The early clinical course of infliximab treatment in rheumatoid arthritis: results from the REMARK observational study

R. Westhovens[1], R.F. van Vollenhoven[2], D.T. Boumpas[3], M. Brzosko[4], K. Svensson[5], O. Bjorneboe[6], C.M. Meeuwisse, S. Srinivasan[7], P. Gaudin[8], J.S. Smolen[9], M.U. Rahman[10], R.L. Nelissen[11], N. Vastesaeger[12]

[1]Skeletal Biology and Engineering Research Center, Department of Development and Regeneration KU Leuven; Rheumatology, University Hospitals Leuven, Belgium; [2]Unit for Clinical Therapy Research, Inflammatory Diseases, Karolinska Institute, Stockholm, Sweden; [3]Rheumatology, Clinical Immunology, and Allergy, Institute of Molecular Biology and Biotechnology, University of Crete School of Medicine, Heraklion, Greece; [4]Department of Rheumatology and Internal Medicine, Pomeranian Medical University, Szczecin, Poland; [5]Skövde Hospital, Skövde, Sweden; [6]Martina Hansens Hospital, Gjettum, Norway; [7]Merck & Company, Inc, Kenilworth, NJ, USA; [8]Department of Rheumatology, University Hospital, Grenoble, CHU Hôpital Sud, Echirolles, France; [9]Division of Rheumatology, Department of Medicine 3, Medical University of Vienna and 2nd Department of Medicine, Hietzing Hospital, Vienna, Austria; [10]Clinical Research, Immunology, Centocor, Malvern, PA, and University of Pennsylvania School of Medicine, Philadelphia, PA, USA; [11]Department of Immune Therapies, Merck, Sharp, & Dohme, Oss, The Netherlands; [12]Department of Immunology, Merck, Sharp, & Dohme, Inc, Brussels, Belgium.

Abstract

Objective

We aimed to describe patterns of disease activity during infliximab plus methotrexate (MTX) treatment and explore C-reactive protein (CRP) as a potential marker of early response.

Methods

REMARK was a phase IV, open-label, observational study of infliximab-naïve adults with rheumatoid arthritis (RA) who received infliximab 3 mg/kg plus MTX for 14 weeks. Treatment response was evaluated in 3 subgroups: patients with <1 year disease duration who were TNF-inhibitor (TNFi)-naïve, patients with ≥1 year disease duration who were TNFi-naïve, and patients who had previous TNFi failure or intolerance. In post hoc analyses, CRP kinetic profiles were analysed by EULAR response (good, moderate, non-response) in REMARK and in an independent replication with data from the ASPIRE study.

Results

In the efficacy-evaluable population (n=662), median 28-joint disease activity score (DAS28) improved from baseline to Week 14 (5.2 vs. 3.6, p<0.0001). Regardless of disease history subgroup, most patients had good or moderate EULAR responses at Weeks 2 (64.9%), 6 (74.1%), and 14 (73.6%). DAS28 and its components did not differ across patient subgroups. Disease flare occurred in 16.2% of patients. CRP levels declined markedly at Week 2, but patients who were EULAR non-responders at Week 14 showed a CRP rebound at Weeks 6 and 14. This CRP pattern was independently replicated in data from ASPIRE. Adverse events were consistent with the known risk profile of infliximab.

Conclusion

Infliximab plus MTX treatment in patients with RA rapidly diminished disease activity. A unique pattern of CRP rebound was found in non-responders early in treatment.

Key words

rheumatoid arthritis, infliximab, C-reactive protein, dose optimisation, TNF inhibitors

Rene Westhovens MD, PhD
Ronald F. van Vollenhoven, MD, PhD
Dimitrios T. Boumpas, MD
Marek Brzosko, MD, PhD
Karin Svensson
Olav Bjorneboe, MD
Cees M. Meeuwisse
Shankar Srinivasan, PhD
Philippe Gaudin
Josef S. Smolen, MD
Mahboob U. Rahman, MD, PhD
Rob L. Nelissen, PhD
Nathan Vastesaeger, MD

Please address correspondence to:
Nathan Vastesaeger, Director,
Medical Affairs,
Merck & Co., Inc.,
Lynx Binnenhof 5,
Brussels B-1200, Belgium.
E-mail: nathan.vastesaeger@merck.com

Received on April 19, 2013; accepted in revised form on November 14, 2013.

Funding: REMARK was sponsored by Integrated Therapeutics Group, Inc., a subsidiary of Schering-Plough Corporation. Additional analyses for this publication were supported by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ.

Competing interests: see page 322.

Introduction

The chronic inflammation of rheumatoid arthritis (RA) progressively leads to joint pain and stiffness, cartilage and bone damage, and decreasing physical function and quality of life (1-3). Current treatment models promote intensively treating inflammation early in the disease course with methotrexate (MTX) and other disease-modifying antirheumatic drugs (DMARDs) (4-6) or bridging glucocorticoids (6). If this strategy is insufficiently effective, control of inflammation, clinical symptoms, radiographic progression, and quality of life can be significantly improved in many patients upon treatment with a combination of MTX and a tumour necrosis factor alpha inhibitor (TNFi) (7-10). However, not all patients respond adequately to treatment with TNFis. In addition, maximising effectiveness of TNFis may require dose increase for some patients (11).

Treatment with the TNFi infliximab is typically initiated with 3 mg/kg infusions in a dense induction series at Weeks 0, 2, and 6, followed with a maintenance dose every 8 weeks (12).

Although the US and European infliximab product labels support dosage increases for patients who lose response or have inadequate response (12, 13), and practice patterns indicate that clinicians sometimes choose to escalate dosages (11, 14, 15), no clear consensus has been reached on the value of dose escalation or which patients might benefit most from it.

