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ORIGINAL ARTICLE

Early Disease Activity or Clinical Response as Predictors of Long-Term Outcomes With Certolizumab Pegol in Axial Spondyloarthritis or Psoriatic Arthritis

D. VAN DER HEIJDE,[1] A. DEODHAR,[2] R. FLEISCHMANN,[3] P. J. MEASE,[4] M. RUDWALEIT,[5] T. NURMINEN,[6] AND O. DAVIES[7]

Objective. **Early identification of patients unlikely to achieve good long-term disease control with anti–tumor necrosis factor therapy in axial spondyloarthritis (SpA) and psoriatic arthritis (PsA) is important for physicians following treat-to-target recommendations. Here we assess associations between disease activity or clinical response during the first 12 weeks of treatment and attainment of treatment targets at week 48 in axial SpA and PsA patients receiving certolizumab pegol.**

Methods. **The relationship between disease activity or clinical response during the first 12 weeks of treatment and achievement of week-48 targets (for axial SpA: inactive disease based on Ankylosing Spondylitis Disease Activity Score [ASDAS] using the C-reactive protein [CRP] level, or Bath Ankylosing Spondylitis Disease Activity Index <2 with normal CRP level; and for PsA: minimal disease activity) was assessed post hoc using RAPID-axSpA and RAPID-PsA trial data.**

Results. **A clear relationship between disease activity from week 2 to 12 and achievement of week-48 treatment targets was observed in both axial SpA and PsA populations. In axial SpA, week-48 ASDAS inactive disease was achieved by 0% of patients (0 of 21) with ASDAS very high disease activity at week 12, compared to 68% of patients (34 of 50) with week-12 ASDAS inactive disease. For PsA, week-48 minimal disease activity was achieved by 0% of patients (0 of 26) with Disease Activity Score in 28 joints (DAS28) using the CRP level >5.1 at week 12, compared to 73% of patients (57 of 78) with DAS28-CRP <2.6. Similar results were observed regardless of the disease activity measure used. Clinical response at week 12 also predicted week-48 outcomes, though to a lesser extent than disease activity.**

Conclusion. **Using disease activity and the clinical response state during the first 12 weeks of certolizumab pegol treatment, it was possible to identify a subset of axial SpA and PsA patients unlikely to achieve long-term treatment goals.**

INTRODUCTION

Recent recommendations have been published to suggest treatment targets for spondyloarthritis (SpA), including axial SpA and psoriatic arthritis (PsA) (1). These recommendations state that a primary goal of treatment in these diseases is to maximize the long-term health-related quality of life and social participation of patients through the preservation of function and prevention of structural damage (1). In

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[1]D. van der Heijde, MD, PhD: Leiden University Medical Center, Leiden, The Netherlands; [2]A. Deodhar, MD: Oregon Health and Science University, Portland; [3]R. Fleischmann, MD: University of Texas SW Medical Center, Dallas; [4]P. J. Mease, MD: Swedish Medical Center and University of Washington, Seattle; [5]M. Rudwaleit, MD: Klinikum Bielefeld and Charité Berlin, Berlin, Germany, and Ghent University, Ghent, Belgium; [6]T. Nurminen, MSocSc: UCB Pharma, Monheim, Germany; [7]O. Davies, BPharm, PhD, MBA: UCB Pharma, Slough, UK.

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Significance & Innovations

- Data from the RAPID-axSpA and RAPID-PsA trials demonstrated that early response to treatment in the first 12 weeks can be used to predict a subset of axial spondyloarthritis (SpA) and psoriatic arthritis (PsA) patients unlikely to achieve long-term treatment goals.
- Predictability analyses were successful in PsA and axial SpA populations, including both the ankylosing spondylitis and nonradiographic axial SpA subpopulations.
- This negative predictability approach was possible when disease activity was assessed using either clinician-scored or patient-reported outcome measures.

addition, the recommendations state that the treatment targets should assess laboratory measures of inflammation, such as C-reactive protein (CRP) levels, alongside clinical outcomes, or that composite outcomes should be used that incorporate both. The treatment targets recommended were clinical remission or inactive disease (1). The treat-to-target recommendations in SpA suggest allowing a maximum of 6 months for reaching the treatment target, but that therapy should be adapted at 3 months if there has been no significant reduction in disease activity by this point (1).

In line with these recommendations, the early identification of patients unlikely to achieve treatment targets (negative predictability) may help avoid unnecessary exposure to treatment, potentially increase cost-effectiveness, and improve the chance of patients achieving long-term goals. To date, negative predictability has not been explored as a primary objective in any analyses in patients with axial SpA or PsA, where axial SpA includes both ankylosing spondylitis and nonradiographic axial SpA patients, referring to the presence or absence of sacroiliac joint changes on radiographs (2). Here we investigated whether the lack of early response or lack of achievement of important disease activity thresholds over the first 12 weeks of treatment could be used to identify patients with axial SpA or PsA receiving certolizumab pegol (CZP) treatment who were unlikely to attain the desired treatment targets at week 48.

