An Exploratory Analysis of the Potential Disconnect Between Objective Inflammatory Response and Clinical Response Following Certolizumab Pegol Treatment in Patients with Active Axial Spondyloarthritis

Martin Rudwaleit,[1] Filip van den Bosch,[2] Helena Marzo-Ortega,[3] Victoria Navarro-Compán,[4] Rachel Tham,[5] Thomas Kumke,[6] Lars Bauer,[6] Mindy Kim,[7] Lianne S. Gensler[8]

Objective

In this post-hoc analysis of the RAPID-axSpA study,[1] we evaluated the relationship between objective measures of inflammation, as measured by MRI/CRP, and clinical outcomes following 12 weeks of certolizumab pegol treatment in patients with active axial spondyloarthritis.

Background

- Axial sponyloarthritis (axSpA) clinical trials use validated composite outcome measures, such as Ankylosing Spondylitis Disease Activity Score (ASDAS), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Assessment of SpondyloArthritis international Society (ASAS) response criteria.
- In clinical practice, ASDAS-based responses are also used to determine response to biologic treatment.[2]
- However, these measures are largely based on patient-reported symptoms, which are likely to be confounded by other factors.
- We hypothesise that patient reported symptoms, as measured by ASAS response criteria, BASDAI and ASDAS may not reflect the degree of reduction of inflammation following treatment with certolizumab pegol (CZP), as evaluated by MRI of the sacroiliac joint (SIJ) and spine, and c-reactive protein (CRP) levels.

Methods

- Outcomes are reported prior to CZP treatment (pre-CZP treatment) and following 12 weeks of treatment (post-CZP treatment) for patients in the MRI set of the RAPID-axSpA study (NCT01087762)[1] initially randomised to either CZP, or to placebo before switching to CZP.
- We report post-CZP clinical measures of disease activity (ASDAS, BASDAI) and objective measures of inflammation (CRP, ASspiMRI-a Berlin Score, SPARCC MRI SIJ score); to improve precision of patient-level estimates, data from two independent readers were pooled in a Mixed Model for Repeated Measures for each response variable.
- In patients with pre-CZP inflammation – defined as either elevated MRI (ASspiMRI-a BERLIN score ≥2 or MRI SPARCC SIJ score ≥2) or elevated CRP (≥15 mg/L) – post-CZP outcomes stratified by ASAS40 response are also reported.

Results

Patients

- 136 patients (radiographic axial spondyloarthritis [r-axSpA]: 76; non-radiographic axial spondyloarthritis [nr-axSpA]: 60) had a pre-CZP and ≥1 post-CZP MRI.
- Baseline demographics for the MRI set are presented in **Table 1**.

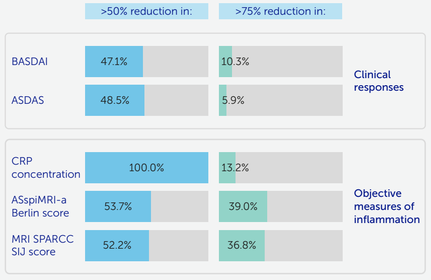
Clinical Outcomes

- Following CZP treatment, CRP, ASspiMRI Berlin score and MRI SPARCC SIJ score were reduced by >50% in the majority of patients (CRP: 136/136 [100.0%]; Berlin: 73/136 [53.7%]; SPARCC: 71/136 [52.2%]), and often by >75% (CRP: 18/136 [13.2%]; Berlin: 53/136 [39.0%]; SPARCC: 50/136 [36.8%]), irrespective of pre-CZP value.
- However, only a minority of both r-axSpA (**Figure 1A**) and nr-axSpA patients (**Figure 1B**), showed a >50% reduction in clinical responses (ASDAS: 66/136 [48.5%]; BASDAI: 64/136 [47.1%]).
- These results were also observed at the individual patient level: >50% improvements in MRI/CRP inflammatory measures did not translate into similar improvements in clinical responses for most patients.
- Similar proportions of patients showed post-CZP improvements in objective measures of inflammation, irrespective of ASAS40 response (**Figure 2**).

Summary

In this post hoc analysis of the RAPID-axSpA trial, we evaluated the relationship between **objective signs of inflammation**, as measured by MRI and CRP, and **clinical responses** following 12 weeks of CZP treatment in patients with active axSpA

Proportion of axSpA patients (n=136) achieving:



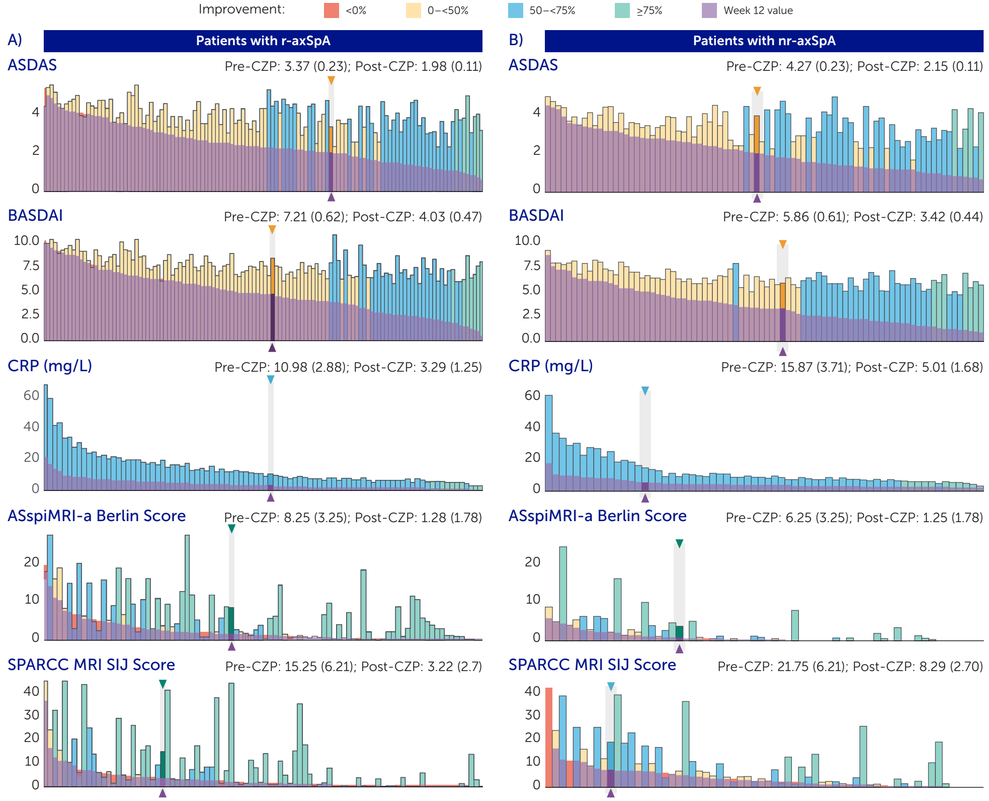
CZP treatment results in a reduction of objective measures of inflammation, irrespective of improvements in clinical symptoms and measures of disease activity

Table 1 Baseline demographics and characteristics

Baseline characteristic, mean (SD), unless otherwise stated	MRI Set N=136	
	r-axSpA N=76	**nr-axSpA N=60**
Age, years	40.4 (11.6)	37.3 (13.0)
Sex, male, n (%)	52 (68.4)	31 (51.7)
HLA-B27, positive, n (%)	59 (77.6)	46 (76.7)
BMI, kg/m²	27.0 (5.2)[a]	26.8 (6.0)[b]
Symptom duration		
Years, median (min, max)	10.3 (0.3, 50.9)	5.9 (0.3, 39.6)
<5 years, n (%)	25 (32.9)	28 (46.7)
ASDAS	4.0 (0.9)	3.8 (0.9)[b]
BASDAI	6.8 (1.5)	6.6 (1.5)
CRP, mg/L	21.2 (27.5)	16.2 (17.0)
CRP, >15 mg/L, n (%)	32 (42.1)	23 (38.3)
ASspiMRI-a Berlin score	6.4 (8.1)	4.5 (8.5)[c]
SPARCC MRI SIJ score	9.5 (14.9)[d]	7.8 (12.4)[e]

MRI set; includes patients evaluable for MRI and who have at least one MRI assessment. [a]n=75; [b]n=59; [c]n=56; [d]n=75; [e]n=55.

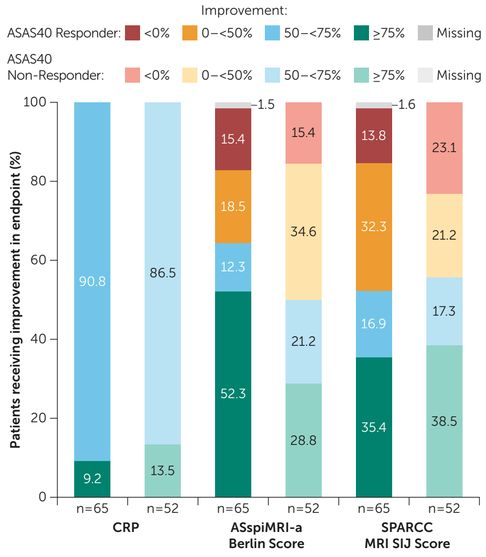
Figure 1 Change following 12 weeks of CZP treatment in clinical response and measures of objective signs of inflammation



Patient treatment sequence: CZP 400 mg at Week 0. Each bar represents a single patient. Across all five endpoints, the same patient is indicated by an arrow. The pre- and post-CZP states are indicated by the step-line (the "skyline") and the dark purple line within each bar (Week 12 value), respectively; the space between these points reflects the change in response. Change in response has been grouped into four categories based on the percentage reduction, as shown by the figure legend. Data presented were obtained from a Mixed Model Repeated Measures that was applied to each response variable: for SPARCC MRI SIJ score, ASspiMRI Berlin score, and ASDAS response variables a linear mixed effect model was used to estimate EBLUP with random effects of: reader j overall, reader j in reading campaign k overall, reader j for subject i and reader j for subject i in reading campaign k, for CRP and BASDAI response variables, a linear mixed effects model was used to estimate EBLUP with spatial autocorrelation (using nearby visits to estimate response variable values).

