Certolizumab pegol treatment in axial spondyloarthritis mitigates fat lesion development: 4-year post-hoc MRI results from a phase 3 study

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Abstract

Objectives. Fat lesions (FLs) on MRI T1 sequences are considered to be early indicators of structural spinal progression in axial spondyloarthritis (axSpA) patients. In this post-hoc analysis from RAPID-axSpA, we assess whether tumour necrosis factor inhibitor (TNFi) treatment over 4 years impacts FLs in spinal vertebral edges (VEs) of patients with axSpA.

Methods. In RAPID-axSpA (NCT01087762), a 4-year, phase 3 randomized trial, participants were randomized to certolizumab pegol (CZP; 400 mg loading dose at Weeks 0/2/4 then 200/400 mg every 2/4 weeks) or placebo (PBO) at baseline; PBO-randomized participants switched to CZP at Week 16/24 (denoted PBO-randomized/CZP). Spinal MRI scans were taken at Weeks 0, 12, 48, 96 and 204. Changes in proportions of VEs with FLs are reported as odds ratios (ORs) between time points.

Results. Overall, 136 participants (CZP: 89, PBO-randomized/CZP: 47) had a baseline and post-baseline MRI. The OR (95% confidence interval) vs baseline of FLs was higher in PBO-randomized/CZP vs CZP-randomized participants at Weeks 48 [3.35 (2.16–5.19) vs 1.45 (1.07–1.97)], 96 [2.62 (1.77–3.88) vs 1.84 (1.36–2.48)] and 204 [2.55 (1.59–4.06) vs 1.71 (1.23–2.37)]. Across 204 weeks, FLs increased more in VEs with baseline inflammation [Week 204 OR: 4.84 (2.56–9.18)] than those without [OR: 1.15 (0.78–1.71)]. VEs in which inflammation was resolved by Week 12 had lower FL prevalence at Weeks 48, 96 and 204 compared with VEs with unresolved inflammation.

Conclusions. Early and sustained suppression of inflammation mitigates the risk of long-term FL development in the spine in study participants with axSpA evaluated over 4 years.

Trial registration. ClinicalTrials.gov, https://clinicaltrials.gov, NCT01087762.

Key words: axial spondyloarthritis, TNF inhibitor, MRI, inflammation, fat lesions

Introduction

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease characterised by inflammation in the sacroiliac (SI) joints and spine [1]. Patients with axSpA have varying degrees of spinal structural damage, often in the form of new bone formation (syndesmophytes), leading to ankylosis and spinal fusion, which impact mobility [2, 3]. Therefore, preventing and reducing new bone formation is an important treatment target for patients across the axSpA spectrum, including radiographic axSpA (r-axSpA/AS) and non-radiographic axSpA (nr-axSpA).
Mechanisms governing the progression of structural damage are thought to involve persistent inflammatory activity in vertebral edges (VEs), accompanied by the development of fat lesions (FLs), ultimately resulting in changes to the bone microenvironment and the promotion of increased osteoblastic activity [4–6]. Eventually, this results in syndesmophyte formation and ankylosis [5, 7]. Such processes are thought to occur over several years; consequently, it has been suggested that there is a window of opportunity for treatment in early axSpA before FLs develop [8]. Early treatment targeting inflammation, before it becomes chronic, has therefore been suggested as the optimal course of action [9].

Previous studies in r-axSpA have suggested that tumour necrosis factor inhibitor (TNFi)-induced resolution of inflammatory lesions (INFls) is associated with increases in FLs, raising concerns that TNFi treatment might promote the process of new bone formation [10, 11]. Although original studies investigating the 2-year effect of TNFi vs conventional treatment on new spinal bone formation concluded no benefits of TNFi [12–14], others have provided evidence that TNFi therapy in r-axSpA can slow down this process when patients are treated over a long-term period (2–8 years) [15, 16]. This has also been shown when treatment is initiated early in disease [17]. However, data relating to FLs from interventional, well-controlled studies in the full axSpA spectrum are absent. Erosions and sclerosis have also been shown to precede development of syndesmophytes in patients with r-axSpA, although they occur infrequently [18].