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Address correspondence to D. van der Heijde, MD, PhD, Department of Rheumatology, Leiden University Medical Center, P.O. Box 9600, Leiden 2300 RC, The Netherlands. E-mail: mail@dvanderheijde.nl.

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PATIENTS AND METHODS

Patients. Analyses were carried out on CZP-treated patients from the RAPID-axSpA (3) and RAPID-PsA (4) trials. Both trials were phase 3, multicenter, randomized trials that were double-blind and placebo-controlled to week 24, dose-blind to week 48, and open-label to week 204 for RAPID-axSpA or week 216 for RAPID-PsA. The analyses reported here use data up to week 48.

In RAPID-axSpA, eligible patients had active axial SpA (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] $\geq$4 and spinal pain $\geq$4) of $\geq$3 months' duration, had to meet the Assessment of SpondyloArthritis international Society classification criteria for axial SpA (5,6), and had failed treatment with, or been resistant to, $\geq$1 nonsteroidal antiinflammatory drug. Eligible patients were stratified at randomization based on the modified New York criteria. The primary clinical end point of RAPID-axSpA (3) and long-term safety and efficacy data (to week 96) (7) have been reported elsewhere.

In RAPID-PsA, eligible patients had PsA as defined by the Classification Criteria for Psoriatic Arthritis (8), had active disease ($\geq$3 tender joints and $\geq$3 swollen joints, and either erythrocyte sedimentation rate [ESR] $\geq$28 mm/hour or CRP level $>$7.9 mg/liter) of $\geq$6 months' duration, and had failed treatment with, or been resistant to, $\geq$1 disease-modifying antirheumatic drug. The primary clinical (4) and radiographic (9) end points of RAPID-PsA have been reported elsewhere, as have long-term (to week 96) (10) outcomes from this trial.

Evaluations. The relationship between disease activity or clinical response during the first 12 weeks of CZP treatment and achievement of a treatment target at week 48 was assessed. Each analysis considered 1 treatment target and 1 predictor, which are described below and shown in Table 1.

Treatment targets: axial SpA. To assess predictability, the achievement of disease activity targets at week 48 was considered. The treatment targets selected were among those suggested in the treat-to-target recommendations (1). For axial SpA, the treatment targets chosen were Ankylosing Spondylitis Disease Activity Score (ASDAS) inactive disease (ASDAS $<$1.3) and BASDAI $<$2 with normal CRP level ($\leq$7.9 mg/liter). ASDAS includes both disease activity components and laboratory investigations of serologic inflammatory response (CRP level). As BASDAI does not contain a CRP component, BASDAI plus normal CRP level (at or below the upper limit of normal of $\leq$7.9 mg/liter) were used as a treatment target, rather than BASDAI alone, as suggested in the treat-to-target recommendations (1).

Treatment targets: PsA. For PsA, minimal disease activity (MDA) was selected as the treatment target. Achievement of MDA (11) is defined as the achievement of 5 of 7 criteria: tender joint count $\leq$1, swollen joint count $\leq$1, psoriasis area and severity index $\leq$1 or body surface area $\leq$3, pain visual analog scale (VAS) $\leq$15, patient's global assessment of disease activity VAS $\leq$20, health assessment questionnaire

Table 1. Definitions and cutoffs used for early predictors investigated for the attainment of week-48 treatment targets*

Target	Predictor: Disease activity (composite measures)	Predictor: Clinical response (composite measures)	Predictor: Clinical response (patient-reported outcomes)
Axial SpA ASDAS inactive disease	ASDAS absolute value thresholds: 1) <1.3, inactive disease 2) ≥1.3 to <2.1, moderate disease activity 3) ≥2.1 to ≤3.5, high disease activity 4) >3.5, very high disease activity	ASDAS improvement from baseline thresholds: 1) ≥2.0, major improvement 2) 1.1 to <2.0, clinically important improvement (CII) but not major improvement 3) <1.1, less than CII	Back pain MCID: 1) ≥1-point decrease from baseline Daily pain diary response: 1) ≥1-point decrease from baseline†
BASDAI <2 and CRP ≤ULN	BASDAI absolute value thresholds: 1) <2, low disease activity 2) ≥2 to <4, moderate disease activity 3) ≥4 to ≤6, high disease activity 4) >6, very high disease activity	BASDAI improvement from baseline thresholds:‡ 1) ≥4 2) ≥2 to <4 3) ≥1 to <2 4) <1	Back pain MCID: 1) ≥1-point decrease from baseline Daily pain diary response: 1) ≥1-point decrease from baseline†
PsA MDA	DAS28-CRP absolute value thresholds:§ 1) <2.6 2) ≥2.6 to ≤3.2 3) >3.2 to ≤5.1 4) >5.1	DAS28-CRP improvement from baseline thresholds:‡ 1) >1.2 2) >0.6 to 1.2 3) ≤0.6 PsARC response: 1) Improvement from baseline in 2 of 4 criteria, 1 of which must be TJC or SJC, and no 1 point ≥30% worsening from baseline in any of the measures	Patient assessment of arthritis pain score MCID: 1) ≥10-point decrease from baseline

* SpA = spondyloarthritis; ASDAS = Ankylosing Spondylitis Disease Activity Score; MCID = minimal clinically important difference; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CRP = C-reactive protein; ULN = upper limit of normal; PsA = psoriatic arthritis; MDA = minimal disease activity; DAS28-CRP = Disease Activity Score in 28 joints using the CRP; PsARC = Psoriatic Arthritis Response Criteria: TJC = tender joint count; SJC = swollen joint count.
† Mean of total and nocturnal spinal pain measures used as baseline score, as the daily pain diary was completed from day 1.
‡ Unvalidated in PsA.
§ Unvalidated in PsA; validated in rheumatoid arthritis (16).

