CZP in axSpA-associated AAU.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.20490063.

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease characterized by involvement of the axial and peripheral skeleton. The disease comprises two subpopulations: those with radiographic axSpA (r-axSpA; ankylosing spondylitis, AS) and those with nonradiographic axSpA (nr-axSpA), with the difference determined by the presence or absence of radiographic sacroiliitis fulfilling the modified New York criteria [1, 2]. Although primarily a musculoskeletal condition, extramusculoskeletal manifestations (EMMs) such as acute anterior uveitis (AAU), psoriasis, and inflammatory bowel disease are important and common systemic features of axSpA that further contribute to the disease burden [3].

AAU, defined as a noninfectious, acute inflammation of the anterior uveal tract and adjacent structures, is the most common EMM in axSpA and affects up to 40% of patients [4, 5]. The onset of AAU symptoms is sudden and includes ocular pain, photophobia, and blurred vision. AAU flares can be recurrent and unpredictable, with variable remission periods spanning from weeks to years [6]. Treatment for AAU with local corticosteroids and mydriatics is often effective, but delayed or inadequate treatment can cause blindness [7, 8]. An efficacious treatment for patients with axSpA that reduces the risk of AAU flares while also targeting axSpA symptoms is, therefore, highly desirable; the importance of treating AAU associated with axSpA has been emphasized in the 2019 American College of Rheumatology (ACR)–Spondylitis Association of America (SAA)–Spondyloarthritis Research and Treatment Network (SPARTAN) and the 2016 ASAS–European League Against Rheumatism (EULAR) guidelines [9, 10].

Biologic disease-modifying antirheumatic drugs (bDMARDs)—especially tumor necrosis factor inhibitors (TNFis)—have been proven effective for the treatment of axSpA. Indeed, the 2016 ASAS–EULAR guidelines recommend bDMARDs for patients with axSpA who failed to respond to conventional treatments, and highlight the initiation of TNFi therapy over other biologics owing to more extensive experience and clinical data [10].

TNFis, especially monoclonal antibodies, have also been shown effective against AAU recurrence, with several studies demonstrating their effectiveness in r-axSpA-related AAU [11–18]. The ACR–SAA–SPARTAN guidelines conditionally recommend treating patients with axSpA and associated AAU with TNFi monoclonal antibodies [9]. Adalimumab is

currently the sole TNFi to have received US Food and Drug Administration (FDA) approval for the treatment of uveitis in adults. However treatment is indicated only for intermediate uveitis, posterior uveitis, and panuveitis, and does not extend to AAU. Additionally, data pertaining to the impact of TNFis on AAU in axSpA are mostly from observational, open-label studies with historical controls and r-axSpA (rather than nr-axSpA) populations [11, 15–17].

Certolizumab pegol (CZP) is a PEGylated Fc-free TNFi, indicated for the treatment of adult patients with active axSpA by several regulatory authorities, and is the only FDA-approved TNFi for both r-axSpA and nr-axSpA [19, 20]. Previous studies have shown CZP to be safe and efficacious for axial symptoms of axSpA; with these studies comes a growing body of evidence describing the impact of CZP on the incidence of axSpA-associated AAU [21–27].

The purpose of this narrative review is to summarize the evidence within the current literature for the effect of CZP treatment on AAU in both subpopulations of patients with axSpA (r- and nr-axSpA), supported by data from four phase 3 or 4 clinical trials. Data are also supplemented by a targeted literature review of studies in patients with axSpA and AAU who received CZP.

PATIENTS AND METHODS

Study Populations

Data in this review have been obtained from one phase 4 and three phase 3 industry-supported, interventional, clinical studies that assessed CZP in axSpA-associated AAU as primary, secondary, or post-hoc outcomes: C-VIEW (NCT03020992), C-axSpAnd (NCT02552212), C-OPTIMISE (NCT02505542), and RAPID-axSpA (NCT01087762, Table 1). Detailed study design and methods have been described previously—data included in this review include both data taken from the original study publications, and data on file [19, 21–27].

