Timing and Magnitude of Initial Change in Disease Activity Score 28 Predicts the Likelihood of Achieving Low Disease Activity at 1 Year in Rheumatoid Arthritis Patients Treated with Certolizumab Pegol: A Post-hoc Analysis of the RAPID 1 Trial

DÉSIRÉE VAN DER HEIJDE, EDWARD C. KEYSTONE, JEFFREY R. CURTIS, ROBERT B. LANDEWÉ, MICHAEL H. SCHIFF, DINESH KHANNA, TORE K. KVIEN, LUCIAN IONESCU, LEON M. GERVITZ, OWEN R. DAVIES, KRISTEL LUIJTENS, and DANIEL E. FURST

ABSTRACT. ***Objective***. To determine the relationship between timing and magnitude of Disease Activity Score [DAS28(ESR)] nonresponse (DAS28 improvement thresholds not reached) during the first 12 weeks of treatment with certolizumab pegol (CZP) plus methotrexate, and the likelihood of achieving low disease activity (LDA) at 1 year in patients with rheumatoid arthritis.

Methods. In a post-hoc analysis of the RAPID 1 study, patients achieving LDA [DAS28(ESR) ≤ 3.2] at Year 1 were assessed according to DAS28 nonresponse at various timepoints within the first 12 weeks.

Results. Seven-hundred eighty-three patients were included (CZP 200 mg, n = 393; CZP 400 mg, n = 390). A total of 86.9% of patients in the CZP 200 mg group had a DAS28 improvement of ≥ 1.2 by Week 12. Of the 13.1% of patients with DAS28 improvement < 1.2 by Week 12, only 2.0% had LDA at Year 1. Failure to achieve LDA at Year 1 depended on timing of nonresponse — 22.3%, 8.4%, and 2.0% of patients with DAS28 improvement < 1.2 by Weeks 1, 6, and 12, respectively, had LDA at Year 1 — and magnitude of initial lack of DAS28 improvement; for example, compared with the patients with DAS28 < 1.2 improvement, fewer patients with DAS28 < 0.6 had LDA at Year 1 (17.4%, 2.4%, and 0.0% at Weeks 1, 6, and 12, respectively).

Conclusion. Failure to achieve improvement in DAS28 within the first 12 weeks of therapy was predictive of a low probability of achieving LDA at Year 1. Moreover, the accuracy of the prediction was found to be strongly dependent on the magnitude and timing of the lack of the response. (Clinical Trial Registration Nos. NCT00152386 and NCT00175877). (First Release May 15 2012; J Rheumatol 2012;39:1326–33; doi:10.3899/jrheum.111171)

Key Indexing Terms:
CERTOLIZUMAB PEGOL RHEUMATOID ARTHRITIS DISEASE ACTIVITY PREDICTION

From the Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands; Rebecca MacDonald Center for Arthritis and Autoimmune Disease, Mount Sinai Hospital, Toronto, Ontario, Canada; Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, Alabama, USA; Academic Medical Center/University of Amsterdam and Atrium Medical Center, Heerlen, The Netherlands; Rheumatology Division, University of Colorado School of Medicine, Denver, Colorado, USA; Division of Rheumatology, University of Michigan, Ann Arbor, Michigan, USA; Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway; UCB Pharma, Brussels, Belgium; UCB Pharma, Smyrna, Georgia, USA; and Division of Rheumatology, UCLA, Los Angeles, California, USA.

Supported by UCB Pharma, which sponsored the clinical trial from which the post-hoc analyses were performed. Prof. van der Heijde has received consultant fees from Abbott, Amgen, BMS, Centocor, Chugai, Merck, Novartis, Pfizer, Roche, Sanofi, UCB Pharma, and Wyeth, and is a member of a Speaker's Bureau for UCB Pharma. Prof. Keystone has received grants/research support from Abbott, Amgen, AstraZeneca, BMS, Centocor, F. Hoffmann-La Roche Inc., Genzyme, Merck, Novartis, Pfizer, and UCB Pharma; and has also received consultancy fees from Abbott, AstraZeneca, Biotest, BMS, Centocor, F. Hoffmann-La Roche Inc., Genentech, Merck, Nycomed, Pfizer, and UCB Pharma; and has received speaker honoraria from Abbott, BMS, F. Hoffmann-La Roche, Merck, Pfizer, and UCB Pharma. Dr. Curtis has received research grants and/or consulting/honoraria from Amgen, Abbott, UCB Pharma, Pfizer, BMS, Centocor, Genentech/Roche, and CORRONA. He also receives support from the NIH (AR053351) and AHRQ (R01HS018517). Prof. Landewé has served as a consultant for Abbott, Amgen, BMS, Centocor, Pfizer, Roche, Schering-Plough, UCB Pharma, and Wyeth. Prof. Schiff has received grant/research support and has served as a consultant for UCB Pharma. Dr. Khanna serves as a consultant for UCB Pharma and is a member of a Speaker's Bureau for UCB Pharma; he also receives support from the American College of Rheumatology and NIH/NIAMS. Prof. Kvien has received grant/research support from UCB Pharma, Abbott, BMS, Roche, Schering-Plough, Wyeth, Pfizer, and MSD; and has served as a consultant/speaker for the same companies. Dr. Gervitz is an employee of UCB Pharma and owns shares of UCB Pharma. Prof. Furst has received grant/research support from Abbott, Actelion, Amgen, BMS, Centocor, Genentech, Gilead, GSK, Novartis, Roche, and UCB Pharma; he has served as a consultant for Abbott, Actelion, Amgen, BMS, Centocor, Genentech, Gilead, Novartis, and UCB Pharma; he is a member of a Speaker's Bureau for Abbott, Actelion, and UCB Pharma (no promotional talks).