≤0.5, and tender entheseal points ≤1 in the Leeds Enthesitis Index (12).

Predictors: disease activity. In order to predict the absence of reaching the treatment target at week 48, a number of possible predictors were considered at early time points (up to week 12), as summarized in Table 1. For axial SpA, ASDAS disease activity was defined using validated (13) cutoff values for inactive, moderate, high, or very high disease activity, while BASDAI disease activity was defined using unvalidated cutoff values for low, moderate, high or very high disease activity. The unvalidated cutoff values for BASDAI disease activity are similar to those previously described in the literature (14,15).

For PsA, in the absence of well-accepted Disease Activity Score in 28 joints (DAS28) using the CRP level thresholds in PsA patients, disease activity was defined using thresholds validated for DAS28-ESR in rheumatoid arthritis (RA) (Table 1) (16). Although these thresholds have not been validated in PsA, and they show poor performance in RA, these have been selected due to the lack of a better alternative (17).

Predictors: clinical response. For axial SpA clinical response, validated (13) ASDAS cutoff values and unvalidated BASDAI cutoff values were used, as shown in Table 1. Patient-reported outcomes were also considered to assess clinical response. For axial SpA, the patient-completed total back pain score (0–10 numerical rating scale)

was used. This outcome was assessed at regular visits and through a daily pain diary from day 0–28 of the trial (the same question was used except that the recall period was modified from "in the last week" for regular assessments to "during the last 24 hours" for the daily pain diary). Clinical response was defined as the achievement or lack of achievement of a minimal clinically important difference (MCID) in pain score (18) or a response in the patient daily pain diary (Table 1).

For PsA, the unvalidated DAS28-CRP clinical response was defined using thresholds validated for DAS28-ESR in RA (16), or as a Psoriatic Arthritis Response Criteria (PsARC) response (19). The patient assessment of arthritis pain score (by VAS) was also considered, with clinical response defined as a pain score MCID (20) (Table 1).

Statistical analysis. Analyses were carried out on all patients originally randomized to CZP at week 0 (200 mg every 2 weeks and 400 mg every 4 weeks, doses combined). For RAPID-axSpA, this analysis included 218 patients and for RAPID-PsA 273 patients. Additional analyses were carried out for the ankylosing spondylitis and nonradiographic axial SpA subpopulations from the RAPID-axSpA trial.

Predictability analyses at a given week were based on all patients continuing treatment at that week. Last observation carried forward estimation was applied for intermittently missing disease activity or clinical response assessments to week 12 (i.e., for all predictors). For treatment targets, for those patients withdrawing between the early disease activity or clinical response assessments and week 48, or otherwise missing week 48 assessments, missing data were imputed by last observation carried forward (ASDAS and BASDAI-CRP) or nonresponder imputation (for MDA).

RESULTS

Disease activity as a predictor of treatment target attainment. *Disease activity in axial SpA, including ankylosing spondylitis and nonradiographic axial SpA patients.* Baseline disease activity, when assessed using either ASDAS or BASDAI, was not strongly associated with the attainment of week 48 treatment targets. However, following treatment initiation, both ASDAS and BASDAI disease activity were strong predictors for the achievement or lack of achievement of week-48 treatment targets, with disease activity as early as week 2 predicting longer-term outcomes in patients treated with CZP.

ASDAS disease activity state at week 2 was associated with the likelihood of achieving ASDAS inactive disease at week 48, with 0% of patients (0 of 27) with ASDAS very high disease activity at week 2 achieving ASDAS inactive disease at week 48, compared to 71% of patients (22 of 31) with ASDAS inactive disease at week 2 achieving ASDAS inactive disease at week 48 (Figure 1). A trend of decreasing

Axial SpA:*

Target	Visit	Disease activity			
		ASDAS ID	ASDAS MD	ASDAS HD	ASDAS vHD
ASDAS ID	Baseline	0/0 (0.0)	1/3 (33.3)	32/70 (45.7)	34/145 (23.4)
	Week 2	22/31 (71.0)	30/59 (50.8)	15/100 (15.0)	0/27 (0.0)
	Week 8	35/49 (71.4)	22/57 (38.6)	10/89 (11.2)	0/20 (0.0)
	Week 12	34/50 (68.0)	20/54 (37.0)	13/86 (15.1)	0/21 (0.0)
		Low	Moderate	High	Very High
BASDAI <2 and CRP ≤ULN		BASDAI <2	BASDAI ≥2 to <4	BASDAI ≥4 to ≤6	BASDAI >6
	Baseline	0/0 (0.0)	2/9 (22.2)	36/79 (45.6)	28/130 (21.5)
	Week 2	20/31 (64.5)	30/62 (48.4)	12/63 (19.0)	4/61 (6.6)
	Week 8	30/45 (66.7)	30/74 (40.5)	5/59 (8.5)	1/37 (2.7)
	Week 12	37/58 (63.8)	19/61 (31.1)	10/54 (18.5)	0/38 (0.0)