It would be helpful to have clearer predictors of early response to help identify patients who are most likely to achieve good response with continued treatment and those who may need dose adjustment. Potential predictors include disease or treatment history, previous TNFi exposure, or various biomarkers. For example, high pretreatment C-reactive protein (CRP) concentrations have been shown to correlate with low serum trough infliximab levels at Week 14 of treatment, suggesting that CRP might be used as a biomarker to identify patients who could benefit from dose escalation (16). Objective predictors reflecting inflammation may be important to justify upward dose adjustments that increase costs.

Here we report the results of REMARK, a prospective, open-label, observational study designed to help describe the course of early treatment with infliximab and evaluate possible predictors of treatment response. Initially, the study analysed disease activity (as measured by the 28-joint disease activity score [DAS28] and its components) in patients who had either failed or did not tolerate a TNFi or were TNFi-naive and had an RA disease duration of <1 year or ≥1 year. In a post hoc analysis, CRP was evaluated as a possible indicator of short-term infliximab treatment response. An independent replication of the results was performed using data from another study of infliximab treatment for early, active RA – the ASPIRE trial (8).

Materials and methods

Study design and procedures

REMARK (NCT00705289, protocol P04250) was a phase IV, 14-week, prospective observational cohort study of infliximab treatment in patients with RA. It was conducted at 91 European sites in 12 countries (Austria, Belgium, Denmark, France, Germany, Greece, Italy, The Netherlands, Norway, Poland, Portugal, and Sweden) from December 2005 to September 2008. Open-label 3 mg/kg infliximab was administered by intravenous infusion at Weeks 0, 2, 6, and 14. All patients received MTX in accordance with product labelling. Other medications were used at the discretion of the treating physician. Treatment was consistent with local country regulations and reimbursement guidelines. Efficacy and safety assessments were collected prior to the baseline infliximab infusion and prior to each subsequent infusion.

Prior to study initiation at each site, the clinical study protocol and the written informed consent form were reviewed and approved by an Independent Ethics Committee. This study was designed and performed in accordance with the Declaration of Helsinki and standards of good clinical research practice.

Patients

The study population included consecutive adult patients with a diagno-

sis of RA (1987 ACR criteria) who had early or established active disease, were naïve to infliximab (but not necessarily all TNFis), and had agreed, on the advice of their physicians, to initiate infliximab treatment in accordance with applicable label and reimbursement criteria.

Efficacy and safety measures

The following efficacy assessments were collected at baseline and Weeks 2, 6, and 14: DAS28 and its components; DAS28 disease activity states (low [DAS28 <3.2], moderate [DAS28 3.2 to 5.1], or high [DAS28 >5.1]); DAS28 remission status (DAS28 <2.6); and European League Against Rheumatism (EULAR) response status (good [DAS28 decrease of >1.2 from baseline with current DAS28 <3.2], moderate [DAS28 decrease >1.2 from baseline with current DAS28 ≥3.2 or a DAS28 decrease of 0.6–1.2 from baseline with current DAS28 ≤5.1], or non-response [DAS28 decrease <0.6 from baseline or DAS28 decrease of 0.6–1.2 from baseline with current DAS28 >5.1]). Individual components of DAS28 were: 28-joint tender joint count (TJC); 28-joint swollen joint count (SJC); CRP concentration (or erythrocyte sedimentation rate [ESR] if no CRP result was available); and patient's self-assessment of general health, as rated on a visual analog scale (VAS) from 0 mm (best possible) to 100 mm (worst possible). Disease flare was defined by using inverse EULAR criteria (DAS28 increase of 0.6–1.2 from Week 6 to Week 14 if the Week-14 DAS28 was >5.1 or any DAS28 increase >1.2 from Week 6 to Week 14). CRP and ESR in serum were analysed at a central laboratory. To assess safety, adverse events were collected and recorded at each infliximab infusion visit. No other safety assessments were performed.

Statistical analysis

The exploratory and descriptive nature of this study precluded a sample size calculation. Because of practical considerations the upper limit was set at 1500 patients.

The efficacy-evaluable population comprised all patients who received ≥1 dose of study drug and provided efficacy data at baseline and ≥1 follow-up visit. The safety population comprised all patients who received ≥1 dose of study drug. Analyses of demographic characteristics included all enrolled patients.

All efficacy analyses were performed using observed data. All tests of significance were 2-sided using a significance level of 0.05. All analyses were conducted using SAS Windows, version 8.2.

Baseline variables and adverse events were summarised using descriptive statistics. The relationship between disease activity (DAS28) and baseline demographic characteristics and disease history were analysed with Pearson correlations.

To evaluate the relationship between disease history and treatment response, patients were divided into 3 categories: patients with early RA (<1 year disease duration) who were naïve to all TNFis; patients with established RA (≥1 year disease duration) who were naïve to all TNFis; and patients who were TNFi-experienced (failed or did not tolerate previous treatment with another TNFi). These 3 groups were then compared with respect to baseline disease activity (mean DAS28) and changes in disease activity during treatment (DAS28 and its components, EULAR response status, and DAS28 remission) using mixed linear regression models controlling for age, sex, and baseline DAS28 and its components. Univariate contrasts were used as appropriate to explore pairwise differences.

To evaluate the usefulness of CRP as a predictor of response, CRP concentrations for patients in each EULAR response category at each visit were calculated. Group differences were analysed using mixed linear models, adjusting for baseline CRP and relevant baseline characteristics.

Results

Patient disposition and baseline characteristics

A total of 728 patients were enrolled, and the efficacy-evaluable population had 662 patients, of whom 84.6% (560/662) completed the 14-week study. In the safety population, 6.8% (49/721) of patients discontinued the study because of AEs; in 2.5% (18/721), the events were classified as serious.

Patients were predominantly female (571/728; 78.4%) with a mean age of 54.1 years and a median RA duration of 6.0 years (Table I). More patients were naïve to TNFis (78.8%, 574/720) than had prior TNFi experience (20.1%, 146/720). Adalimumab, etanercept, or other TNFis had been used previously by 11.8%, 10.6%, and 1.1% of patients, respectively.