C-VIEW

C-VIEW was a 104-week (96 weeks plus 8-week safety follow-up), open-label, multicenter phase 4 study. Eligible patients had high axSpA disease activity at baseline (defined as a Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] score ≥ 4 and spinal pain [BASDAI item 2] ≥ 4) and were at high risk for recurrent AAU flares (a history of recurrent AAU [two or more AAU flares in total; one or more flares in the year prior to baseline]). The primary efficacy outcome was the AAU flare event rate—assessed by counting distinct episodes of AAU flares—during 96 weeks CZP versus 2 years pre-baseline. Patients were requested to contact their ophthalmologist when they suspected an AAU flare at any time during the study. Patients received CZP 400 mg at weeks 0, 2, and 4, then 200 mg every 2 weeks to week 96 [24, 25].

C-axSpAnd

C-axSpAnd was a 3-year, multicenter phase 3 study including a 52-week double-blind, placebo-controlled period reporting uveitis data as a secondary outcome. Adults ($n = 317$) with nr-axSpA fulfilling the Assessment of SpondyloArthritis international Society (ASAS) classification criteria and with objective signs of inflammation (C-reactive protein [CRP] $\geq$ upper limit of normal [CRP^+] and/or evidence of sacroiliitis on MRI [MRI^+]) were randomized 1:1 to placebo (PBO) or CZP (400 mg at weeks 0, 2, and 4, then 200 mg every 2 weeks [Q2W]) for 52 weeks. AAU outcomes included the number of patients reporting AAU flares as recorded on EMM and adverse event forms [27].

C-OPTIMISE

C-OPTIMISE was a two-part, multicenter phase 3 study in adults with early active axSpA (radiographic or nonradiographic) where AAU data were reported as a secondary outcome. During the 48-week open-label induction period, patients received CZP 200 mg every 2 weeks (Q2W). At week 48, patients in sustained remission (Ankylosing Spondylitis Disease Activity Score [ASDAS] < 1.3 at weeks 32/36 and 48) were randomized to receive double-blind CZP 200 mg Q2W (full maintenance dose), CZP

Table 1 Overview of publications reporting data on the impact of CZP on AAU incidence in patients with axSpA from phase 3 or 4 clinical studies

References	Population	*N*	Study length (weeks)	History of AAU (%)	Duration of AAU assessment (weeks)	AAU assessment	Study type
C-VIEW—van der Horst-Bruinsma 2020 [24]	axSpA	89	96	100	48	Primary outcome	Prospective, open-label study (results of first 48 weeks)
C-VIEW—van der Horst-Bruinsma 2021 [25]	axSpA	89	96	100	96	Primary outcome	Prospective, open-label study (final results)
C-axSpAnd—Deodhar 2019 [27]	nr-axSpA	317	52	15	52	Secondary outcome	Placebo-controlled trial
C-OPTIMISE—Landewé 2020 [23]	axSpA	736	96	15	48	Secondary outcome	Open-label induction period of trial
C-OPTIMISE—Landewé 2020 [22]	axSpA	313	96	17	96	Secondary outcome	Placebo-controlled period of the trial
RAPID-axSpA—Rudwaleit 2016 [21]	axSpA	325	204	21	96	Post-hoc outcome	Placebo-controlled trial with open-label follow-up
RAPID-axSpA—van der Heijde 2017 [26]	axSpA	315	204	20	204	Post-hoc outcome	Placebo-controlled trial with open-label follow-up

AAU acute anterior uveitis, *axSpA* axial spondyloarthritis, *nr-axSpA* nonradiographic axSpA

200 mg every 4 weeks (Q4W; reduced maintenance dose) or placebo (withdrawal) for a further 48 weeks. AAU outcomes included the number of patients reporting AAU flares as recorded on EMM and adverse event forms, and were stratified by history of uveitis at baseline [22, 23].

RAPID-axSpA

RAPID-axSpA was a double-blind and placebo-controlled to week 24, dose-blind to week 48, and open-label to week 204 phase 3 study. In this multicenter study in adults with active axSpA (radiographic or nonradiographic), patients were randomized to CZP or placebo; placebo patients entering the dose-blind phase were rerandomized to CZP. AAU outcomes included number of patients reporting AAU flares and were recorded on EMM or adverse event forms. Events were stratified by history of uveitis at baseline, and rates were reported per 100 patient-years [21, 26].