PsA: †

		DAS28-CRP <2.6	DAS28-CRP ≥2.6 to 3.2	DAS28-CRP >3.2 to 5.1	DAS28-CRP >5.1
MDA	Baseline	1/1 (100.0)	2/6 (33.3)	64/145 (44.1)	32/120 (26.7)
	Week 2	17/25 (68.0)	22/34 (64.7)	55/159 (34.6)	5/52 (9.6)
	Week 8	50/71 (70.4)	23/38 (60.5)	25/114 (21.9)	1/39 (2.6)
	Week 12	57/78 (73.1)	23/47 (48.9)	19/105 (18.1)	0/26 (0.0)

Key to probability of reaching defined target:	80–100%	60–80%	40–60%	20–40%	10–20%	0–10%

Figure 1. Proportion of patients achieving disease activity targets at week 48 based on classification of disease activity at baseline, week 2, week 8, and week 12. Values are the number/total number (percentage). * = the number of axial spondyloarthritis (SpA) patients at each visit: 218 at baseline, 217 at week 2, 215 at week 8, and 211 at week 12. † = the number of psoriatic arthritis (PsA) patients at each visit: 272 at baseline, 270 at week 2, 262 at week 8, and 256 at week 12. ASDAS = Ankylosing Spondylitis Disease Activity Score; ID = inactive disease; MD = moderate disease; HD = high disease; vHD = very high disease; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CRP = C-reactive protein; ULN = upper limit of normal; MDA = minimal disease activity; DAS28 = Disease Activity Score in 28 joints.

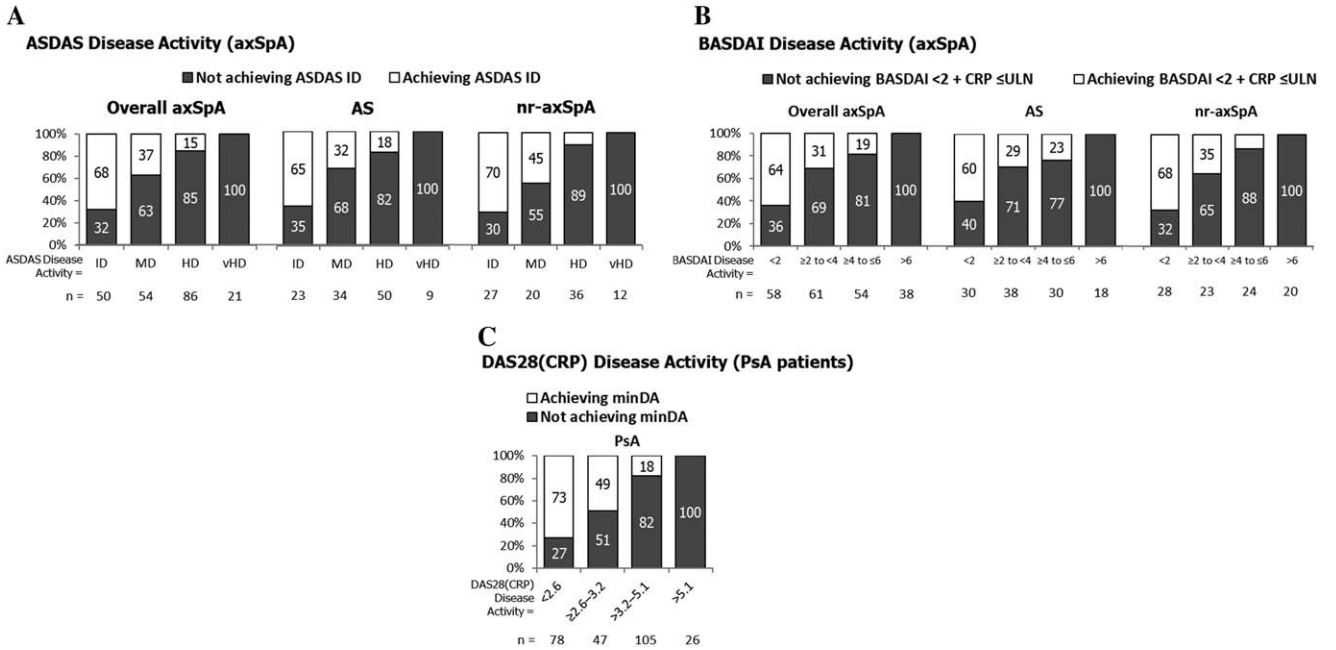

Figure 2. Disease activity at week 12 successfully predicts lack of attainment of treatment targets. axSpA = axial spondyloarthritis; AS = ankylosing spondylitis; nr = nonradiographic; PsA = psoriatic arthritis; minDA = minimal disease activity. See Figure 1 for other definitions.

achievement of ASDAS inactive disease was observed with higher disease activity at week 2, from inactive disease through to moderate, high, and very high disease activity. A similar trend was observed at week 8 and week 12, although fewer patients had high and very high disease activity, and more patients had inactive disease at later time points.