The phase 3 RAPID-axSpA study assessed the safety and efficacy of the TNFi certolizumab pegol (CZP) in patients with r- and nr-axSpA compared with placebo (PBO) [19]. Four-year MRI outcomes from this study have previously shown that CZP rapidly suppresses active inflammation in the spine and SI joints, with effects sustained over time [20]. In addition, it was previously reported that limited spinal radiographic progression was observed in study participants during the first 2 years of treatment, with a reduced rate of progression from years 2–4 [20].

In this analysis from RAPID-axSpA, we explore MRI spinal lesion data in participants who had MRI scans taken during the 4-year study period. The analysis aims, first, to evaluate whether CZP treatment, by reducing spinal inflammation, mitigates the development of chronic lesions, including FLs, erosions and sclerosis. Second, we investigate whether the risk of developing FLs is affected by baseline presence and Week 12 resolution of inflammation. Finally, we explore changes in lesion prevalence by axSpA subpopulation and disease duration.

**Methods**

**RAPID-axSpA study design**

RAPID-axSpA (NCT01087762) was a 4-year, phase 3, randomized, multicentre trial that investigated the efficacy and safety of CZP treatment in participants with r- and nr-axSpA. The trial was double-blind and PBO-controlled to Week 24, dose-blind to Week 48 and open-label to Week 204. At baseline, participants were randomized to CZP (400 mg loading dose at Weeks 0, 2 and 4, then 200 mg every 2 weeks [Q2W] or 400 mg every 4 weeks [Q4W]) or PBO. Participants initially randomized to CZP continued their assigned dose to Week 204, while those initially randomized to PBO were re-randomized 1:1 to CZP 200 mg Q2W or 400 mg Q4W at Week 16/24 (denoted PBO-randomized/CZP throughout). Further details on RAPID-axSpA study design and eligibility criteria have been previously reported [19, 20].

Local X-ray assessment of the SI joints prior to screening performed locally by rheumatologists or radiologists was used for the determination of radiographic sacroiliitis to define the r-axSpA and nr-axSpA subpopulations [19].

**Ethical approval information**

The study was approved by institutional review boards and independent ethics committees at participating sites and was conducted in accordance with local regulations and the International Conference on Harmonization Good Clinical Practice requirements, based on the Declaration of Helsinki. All patients provided written informed consent to participate.

**MRI assessments**

This substudy of RAPID-axSpA involved participants recruited from sites with MRI facilities who could undergo spinal MRI scans at baseline and Weeks 12, 48, 96 and 204. The imaging protocol of the study has been described previously [21]. For this post-hoc analysis, spinal MRI scans of all 23 vertebral units (C2/3 to L5/S1) from each participant were assessed independently by two central readers who were blinded to all clinical information, treatment and image time point. Two experienced readers with >8 years of experience in the evaluation of spinal MRIs assessed the presence or absence of active INFls (by sagittal short-tau inversion recovery [STIR] sequence technique) and FLs, sclerosis and erosions (by sagittal T1-weighted sequence technique) in VEs for all time points [21]. Definitions of the spinal lesions were applied as described in the Assessment of SpondyloArthritis international Society (ASAS) handbook [22]. Abnormalities not related to axSpA according to the readers were not registered [22]. Each vertebral unit was divided into four quadrants (upper anterior, upper posterior, lower posterior, lower anterior). Prior to the image evaluation, both readers underwent consensus training for alignment on the identification of lesions by using a set of 30 reference images including axSpA patients [22]. Lesions were only considered present if observed by both readers. Inter-reader agreement was assessed using Cohen’s Kappa statistic, measured by the kappa coefficient (ranging
from −1 to +1, where ≤0 represents no agreement and 1 represents perfect agreement between the two raters).

**Statistical analysis**

Participants were included in the post-hoc statistical analyses if they had a valid MRI assessment at baseline and ≥1 post-baseline MRI assessment.