D. van der Heijde, MD, PhD, Professor, Department of Rheumatology, Leiden University Medical Center; E.C. Keystone, MD, FRCPC, Professor of Medicine, University of Toronto; J.R. Curtis, MD, Associate

Professor of Medicine, Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham; R.B. Landewé, MD, PhD, Professor, Academic Medical Center/University of Amsterdam and Atrium Medical Center; M.H. Schiff, MD, Clinical Professor of Medicine, Rheumatology Division, University of Colorado School of Medicine; D. Khanna, MD, MS, Associate Professor of Medicine, Division of Rheumatology, University of Michigan; T.K. Kvien, MD, PhD, Professor of Rheumatology, Department of Rheumatology, Diakonhjemmet Hospital; L. Ionescu, MD, UCB Pharma; L.M. Gervitz, PhD, UCB Pharma; O. Davies, PhD, UCB Pharma; K. Luijtens, PhD, UCB Pharma; D.E. Furst, MD, Carl M. Pearson Professor of Rheumatology, Division of Rheumatology, UCLA.

Address correspondence to Prof. D. van der Heijde, Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands. E-mail: d.vanderheijde@kpnplanet.nl

Accepted for publication March 21, 2012.

Studies have demonstrated the importance of early control of disease activity in rheumatoid arthritis (RA) using intensive treatment and management strategies to obtain longterm clinical benefit[1]. Swift identification of patients who are unlikely to have a longterm response allows for early adjustment of treatment and may result in better control of disease activity[2]. Nevertheless, there are currently no good biomarkers or other indicators capable of predicting response or longer-term benefit[3]. In the absence of such indicators, timing of onset of response to drug therapy has emerged as one of the strongest predictors of longterm outcomes[4,5,6,7,8]. However, the use of clinical data collected soon after initiation of treatment to act as a predictor of nonresponse [i.e., failing to achieve low disease activity (LDA) at 1 year] has received far less attention[2]. This is important since it would limit exposure to potentially expensive therapies that patients are unlikely to benefit from.

The negative predictive value of failing to achieve improvement in disease activity — measured by Disease Activity Score [DAS28(ESR)] — during the first 12 weeks of certolizumab pegol (CZP) therapy was investigated in this post-hoc analysis of the Rheumatoid Arthritis PreventIon of structural Damage (RAPID) 1 trial[9]. This was accomplished by observing the effect of timing and magnitude of DAS28(ESR) nonresponse on the likelihood of achieving LDA (DAS28 ≤ 3.2) at Year 1.

MATERIALS AND METHODS

Patient population. The RAPID 1 study (NCT00152386) is described in detail[9]. Briefly, eligible patients were randomized to methotrexate (MTX) plus (1) placebo, or subcutaneous CZP 400 mg at Weeks 0, 2, and 4, then (2) 200, or (3) 400 mg every other week (EOW) for 52 weeks. Patients who completed 52 weeks of RAPID 1 (completers), or who failed to achieve an ACR20 response at both Weeks 12 and 14 and had to be withdrawn at Week 16 per study protocol (withdrawers), were given the option to enter an open-label extension (OLE) study of CZP 400 mg EOW plus MTX (NCT00175877).

Assessments. Analyses were performed in patients initially randomized to active treatment with CZP to examine the relationship between initial lack of improvements in disease activity and likelihood of achieving LDA at Year 1. The proportion of patients who had LDA at Year 1 and at both Years 1 and 2 was cross-tabulated according to magnitude of DAS28 nonresponse up to Weeks 1, 2, 4, 6, 8, 10, and 12 and DAS28 improvement thresholds (0.3, 0.6, 0.9, 1.2, 1.5, and 1.8 points). LDA at Year 1 was also evaluated according to DAS28 baseline quartiles (≤ 6.34, > 6.34 to ≤ 6.95, > 6.95 to ≤ 7.48, > 7.48).