Targeted Literature Review

To capture any data on CZP in axSpA-associated AAU beyond the C-VIEW, C-axSpAnd, C-OPTIMISE, and RAPID-axSpA studies, a targeted

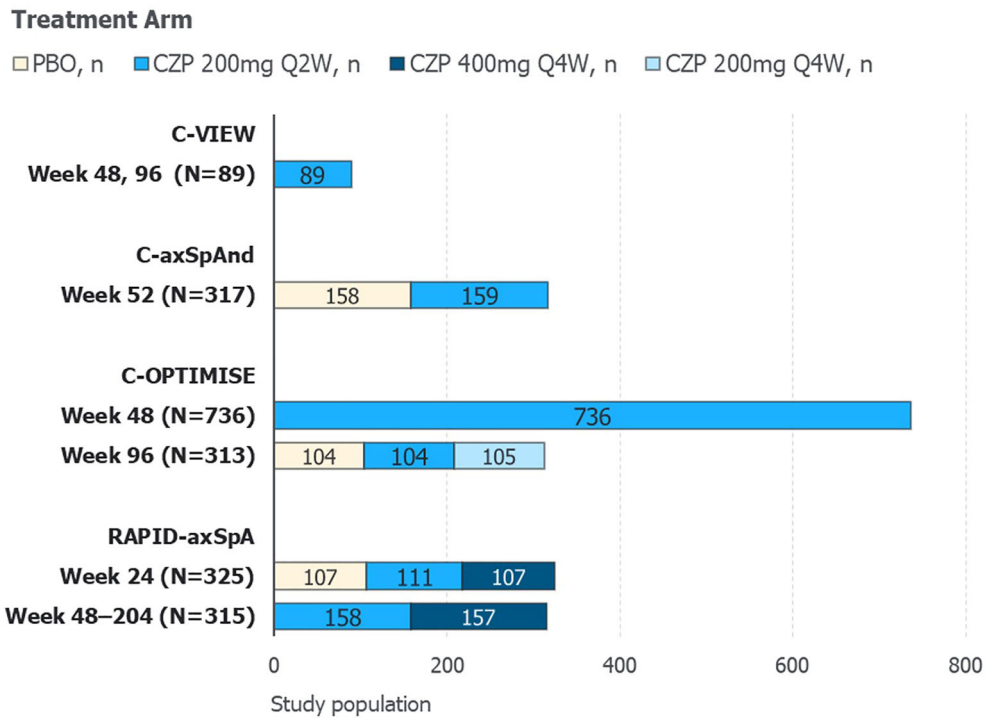


Fig. 1 Study populations and CZP dosage of phase 3 clinical studies assessing the impact of CZP on AAU incidence in patients with axSpA. *CZP* certolizumab pegol, *PBO* placebo, *Q2W* every 2 weeks, *Q4W* every 4 weeks

literature search was performed on 19 July 2021, in the Ovid MEDLINE and Embase databases. Search terms included "axial spondyloarthritis," "spondylarthropathies," ["certolizumab pegol" OR "CZP"], ["uveitis" OR "iritis" OR "AU" or "AAU"]; the full search strategy is outlined in Supplementary Table S1. A supplementary search of the bibliographies of relevant review articles identified through the database searches was also performed.

To be eligible, studies had to be in English and report AAU outcomes in adults with axSpA who had received CZP. Review articles, conference abstracts where data had subsequently been reported in a full manuscript, and abstracts and manuscripts pertaining to the clinical studies detailed above were excluded.

RESULTS

Study Populations

Across the phase 3 and 4 clinical studies reporting on the impact of CZP in axSpA-associated AAU, data have been reported for 1467 patients (Fig. 1). Baseline characteristics for patients included in the phase 3/4 clinical studies are provided in Table 2. These studies confirmed the safety and efficacy profile of CZP in both r-axSpA and nr-axSpA populations; data pertaining to the treatment of axial symptoms in axSpA are reported in the original publications [21–27].