For efficacy-evaluable patients (n=662) at baseline, mean DAS28 was 5.2 (SD=1.15; median 5.2), and 53.3% of patients had high disease activity (DAS28 >5.1). Weak, but statistically significant, positive correlations with baseline DAS28 were found for age (r=0.1402, $p<0.005$) and weight (r=0.1152, $p<0.005$), but not gender ($p=0.715$) or time since diagnosis ($p=0.799$).

Analyses of baseline disease activity by disease history subgroups

When the efficacy-evaluable patients were divided into the disease history subgroups, 76/662 (11.5%) were in the TNFi-naïve/early-RA subgroup, 447 (67.5%) were in the TNFi-naïve/established-RA subgroup, and 123 (18.6%) were in the TNFi-experienced subgroup. Sixteen patients could not be classified into a disease history subgroup because their date of diagnosis was missing. Median DAS28 was similar across the 3 disease history subgroups at baseline (Table I). Percentage of patients with each DAS28 disease activity level (high, medium, or low) at baseline was also determined for each of the subgroups. Baseline disease activity was high in 48.7% (37/76) of the TNFi-naïve/early RA subgroup, 51.9% (232/447) of the TNFi-naïve/established RA subgroup, and 61.0% (75/123) of the TNFi-experienced subgroup. Less than 5% of patients in any of the subgroups had low disease activity (DAS28 <3.2) at baseline.

Relationships between disease history and infliximab response

Overall, median DAS28 scores decreased by 25% at Week 2 of infliximab treatment and were stable until

Week 14 (baseline, 5.2; Week 2, 3.9; Week 6, 3.6; Week 14, 3.6; $p<0.0001$ for each visit *vs*. baseline). Each of the 3 disease history subgroups had a similar DAS28 pattern across visits (whether measured as mean or median scores), although the TNFi-experienced subgroup appeared to have the smallest numeric improvement at each visit after baseline (Fig. 1). Overall, reductions in all DAS28 components were similar across the 3 disease history subgroups at Weeks 2, 6, and 14, with more fluctuating courses for ESR and CRP and more stable improvements in SJC, TJC, and the VAS self-assessment of general health (Table II).

For a majority of patients, EULAR response was either good or moderate at Week 2 (64.9% [406/626]), Week 6 (74.1% [463/625]), and Week 14 (73.6% [415/564]). Although all 3 subgroups had similar initial responses, they differed somewhat in the pattern of good/moderate response from Week 6 to Week 14; the TNFi-naïve/early-RA subgroup had continued improvement (72.2% [52/72] to 81.8% [54/66]), the TNFi-naïve/established group stayed the same (75.1% [317/422] to 74.1% [281/379]), and the TNFi-experienced subgroup declined somewhat (72.2% [83/115] to 67.3% [70/104]) (Fig. 2A).

Disease flare at Week 14 was experienced by 16.2% of patients (75/463) who had a good or moderate EULAR response at Week 6. As shown in Fig. 2B, when disease history subgroups were compared, patients with TNFi experience appeared to be more likely to experience a flare (17/83 patients; 20.5%) than TNFi-naïve/early RA patients (7/52 patients; 13.5%) or TNFi-naïve/established RA patients (48/317 patients; 15.1%).

Analysis of DAS28 remission (DAS28 <2.6) indicated that approximately 23% of all efficacy-evaluable patients achieved remission at Weeks 6 and 14. At Week 6, the remission rates were 25.0% (18/72), 24.6% (104/422), and 15.7 (18/115), respectively, for the TNFi-naïve/early-RA, TNFi-naïve/established-RA, and TNFi-experienced groups. At Week 14, the rates were 19.7% (13/66), 24.5% (93/379), and 18.3% (19/104), respectively.

Table I. REMARK: baseline characteristics.

	All patients	Disease history subgroup		
		Early RA* + TNFi naïve	Established RA† + TNFi naïve	Failed/did not tolerate prior to TNFi
Demographic characteristics‡				
Gender	n=728	n=81	n=490	n=134
Male, n (%)	157 (21.6	25 (30.9))	105 (21.4)	20 (14.9)
Female, n (%)	571 (78.4)	56 (69.1)	385 (78.6)	114 (85.1)
Age, yrs	n=728	n=81	n=490	n=134
Mean (SD)	54.1 (13.08)	51.4 (13.49)	54.0 (13.10)	55.2 (11.98)
Weight, kg	n=719	n=81	n=489	n=132
Mean (SD)	71. 7 (14.92)	72.1 (13.50)	72.1 (15.39)	69.7 (13.71)
Height, cm	n=675	n=77	n=461	n=121
Mean (SD)	165.2 (8.36)	168.0 (7.89)	165.1 (8.42)	164.4 (7.92)
Disease and treatment history‡				
Duration of RA, yrs	n=703	n=81	n=489	n=133
Mean (SD)	9.0 (8.99)	0.5 (0.30)	9.8 (8.85)	11.5 (9.32)
Median	6.0	0.4	7.2	9.5
Radiographic				
Damage#	n=703	n=80	n=487	n=133
No, n (%)	224 (30.8)	48 (60.0)	144 (29.6)	32 (24.1)
Yes, n (%)	479 (65.8)	32 (40.0)	343 (70.4)	101 (75.9)
Disease activity at baseline¶				
DAS28	n=662	n=76	n=447	n=123
Mean (SD)	5.2 (1.15)	5.3 (1.16)	5.2 (1.14)	5.3 (1.16)
Median	5.2	5.1	5.2	5.4
$25^{th}/75^{th}$ percentiles	4.5/6.0	4.5/6.2	4.5/6.0	4.5/6.3
CRP (mg/dL)	n=617	n=72	n=416	n=115
Median	9.8	12.1	9.6	10.0
$25^{th}/75^{th}$ percentiles	4/26.5	3.6/36.5	4/26	4/29.7

*<1 year disease duration at baseline; †≥1 year disease duration at baseline; ‡All enrolled patients; #Erosion or bony decalcification as judged by the treating rheumatologist; ¶Efficacy-evaluable population. CRP: C-reactive protein; DAS28: disease activity score based on the assessment of 28 joints; max: maximum; min: minimum; RA: rheumatoid arthritis; SD: standard deviation; TNFi: tumour necrosis factor inhibitor; yrs: years.

