The impact of prior biologic therapy on adalimumab response in patients with rheumatoid arthritis

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Abstract

Objective

The aim of this study is to use data from a non-interventional study of adalimumab in patients with rheumatoid arthritis (RA) during routine clinical practice to evaluate the impact of prior treatment with biologics on the effectiveness of current therapy.

Methods

Efficacy parameters were evaluated for all patients with values at baseline and month 12. Subgroup analyses were performed on patients with 0, 1, or ≥2 prior biologic agents. Key outcome measures included Disease Activity Score-28 joints (DAS28) and Funktionsfragebogen Hannover (FFbH) functional ability score.

Results

A total of 4700 RA adalimumab-treated patients were included in this analysis. Baseline disease activity increased with an increasing number of prior biologic agents and therapeutic response diminished. After 12 months of adalimumab therapy, DAS28 and FFbH scores showed improvements in all groups, but the group with 0 prior biologic agents had the best outcomes, while the group with ≥2 prior biologic agents had the worst. Clinical response (EULAR and DAS28-d_{crit}) and remission rates showed a similar pattern. Nevertheless, 44% to 67% of patients treated with ≥2 prior biologic agents achieved a clinical response. Multiple regression analyses identified prior biologic therapy as a significant negative predictor for response to therapy.

Conclusion

Treatment with adalimumab leads to decreases in disease activity and improvements in function. Improvements are most pronounced in patients with 0 or 1 prior biologic agent, but a substantial proportion of patients treated with ≥2 prior biologic agents experience significant benefit from adalimumab therapy.

Key words

adalimumab, biologic therapy, tumour necrosis factor-alpha, anti-rheumatic agents, rheumatoid arthritis, treatment outcome, treatment effectiveness

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease leading to progressive joint destruction, pain, and loss of functionality, which is accompanied by decreasing quality of life and increased mortality (1). Tumour necrosis factor (TNF)-α is a key mediator of inflammation in RA (2). Introduction of TNF-α inhibitors more than 10 years ago revolutionised RA therapeutic options and led to the development of further biologic agents for use in the treatment of RA. Multiple clinical trials have shown that adalimumab, a human monoclonal anti-TNF-α antibody, reduces RA symptoms, slows or prevents radiographic progression, and improves health-related quality of life (3-10). On the basis of these data, adalimumab received regulatory approval for use as RA therapy in the US (2002) and in the EU (2003). Concomitant treatment with methotrexate (MTX) improves outcomes (3) and is recommended by the Summary of Product Characteristics unless it is considered inappropriate (11).

Prospective, observational, non-interventional studies can supplement clinical trials by providing data on the "real-world" clinical effectiveness and safety of a therapeutic agent (12). The large patient populations utilised in such studies can also provide insights into factors that affect treatment response. Kleinert *et al.* have recently reported findings from a non-interventional study of RA patients treated with adalimumab during routine clinical practice (13). This study found that disease activity decreased, functional capacity increased, and fewer patients required concomitant RA medications during adalimumab therapy. Further analysis of these results identified a high number of previous biologic therapies as a negative predictor for therapeutic gain. To further investigate this issue, we have utilised an expanded data set from the same adalimumab non-interventional study (13) to provide an in-depth analysis of the effectiveness of adalimumab in patients previously treated with other biologics in routine clinical practice, and to explore the potential impact of prior biologic therapy on disease activity and functional improvement during adalimumab therapy.

Materials and methods

Study design

This report utilises data from a single-arm, multicentred, non-interventional study of patients treated with adalimumab during routine clinical practice at 374 rheumatology centres and clinical practices in Germany. We present results for up to 12 months of adalimumab therapy, including all patients who enrolled between June 2003 and March 2009 and had documentation at baseline and month 12 for the specified parameter. The primary objectives of this study were to evaluate the effectiveness of adalimumab in RA patients who had been treated with 0, 1, or ≥2 biologic therapies (primarily infliximab, etanercept, or anakinra) prior to initiation of adalimumab, and to explore the potential impact of prior biologic treatment on therapeutic response as evaluated by disease activity, functional activity, and the proportions of patients achieving improvement criteria.