AAU Flare Incidence and Event Rate and Duration

Across all studies, CZP led to a reduction in the number of patients reporting AAU flares compared with placebo or the pretreatment period

Table 2 Study baseline characteristics

	C-VIEW	C-axSpAnd	C-OPTIMISE		RAPID-axSpA	
	Weeks 48, 96 *n* = 89	Week 52 *n* = 317	Week 48 *n* = 736	Week 96 *n* = 313	Week 24 *n* = 325	Weeks 48–204 *n* = 315
Age, years (mean ± SD)	46.5 ± 11.2	37.3 ± 10.6	32.9 ± 7.0	32.0 ± 6.9	39.6 ± 11.9	39.7 ± 12.0
Male sex, *n* (%)	56 (62.9)	154 (48.6)	513 (69.7)	247 (78.9)	200 (61.5)	196 (62.2)
axSpA subpopulation						
r-axSpA, *n* (%)	76 (85.4)	0 (0)	407 (55.3)	–	178 (54.8)	174 (55.2)
nr-axSpA, *n* (%)	13 (14.6)	317 (100)	329 (44.7)	–	147 (45.2)	141 (44.8)
axSpA disease duration, years (mean ± SD)	9.1 ± 8.6	3.8 ± 5.1	2.2 ± 1.7	2.2 ± 1.7	6.7 ± 7.5	6.8 ± 7.5
r-axSpA (mean ± SD)	–	–	2.5 ± 1.8	–	8.2 ± 8.1	8.3 ± 8.1
nr-axSpA (mean ± SD)	–	3.8 ± 5.1	1.8 ± 1.6	–	4.9 ± 6.2	5.0 ± 6.2
HLA-B27 positive, *n* (%)	89 (100)	261 (82.3)	611 (83.0)	280 (89.5)	255 (78.5)	248 (78.7)
Past TNFi medication, *n* (%)	5 (5.6)	18 (5.7)	32 (4.3)	17 (5.4)	52 (16.0)	49 (15.6)
CRP, mg/L (mean ± SD)	–	15.8 ± 17.7	–	–	18.9 ± 23.3	18.8 ± 23.4
Concomitant medication						
Systemic corticosteroids, *n* (%)	15 (16.9)	56 (17.7)	98 (13.3)	49 (15.7)[a]	55 (16.9)	58 (18.5)[b]
csDMARDs, *n* (%)	16 (18.0)	103 (32.5)	166 (22.6)	69 (22.1)[a]	105 (32.3)	98 (31.2)[b]
NSAIDs, *n* (%)	76 (85.4)	276 (87.1)	618 (84.0)	262 (84.0)[a]	285 (87.7)	276 (87.9)[b]
AAU						
History of AAU, *n* (%)						
All patients, *n* (%)	89 (100)	47 (14.8)	110 (14.9)	53 (16.9)	68 (20.9)	63 (20.0)
nr-axSpA, *n* (%)	13 (100)	47 (14.8)	48 (14.6)	–	31 (21.1)	–
r-axSpA, *n* (%)	76 (100)	–	62 (15.2)	–	37 (20.8)	–
Current AAU at baseline, *n* (%)	5 (5.6)	17 (5.4)	15 (2.0)	5 (1.6)	16 (4.9)	15 (4.8)
Time since onset of first AAU flare, years (mean ± SD)	10.1 ± 9.2	–	–	–	–	–

AAU acute anterior uveitis, *axSpA* axial spondyloarthritis, *CRP* C-reactive protein, *csDMARDs* conventional synthetic disease-modifying antirheumatic drugs, *nr-axSpA* nonradiographic axSpA, *NSAIDs* nonsteroidal anti-inflammatory drugs, *r-axSpA* radiographic axSpA, *SD* standard deviation, *TNFi* tumor necrosis factor inhibitors

[a]Safety set, *n* = 312

[b]Full analysis set, *n* = 314

(Table 3, Supplementary Fig. 1), with larger reductions in AAU flares observed in groups receiving a continuous maintenance dose of CZP (200 mg Q2W), compared with those who had a dose reduction (200 mg Q4W). During the C-OPTIMISE double-blind period, 6/104 (5.8%) patients experienced an AAU flare in the placebo group. This compares to the 3/105 (2.9%) of patients who experienced an AAU flare in the group receiving 200 mg CZP Q4W; in the group receiving the full maintenance dose, no flares were reported (data on file). In C-axSpAnd, where all patients had nr-axSpA, 4/159 (2.5%) patients receiving CZP 200 mg Q2W reported an AAU flare by week 52 compared with 8/158 (5.1%) of those in the placebo group [27].