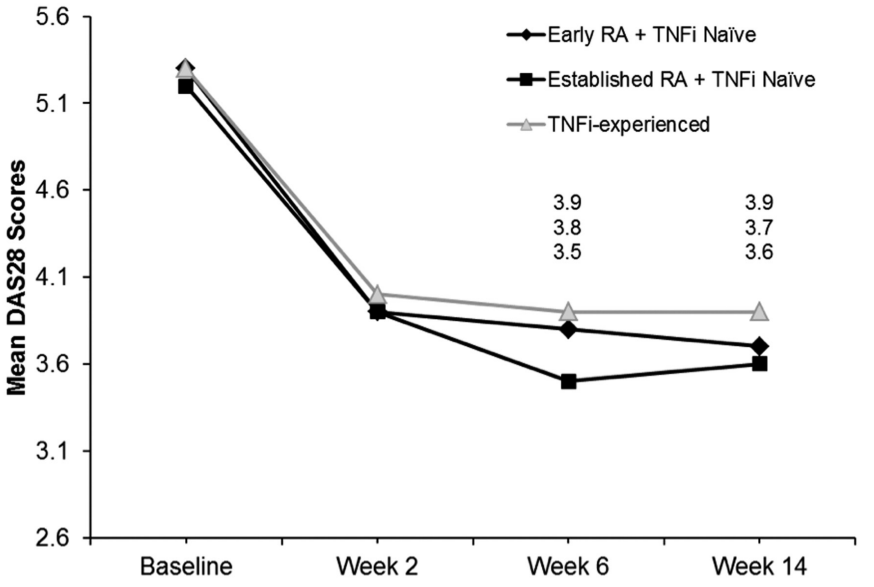

Fig. 1. DAS28 scores for each disease history group during infliximab treatment. DAS28: 28-joint disease activity score; RA: rheumatoid arthritis; TNFi: tumour necrosis factor inhibitor.

Table II. Disease activity improvements: reductions from baseline in DAS28 components.

DAS28 component	Disease history subgroup								
	Early RA* + TNFi naïve n=76			Established RA† + TNFi naïve n=447			Failed/did not tolerate prior to TNFi n=123		
	Wk 2	Wk 6	Wk 14	Wk 2	Wk 6	Wk 14	Wk 2	Wk 6	Wk 14
TJC28, n	76	73	67	440	433	388	119	117	109
Median	4.0	5.0	5.0	3.0	5.0	5.0	4.0	5.0	5.0
25th/75th percentile	6/1	9/1	10/0	7/0	9/1	9.5/1	8.4/0	10/1	10/1
SJC28, n	76	73	67	438	433	388	119	117	109
Median	2.0	4.0	4.0	3.0	4.0	4.0	2.0	3.0	4.0
25th/75th percentile	5/1	7/1	8/1	6/0	8/1	8/1	5.6/0	7/1	7.5/1
General health VAS,‡ n	76	73	66	402	392	347	108	107	95
Mean	19.4	20.2	20.6	16.4	22.4	21.9	15.2	16.1	18.3
(SD)	(20.97)	(27.45)	(30.19)	(26.34)	(27.0)	(27.78)	(21.68)	(23.49)	(24.64)
ESR (mm/hr), n	68	67	59	394	391	355	104	107	96
Median	7.5	5.0	5.0	8.0	7.0	4.0	8.0	4.0	3.0
25th/75th percentile	17/1	16/2	14/5	18/2	18/1	15/3	19.5/0	18/3	14.5/6.5
CRP (mg/dL), n	69	68	63	386	385	345	104	107	95
Median	6.0	2.5	2.0	5.0	3.9	2.3	5.3	2.0	2.0
25th/75th percentile	21.0/0.2	16/0	19/0.5	16.9/0.1	15/0	10.4/0	16.2/0.1	13/0	9/2.2

*<1 year disease duration at baseline; †≥1 year disease duration at baseline; ‡Patient's self-assessment of general health based on a 100 mm VAS (0=best possible to 100=worst possible).
CRP: C-reactive protein; DAS28: disease activity score, based on 28 specified joints; ESR: erythrocyte sedimentation rate; max: maximum; min: minimum; RA: rheumatoid arthritis; SD, standard deviation; SJC28: swollen joint count in 28 joints; TJC28: tender joint count in 28 joints; TNFi: tumour necrosis factor inhibitor; VAS: visual analogue scale; Wk: week.

Safety

Treatment-emergent AEs occurred in 33.8% (244/721) of patients in the safety population (Table III). AE severity was mild in 13.5% of patients, moderate in 16.5% of patients, and severe in 3.3% of patients. AEs observed in ≥1% of patients are listed in Table III. The most commonly reported category of AEs was infections and infestations (13.2%).

Serious AEs occurred in 40 (5.5%) patients, and no deaths occurred. The most frequently reported category of serious AE was infections and infestations (13 patients, 1.8%). AEs led to treatment discontinuation in 6.8% of patients (49/721); the events were serious in 2.5% of patients (18/721). AEs that led to discontinuation in more than 1 patient were rash (4 patients), hypersensitivity reaction (3 patients; serious in 1), and infusion-related reaction (3 patients; serious in 2).

Overall, the reported AEs were consistent with the known risk profile of infliximab, and no unexpected AEs were identified in this clinical practice setting.