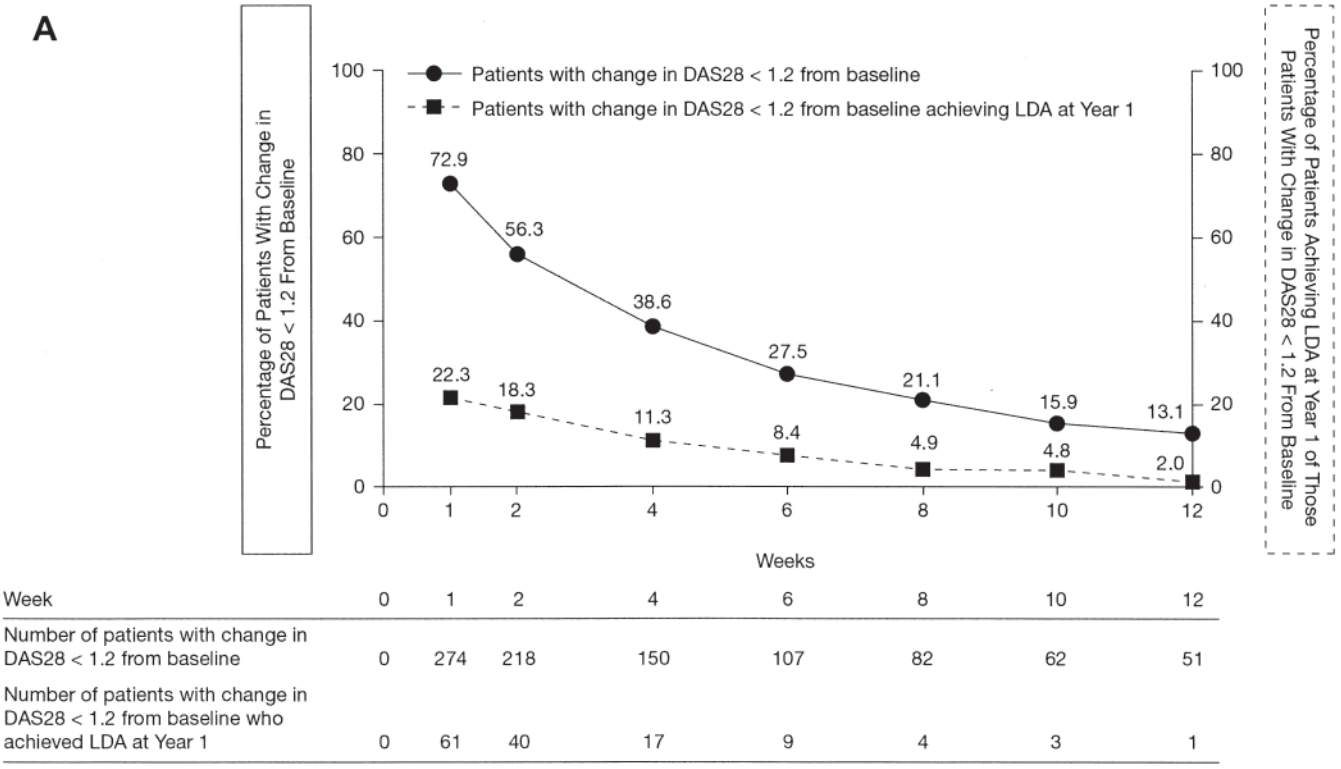
Statistical analyses. The analysis was conducted on the intent-to-treat (ITT) population. The number of patients at each timepoint varies slightly from the ITT numbers owing to nonimputable missing data for the predictor variables. For assessment of LDA at Year 1, last observation carried forward (LOCF) was used to account for missing data (e.g., after withdrawal from RAPID 1 or use of rescue medication). LOCF was also used for assessment of LDA at Years 1 and 2 (patients who did not reconsent to enter the OLE, received rescue medication, or withdrew from the OLE). Nonresponder populations of patients evaluated according to improvements in DAS28 up to each timepoint were not mutually exclusive, e.g., the group of nonresponders at the 1.2-point level (i.e., decrease < 1.2) included < 0.3, < 0.6, and < 0.9 nonresponders.

RESULTS

A total of 783 patients were included in this post-hoc analysis (CZP 200 mg, n = 393; CZP 400 mg, n = 390). The mean baseline DAS28 was 6.9, with 98% of patients in high disease activity (DAS28 > 5.1). The average disease duration at baseline was 6.1 years.