Data pertaining to AAU flare event rate have also been reported [24, 25]. In C-VIEW, the adjusted event rate was 1.87 in the pretreatment period compared with 0.34 in the 96-week treatment period (Fig. 2). This represents an 82% reduction (rate ratio 0.18, 95% confidence interval [95% CI] 0.12–0.28) and is noteworthy since patients were selected on the basis of criteria that predicted the highest recurrence risk of AAU (both prior history of AAU and human leukocyte antigen B27 [HLA-B27] positivity) [25].

AAU flare event rate data—assessed by counting distinct episodes of AAU flares—for CZP versus placebo were reported in RAPID-axSpA, where the rate of uveitis flares to week 24 was lower in patients treated with CZP (3.0 per 100 patient-years; 95% CI 0.6–8.8; 200 mg Q2W or 400 mg Q4W) compared with placebo (10.3 per 100 patient-years; 95% CI 2.8–26.3). Furthermore, data pertaining to the long-term incidence of uveitis—collected to week 96 of the RAPID-axSpA trial—suggested that the overall rate of AAU flares remained similar at weeks 48 and 96 of CZP treatment compared with that observed over 24 weeks of CZP treatment (4.9 per 100 patient-years at week 48 [95% CI 2.5–8.6] and 4.9 per 100 patient-years at week 96 [95% CI 3.2–7.4]) [21].

The final measure of the impact of CZP on AAU in patients with axSpA reported in the literature is flare duration, defined as total days of active AAU per patient. In C-VIEW, 18/89 patients (20%) experienced AAU flares during the 96-week treatment period: for these patients, the mean (SD) duration of total days active inflammation per patient was 97.3 (66.7) days in the 2-year prebaseline period, compared with 74.4 (55.3) days during 96 weeks of CZP treatment (mean reduction of 22.9 days) [25].

AAU Outcomes Stratified by History of AAU at Baseline

AAU flares are often recurrent in patients with axSpA, yet effective treatments for relapsing AAU are limited [28]. All patients enrolled in the C-VIEW trial had at least one AAU flare in the 104-week prestudy period, with 53/89 patients (59.6%) experiencing two or more AAU flares. Over the 96-week CZP treatment period, the proportion of patients experiencing two or more flares was reduced to 11.2% (10/89); 9.0% of patients (8/89) experienced a single flare, whilst 79.8% of patients (71/89) had no AAU flares while receiving CZP [25]. Similar AAU outcomes were reported in C-OPTIMISE and RAPID-axSpA (Table 4). Of those with a history of AAU at baseline, patients who received CZP reported no AAU flares compared with 4/17 (23.5%) of those who received placebo at week 96 in C-OPTIMISE (data on file); comparably, at week 24 in RAPID-axspA, 3/38 (7.9%) patients with a history of AAU who received CZP reported flares, compared with 4/31 (12.9%) of those in the placebo group [21, 22].

Comparator data are limited for patients without a history of AAU at baseline, although no patients in this group reported AAU flares in RAPID-axSpA (with either CZP or placebo treatment) [21].

AAU Outcomes by Disease Classification

AAU is known to have a greater prevalence in patients with r-axSpA compared with nr-axSpA: as many as 40% of patients with r-axSpA will experience at least one AAU flare during the course of their disease. A lower prevalence has been reported for patients with nr-axSpA, but data are more limited [29–32]. Across the C-VIEW, C-axSpAnd, C-OPTIMISE, and RAPID-axSpA studies, AAU data are reported for 806

Table 3 Number of patients reporting AAU flares

Number of patients reporting AAU flares *n* (%), [#, PEY, EAIR[a]]	24 month pretreatment period	PBO	CZP 200 mg Q2W	CZP 400 mg Q4W	CZP 200 mg Q4W
C-VIEW					
Week 48	89 (100)	–	13 (14.6)	–	–
	[–, –, 132.7]		[15, –, 18.6]		
Week 96	89 (100)	–	18 (20.2)	–	–
	[–, –, 97.5]		[28, –, 17.7]		
C-axSpAnd					
Week 52	–	8 (5.1)	4 (2.5)	–	–
C-OPTIMISE					
Part A—week 48	–	–	10 (1.4)	–	–
			[13, –, –]		
Part B—week 96	–	6 (5.8)	0 (0)	–	3 (2.9)
		[6, 53, 11.7]	[0, 101, 0]		[3, 96, 3.2]
RAPID-axSpA					
Week 24	–	4 (3.7)	3 (2.7)	0 (0)	–
		[4, 38.9, 10.4]	[3, 51.2, 6.0]	[0, 48.7, 0]	
Week 48	–	–	9 (5.7)	2 (1.3)	–
			[10, 123.6, 7.5]	[2, 120.5, 1.7]	
Week 96	–	–	13 (8.2)	10 (6.4)	–
			[14, 245.5, 5.5]	[10, 240.2, 4.3]	
Week 204	–	–	18 (11.4)	12 (7.6)	–
			[25, 496.0, 3.9]	[21, 484.7, 2.6]	