Analysis of the relationship between EULAR response and CRP kinetics

One goal of REMARK was to explore possible markers of response that might be useful for assessing likelihood of continued response and guiding therapeutic decisions. Data from the planned analyses of REMARK showed substantial variability in CRP concentrations during infliximab treatment. After an initial overall decrease in median CRP from baseline (9.8 mg/dL) to Week 2 (4.0 mg/dL), CRP increased at Week 6 (4.9 mg/dL) and Week 14 (5.0 mg/dL), while most other DAS28 components were stable or continued to improve. Therefore, the value of CRP as a marker of response was evaluated by further exploring patterns of change in CRP concentrations during treatment in each EULAR response group. This post hoc analysis included only REMARK patients whose serum was available for CRP analysis at the central laboratory (n=481). Baseline characteristics in this subpopulation were representative of the total REMARK population. The percentages of patients in this subpopulation in each EULAR response category at Week 14 were as follows: good responders (34.5%, 166/481), moderate responders (41.1%, 198/481), and non-responders (24.3%, 117/481).

In all of the EULAR response groups, CRP concentrations steeply declined from baseline to Week 2, and the groups were not statistically different (Fig. 3A). In the good EULAR responder group, CRP remained stable at low levels through Week 14. In contrast, in the non-responder group, CRP concentration increased significantly from Weeks 2 to 6 (4.1 mg/dL to 6.8 mg/dL) and again at Week 14 (10.7 mg/dL). CRP levels in the moderate response group were intermediate compared with the other groups, increasing from 4.1 mg/dL to 6.0 mg/dL from Week 2 to Week 14. The good and moderate responder groups had statistically significantly lower CRP concentrations than the non-responder group at Weeks 6 and 14 (all $Ps < 0.001$).

Independent replication of CRP analysis

We sought to further validate the results from REMARK by replication

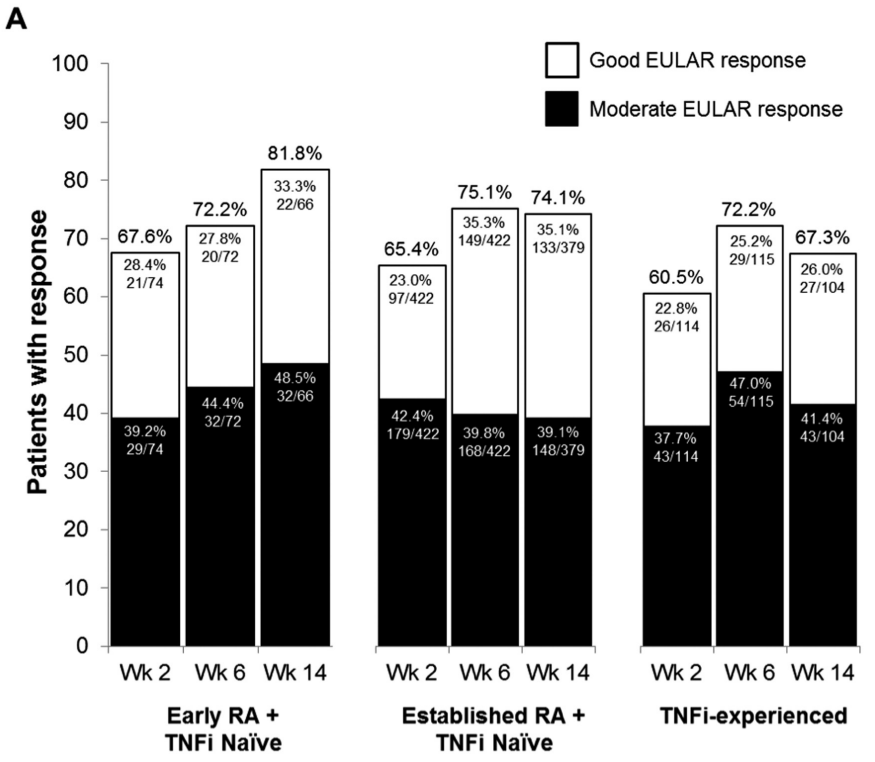

Fig. 2A. Percentage of patients with good and moderate EULAR responses to infliximab at Weeks 2, 6, and 14. Patients are grouped by disease history subgroups. Numbers at the top of the bars represent the sum of the percentages of patients who had good and moderate EULAR response in each group. EULAR: European League Against Rheumatism; RA: rheumatoid arthritis; TNFi: tumour necrosis factor inhibitor; Wk: week.

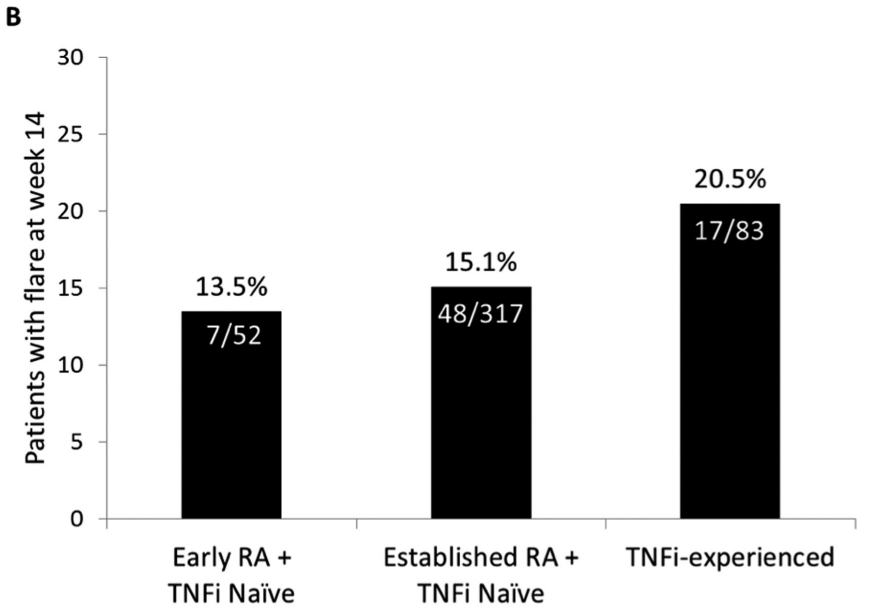

Fig. 2B. Disease Flare. Proportion of patients with flare, defined as good or moderate EULAR response at Week 6 followed by inverse EULAR response at Week 14. EULAR: European League Against Rheumatism; RA: rheumatoid arthritis; TNFi: tumour necrosis factor inhibitor.