Model-based inferential analyses of INFLs and FLs were performed with VE-level data using a logistic generalised linear mixed model. For each analysis, patient-level random effects were used. Within-VE correlation over time points was modelled with a random intercept specific to each VE (within patient), and a Toeplitz correlation structure was applied to account for the observed correlations of data between nearby VEs.

Given the negligible between-VE correlation of post-baseline FL data when adjusted for baseline status, the analysis of FL prevalence according to Week 12 INFL status was performed using a generalised estimating equation model. VEs were assumed to be independent, and within-VE correlation was assumed to remain constant over time (compound symmetry) [23]. A generalised estimating equation model was also used to estimate the odds ratio (OR) of FLs at baseline between VEs with vs without active inflammation to account for the fact that VE-level data from the same participant are correlated.

ORs and 95% confidence intervals (CIs) between time points are provided as ratio of odds (probability of lesion observed/probability of lesion not observed) between time points/baseline. ORs between randomized treatments are provided as the ratio of odds between randomized CZP/PBO. Per-patient mean number of VEs with a lesion were estimated by averaging out observations for sclerotic lesions and 0.749 to 1.000 for erosions; Supplementary Table S1, available at *Rheumatology* online). Inter-reader agreement of assessments was strong (kappa coefficients ranged from 0.966 to 0.976 for INFLs, 0.982 to 0.992 for FLs, 0.817 to 0.923 for sclerotic lesions and 0.749 to 1.000 for erosions; Supplementary Table S1, available at *Rheumatology* online).

**Changes in lesion prevalence by randomized treatment over 4 years**

*Inflammatory lesions*

For CZP-randomized participants, a considerable reduction in INFLs was observed at Week 12 (mean count of 5.0 lesions per participant to 2.7) and maintained to Week 204 (Fig. 1a). For PBO-randomized/CZP participants, INFLs remained relatively unchanged between baseline and Week 12 (5.2 to 4.8) but a substantial reduction was observed at Week 48 and maintained to Week 204, following CZP treatment initiation at Week 16/24 (Fig. 1a).

After adjustment for baseline inflammation, CZP-randomized participants showed reduced inflammation at Week 12 [OR 0.33 (95% CI: 0.21, 0.54)] and Week 48 [OR 0.55 (0.33, 0.93)] compared with PBO-randomized/ CZP participants (an OR of <1 indicates reduced risk and vice versa). At Weeks 96 and 204 (by which point PBO-randomized/CZP participants had received CZP treatment for ≥72 and ≥180 Weeks, respectively), the risk of having INFLs was similar for both treatment groups [OR 1.07 (0.64, 1.79) and 0.95 (0.54, 1.66), respectively].

*Fat lesions*

Over the 204 weeks there were slight increases in FLs in both the CZP-randomized and PBO-randomized/CZP
participants compared with baseline. In CZP-randomized participants, mean FL counts increased from 6.8 at baseline to 7.3 by Week 12 but remained generally unchanged through Week 204. In PBO-randomized/CZP participants, the mean FL count increased from 6.4 at baseline to 6.9 at Week 12 then 8.0 at Week 48, with no further increase at the later time points (Fig. 1b).

A formal comparison between CZP-randomized and PBO-randomized/CZP VEs is presented in the section Comparison of fat lesions between treatment groups.

Erosions and sclerosis
Across all participants, erosions and sclerosis were observed in only 5 and 10 VEs at baseline, respectively, with only minimal changes observed over 204 weeks (Fig. 1c).

The impact of baseline inflammation on fat lesion development
To better understand the link between inflammation and FL development, prevalence of FL over 4 years was assessed in VEs with and without active inflammation at baseline.

At baseline, in 2047 VEs from CZP-randomized participants, FLs were present in 49.8% (216/434) of those with active inflammation and in 24.5% (395/1613) of those without (Fig. 2a); the OR of FLs in VEs with vs without INFL was 3.06 (95% CI: 2.14, 4.35), indicating that the presence of inflammation in VEs increases the risk of FLs in the same location.

VEs with active inflammation at baseline also had a greater increase in FLs over the 204-week treatment period compared with those without baseline inflammation. In VEs with baseline inflammation, the OR (95% CI) of FLs at Week 204 vs baseline was 4.84 (2.56, 9.18), while in VEs with no baseline inflammation it was 1.15 (0.78, 1.71) (Fig. 2b).