AAU acute anterior uveitis, *CZP* certolizumab pegol, *EAIR* exposure-adjusted incidence rates, *PEY* patient exposure years, *PBO* placebo, *Q2W* every 2 weeks, *Q4W* every 4 weeks

[a]EAIR calculated as incidence of new cases per 100 exposure years.

patients with nr-axSpA. Data from C-axSpAnd—where all 317 enrolled patients had nr-axSpA—show CZP to be effective at reducing the number of patients reporting AAU flares when compared with placebo [CZP 200 mg Q2W: $n = 4$ (2.5%); placebo: $n = 8$ (5.1%); Table 3] [27].

Furthermore, no significant differences in AAU flare event rate data between nr-axSpA ($n = 13$) and r-axSpA ($n = 76$) subpopulations were reported in C-VIEW (Fig. 2)—after 96 weeks of receiving CZP, both groups achieved an 82% reduction in AAU flare event rate [25]. C-OPTIMISE and RAPID-axSpA also

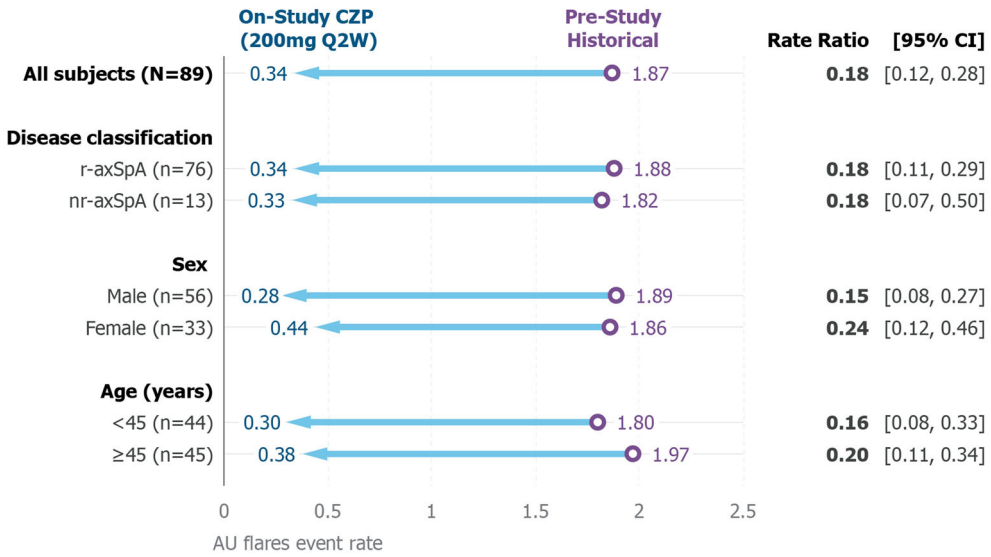


Fig. 2 AAU flares event rate per 96 weeks stratified by disease diagnosis, sex, and age. All data from C-VIEW [25]. "Pre-Study Historical": week—104 to baseline; "On-study CZP": baseline to week 96. *CI* confidence interval, *CZP* certolizumab pegol, *nr-axSpA* nonradiographic axSpA, *r-axSpA* radiographic axSpA

included patients with both nr-axSpA (C-OPTIMISE: $n = 329$; RAPID-axSpA: $n = 147$) and r-axSpA (C-OPTIMISE: $n = 407$; RAPID-axSpA: $n = 178$); AAU outcome data specific to patients with nr-axSpA from these trials are not available, however, as data were pooled with those from the r-axSpA subpopulations [21–23, 26].