The nonresponder population was examined to determine if the magnitude of lack of change in DAS28 or the timepoint at which it is measured could be used to predict likelihood of achieving LDA at Year 1. Patients who failed to achieve a DAS28 improvement of ≥ 1.2 units at later timepoints of the first 12 weeks of treatment with CZP were less likely to have LDA at Year 1 than those who failed to achieve DAS28 improvement ≥ 1.2 at earlier timepoints (Figure 1A). In the CZP 200 mg group, 86.9% (338/389) had an improvement in DAS28 of ≥ 1.2 by Week 12. Specifically, of the 13.1% of patients with DAS28 improvement < 1.2 (51/389) by Week 12, only 1 patient (2.0%) achieved LDA at Year 1. Of the 107 patients with DAS28 improvement < 1.2 by Week 6 (27.5%), 9 patients (8.4%) had LDA at Year 1. For DAS28 magnitude, patients who failed to achieve lower improvements in DAS28 units at selected timepoints (Weeks 1, 6, and 12) were less likely to achieve LDA at Year 1 compared with those who failed to achieve greater reductions in disease activity (Figure 1B). For example, at Weeks 1, 6, and 12, respectively, 17.4%, 2.4%, and 0.0% of patients with DAS28 improvement < 0.6 had LDA at Year 1 compared with 22.3%, 8.4%, and 2.0% of those with DAS28 improvement < 1.2 (Figure 1B). These DAS28 data are also tabulated to illustrate in more detail the relationship between magnitude and timepoint of failure to achieve a DAS28 change as a function of the probability to achieve LDA at Year 1. DAS28 changes of < 0.3 by Week 4, < 1.2 by Week 8, or < 1.8 by Week 12 were associated with a < 5% chance of LDA at Year 1 (Table 1). Similar findings were also observed in those patients who received CZP 400 mg (data not shown).

As a sensitivity analysis the likelihood of LDA at Year 1 was also evaluated according to disease activity at baseline (by DAS28 baseline quartiles). The timing and magnitude of



Week	0	1	2	4	6	8	10	12
Number of patients with change in DAS28 < 1.2 from baseline	0	274	218	150	107	82	62	51
Number of patients with change in DAS28 < 1.2 from baseline who achieved LDA at Year 1	0	61	40	17	9	4	3	1

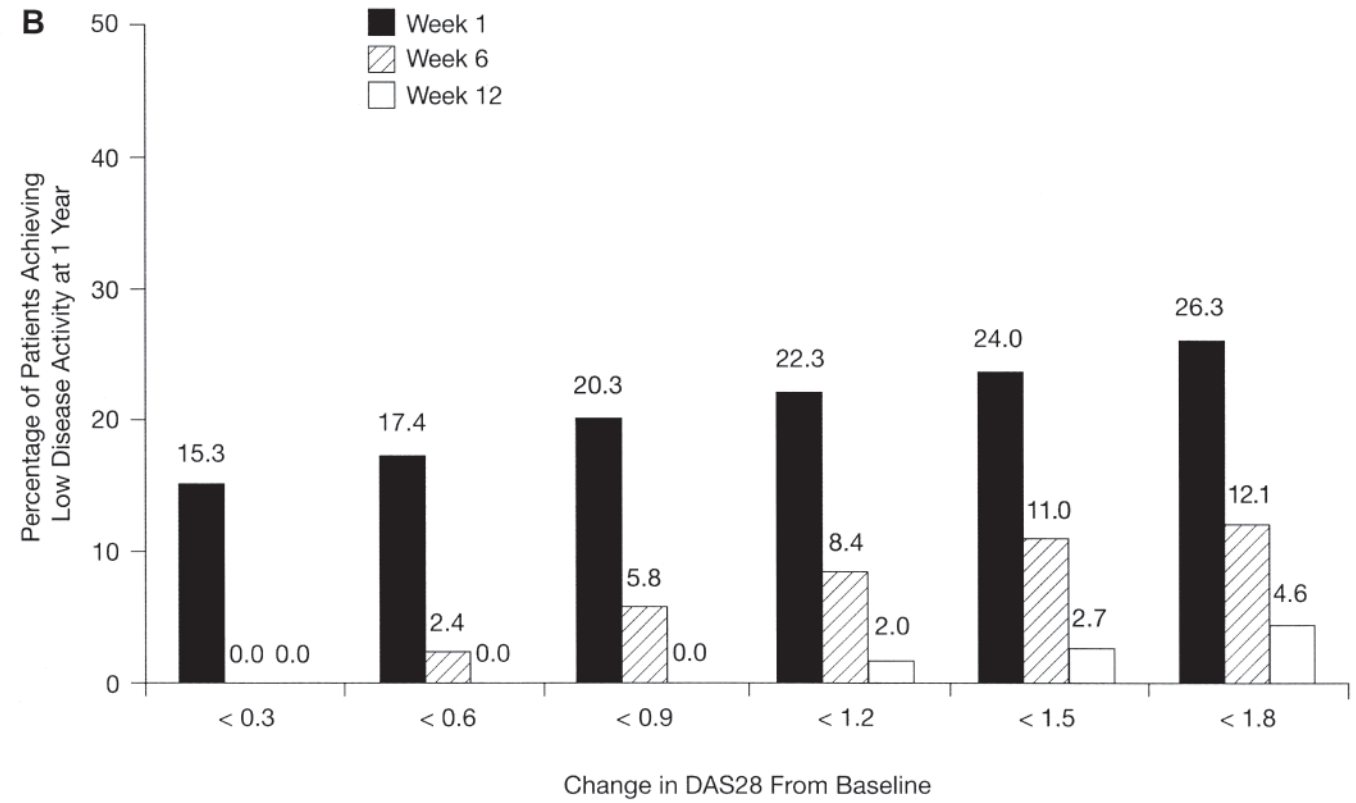


Figure 1. Response with certolizumab pegol (CZP) 200 mg plus methotrexate. A. Percentage of patients with DAS28 improvement < 1.2 up to Week 12 and percentage who subsequently had LDA at Year 1. B. Percentage of patients who achieved LDA at Year 1 by time to and magnitude of initial DAS28 response. LDA: low disease activity defined as DAS28(ESR) ≤ 3.2.