The impact of inflammation resolution on fat lesion development
Having shown a substantial reduction in inflammation following CZP treatment and that FLs are more likely to be present in VEs with active baseline inflammation, we next assessed whether early resolution of inflammation at Week 12 impacted further FL development. Week 12 was evaluated because all participants were still on double-blind randomized treatment, and by Week 12 there had been a substantial reduction in inflammation in the CZP-randomized group (Fig. 1a). By Week 12, the percentage of VEs with INFs in the CZP-randomized participants had decreased from 21.2% (baseline) to 12.3%. Comparing FL prevalence between VEs with vs without Week 12 resolution of inflammation, there was little difference in FLs at Week 12 [OR 0.93 (0.61, 1.42)], but at subsequent time points the risk of FLs was higher in VEs without Week 12 resolution of inflammation, increasing to Week 204 (Fig. 3; counts reported in Supplementary Table S2, available at Rheumatology online). A similar trend was observed when this analysis was repeated for Week 48, with increased prevalence of

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**Table 1** Baseline and disease characteristics for study participants with eligible MRI outcomes and all subjects in the RAPID-axSpA study

| Study participants | PBO-randomized/CZP (N = 136) | CZP-randomized (N = 47) | All subjects (N = 325) |
|--------------------|-------------------------------|------------------------|-----------------------|
| Age, mean (s.d.), years | 39.1 (12.3) | 38.7 (14.1) | 39.2 (11.3) | 39.6 (11.9) |
| Male, n (%) | 83 (61.0) | 32 (68.1) | 51 (57.3) | 200 (61.5) |
| r-axSpA, n (%) | 76 (55.9) | 27 (57.4) | 49 (55.1) | 178 (54.8) |
| nr-axSpA, n (%) | 60 (44.1) | 20 (42.6) | 40 (44.9) | 147 (45.2) |
| HLA-B27 positive, n (%) | 105 (77.2) | 39 (83.0) | 66 (74.2) | 255 (78.5) |
| Racial group: Caucasian, n (%) | 130 (95.6) | 45 (95.7) | 85 (95.9) | 293 (90.2) |
| BMI (kg/m²), mean (s.d.) | 26.9 (5.5) | 26.5 (5.4) | 27.1 (5.6) | 27.6 (5.8) |
| Time since axSpA diagnosis (years), mean (s.d.) | 6.9 (7.4) | 8.0 (8.5) | 6.3 (6.8) | 6.7 (7.5) |
| Symptom duration (years), median (range) | 8.1 (0.3–50.9) | 9.0 (0.5–50.9) | 8.0 (0.3–36.8) | 10.4 (0.3–50.9) |
| CRP mg/l, median (range) | 14.0 (0.1–159.9) | 15.0 (1.4–155.6) | 12.0 (0.1–159.9) | 13.9 (0.1–174.8) |
| Patients with CRP > 15 mg/l, n (%) | 55 (40.4) | 23 (48.9) | 32 (36.0) | 133 (40.9) |
| ASDAS, mean (s.d.) | 3.9 (0.9) | 4.1 (1.0) | 3.8 (0.8) | 3.8 (0.9) |
| BASDAI, mean (s.d.) | 6.7 (1.5) | 6.7 (1.6) | 6.6 (1.5) | 6.4 (1.6) |
| BASFI, mean (s.d.) | 5.5 (2.2) | 5.7 (2.0) | 5.4 (2.3) | 5.4 (2.3) |
| BASMI, mean (s.d.) | 3.7 (1.6) | 3.9 (1.7) | 3.6 (1.5) | 3.8 (1.7) |
| Inflammatory lesions per patient, mean (s.d.) | 5.0 (5.0) | 5.1 (5.1) | 4.9 (4.9) | — |
| Fat lesions per patient, mean (s.d.) | 6.7 (6.6) | 6.5 (6.3) | 6.9 (6.8) | — |
| Erosive lesions per patient, mean (s.d.) | 0.0 (0.2) | 0.0 (0.2) | 0.0 (0.2) | — |
| Sclerotic lesions per patient, mean (s.d.) | 0.1 (0.3) | 0.1 (0.3) | 0.1 (0.4) | — |