AAU Outcomes Stratified by Sex and Age

The efficacy of TNFis has been observed to be lower in females with axSpA compared with males for subjective outcome measures [33], but little has been reported on sex differences in the treatment of AAU. In C-VIEW, the male and female subgroups achieved reductions in AAU flare event rate of 85% and 76%, respectively: the AAU flare event rate was reduced from 1.89 to 0.28 per 96 weeks (rate ratio 0.15; 95% CI 0.08–0.27) in male patients ($n = 56$), compared with a reduction of 1.86–0.44 (rate ratio 0.24; 95% CI 0.12–0.46) in female patients ($n = 33$; Fig. 2) [25]. No significant differences have been reported for the impact of age on the effectiveness of CZP in AAU associated axSpA, although data are limited to a small subgroup analysis performed in C-VIEW where AAU flare event rates were reported for patients older or younger than 45 years (Fig. 2).

Targeted Literature Review

We performed a targeted literature search of the Ovid MEDLINE and Embase databases to identify data on the effects of CZP in axSpA-associated AAU beyond the RAPID-axSpA, C-OPTIMISE, C-axSpAnd, and C-VIEW studies. After deduplication, the electronic database search identified 80 records; 25 were included for full-text review, of which 2 publications fulfilled the eligibility criteria and were included. The supplementary search of excluded review article bibliographies identified four further publications, giving a total of six (Supplementary Fig. 2) [34–39]. However, of these six included studies, only one was specific to CZP in axSpA-associated AAU—an observational, multicenter, retrospective study in 13 patients with SpA (8 axSpA) with refractory uveitis, who had received CZP for at least 6 months [34]. The results of this study suggest that CZP provides a benefit to patients with uveitis associated with SpA refractory to previous TNFi treatment: improvements (although

Table 4 Number of patients reporting AU flares by uveitis history

Number of patients reporting AAU flares, *n* (%) [#, PEY, EAIR[a]]	CZP		Comparator[b]	
	History of and/or current uveitis	No history	History of and/or current uveitis	No history
C-VIEW				
Week 48	13 (14.6)	–	89 (100)	–
	[15, –, 18.6]		[–, –, 132.7]	
Week 96	18 (20.2)	–	89 (100)	–
	[28, –, 17.7]		[–, –, 97.5]	
C-OPTIMISE				
Week 48	8 (7.2)	2 (0.3)	–	–
Week 96	0 (0)	200 mg Q4W: 3 (3.5); 200 mg Q2W: 0 (0)	4 (23.5)	2 (2.3)
			[–, –, 45.09]	
RAPID-axSpA				
Week 24	3 (7.9)	0 (0)	4 (12.9)	0 (0)
	[3, 17.5, 18.0]	[0, 82.5, –]	[4, 10.4, 39.6]	[0, 28.5, –]
Week 48	9 (14.3)	2 (0.8)	–	–
	[10, 48.0, 20.2]	[2, 196.1, 1.0]		
Week 96	15 (23.8)	8 (3.2)	–	–
	[16, 97.3, 17.8]	[8, 388.4, 2.1]		
Week 204	–	–	–	–

AAU acute anterior uveitis, *CZP* certolizumab pegol, *EAIR* exposure-adjusted incidence rates, *PEY* patient exposure years
[a]EAIR calculated as incidence of new cases per 100 exposure years
[b]Comparator C-VIEW: 96-week prestudy period; C-OPTIMISE and RAPID-axSpA: placebo

not quantified) were observed in both SpA activity and visual acuity. The remaining five studies included a very low number of patients from several subpopulations across the SpA disease spectrum, including psoriatic spondylitis and inflammatory bowel disease-associated spondyloarthritis. As the study populations comprised patients who are not the topic of this review, it is difficult to draw any conclusions on the efficacy of CZP in uveitis specifically associated with axial SpA from these studies.