ASDAS: Ankylosing Spondylitis Disease Activity Score; **ASspiMRI:** Ankylosing Spondylitis spine MRI score; **BASDAI:** Bath Ankylosing Spondylitis Disease Activity Index; **BMI:** body mass index; **CRP:** C-reactive protein; **CZP:** certolizumab pegol; **EBLUP:** empirical best linear unbiased predictor; **HLA-B27:** human leukocyte antigen B27; **MRI:** magnetic resonance imaging; **nr-axSpA:** non-radiographic axial spondyloarthritis; **r-axSpA:** radiographic axial spondyloarthritis; **SD:** standard deviation; **SIJ:** sacroiliac joints; **SPARCC:** Spondyloarthritis Research Consortium of Canada.

Figure 2 Objective measures of inflammation in patients with pre-CZP inflammation, stratified by post-CZP ASAS40 achievement



Data reported for patients with pre-CZP inflammation only, defined as either elevated MRI (either ASspiMRI-a BERLIN score ≥2 or MRI SPARCC SIJ score ≥2) or elevated CRP (≥15 mg/L). Patients with both nr-axSpA and r-axSpA are included.

Conclusions

This analysis revealed a potential disconnect between objective measures of inflammation, as measured by MRI and CRP, and clinical outcome responses. In most patients, CZP treatment resulted in a reduction of objective measures of inflammation, irrespective of improvements in clinical symptoms and measures of disease activity.

The use of clinical response measures as clinical trial endpoints may therefore underestimate anti-inflammatory treatment effects.

Institutions: [1]University of Bielefeld, Klinikum Bielefeld, Bielefeld, Germany; [2]Department of Internal Medicine and Pediatrics, Ghent University and VIB Center for Inflammation Research, Ghent, Belgium; [3]NIHR Leeds Biomedical Research Centre, Leeds Teaching Hospitals NHS Trust and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK; [4]Department of Rheumatology, La Paz University Hospital, IdiPaz, Madrid, Spain; [5]UCB Pharma, Slough, UK; [6]UCB Pharma, Monheim, Germany; [7]UCB Pharma, Smyrna, GA, USA; [8]University of California San Francisco, San Francisco, CA, USA

References: [1]van der Heijde D. et al. Ann Rheum Dis 2017;77:699–705; [2]Ramiro S. et al. Arthritis Rheumatol 2022; 74 (Suppl 9) 2022; doi:10.1136/ard-2022-223296. **Author Contributions:** Substantial contributions to study conception/design, or acquisition/analysis/interpretation of data: **MR, FvdB, HMO, VNC, RT, TK, LB, MK, LSG**; Drafting of the publication, or revising it critically for important intellectual content: **MR, FvdB, HMO, VNC, RT, TK, LB, MK, LSG**; Final approval of the publication: **MR, FvdB, HMO, VNC, RT, TK, LB, MK, LSG**. **Author Disclosures: MR:** Speakers bureau from AbbVie, Boehringer Ingelheim, Chugai, Eli Lilly, Janssen, Novartis, Pfizer, and UCB Pharma; consultancy fees from AbbVie, Eli Lilly, Novartis, and UCB Pharma. **FvdB:** Consultancy fees from AbbVie, Amgen, Eli Lilly, Galapagos, Janssen, Merck, Novartis, Pfizer and UCB Pharma; Speakers bureau from AbbVie, Bristol Myers Squibb, Celgene, Janssen, Merck, Novartis, Pfizer and UCB Pharma. **HMO:** Research grants from Janssen, Novartis, and UCB Pharma; Speakers bureau and/or consultancy fees from AbbVie, Biogen, Eli Lilly, Janssen, Moonlake, Novartis, Pfizer, Takeda, and UCB Pharma. **VNC:** Speakers bureau from AbbVie, Eli Lilly, Janssen, MSD, Novartis, Pfizer, and UCB Pharma; Consultancy fees from AbbVie, Eli Lilly, MSD, Novartis, Pfizer, and UCB Pharma; Research grants from AbbVie and Novartis. **RT:** Veramed statistical consultant for UCB Pharma. **TK, LB, MK:** Employees and stockholders of UCB Pharma. **LSG:** Grants from Novartis, Pzifer and UCB Pharma (paid to institution); Consultancy fees from AbbVie, Acelyrin, Eli Lilly, Fresenius Kabi, Janssen, Novartis, Pfizer, and UCB Pharma. **Acknowledgements:** We would like to thank the patients and their caregivers in addition to all the investigators and their teams who contributed to this study. The authors acknowledge Simone E. Auteri MSc EMS PhD, UCB Pharma, for publication coordination, Alexandra Quinn-Savory, MPH, Costello Medical, Cambridge, UK, for medical writing and editorial assistance, and the Costello Medical Creative Team for design support. This study was funded by UCB Pharma. All costs associated with development of this presentation were funded by UCB Pharma.

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