* n = 134. ^b n = 87. ^n = 319. ^n = 324. ^n = 323. axSpA: axial SpA; ASDAS: Ankylosing Spondylitis Disease Activity Score; CZP: certolizumab pegol; nr-axSpA: non-radiographic axSpA; PBO: placebo; r-axSpA: radiographic axSpA.
**Fig. 1** Changes in lesion prevalence over time by randomized treatment group

**a) Inflammatory lesions** (CZP-randomized and PBO-randomized/CZP participants)

- Odds ratios for INFLs/FLs vs baseline were estimated using a logistic generalised linear mixed model (Laplace estimation) with treatment group by time point as a fixed effect and patient and vertebral edge (within patient) as random effects; an odds ratio >1 represents an increase compared with baseline.

**b) Fat lesions** (CZP-randomized and PBO-randomized/CZP participants)

- Odds ratios for fat lesions were estimated using a mixed model with the actual value as the dependent variable and week as a fixed factor.

**c) Erosive and sclerotic lesions** (CZP-randomized participants only)

- LS means have been estimated using a mixed model with the actual value as the dependent variable and week as a fixed factor.

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Odds ratios for INFLs/FLs vs baseline were estimated using a logistic generalised linear mixed model (Laplace estimation) with treatment group by time point as a fixed effect and patient and vertebral edge (within patient) as random effects; an odds ratio >1 represents an increase compared with baseline. Given the small numbers of sclerotic and erosive lesions, LS means have been estimated using a mixed model with the actual value as the dependent variable and week as a fixed factor. CZP: certolizumab pegol; INFL: inflammatory lesion; FL: fat lesion; LS: least squares; PBO: placebo.
FLs at later time points in VEs in which inflammation persisted at Week 48; however, findings did not reach nominal statistical significance (Supplementary Fig. S2, available at Rheumatology online).

Comparison of fat lesions between treatment groups
To assess the impact of CZP treatment, we compared the proportion of VEs with FLs between CZP-randomized and PBO-randomized/CZP participants, adjusted for both baseline INFLs and FLs. VEs from CZP-randomized participants had a numerically higher prevalence of FLs at Week 12 compared with the PBO-randomized/CZP participants [OR 1.79 (0.85, 3.77); Fig. 4; counts reported in Supplementary Table S3, available at Rheumatology online]. However, at Week 48 CZP-randomized VEs showed a significantly lower prevalence of FLs compared with PBO-randomized/CZP VEs [OR 0.42 (0.20, 0.87)]. By Weeks 96 and 204 (after ≥72 and ≥180 weeks’ CZP treatment in PBO-randomized/CZP participants, respectively), baseline-adjusted FL levels were similar between groups [OR 0.98 (0.48, 2.00) and 0.82 (0.38, 1.78), respectively]. These results were largely similar when the model was adjusted to account for patient-level features (sex, HLA-B27 status, disease duration, syndesmophyte presence) (Supplementary Fig. S3, available at Rheumatology online).

Changes in lesion prevalence over 4 years by subgroups
Radiographic and non-radiographic axSpA
For CZP-randomized participants, INFL counts were comparable between r-axSpA and nr-axSpA at baseline (5.1 and 4.7 per participant, respectively). Following CZP treatment onset, similar reductions in INFLs were...
observed in both groups (Supplementary Fig. S4a, available at Rheumatology online). Conversely, a higher number of FLs was observed in r-axSpA per participant at baseline compared with nr-axSpA (8.1 and 5.2, respectively), but a negligible increase in FLs was observed over time in both groups, similar to observations in the overall axSpA population (Fig. 5a).

**Disease duration**

At baseline, CZP-randomized participants with shorter disease duration (≤3 years) had a higher mean number of INFLs than those with disease duration >3 years (5.7 and 4.3 per participant, respectively). However, between Weeks 12 and 204 mean INFL counts were similar in both groups (Supplementary Fig. S4b, available at Rheumatology online).