of the analysis in an independent data set from a population of patients with RA who were treated with infliximab. Data from the ASPIRE trial were used for this analysis. Methods and results of the ASPIRE study have been previously described by St. Clair *et al*. (8). Briefly, ASPIRE was a phase-III, 54-week, double-blinded randomised, controlled trial in patients with early (3-year duration), active RA, as defined by the number of tender and swollen joints (6 or more) and the presence of other disease characteristics such as elevated CRP and morning stiffness. Patients in ASPIRE had no prior treatment with MTX or TNFis. During the ASPIRE trial, patients were randomly assigned to receive placebo plus MTX, infliximab 3 mg/kg plus MTX, or infliximab 6 mg/kg plus MTX. As in REMARK, serum was collected prior to infliximab infusion, and CRP analysis occurred at a central laboratory.

Patients from ASPIRE were included in this post hoc analysis if they had documented EULAR outcomes, were in the 3-mg/kg infliximab plus MTX arm of ASPIRE, and had CRP data available from the pertinent visits (n=277). As previously reported, patients in the ASPIRE group treated with 3-mg/kg infliximab plus MTX (n=359) were predominantly female (71%) with a mean age of 51 years (SD=12) and a mean disease duration of 0.8 years (SD=0.7). At baseline, this ASPIRE treatment group had a mean DAS28 of 6.6 (SD=1.1) and mean CRP of 2.9 mg/dL (SD=3.3). (8)

The percentages of patients who were in each EULAR response category at Week 14 were similar in ASPIRE and REMARK. Results for the ASPIRE subpopulation were as follows: good responders, 27.4% (n=76); moderate responders, 46.9% (n=130); and non-responders, 25.6% (n=71). The patterns of CRP concentrations in each of the 3 EULAR response groups during the first 14 weeks of treatment were similar to those reported for REMARK. In all 3 ASPIRE EULAR response groups, CRP improved from baseline to Week 2 of treatment, and the groups were similar at this early point in treatment. After Week 2, the good and moderate responders maintained low CRP until Week 14, while the non-responder group had a substantial increase in CRP at Weeks 6 and 14 (Fig. 3B).

Discussion

REMARK was a phase IV, 14-week, observational study that investigated early treatment response patterns in in-

Table III. Treatment-emergent adverse events in the safety population.

Type of TEAE	Patients with TEAEs n=721 n (%)	
Any TEAE	244	(33.8)
Relatedness to study medication:		
Unlikely	112	(15.5)
Possible	90	(12.5)
Probable	42	(5.8)
Severe or life-threatening TEAE	28	(3.9)
AE leading to treatment discontinuation	49	(6.8)
Serious TEAEs	40	(5.5)
Serious TEAEs leading to treatment discontinuation	18	(2.5)
Infusion-related reaction	2	(0.3)
Angioedema	1	(0.1)
Arthritis	1	(0.1)
Bronchopneumonia	1	(0.1)
Cellulitis	1	(0.1)
Cholecystitis	1	(0.1)
Device failure	1	(0.1)
Diabetes mellitus inadequate control	1	(0.1)
Disseminated tuberculosis	1	(0.1)
Esophageal neoplasm	1	(0.1)
Gait disturbance	1	(0.1)
Hypersensitivity	1	(0.1)
Hypertension	1	(0.1)
Hyperthermia	1	(0.1)
Joint prosthesis	1	(0.1)
Nausea	1	(0.1)
Oropharyngeal pain	1	(0.1)
Pneumocystis jiroveci pneumonia	1	(0.1)
Pneumonia legionella	1	(0.1)
Pyrexia	1	(0.1)
Speech disorder	1	(0.1)
Thrombosis	1	(0.1)
Deaths	0	
TEAEs reported by ≥1% of patients*		
Infections and infestations		
Bronchitis	16	(2.2)
Urinary tract infection	12	(1.7)
Nasopharyngitis	11	(1.5)
Rhinitis	7	(1.0)
Gastrointestinal disorders		
Nausea	12	(1.7)
Diarrhoea	9	(1.2)
General disorders and administration site conditions		
Pyrexia	11	(1.5)
Skin and subcutaneous tissue disorders		
Rash	17	(2.4)
Nervous system disorders		
Headache	23	(3.2)
Vascular disorders		
Hypertension	10	(1.4)
Cardiac disorders		
Tachycardia	7	(1.0)

*An additional 2 serious AEs include a malignancy (breast cancer) that occurred 11 days after the last dose of study medication and an esophageal neoplasm that occurred 21 days after the last dose of study medication.
AE: adverse events; TEAE: treatment-emergent adverse events.

fliximab-naïve RA patients. Treatment with infliximab 3mg/kg plus MTX resulted in diminished disease activity (measured by DAS28 and EULAR response) as early as Week 2. By Week 14, 74% of patients had achieved good or moderate EULAR response and 23% had achieved DAS28 remission. This observational study yielded treatment responses that were similar to those reported in ATTRACT, a randomised, controlled trial (7).