A similar association between disease activity during the first 12 weeks of therapy and achievement of treatment targets was observed when BASDAI was considered. Very high disease activity (BASDAI >6) successfully predicted the lack of attainment of the treatment target BASDAI <2 and CRP at or below the upper limit of normal (Figure 1). Disease activity was a strong negative predictor for the achievement of week-48 treatment targets across the ankylosing spondylitis and nonradiographic axial SpA subpopulations (Figure 2A and 2B).

Sensitivity analyses were performed using nonresponder imputation, rather than last observation carried forward. Only 3 fewer patients achieved ASDAS inactive disease when the more conservative imputation method (nonresponder) was used, and therefore a change in imputation methodology is unlikely to have affected the outcomes of this analysis.

Disease activity in PsA. Higher DAS28-CRP was a strong negative predictor for achievement of the treatment target in PsA. A clear relationship between disease activity state at week 2 and MDA at week 48 was observed, with 10% of patients (5 of 52) with week 2 DAS28-CRP >5.1 achieving week-48 MDA, compared with 68% of patients (17 of 25) with DAS28-CRP <2.6 at week 2 (Figure 1). As with axial SpA, a trend was seen across the various levels of disease activity, with a decreasing proportion of patients achieving MDA in progressively higher disease activity states. This trend was maintained to week 12, at which point more patients had lower disease activity. At week 48, MDA was achieved by 0% of patients (0 of 26) with week-12 DAS28-CRP >5.1, compared to 73% of patients (57 of 78) with week-12 DAS28-CRP <2.6.

Clinical response predicts achievement of treatment targets. *Clinical response in axial SpA, including ankylosing spondylitis and nonradiographic axial SpA patients.* A lack of early clinical response to CZP was also an effective negative predictor of week-48 disease activity. In axial SpA, only 7% of patients (3 of 45) with week 12 BASDAI improvement <1 achieved week-48 disease activity of BASDAI <2 and CRP at or below the upper limit of normal (Figure 3).

When ASDAS inactive disease was used as the treatment target, 18% of patients (12 of 65) with week-12 ASDAS less than clinically important improvement achieved the treatment target at week 48, compared to 47% of patients (39 of 83) with week-12 major improvement (Figure 3). A similar trend was seen in the ankylosing spondylitis and nonradiographic axial SpA subpopulations, whether using ASDAS or BASDAI to define clinical response and treatment target (Figure 4A and 4B).

Lack of early improvement in pain score was also a negative predictor of achievement of week-48 treatment targets. Just 12% of patients (9 of 74) not achieving a daily pain response by day 7 went on to achieve ASDAS inactive disease at week 48, compared to 41% of patients (57 of 138) achieving a daily pain response (Figure 3).

At week 12, 6% of patients (2 of 36) not achieving week-12 pain MCID went on to achieve week-48 ASDAS inactive disease, compared to 37% of patients (65 of 175) with pain MCID. When BASDAI <2 and CRP at or below the upper limit of normal were considered as the treatment target, only 3% (1 of 36) of week-12 MCID nonresponders achieved the week-48 treatment target (Figure 3).

Axial SpA:*

Target	Visit	Clinical response			
		ASDAS-MI	**ASDAS-CII**		**ASDAS<CII**
ASDAS ID	Week 2	30/65 (46.2)	23/71 (32.4)		14/81 (17.3)
	Week 8	36/78 (46.2)	21/74 (28.4)		10/63 (15.9)
	Week 12	39/83 (47.0)	16/63 (25.4)		12/65 (18.5)
		BASDAI improvement ≥4	**BASDAI improvement ≥2 to <4**	**BASDAI improvement ≥1 to <2**	**BASDAI improvement <1**
BASDAI <2 and CRP ≤ULN	Week 2	18/32 (56.3)	28/62 (45.2)	13/56 (23.2)	7/67 (10.4)
	Week 8	28/52 (53.8)	26/77 (33.8)	9/39 (23.1)	3/47 (6.4)
	Week 12	32/65 (49.2)	23/66 (34.8)	8/35 (22.9)	3/45 (6.7)
		Achievement of daily pain diary response		**Nonachievement of daily pain diary response**	
ASDAS ID	Day 3	50/136 (36.8)		16/76 (21.1)	
	Day 7	57/138 (41.3)		9/74 (12.2)	
	Day 14	56/144 (38.9)		10/68 (14.7)	
	Day 28	59/160 (36.9)		7/52 (13.5)	
		Achievement of daily pain diary response		**Nonachievement of daily pain diary response**	
BASDAI <2 and CRP ≤ULN	Day 3	51/136 (37.5)		13/76 (17.1)	
	Day 7	57/138 (41.3)		7/74 (9.5)	
	Day 14	56/144 (38.9)		8/68 (11.8)	
	Day 28	58/160 (36.3)		6/52 (11.5)	
		Achievement of pain MCID		**Nonachievement of pain MCID**	
ASDAS ID	Week 2	59/147 (40.1)		8/70 (11.4)	
	Week 8	61/176 (34.7)		6/39 (15.4)	
	Week 12	65/175 (37.1)		2/36 (5.6)	
		Achievement of pain MCID		**Nonachievement of pain MCID**	
BASDAI <2 and CRP ≤ULN	Week 2	60/147 (40.8)		6/70 (8.6)	
	Week 8	61/176 (34.7)		5/39 (12.8)	
	Week 12	65/175 (37.1)		1/36 (2.8)	