Baseline mean counts of FLs were higher in axSpA patients with longer disease duration (7.9 vs 5.8 for >3 years and ≤3 years, respectively). In participants with longer disease duration, mean FL counts increased to 8.5 and 8.9 by Weeks 12 and 204, respectively, while for participants with ≤3 years disease duration, the mean FL count remained largely unchanged through Week 204 (Fig. 5b).

**Discussion**

To our knowledge, this analysis is the first to report the impact of TNF inhibition on inflammatory and chronic lesions (FLs, erosions and sclerosis) in the VEs of patients across the broad axSpA spectrum and over a
long-term (4-year) period in a controlled setting. Furthermore, data are reported for subgroups of interest, including r-axSpA and nr-axSpA subpopulations, and for patients stratified by disease duration. Given the small number of erosive and sclerotic lesions identified, this analysis focused primarily on FL development. Our findings support the hypothesis that the rapid and sustained anti-inflammatory effect of CZP largely mitigates the development of FLs over a 4-year treatment period.

In this analysis of VE MRI data from the RAPID-axSpA study, a considerable reduction in inflammation was shown in VEs, which was maintained over 4 years following CZP treatment initiation at Week 0 or Week 16/24, confirming the efficacy of CZP in reducing active MRI inflammation and supporting previously published results from RAPID-axSpA and other studies reporting CZP in axSpA data [20, 21, 25, 26]. Previously published MRI data from this study investigated overall inflammation on a patient-level using Spondyloarthritis Research Consortium of Canada (SPARCC) SI joint and Berlin scores, while data here are reported by VEs [20]. Although a slight increase in FL count was observed in both CZP-randomized and PBO-randomized/CZP participants to Week 12, the subsequent increase was negligible in CZP-randomized participants and greater in PBO-randomized/CZP participants at Week 48, despite

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**Fig. 5** Changes in fat lesion prevalence in CZP-randomized participants stratified by axSpA subpopulation and disease duration

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**a) FLs by axSpA subpopulation (CZP-randomized participants)**

| Week | Odds ratio (95% CI) |
|------|---------------------|
| 12   | 1.36 (0.94, 1.98)   |
| 48   | 1.54 (1.01, 2.35)   |
| 96   | 1.64 (0.98, 2.46)   |
| 204  | 1.58 (1.01, 2.46)   |

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**b) FLs by disease duration (CZP-randomized participants)**

| Week | Odds ratio (95% CI) |
|------|---------------------|
| 12   | 1.24 (0.83, 1.86)   |
| 48   | 1.08 (0.67, 1.63)   |
| 96   | 1.40 (0.91, 2.15)   |
| 204  | 1.22 (0.77, 1.92)   |

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*Odds ratios for FLs vs baseline were estimated using a logistic generalised linear mixed model (Laplace estimation) with treatment group by time point as a fixed effect and patient and vertebral edge (within patient) as random effects, fitted for each subgroup; an odds ratio of >1 represents an increase in FLs compared with baseline. axSpA: axial spondyloarthritis; CZP: certolizumab pegol; FL: fat lesion; nr-axSpA: non-radiographic axSpA; r-axSpA: radiographic axSpA.*
switching to CZP at Week 16/24. These findings indicate a relationship between inflammation and later FL development, supporting earlier preliminary findings [27, 28].

In CZP-randomized participants, it was shown that FLs were more likely to be present in VEs with baseline inflammation (vs those without), with further gradual increases over time. This again supports a link between inflammation and FLs, even after a short period of evaluation. Early resolution of inflammation (by Week 12) was associated with a reduced risk of FL development at Weeks 96 and 204 compared with VEs with persisting inflammation at Week 12. Inflammation that persisted at Week 48 was also associated with an increased risk of FLs at later time points, although the ORs were not nominally significant, which may be due to patient dropout.