Table 1. LDA at Year 1 among patients treated with certolizumab pegol (CZP) 200 mg plus methotrexate (MTX), who failed to achieve certain DAS28 decreases within the first 12 weeks of treatment (ITT population; N = 393). LDA: low disease activity defined as DAS28(ESR) ≤ 3.2; n: number of patients not achieving a particular DAS28 threshold (row) up to a particular timepoint (column). Grey, white, and black shading indicate > 10%, 5%–10%, and < 5% probability of achieving LDA at 1 year, respectively. ITT: intent-to-treat.

DAS28 change from baseline	Percentage of patients achieving LDA at Year 1 out of patients (n) with a given DAS28 change up to a particular week (CZP 200 mg plus MTX)						
<0.3	15.3 (n=118)	11.9 (n=59)	2.8 (n=36)	0 (n=25)	0 (n=15)	0 (n=11)	0 (n=8)
<0.6	17.4 (n=178)	15.1 (n=106)	9.0 (n=67)	2.4 (n=42)	3.0 (n=33)	0 (n=25)	0 (n=18)
<0.9	20.3 (n=231)	15.1 (n=166)	9.3 (n=107)	5.8 (n=69)	3.8 (n=52)	0 (n=35)	0 (n=32)
<1.2	22.3 (n=274)	18.3 (n=218)	11.3 (n=150)	8.4 (n=107)	4.9 (n=82)	4.8 (n=62)	2.0 (n=51)
<1.5	24.0 (n=304)	19.9 (n=251)	14.1 (n=191)	11.0 (n=145)	6.1 (n=115)	6.5 (n=93)	2.7 (n=73)
<1.8	26.3 (n=331)	24.0 (n=292)	16.0 (n=231)	12.1 (n=182)	9.4 (n=149)	8.6 (n=128)	4.6 (n=108)
	1	2	4	6	8	10	12
	Week						

lack of DAS28 improvements influenced outcomes regardless of baseline disease activity; patients with lower baseline disease activity who failed to achieve DAS28 thresholds within the first 12 weeks were more likely to have LDA at Year 1 compared with those patients with higher levels of disease activity at baseline (Tables 2-5).

The analyses were repeated to examine the influence of DAS28 nonresponse on the ability to predict sustained longterm outcomes defined as LDA at both Years 1 and 2. A total of 670 patients went on to enter the OLE study, 334 randomized to CZP 200 mg and 336 to CZP 400 mg, with 574 (CZP 200 mg, n = 277; CZP 400 mg, n = 297) remain-

Table 2. Probability to achieve LDA at Year 1 among patients treated with certolizumab pegol (CZP) 200 mg plus methotrexate (MTX) according to baseline DAS28 ≤ 6.34. LDA: low disease activity defined as DAS28(ESR) ≤ 3.2; n: number of patients not achieving a particular DAS28 threshold (row) up to a particular timepoint (column). Grey, white, and black shading indicate > 10%, 5%–10%, and < 5% probability of achieving LDA at 1 year, respectively.

DAS28 change from baseline	Percentage of patients with baseline DAS28 ≤6.34 achieving LDA at Year 1 out of patients (n) with a given DAS28 change up to a particular week (CZP 200 mg plus MTX)						
<0.3	15.6 (n=32)	11.8 (n=17)	8.3 (n=12)	0 (n=9)	0 (n=5)	0 (n=3)	0 (n=2)
<0.6	22.0 (n=41)	15.4 (n=26)	10.0 (n=20)	0 (n=13)	0 (n=9)	0 (n=7)	0 (n=5)
<0.9	30.2 (n=53)	20.5 (n=39)	12.9 (n=31)	5.0 (n=20)	7.7 (n=13)	0 (n=9)	0 (n=8)
<1.2	33.3 (n=60)	28.8 (n=52)	18.4 (n=38)	6.9 (n=29)	4.5 (n=22)	0 (n=16)	0 (n=14)
<1.5	36.1 (n=72)	31.1 (n=61)	26.0 (n=50)	14.3 (n=35)	10.7 (n=28)	8.7 (n=23)	5.0 (n=20)
<1.8	38.0 (n=79)	37.1 (n=70)	28.3 (n=60)	20.8 (n=48)	17.1 (n=41)	15.4 (n=39)	11.1 (n=36)
	1	2	4	6	8	10	12
	Week						

Table 3. Probability to achieve LDA at Year 1 among patients treated with certolizumab pegol (CZP) 200 mg plus methotrexate (MTX) according to baseline DAS28 > 6.34 to ≤ 6.95. LDA: low disease activity defined as DAS28(ESR) ≤ 3.2; n: number of patients not achieving a particular DAS28 threshold (row) up to a particular timepoint (column). Grey, white, and black shading indicate > 10%, 5%–10%, and < 5% probability of achieving LDA at 1 year, respectively.