One goal of REMARK was to identify variables that might predict infliximab response. To that end, treatment response patterns were evaluated in patients with 3 different disease/treatment histories: patients who were TNFi-naïve with <1-year disease duration, patients who were TNFi-naïve with ≥1-year disease duration, and patients with previous TNFi failure/intolerance. Overall, the 3 groups had similar patterns of disease activity during treatment, as measured by DAS28, DAS28 components, and EULAR response. It should be noted that, although the group differences were not statistically significant, the TNFi-experienced group had the least improvement in DAS28 at Weeks 6 and 14, the lowest rate of good/moderate EULAR response at Week 14 (67.3%), and the highest rate of flare (20.5%).

Although overall EULAR response rates in the REMARK study were good, 16.2% of patients lost response at Week 14. Examination of the individual components of DAS28 indicated that most components were stable or continued to improve to Week 14. However, CRP showed a pattern of initial improvement from baseline (9.8 mg/dL) to Week 2 (4.0 mg/dL), followed by an increase at Weeks 6 (4.9 mg/dL) and 14 (5.0 mg/dL). The loss of response and increase in CRP coincided with the timing of the increased infliximab dosing intervals, suggesting that the loss of response may be explained by decreased dosing frequency rather than by disease activity fluctuation, especially given the rapid improvement in DAS28 that was observed following initiation of infliximab treatment.

In clinical practice, physicians sometimes observe that patients benefit for about 6 weeks after an infliximab in-

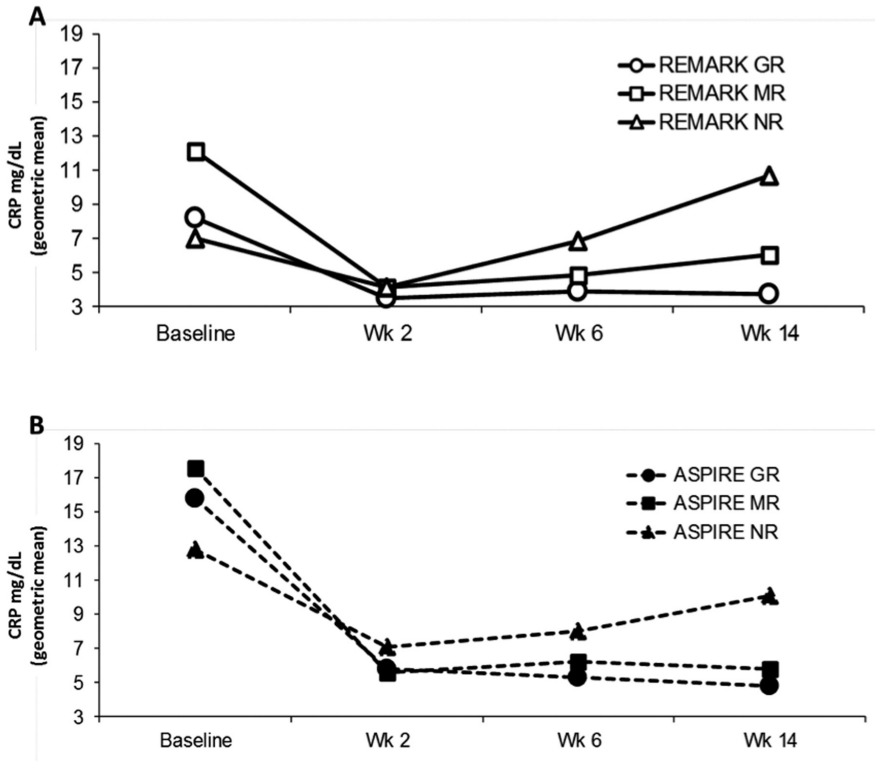

Fig. 3. A. Estimated CRP concentrations in each EULAR response group in REMARK. B. Estimated CRP concentrations in each EULAR response group in ASPIRE. Estimated CRP concentrations are geometric means and are adjusted for baseline CRP and patient characteristics. ASPIRE; CRP: C-reactive protein; EULAR: European League Against Rheumatism; GR: Good EULAR response; MR: Moderate EULAR response; NR: EULAR non-response; Wk: week.

fusion, but worsen during the 2 weeks prior to the next infusion. In such situations, a biomarker that identifies patients who would benefit from increased infliximab dosages or increased infusion frequency would be a valuable tool for clinicians. Of the 5 DAS28 components that were evaluated in this study, CRP is the most objective measure of inflammation and the most sensitive to change, making it a plausible potential biomarker to guide treatment adjustments with an expensive anti-inflammatory agent such as infliximab. Because the relative contribution of CRP to the composite measures of disease activity is small, it is important that physicians monitor this marker as well when considering increasing the dose intensity of an expensive anti-inflammatory therapy (17). In the independent REMARK and ASPIRE populations, patients who were EULAR non-responders showed a unique pattern of change in CRP over time—a pattern that was different from the pattern shown by responders. Good and moderate EULAR responders had an initial decrease in CRP at Week 2 of treatment that was generally stable until Week 14. In contrast, non-responders had an initial decrease in CRP, followed by a rebound that nearly reached baseline levels at Week 14. This unique pattern of CRP may be a marker of clinical non-response that could be used to identify patients who may need dose optimisation, especially for patients who also report feeling well after an infusion but not throughout the 8 weeks between doses. Of course, the treating physician would need to evaluate CRP in light of other potentially important factors, such as co-occurring infection. One limitation of the study is that several factors that are potentially associated with outcomes, such as rheumatoid factor, anti-cyclic citrullinated peptide, and smoking history, were not collected. In addition, because REMARK was an observational study that was not designed to guide therapy or to evaluate the clinical benefit or risks of treatment optimisation, further studies will need to rigorously explore the consequences of using CRP to guide dose optimisation during treatment with biologics. A strength of this study is that the pattern of CRP and its association with non-response was replicated in 2 independent patient populations in 2 different clinical studies.