Patients in the adalimumab non-interventional study were required to: 1) be at least 18 years of age with active RA as determined by the treating physician; 2) have a clinical indication for treatment with a TNF-α inhibitor and no contra-indication; 3) have not been given adalimumab previously; and 4) provide written consent for participation. No other selection criteria were applied. All patients were informed about the objectives of the study and gave written consent for their voluntary participation and the anonymous use of their personal data in statistical analyses. Because of the non-interventional, observational nature of this study, ethics approval was not required by German law.

RA treatment was performed according to routine clinical practice at the discretion of the treating clinician. The recommended dosage of adalimumab was 40 mg administered subcutaneously every other week in combination with MTX unless MTX is inappropriate, as stated in the Summary of Product Characteristics (11).

Assessments of effectiveness

RA disease activity and functional capacity were the primary effectiveness outcomes. RA disease activity was as-

sessed by the Disease Activity Score using 28 joints (DAS28) (14). The Funktionsfragebogen Hannover (FFbH) was used to assess functional capacity. The FFbH is a self-administered patient questionnaire that evaluates the degree of remaining functional capacity on a scale of 0% (maximal impairment) to 100% (maximal functionality) (15). The FFbH has been validated in RA and is comparable to the Health Assessment Questionnaire-Disability Index (16).

Other variables assessed included inflammatory markers (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]), joint counts, subjective assessments of pain and fatigue, and the proportion of patients achieving various improvement criteria, including European League Against Rheumatism (EULAR) response (DAS28 decrease of >1.2 points and a current DAS28 state of ≤3.2 for a good response and DAS28 decrease of >0.6 and current state ≤5.1 for a moderate response) (17), disease remission (DAS28 <2.6) (18), FFbH increase of ≥11 (15), and DAS28-$d_{crit,}$ the change in DAS28 scores that exceeds the level of random variation observed in RA patients with stable disease activity under a fixed treatment regimen. For a nationwide cohort of German patients, the DAS28-d_{crit} was conservatively determined to be ≥1.8 points (19).

Data analyses

Analyses were conducted on adalimumab-treated RA patients who had DAS28 and FFbH measurements at baseline (within 14 days of start of therapy) and were not receiving concomitant therapy with other biologic agents in addition to adalimumab. Patients with low disease activity (DAS28 score <3.2 at baseline) were excluded (n=185). Changes in effectiveness parameters were evaluated in all patients who had documentation for that parameter at baseline and month 12 to allow a more detailed examination of the effect of therapy on treatment outcomes. Last observation carried forward (LOCF) analyses based on month 3 data were performed as confirmatory analyses. LOCF analyses used the last available data from all patients with a documented withdrawal at or before month 12.

Table I. Disposition and discontinuation rates from baseline to month 12. Withdrawals are shown as cumulative numbers and rates.

Number of prior biologics	Disposition	Months after inclusion			
		0	3	6	12
0	Full analysis set	3213	2624	2240	1926
	Reasons for withdrawals				
	Adverse drug reaction		79	143	187
	Lack of efficacy		133	261	375
	Both adverse drug reaction and lack of efficacy		11	18	21
	Other		43	89	132
	Cumulative withdrawals		266	511	715
	(discontinuation rates)		(8.3%)	(15.9%)	(22.3%)
	Lost to follow-up (cumulative)		212	348	470
			(6.6%)	(10.8%)	(14.6%)
	Missing documentation*		111	114	102
1	Full analysis set	1149	916	774	661
	Reasons for withdrawals				
	Adverse drug reaction		26	46	59
	Lack of efficacy		49	103	140
	Both adverse drug reaction and lack of efficacy		5	11	12
	Other		14	29	46
	Cumulative withdrawals		94	189	257
	(discontinuation rates)		(8.2%)	(16.4%)	(22.4%)
	Lost to follow-up (cumulative)		93	142	189
			(8.1%)	(12.4%)	(16.4%)
	Missing documentation*		46	44	42
≥2	Full analysis set	338	259	207	163
	Reasons for withdrawals				
	Adverse drug reaction		11	14	19
	Lack of efficacy		23	37	60
	Both adverse drug reaction and lack of efficacy		3	6	7
	Other		3	9	12
	Cumulative withdrawals		36	66	98
	(discontinuation rates)		(11.8%)	(19.5%)	(29.0%)
	Lost to follow-up (cumulative)		28	49	66
			(8.3%)	(14.5%)	(19.5%)
	Missing documentation*		11	16	11
Total	Full analysis set	4700	3799	3221	2750
	Reasons for withdrawals				
	Adverse drug reaction		116	203	265
	Lack of efficacy		205	401	575
	Both adverse drug reaction and lack of efficacy		19	35	40
	Other		60	127	190
	Cumulative withdrawals		382	725	1012
	(discontinuation rates)		(8.1%)	(15.4%)	(21.5%)
	Lost to follow-up (cumulative)		333	539	725
			(7.1%)	(11.5%)	(15.4%)
	Missing documentation*		168	174	155

*Patients had documentation for later visits.