DAS28 change from baseline	Percentage of patients with baseline DAS28 >6.34–≤6.95 achieving LDA at Year 1 out of patients (n) with a given DAS28 change up to a particular week (CZP 200 mg plus MTX)						
<0.3	15.6 (n=32)	11.1 (n=18)	0 (n=11)	0 (n=8)	0 (n=5)	0 (n=5)	0 (n=3)
<0.6	17.5 (n=40)	11.1 (n=27)	5.6 (n=18)	0 (n=11)	0 (n=10)	0 (n=8)	0 (n=6)
<0.9	22.0 (n=50)	10.0 (n=40)	4.0 (n=25)	0 (n=16)	0 (n=12)	0 (n=10)	0 (n=8)
<1.2	27.4 (n=62)	17.6 (n=51)	8.3 (n=36)	8.0 (n=25)	4.8 (n=21)	5.9 (n=17)	0 (n=11)
<1.5	31.0 (n=71)	21.7 (n=60)	12.5 (n=48)	10.3 (n=39)	3.3 (n=30)	3.8 (n=26)	0 (n=18)
<1.8	32.1 (n=78)	25.7 (n=74)	15.0 (n=60)	10.0 (n=50)	7.3 (n=41)	5.7 (n=35)	0 (n=26)
	1	2	4	6	8	10	12
	Week						

Table 4. Probability to achieve LDA at Year 1 among patients treated with certolizumab pegol (CZP) 200 mg plus methotrexate (MTX) according to baseline DAS28 > 6.95 to ≤ 7.48. LDA: low disease activity defined as DAS28(ESR) ≤ 3.2; n: number of patients not achieving a particular DAS28 threshold (row) up to a particular timepoint (column). Grey, white, and black shading indicate > 10%, 5%–10%, and < 5% probability of achieving LDA at 1 year, respectively.

DAS28 change from baseline	Percentage of patients with baseline DAS28 >6.95–≤7.48 achieving LDA at Year 1 out of patients (n) with a given DAS28 change up to a particular week (CZP 200 mg plus MTX)						
<0.3	22.2 (n=27)	14.3 (n=14)	0 (n=5)	0 (n=2)	0 (n=1)	0 (n=1)	0 (n=1)
<0.6	22.0 (n=50)	24.1 (n=29)	21.4 (n=14)	14.3 (n=7)	16.7 (n=6)	0 (n=3)	0 (n=2)
<0.9	20.3 (n=69)	20.0 (n=50)	17.2 (n=29)	17.6 (n=17)	9.1 (n=11)	0 (n=7)	0 (n=7)
<1.2	21.3 (n=80)	19.0 (n=63)	11.9 (n=42)	17.9 (n=28)	11.8 (n=17)	15.4 (n=13)	8.3 (n=12)
<1.5	20.9 (n=86)	19.2 (n=73)	11.5 (n=52)	14.6 (n=41)	10.7 (n=28)	15.0 (n=20)	6.7 (n=15)
<1.8	23.2 (n=95)	22.5 (n=80)	14.8 (n=61)	13.3 (n=45)	11.1 (n=36)	11.5 (n=26)	4.8 (n=21)
	1	2	4	6	8	10	12
	Week						

ing in the OLE at the end of Year 2 (73% of the ITT population). At Year 2, LDA was achieved in 35.2% of the combined starting ITT population (274/778) and 26.0% of patients (202/778) had LDA at both Years 1 and 2. In the CZP 200 mg group, the timing and magnitude of a DAS28 nonresponse predicted LDA at both Years 1 and 2 (Table 6). The proportions of DAS28 nonresponders with LDA at both Years 1 and 2 were similar to the proportions of nonresponders with LDA at Year 1, particularly for patients with failure to achieve improvement in DAS28 between Weeks 6 and 12 (Table 6). Results were similar in patients treated with either CZP 200 mg or 400 mg (data not shown).

Table 5. Probability to achieve LDA at Year 1 among patients treated with certolizumab pegol (CZP) 200 mg plus methotrexate (MTX) according to baseline DAS28 > 7.48. LDA: low disease activity defined as DAS28(ESR) ≤ 3.2; n: number of patients not achieving a particular DAS28 threshold (row) up to a particular timepoint (column). Grey, white, and black shading indicate > 10%, 5%–10%, and < 5% probability of achieving LDA at 1 year, respectively. ITT: intent-to-treat.