DISCUSSION

AAU is the most frequent extramusculoskeletal manifestation of axSpA and can represent a significant clinical burden; the management of AAU therefore represents an important aspect of axSpA disease treatment. Some observational data suggest that conventional synthetic DMARDs (csDMARDs) such as sulfasalazine could have potential in the management of highly recurrent AAU [4, 6]. Data demonstrating the impact of CZP treatment on the incidence of AAU are available for 1467 patients across the C-VIEW, C-axSpAnd, C-OPTIMISE, and RAPID-axSpA clinical trials and show CZP

to be effective in patients with axSpA-associated AAU across the full axSpA spectrum, including both r- and nr-axSpA. In these trials, concomitant use of csDMARDs was comparable across CZP and placebo groups; greater improvements in AAU symptoms in groups receiving CZP compared with placebo cannot be ascribed to differing rates of csDMARD administration [21–27].

Our targeted literature review highlighted that, outside of the industry-supported phase 3 and 4 clinical studies—and similar to other biologics for the treatment of axSpA—there remains a paucity of data that are specific to CZP in axSpA and related AAU. Those few studies that are available have a limited number of patients and are predominantly case reports. In our analysis, the earliest report of CZP use in a patient with AAU associated with r-axSpA was from a single retrospective case series of seven patients with uveitis, one of whom had anterior uveitis and r-axSpA [35]. After CZP commencement, rapid ocular quiescence and improvement in axial symptoms were achieved in the patient with r-axSpA and maintained until 6 months of follow-up. However, the patient also had relapsing polychondritis, and so was excluded from our analysis.

This review demonstrates that subsequent data beyond the industry-supported clinical trials are still limited and highlights data from C-VIEW, C-axSpAnd, C-OPTIMISE, and RAPID-axSpA trials as the most robust and consistent pertaining to the efficacy of CZP on axSpA-associated AAU. C-VIEW was the first study to assess AAU flares as a primary outcome in a population of patients with axSpA who were at a high risk of AAU (both HLA-B27 positive and with a history of AUU). One limitation of C-VIEW was the open-label study design without a parallel control group. A placebo control, however, was considered unethical owing to enrolling patients at a high risk of developing recurrent AAU and with high axSpA disease activity at baseline. While the within-patient historical control in C-VIEW offered a good solution, the availability of data from comparative studies would further enhance the body of evidence on the effects of CZP in patients with axSpA and associated AAU.

AAU is known to have a greater prevalence in patients with r-axSpA than in those with nr-axSpA: one 2016 study performed a pooled meta-analysis comprising 2236 patients and reported a difference in the pooled prevalence of history of uveitis between patients with r-axSpA (23%) and those with nr-axSpA (16%) [31]. The increased incidence of AAU with axSpA disease duration is likely to contribute to this difference; the prevalence of AAU in axSpA has been shown to reach over 50% in patients with r-axSpA with a disease duration $\geq$ 30 years [40]. An alternative explanation for these differences in prevalence is HLA-B27 positivity being lower in nr-axSpA populations: a key genetic marker for axSpA, HLA-B27 has been associated with a substantially increased risk (2.6- to 4.2-fold) of developing AAU [41]. Patients with HLA-B27-positive axSpA also often have more frequent and severe episodes of AAU than those who are HLA-B27 negative [3].

To date, there has been a paucity of data specific to the effect of biologics in nr-axSpA and AAU, with most studies specific to r-axSpA populations. Studies report that about 10–40% of patients with nr-axSpA progress to r-axSpA over a period of 2–10 years, though there remains some debate on whether nr-axSpA should be seen as an early form of r-axSpA, or as two distinct conditions [42–44]. This review collates AAU outcome data for 806 patients with nr-axSpA, with the C-axSpAnd study being the first to incorporate a 52-week placebo-controlled time period to investigate the efficacy of an anti-TNF agent in a population of nr-axSpA patients and report the impact of CZP on axSpA disease activity and AAU flare rates.

Other reported subgroup analyses (age greater or less than 45 years; sex) found no significant differences between groups, although the sample sizes were too small to be sufficiently powered to draw conclusions by subgroup [25]. To our knowledge, these are the only data in the literature pertaining to CZP efficacy in axSpA-associated AAU stratified by age or sex.

CONCLUSION

The management of AAU manifestation is an important aspect of axSpA disease treatment. Data showing CZP to be effective in AAU in patients through the full axSpA spectrum, including both r-axSpA and nr-axSpA, are available for 1467 patients across the C-VIEW, C-axSpAnd, C-OPTIMISE, and RAPID-axSpA clinical trials. Outside of these studies, however, there remains a paucity of data that are specific to CZP in axSpA and related AAU.

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