Descriptive statistics or frequencies were computed for all data as appropriate. Comparisons among groups were numerical; *p*-values were not assessed due to multiple confounding factors. Changes in DAS28 and FFbH from baseline to month 12 were used as outcome measures of therapeutic effectiveness. Because the patient groups were heterogeneous and not matched with respect to potentially confounding factors such as age, disease duration, and disease activity, multiple regression analysis is the statistical method of choice to identify associations among relevant variables (20, 21). Stepwise and back-

ward regression models were used to determine whether previous biologic treatment had a statistically significant impact on therapeutic response parameters (DAS28 and FFbH changes, EULAR and DAS28-d_{crit} responses, and remission) during 12 months of adalimumab therapy. For EULAR response, DAS28-d_{crit} response, and remission rates, odds ratios were also calculated.

Results

Patient disposition and characteristics

A total of 4700 patients in 374 rheumatology clinics and specialised medical practices in Germany were included in the documentation to date: 3213 with 0 prior biologics, 1149 with 1 prior biologic, and 336 with ≥2 prior biologics (Table I). At month 12, data from 2750 patients were available: 1926 with 0 prior biologic, 661 with 1 prior biologic, and 163 with ≥2 prior biologics. Discontinuation rates during the 12 months of adalimumab therapy were nearly identical among groups with 0 (22.3%) and 1 (22.4%) prior biologic agent, but higher in the group with ≥2 prior biologic therapies (29.0%; Table I). In particular, patients with ≥2 prior biologic therapies had a numerically higher rate of discontinuations for lack of efficacy (17.8%) compared with patients with 0 (11.7%) or 1 (12.2%) prior biologic therapy.

Table II presents demographic characteristics of the study population by number of previous biologic therapies. Comparisons among groups must be treated with caution due to multiple confounding factors. Patients in the group treated with ≥2 prior biologic agents were slightly younger than patients in the other groups, but had longer disease duration. Compared with patients with 0 or 1 prior biologic therapies, patients with ≥2 prior biologic therapies had more severe disease, as indicated by more extensive joint involvement, higher levels of inflammatory markers, higher DAS28 scores, and lower functional capacity. Patients who received 0 or 1 prior biologic agent had generally comparable mean baseline characteristics, although patients with 1 prior agent had longer disease duration and lower functional capacity. Most (94.4%) of the patients with 1 prior biologic agent had received treatment with an anti-TNF-α agent and approximately 60% of the patients with ≥2 prior biologic therapies had received treatment with two anti-TNF-α agents.

Table II. Demographic and disease characteristics at initiation of adalimumab therapy. Mean data are presented unless otherwise indicated. Tender and swollen joint counts were based on evaluations of 28 joints. Not all patients provided data for each parameter. BMI: body mass index; SD: standard deviation.

Parameter	Number of prior biologic therapies		
	0 (n=3213)	1 (n=1149)	≥2 (n=338)
Age, yrs (SD)	54.8 (12.9)	55.2 (12.5)	53.0 (13.6)
Females, %	77.2%	77.9%	76.6%
BMI, kg/m^2 (SD)	26.1 (4.8)	25.9 (4.9)	26.1 (5.0)
Disease duration, yrs (SD)	11.0 (9.3)	13.0 (9.2)	13.5 (9.5)
Number of prior DMARDs (SD)	2.6 (1.3)	2.9 (1.4)	3.1 (1.4)
Tender joint count (SD)	12.2 (7.2)	12.6 (7.4)	13.3 (7.5)
Swollen joint count (SD)	9.4 (6.2)	9.6 (6.3)	10.3 (6.8)
CRP, mg/L (SD)	32.8 (64.9)	34.2 (59.1)	41.6 (66.6)
ESR, mm/h (SD)	33.8 (22.5)	35.7 (24.7)	38.9 (24.4)
DAS 28 (SD)	5.8 (1.1)	5.9 (1.2)	6.1 (1.2)
FFbH, % remaining functional capacity (SD)	59.3 (23.0)	54.0 (23.0)	52.0 (22.5)
Prior biologic therapy, %			
Etanercept	0	63.4%	88.5%
Infliximab	0	31.0%	83.1%
Anakinra	0	4.8%	37.6%
Other	0	0.8%	3.6%