DAS28 change from baseline	Percentage of patients with baseline DAS28 >7.48 achieving LDA at Year 1 out of patients (n) with a given DAS28 change up to a particular week (CZP 200 mg plus MTX)						
<0.3	7.4 (n=27)	10.0 (n=10)	0 (n=8)	0 (n=6)	0 (n=4)	0 (n=2)	0 (n=2)
<0.6	8.5 (n=47)	8.3 (n=24)	0 (n=15)	0 (n=11)	0 (n=8)	0 (n=7)	0 (n=5)
<0.9	10.2 (n=59)	8.1 (n=37)	0 (n=22)	0 (n=16)	0 (n=16)	0 (n=9)	0 (n=9)
<1.2	9.7 (n=72)	7.7 (n=52)	5.9 (n=34)	0 (n=25)	0 (n=22)	0 (n=16)	0 (n=14)
<1.5	9.3 (n=75)	7.0 (n=57)	4.9 (n=41)	3.3 (n=30)	0 (n=29)	0 (n=24)	0 (n=20)
<1.8	12.7 (n=79)	10.3 (n=68)	4.0 (n=50)	2.6 (n=39)	0 (n=31)	0 (n=28)	0 (n=25)
	1	2	4	6	8	10	12
	Week						

Table 6. LDA at both Years 1 and 2 among patients treated with certolizumab pegol (CZP) 200 mg plus methotrexate (MTX) who failed to achieve DAS28 decreases within the first 12 weeks of treatment (ITT population; N = 393). LDA: low disease activity defined as DAS28(ESR) ≤ 3.2; n: number of patients not achieving each DAS28 threshold (row) up to a particular timepoint (column). Grey, white, and black shading indicate > 10%, 5%–10%, and < 5% probability of achieving LDA at 1 year, respectively. ITT: intent-to-treat.

DAS28 change from baseline	Percentage of patients achieving LDA at Years 1 and 2 out of patients (n) with a given **DAS28** change up to a particular week (CZP 200 mg plus MTX)						
<0.3	13.7 (n=117)	10.5 (n=57)	2.9 (n=35)	0 (n=25)	0 (n=15)	0 (n=11)	0 (n=8)
<0.6	14.8 (n=176)	10.6 (n=104)	7.7 (n=65)	2.4 (n=41)	3.1 (n=32)	0 (n=24)	0 (n=17)
<0.9	16.8 (n=232)	10.8 (n=166)	8.3 (n=108)	5.8 (n=69)	3.8 (n=52)	0 (n=35)	0 (n=32)
<1.2	18.2 (n=274)	12.5 (n=216)	8.7 (n=149)	7.5 (n=106)	4.9 (n=82)	4.8 (n=62)	2.0 (n=51)
<1.5	20.1 (n=304)	14.4 (n=250)	12.0 (n=192)	9.1 (n=143)	6.1 (n=114)	7.6 (n=92)	4.1 (n=73)
<1.8	22.7 (n=331)	19.2 (n=291)	13.0 (n=230)	9.9 (n=182)	8.2 (n=146)	8.0 (n=125)	4.7 (n=107)
	1	2	4	6	8	10	12
	Week						

DISCUSSION

This post-hoc analysis demonstrates that the timing and magnitude of DAS28 nonresponse can be used to predict LDA at Year 1. Previous studies have demonstrated the role of early response as a marker of longterm clinical outcomes[4,5,6,7,8]. In our analysis, these observations were extended to focus on DAS28 nonresponse by Week 12 as a predictor of longterm outcomes. LDA was selected as the target in our analysis because the population had high disease activity at baseline and longstanding disease duration.

Although American College of Rheumatology/European League Against Rheumatism recommendations highlight the importance of remission as a therapeutic goal[10], LDA is suggested as an acceptable alternative in this patient population[2,11].

In patients who did not achieve certain DAS28 improvement thresholds, the timing of this nonresponse affected achievement of LDA at Year 1, with nonresponses up to later timepoints associated with a reduced likelihood for LDA. Additionally, the magnitude of DAS28 nonresponse up to Week 12 could predict lack of attainment of LDA at Year 1. Patients achieving changes in DAS28 < 1.8 units within the first 12 weeks of treatment were more likely to achieve LDA at Year 1 than those with lesser changes of < 1.5, < 1.2, or < 0.9 units. The timing and magnitude of the DAS28 nonresponse also consistently predicted the probability of achieving LDA at both Years 1 and 2. Early prediction of longterm disease activity may reduce costs, decrease unnecessary drug exposure, and allow prompt access to more effective treatment, especially if used with other methods (e.g., intensive imaging or biomarkers)[3].