PsA:†

		DAS28-CRP improvement >1.2	**DAS28-CRP improvement >0.6 to 1.2**	**DAS28-CRP improvement ≤0.6**
MDA	Week 2	55/98 (56.1)	15/61 (24.6)	29/111 (26.1)
	Week 8	76/140 (54.3)	14/54 (25.9)	9/68 (13.2)
	Week 12	76/153 (49.7)	17/53 (32.1)	6/50 (12.0)
		PsARC responder		**PsARC nonresponder**
MDA	Week 2	70/138 (50.7)		29/129 (22.5)
	Week 8	90/191 (47.1)		9/70 (12.9)
	Week 12	93/199 (46.7)		6/56 (10.7)
		Achievement of pain MCID		**Nonachievement of pain MCID**
MDA	Week 2	59/127 (46.5)		40/143 (28.0)
	Week 8	80/159 (50.3)		19/103 (18.4)
	Week 12	89/184 (48.4)		10/72 (13.9)

Key to probability of reaching defined target:	80–100%	60–80%	40–60%	20–40%	10–20%	0–10%

Figure 3. Likelihood of achieving disease activity targets at week 48 based on clinical response or on achievement of patient-reported outcome responses at early time points. Values are the number/total number (percentage). * = the number of axial spondyloarthritis (SpA) patients at each visit: 218 at baseline, 217 at week 2, 215 at week 8, and 211 at week 12. † = the number of PsA patients at each visit: 272 at baseline, 270 at week 2, 262 at week 8, and 256 at week 12. MI = major improvement; CII = clinically important improvement; MCID = minimal clinically important difference; PsARC = Psoriatic Arthritis Response Criteria. See Figure 1 for other definitions.

Clinical response in PsA. Clinical response at week 12 was also associated with the likelihood of attaining treatment targets at week 48 in PsA patients. At week 48, MDA was achieved by only 12% of patients (6 of 50) with week-12 DAS28-CRP improvement from baseline ≤0.6, compared with 50% of patients (76 of 153) with week 12 DAS28-CRP improvement from baseline >1.2. Similar results were seen when using early PsARC response as a predictor, with fewer week-12 PsARC nonresponders achieving week-48 MDA than responders (Figure 3). At week 12, only 14% of patients (10 of 72) without week-12 pain MCID achieved week-48 MDA, whereas 48% of patients (89 of 184) with week-12 pain MCID went on to achieve MDA at week 48.

Maintained achievement or lack of achievement of treatment targets. Treat-to-target recommendations emphasize the importance of the maintenance of targets throughout the disease course (1). To this end, a heat-map approach is presented, where individual patient disease activity scores are shown by visit, sorted according to their week-12 disease activity score (Figure 5).