Therapeutic response

Response to adalimumab treatment was assessed by DAS28 scores, FFbH functional capacity scores, joint counts, and inflammatory markers in patients with data for that parameter at baseline and month 12 (Table III). The same pattern was generally seen with all effectiveness assessments, including patient-reported subjective outcomes: baseline values worsened and the magnitude of response decreased with a greater number of previous biologic therapies. LOCF analyses of DAS28 and functional capacity in all treated patients also showed less favourable outcomes with an increasing number of previous biologic therapies (month 12 mean DAS28 scores of 4.0, 4.4, and 4.8 and month 12 mean FFbH scores of 67.7, 61.3, and 57.4 for patients treated with 0, 1, and ≥2 previous biologics, respectively). Multiple regression analyses (n=2827 for regression models) found that the number of previous biologic therapies was a significant negative predictor ($p \leq 0.0001$) for improvements in DAS28 and FFbH during 12 months of therapy.

Concomitant treatment with MTX

At baseline, 53.6% of patients (2517/4700) were treated with concomitant MTX as recommended by the Summary of Product Characteristics (11) (54.6%, 51.5%, and 50.6% for groups with 0, 1, and ≥2 prior biologic agents, respectively). Concomitant leflunomide was used by 20.7% of patients; 26.8% of patients received adalimumab as monotherapy at baseline. MTX use remained relatively constant in the three patient groups, although slight increases in use from baseline to Month 12 were observed for patients with 1 or ≥2 prior biologic therapies (to 53.8% and 56.4%, respectively). Patients treated with concomitant MTX achieved slightly lower mean DAS28 scores (3.6, 4.1, and 4.3 for 0, 1, and ≥2 prior biologics) and higher mean functional capacity scores (72.6, 66.2, and 63.4 percentage points) at 12 months than patients who did not receive MTX (mean DAS28 of 3.9, 4.3, and 4.8 and mean FFbH of 68.6, 60.1, and 53.4, respectively). The previously identified pattern of response was retained irrespective of MTX use: patients treated with 0 prior biologic agents showed the best responses at 12 months, while patients treated with ≥2 prior biologic agents showed the worst.

Table III. Effect of adalimumab therapy on outcomes in patients treated with 0, 1, or 2 or more prior biologic agents. Outcome measures were evaluated in patients with values at baseline and month 12. SD: standard deviation.