The limitations of this report include the post-hoc design of our analyses compared with prospective approaches. Additionally, the generalizability of the results is potentially limiting because patients were difficult to treat and had high disease activity at baseline. To address this point we investigated the influence of baseline disease activity using the same approach. Analysis of DAS28 baseline quartiles demonstrated that the results are applicable to patients who have lower disease activity at baseline. For those patients in the lowest DAS28 baseline quartile (DAS28 ≤ 6.34) who failed to achieve a DAS28 improvement of ≥ 1.2 units by Week 12, none achieved LDA at Year 1. Indeed, no patient in this quartile who failed to achieve a DAS28 improvement of ≥ 1.2 units by Week 10 reached LDA at Year 1. Although 6.34 is still higher than the average disease activity of patients typically seen in clinical practice in Europe and the United States, the findings suggest that the modeling approach may be applicable to RA patients with lower disease activity. Nevertheless, further work in a broader population of patients more reflective of routine clinical practice, including patients with different disease duration and disease activity and receiving a range of concomitant therapies, is required to confirm the findings.

Initial observations examining the likelihood of LDA based on responses according to the Clinical Disease Activity Index are similar to the DAS28 findings reported here, although further work is warranted. It would also be interesting to examine the ability of the timing and magnitude of response to predict remission and to validate the current results using registry data.

The final limitation of this analysis is that the ability to predict nonresponse with high probability (< 5% misclassification) at Week 12 based on a DAS28 change of < 1.2 units applied to only 13% of the RAPID 1 population. Although the prediction of failure to reach LDA applies to a small cohort of patients, the model is useful for patients within the cohort. Additionally, at timepoints earlier than 12 weeks, the negative predictive value is high, and applies to a considerably higher percentage of this patient population than at the 12-week point. A compromise between acceptable risk of misclassification and the size of the population that experiences the nonresponse will ultimately depend on physician judgment.

These results demonstrate that the likelihood of LDA at Year 1 can be predicted early in the course of treatment with CZP based on the timing and magnitude of initial change in DAS28. Attaining either slower and/or a lower magnitude of response (greater magnitude of nonresponse) was associated with a lower rate of LDA at Year 1. These findings suggest that early response may be important in estimating longterm effectiveness of therapy and could be used to optimize "tight control" treatment strategies[11]. Identifying nonresponders early is potentially more useful than identifying responders; it will facilitate timely stopping of ineffective treatment at the individual patient level and allow exploration of alternative therapy options. For CZP, the findings suggest that patients who have not responded with a DAS28 improvement of at least 1.2 units by Week 12 are unlikely to have LDA after 1 year. Assuming that LDA is the (minimum) target of treatment, this information should facilitate decisions to halt CZP beyond Week 12.

ACKNOWLEDGMENT

We thank Marine Champsaur from UCB Pharma for critical review of the manuscript. We acknowledge the editorial services of Andrew Richardson from PAREXEL, which were funded by UCB Pharma.

REFERENCES

1. Knevel R, Schoels M, Huizinga TW, Aletaha D, Burmester GR, Combe B, et al. Current evidence for a strategic approach to the management of rheumatoid arthritis with disease-modifying antirheumatic drugs: A systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2010;69:987-94.
2. Smolen JS, Landewé R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 2010;69:964-75.
3. Smolen JS, Aletaha D, Grisar J, Redlich K, Steiner G, Wagner O. The need for prognosticators in rheumatoid arthritis. Biological and clinical markers: Where are we now? Arthritis Res Ther 2008;10:208.
4. Aletaha D, Funovits J, Keystone EC, Smolen JS. Disease activity early in the course of treatment predicts response to therapy after one year in rheumatoid arthritis patients. Arthritis Rheum 2007;56:3226-35.
5. Gulfe A, Kristensen LE, Geborek P. Six and 12 weeks treatment response predicts continuation of tumor necrosis factor blockade in rheumatoid arthritis: An observational cohort study from southern Sweden. J Rheumatol 2009;36:517-21.

6. Schiff M, Keystone E, Kvien T, Curtis J, Emery P, Luijtens K, et al. DAS28(ESR) response at week 12 is predictive of long-term disease activity in rheumatoid arthritis patients treated with certolizumab pegol. Ann Rheum Dis 2009;68 Suppl 3:543.
7. Ichikawa Y, Saito T, Yamanaka H, Akizuki M, Kondo H, Kobayashi S, et al; Study Group for the Japanese Ministry of Health, Labor and Welfare, Research for Establishment of Therapeutic Guidelines in Early Rheumatoid Arthritis Program. Clinical activity after 12 weeks of treatment with nonbiologics in early rheumatoid arthritis may predict articular destruction 2 years later. J Rheumatol 2010;37:723-9.
8. Keystone EC, Curtis JR, Fleischmann RM, Furst DE, Khanna D, Smolen JS, et al. Rapid improvement in the signs and symptoms of rheumatoid arthritis following certolizumab pegol treatment predicts better longterm outcomes: Post-hoc analysis of a randomized controlled trial. J Rheumatol 2011;38:990-6.
9. Keystone E, van der Heijde D, Mason D Jr, Landewé R, Vollenhoven RV, Combe B, et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: Findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum 2008;58:3319-29.
10. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis 2011;70:404-13.
11. Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G, et al.; T2T Expert Committee. Treating rheumatoid arthritis to target: Recommendations of an international task force. Ann Rheum Dis 2010;69:631-7.