Overall, our results confirm that treatment of RA with infliximab plus MTX in routine clinical practice results in diminished disease activity as measured by DAS28, EULAR response, and a low rate of disease flare. Future work will need to confirm whether the distinctive pattern of CRP changes found in non-responders may be useful in prospectively guiding dose optimisation.

Ackowledgements

Medical writing and editorial assistance was provided by Ellen Stoltzfus, PhD, of JK Associates, Inc., and Jacqueline M. Mahon, MA, of Synergy Medical Education, LLC. This assistance was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ.

Competing interests

D. Boumpas has nothing to disclose.

O. Bjorneboe has nothing to disclose.

M. Brzosko has received payment for lectures including service on speaker bureaus from Abbott, Amgen, MSD, Novartis, Pfizer, Roche, Sanofi-Aventis, and Schering-Plough.

P. Gaudin has received payment for consulting work from Abbott, Chugai, and Roche; payment for lectures including service on speaker bureaus and reimbursement for travel from Abbott, Amgen, Chugai, Ipsen, MSD, Pfizer, and Roche; and payment for manuscript preparation for Roche.

C. Meeuwisse was an employee of MSD when the REMARK study was conducted.

R. Nelissen is an employee of MSD and owns stock in the company.

M.U. Rahman was an employee of Johnson & Johnson, a division of MSD, when the REMARK study was conducted. He owns Johnson & Johnson stock.

J. Smolen has received payment for consulting work and for lectures including service on speaker bureaus from Janssen, MSD, Pfizer, and UCB; and has received a grant and/or has a grant pending from Pfizer, MSD, and UCB.

S. Srinivasan was an employee of MSD when the REMARK study was conducted.

K. Svensson has nothing to disclose.

N. Vastasaeger is an employee of MSD and owns stock in the company.
R. van Vollenhoven has received payment for consulting work from Abbott, GlaxoSmithKline, Merck, Pfizer, Roche, and UCB; and his institution, Karolinska University Hospital, has received payment for clinical trial support related to the present study and has received grants and/or has grants pending from Abbott, GlaxoSmithKline, Merck, Pfizer, Roche, and UCB.
R. Westhovens has received payment for lectures including service on speaker bureaus from BMS; and his institution, Katholieke Universiteit, has received payment from BMS and Centocor for his consulting work and/or also has grants pending from Roche and UCB.

References

1. O'DELL JR: Therapeutic strategies for rheumatoid arthritis. *N Engl J Med* 2004; 350: 2591-602.
2. KLINKHOFF A: Biological agents for rheumatoid arthritis: targeting both physical function and structural damage. *Drugs* 2004; 64: 1267-83.
3. LEE DM, WEINBLATT ME: Rheumatoid arthritis. *Lancet* 2001; 358: 903-11.
4. SCOTT DL: Pursuit of optimal outcomes in rheumatoid arthritis. *Pharmacoeconomics* 2004; 22 (2 Suppl.): 13-26.
5. BREEDVELD FC, KALDEN JR: Appropriate and effective management of rheumatoid arthritis. *Ann Rheum Dis* 2004; 63: 627-33.
6. AMERICAN COLLEGE OF RHEUMATOLOGY SUBCOMMITTEE ON RHEUMATOID ARTHRITIS GUIDELINES: Guidelines for the management of rheumatoid arthritis: 2002 update. *Arthritis Rheum* 2002; 46: 328-46.
7. MAINI R, ST CLAIR EW, BREEDVELD F *et al*.: Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. *Lancet* 1999; 354: 1932-9.
8. ST CLAIR EW, VAN DER HEIJDE DM, SMOLEN JS *et al*.: Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: A randomized, controlled trial. *Arthritis Rheum* 2004; 50: 3432-43.
9. KEYSTONE EC, KAVANAUGH AF, SHARP JT *et al*.: Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. *Arthritis Rheum* 2004; 50: 1400-11.
10. KLARESKOG L, VAN DER HEIJDE D, DE JAGER JP *et al*.; TEMPO (TRIAL OF ETANERCEPT AND METHOTREXATE WITH RADIOGRAPHIC PATIENT OUTCOMES) STUDY INVESTIGATORS: Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet* 2004; 363: 675-81.
11. RAMÍREZ-HERRÁIZ E, ESCUDERO-VILLA-PLANA V, ALAÑÓN-PLAZA E *et al*.: Efficiency of adalimumab, etanercept and infliximab in rheumatoid arthritis patients: dosing patterns and effectiveness in daily clinical practice. *Clin Exp Rheumatol* 2013; 31: 559-65.
12. SCHERING-PLOUGH, LTD (Merck Sharp & Dohme Limited). Remicade (infliximab) Summary of Product Characteristics. [30 March 2012]. Available from: www.ema.europa.eu/docs/en_GB /document_library/EPAR_-_Product_Information /human/000240/WC500050888.pdf.
13. JANSSEN BIOTECH, INC: Remicade (Infliximab) Prescribing Information. [October, 2011]. Available from: www.remicade.com/remicade/assets/hcp_ppi.pdf.
14. STERN R, WOLFE F: Infliximab dose and clinical status: results of 2 studies in 1642 patients with rheumatoid arthritis. *J Rheumatol* 2004; 31: 1538-45.
15. ARIZA-ARIZA R, NAVARRO-SARABIA F, HERNÁNDEZ-CRUZ B *et al*.: Dose escalation of the anti-TNF-alpha agents in patients with rheumatoid arthritis. A systematic review. *Rheumatology* 2007; 46: 529-32.
16. WOLBINK GJ, VOSKUYL AE, LEMS WF *et al*.: Relationship between serum trough infliximab levels, pretreatment C reactive protein levels, and clinical response to infliximab treatment in patients with rheumatoid arthritis. *Ann Rheum Dis* 2005; 64: 704-7.
17. ALETAHA D, NELL VP, STAMM T *et al*.: Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. *Arthritis Res Ther* 2005; 7: R796-R806.