Although a previous study suggested that resolution of inflammation with TNFis was linked to increased occurrence of FLs as markers of chronic damage caused by INFLs, their conclusions were based on just 48 weeks of treatment [11]. In comparison, our study followed participants for 4 years, revealing that early resolution of inflammation with CZP decreased FL prevalence in the long term, and supporting evidence from previous studies in r-axSpA that showed association between advanced or persistent inflammation and syndesmophyte development [4, 10]. Furthermore, CZP-randomized participants with longer disease duration (>3 years) had higher FL prevalence at baseline and more FL development over 204 weeks compared with those with a disease duration ≤3 years, although INFLs were detected at comparable levels at baseline and reduced to the same degree across subgroups. The findings support the idea of a window of opportunity for targeting inflammation early to limit further FL development and prevent irreversible chronic damage of the spine in axSpA patients [8, 10].

Our analysis adjusted for baseline VE status, with respect to INFL and FL levels, showed that the risk of FLs at Week 48 was lower in the CZP-randomized VEs vs PBO-randomized/CZP VEs, but that at later time points there was no difference between the treatment groups. Given that the PBO-randomized/CZP participants switched to active TNFi treatment at Week 16/24, these results indicate that CZP treatment can effectively reduce FL development over a long-term period, supporting previous evidence of TNF inhibition limiting radiographic progression [20, 21, 29].

We also evaluated FLs in patients according to axSpA subpopulations; given the paucity of data on chronic structural changes in nr-axSpA, this subpopulation is of particular interest. At baseline, mean INFL counts were comparable between CZP-randomized participants with r-axSpA and nr-axSpA, but mean FL counts were higher in those with r-axSpA. During the 204 weeks, changes in INFLs and FLs were comparable in both subpopulations, indicating that nr-axSpA patients experience similar long-term benefits of CZP treatment on chronic lesions to those with r-axSpA. These findings also support prior evidence of CZP clinical efficacy in patients across the axSpA spectrum [20, 25].

There were minimal erosions and sclerosis observed in VEs at baseline and throughout the study. These lesions appeared to be unaffected by treatment, but given their small numbers, assessment of treatment impact is difficult, and a longer observation time may be needed to capture changes at a spinal level.

A limitation of this study was the relatively small number of eligible participants, which may pose a risk of selection bias. Despite the small proportion of eligible participants from the overall study, baseline and disease characteristics between the overall study participants and those with MRI were comparable. Patient numbers were similar to those used in previous studies on the same topic (but with shorter time periods) [10, 11]. There were participant dropouts and missing MRIs, with the number of CZP-randomized participants reducing considerably by Week 204, and a larger dropout of participants initially randomized to placebo, which may introduce bias. It has been reported previously that withdrawal from the study was weakly associated with clinical disease activity, leading to selection bias in favour of participants with better clinical status [20]. However, given the weak correlation between clinical and MRI disease activity, dropouts would have introduced little selection bias affecting the MRI results, while the use of statistical models that account for information from dropout participants would have mitigated the impact of selection bias [21]. Overall, the number of analysed VEs was deemed sufficient to allow useful conclusions to be made.

To conclude, our findings confirm that CZP is an effective treatment for the reduction of INFLs and the mitigation of increased FL prevalence in the spine of patients with axSpA. Baseline inflammation was associated with increased risk of FLs, with early suppression of inflammation shown to alleviate the risk of further FL development. Given its efficacy in reducing inflammation and limiting chronic changes such as FLs in patients with axSpA, early CZP treatment may therefore contribute to limiting future structural spinal damage.

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Data availability statement

Underlying data from this manuscript may be requested by qualified researchers 6 months after product approval in the USA and/or Europe, or global development is discontinued, and 18 months after trial completion. Investigators may request access to anonymised individual patient data and redacted study documents, which may include: raw datasets, analysis-ready datasets, study protocol, blank case report form, annotated case report form, statistical analysis plan, dataset specifications, and clinical study report. Prior to use of the data, proposals need to be approved by an independent review panel at www.Vivli.org, and a signed data-sharing agreement will need to be executed. All documents are available in English only, for a pre-specified time, typically 12 months, on a password-protected portal.

Supplementary data

Supplementary data are available at Rheumatology online.

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