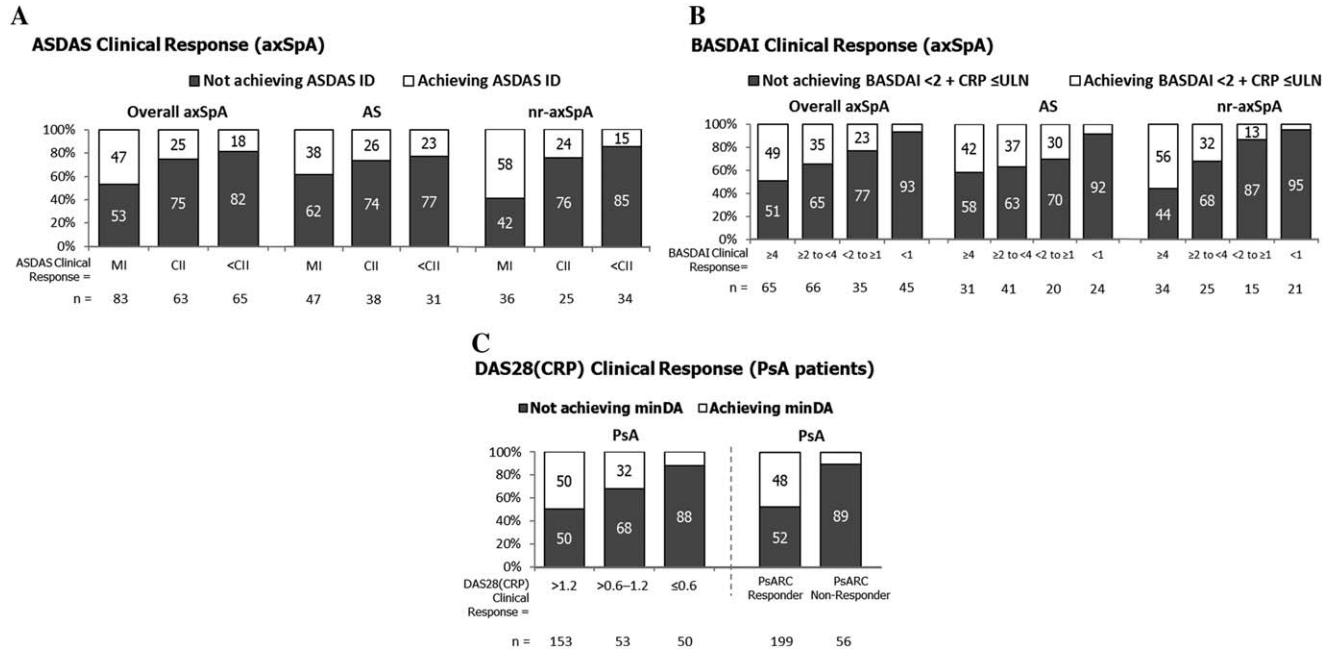

Figure 4. Clinical response at week 12 predicts lack of attainment of treatment targets moderately well. axSpA = axial spondyloarthritis; AS = ankylosing spondylitis; nr = nonradiographic; MI = major improvement; CII = clinically important improvement; PsA = psoriatic arthritis; minDA = minimal disease activity; PsARC = Psoriatic Arthritis Response Criteria. See Figure 1 for other definitions.

This heat map shows that the level of disease activity achieved at week 12 is maintained relatively consistently over time. However, some variation in disease activity is observed between visits, with some patients experiencing worsening disease activity and some seeing greater improvements. This variability likely represents the natural fluctuating course of these inflammatory diseases.

DISCUSSION

The prediction of response in axial SpA and PsA patients has not been studied extensively. The majority of work in the literature has focused on prediction of response in patients with ankylosing spondylitis, PsA, RA, or psoriasis, and has focused on the use of baseline characteristics to identify patients likely to achieve a good therapeutic response (21–25), or else the use of early treatment response to predict those patients likely to achieve treatment targets at later time points (positive predictability) (26–30). These studies have consistently found that long-term clinical improvements are predicted by raised inflammatory markers (such as CRP level) at baseline, and by an early clinical response to treatment. Other factors predictive of long-term improvements in some of these studies were better function (lower Bath Ankylosing Spondylitis Functional Index score), lower enthesitis score, younger age, HLA–B27 positivity, male sex and anti–tumor necrosis factor naivety at baseline in ankylosing spondylitis (22–25), and baseline health assessment questionnaire in PsA (21).

The use of baseline characteristics to predict those patients likely to respond well to a given therapy can be used to tailor treatments to specific patients, thus increasing the likelihood of a patient responding well to their initial treatment and reducing the need to switch therapies. Positive prediction based on early response provides clinicians with reassurance when continuing a patient on their current treatment. Complementary to these ideas is the concept of negative prediction, which can inform a clinician whether or not to consider stopping treatment in a patient who is not responding or who is having a suboptimal response to therapy.

The concept of negative predictability has previously been demonstrated in RA patients treated with CZP (31,32). In RA, clinically applicable models were used to successfully identify which patients may benefit from switching therapy after 12 weeks of CZP treatment. These patients were predicted to be nonresponders at week 52 (patients with a very low likelihood of achieving low disease activity) with a high degree of specificity, based on the improvement in their disease activity level at week 12 (DAS28 improvement from baseline) (31,32). Here we demonstrate that this approach is also applicable to axial SpA and PsA patients treated with CZP. The axial SpA data reported here demonstrate that the prediction of long-term nonresponse (based on remission or low disease activity) was independent of the presence of radiographic sacroiliitis and provides further evidence that the use of treat-to-target methods can be applied across the spectrum of axial SpA patients, inclusive of both the ankylosing spondylitis and nonradiographic axial SpA subpopulations. Furthermore, these concepts were applicable when using either clinician-rated outcomes or patient self-reported outcomes as the predictor.

In this article we present individual patient data, which show that very few patients with high or very high disease activity at week 12 had moderate or inactive disease at any

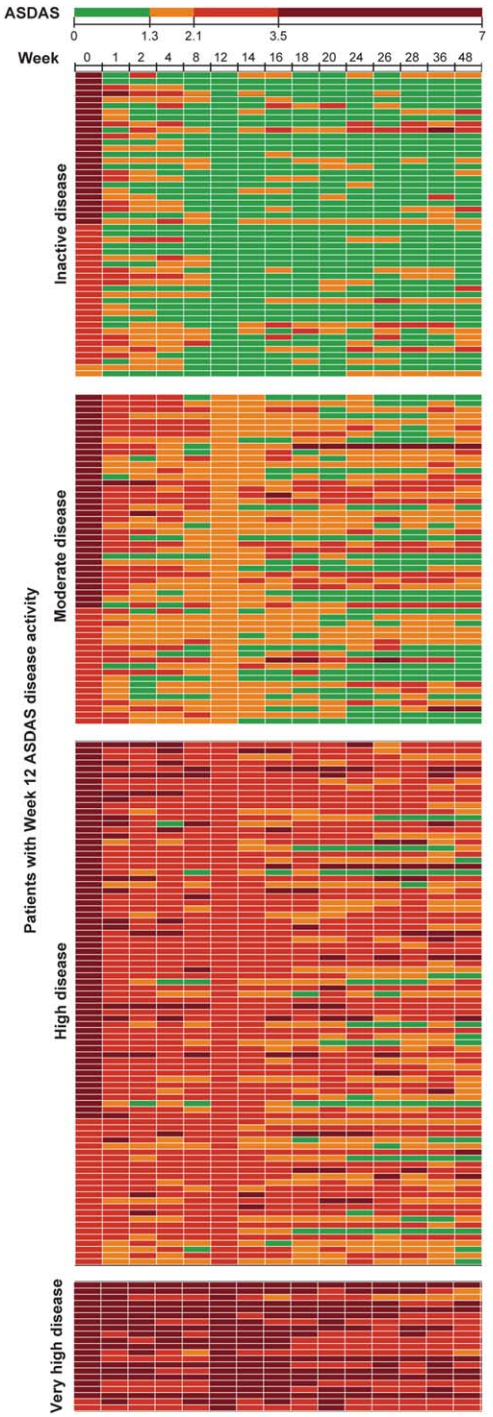

Figure 5. Heat map representing Ankylosing Spondylitis Disease Activity Score (ASDAS) disease activity at each visit grouped by patients' week-12 ASDAS category and sorted by baseline ASDAS.

time point thereafter, and that the majority of patients with inactive disease at week 12 maintained this result throughout. This finding suggests that following initial CZP treatment, disease activity states are maintained over time, thus lending credibility to the prediction model used here, in which only one future time point is considered.

The analyses reported here have a number of limitations. One such limitation is the lack of validated thresholds for DAS28-CRP and BASDAI. Although the DAS28-CRP is not validated in PsA, most patients in the study had polyarticular disease and therefore DAS28-CRP was felt to be the most appropriate measure in the absence of another well-accepted and validated measure in PsA to assess disease activity, although there is also debate about the thresholds of remission and low disease activity in RA. A second potential limitation in these analyses is the use of last observation carried forward imputation for axial SpA analyses for the ASDAS and BASDAI outcome measures, as has been previously used when reporting these outcomes from the RAPID-axSpA trial (7). However, the number of patients achieving ASDAS inactive disease remained similar when an alternative, more conservative imputation method (nonresponder) was used. As the number of patients affected was so low, the outcomes of this investigation were unlikely to be impacted by a change in imputation methodology. A further limitation is the use of data from clinical trials, which may mean that these results are not representative of the wider axial SpA and PsA patient populations, as clinical trial populations tend to have worse disease activity and fewer comorbidities than the general patient population. Finally, the results are restricted by the limited number of patients in the ankylosing spondylitis and nonradiographic axial SpA subpopulations.

Here we have shown that by using disease activity state or, to a lesser extent, clinical response during the first 12 weeks of CZP treatment, we were able to identify a subset of axial SpA or PsA patients who are unlikely to achieve long-term treatment goals. For the treating clinician in practice, discontinuation of CZP treatment should be considered in axial SpA patients with ASDAS very high disease activity or BASDAI >6 after 12 weeks of CZP treatment, as these patients are very unlikely to achieve treatment targets (ASDAS inactive disease or BASDAI <2 and normal CRP) at later time points. Moreover, patients at week 12 who still have ASDAS high disease activity or BASDAI >4 have only a small chance to reach the treatment target and stopping treatment should be considered. Similarly, for PsA patients with DAS28-CRP >5.1 after 12 weeks of CZP treatment, careful consideration should be given before continuing treatment with CZP, as these patients are unlikely to go on to achieve MDA. Also for patients with DAS28-CRP >3.2 to 5.1, the risk/benefit of continuation should be carefully considered, as reaching the target is achieved by a small percentage of patients. Although early clinical response was not as strong a negative predictor for the lack of achievement of long-term treatment targets, these results support discontinuation of CZP treatment after 12 weeks in axial SpA patients with <1 unit improvement in BASDAI at week 12, as they are also unlikely to achieve later treatment targets. This negative prediction approach may enable physicians adopting a treat-to-target strategy to determine early on when to change therapy in patients not responding to CZP.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. van der Heijde had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Deodhar, Nurminen, Davies.

Acquisition of data. van der Heijde, Deodhar, Fleischmann, Mease, Rudwaleit.

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