Outcome measure	Number of prior biologic therapies					
	0		1		≥2	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
DAS28						
Baseline	2004	5.9 (1.1)	667	5.9 (1.2)	178	6.2 (1.2)
3 months	1861	4.0 (1.4)	597	4.5 (1.4)	164	4.8 (1.4)
6 months	1831	3.8 (1.4)	595	4.2 (1.4)	159	4.7 (1.6)
12 months	2004	3.8 (1.4)	667	4.2 (1.4)	178	4.6 (1.5)
FFbH, % remaining functional capacity						
Baseline	2072	60.8 (22.9)	700	55.2 (23.2)	187	51.7 (23.0)
3 months	1962	69.6 (22.3)	653	63.7 (23.1)	177	59.3 (24.1)
6 months	1962	71.1 (22.5)	649	64.8 (23.3)	170	59.9 (24.2)
12 months	2082	70.5 (22.9)	700	64.2 (23.7)	187	59.5 (25.2)
Tender joint count						
Baseline	2102	12.2 (7.1)	713	12.9 (7.5)	190	13.9 (7.5)
3 months	2021	5.5 (6.0)	672	6.6 (6.7)	183	8.4 (7.8)
6 months	2001	4.6 (5.7)	672	5.8 (6.3)	175	7.6 (7.5)
12 months	2102	4.5 (5.6)	713	5.7 (6.3)	190	7.5 (7.7)
Swollen joint count						
Baseline	2102	9.4 (6.1)	713	9.8 (6.4)	190	11.1 (6.9)
3 months	2021	4.0 (4.8)	672	5.1 (5.3)	183	6.3 (6.5)
6 months	2001	3.3 (4.3)	672	4.3 (4.9)	175	5.5 (6.1)
12 months	2102	3.2 (4.3)	713	4.0 (4.8)	190	5.3 (5.8)
CRP (mg/L)						
Baseline	1414	33.6 (68.0)	493	33.6 (50.0)	144	42.3 (72.0)
3 months	1222	17.6 (65.6)	441	22.5 (56.9)	129	30.3 (88.0)
6 months	1226	14.6 (27.9)	430	17.2 (27.5)	127	20.3 (30.0)
12 months	1414	17.1 (107.8)	493	15.9 (33.5)	144	27.1 (67.7)
ESR (mm/h)						
Baseline	2061	33.4 (22.0)	697	35.2 (24.5)	186	37.3 (22.2)
3 months	1953	22.1 (18.2)	648	25.9 (20.0)	179	28.4 (20.9)
6 months	1923	21.5 (18.1)	640	25.0 (19.6)	171	28.8 (22.5)
12 months	2061	21.8 (18.3)	697	24.4 (19.6)	186	28.4 (20.7)
Fatigue (VAS)						
Baseline	2051	5.8 (2.6)	689	6.1 (2.5)	185	6.3 (2.4)
3 months	1948	4.0 (2.6)	644	4.5 (2.5)	175	4.8 (2.4)
6 months	1929	3.8 (2.6)	639	4.1 (2.4)	169	4.8 (2.6)
12 months	2051	3.9 (2.6)	689	4.2 (2.5)	185	4.7 (2.5)
Pain (VAS)						
Baseline	2059	6.7 (2.0)	693	6.7 (2.1)	186	7.1 (1.9)
3 months	1952	4.2 (2.3)	649	4.6 (2.3)	177	5.0 (2.1)
6 months	1936	4.0 (2.3)	642	4.4 (2.2)	169	5.0 (2.2)
12 months	2059	4.0 (2.3)	693	4.4 (2.3)	186	4.9 (2.3)

Improvement criteria

Although mean values summarise the average amount of improvement in a patient cohort, they are less useful in estimating the number of patients with a clinically significant improvement in response to treatment. We thus utilised established improvement criteria (EULAR response criteria [17], disease remission [18], significant increase in FFbH percentage points [15]) and a new statistically-determined therapeutic response criterion, the DAS28-d_{crit} (DAS28 decrease of ≥1.8 points) (19), to evaluate patient response during adalimumab treatment (Fig. 1). For EULAR response (Fig. 1A), the group treated with 0 prior biologic agents had the highest proportion of patients meeting improvement criteria, while the group treated with ≥2 prior biologic agents had the lowest proportion of patients meeting improvement criteria. Despite the overall lower response among patients treated with ≥2 prior biologic agents, at 12 months 66.8% experienced a EULAR response (moderate or good). Evaluation of these data using the DAS28-d_{crit} criterion (19) showed a similar pattern of response, but the disparity between patients treated with 0 prior biologic agents and those treated with ≥2 was reduced (56% and 44% with a significant DAS28 decrease, respectively) (Fig. 1B). The proportions of patients achieving a significant increase in FFbH (≥11 points) (15) showed only slight changes among the 3 patient groups (Fig. 1C), with more than 40% of patients in all groups achieving significant functional improvements.

The proportion of patients in remission (DAS <2.6; [18]) was also examined. At month 12, 22.1% of patients treated with 0 prior biologics were in remission compared with 14.2% and 9.0% of patients treated with 1 and ≥2 prior biologic agents, respectively. The characteristics of patients who had been treated with ≥2 prior biologic agents and achieved remission were examined in more detail. Analyses to determine statistical significance were not performed due to the small sample size. As most patients who achieve remission during adalimumab therapy do so by 3 months, we compared characteristics of the 16 patients who achieved remission at 3 months with those of the 259 who did not. There were several notable differences between these groups, including mean age at study enrollment (39.6 years for patients in remission *vs*. 54.0 for patients not in remission), mean age at disease onset (27.5 *vs*. 40.5 years), and gender (37.5% *vs*. 22.0% male). Despite the differences in age, the mean duration of RA was similar between the 2 groups (12.0 *vs*. 13.6 years). At baseline, patients who achieved remission had lower disease activity (DAS28 of 5.1 *vs*. 6.2), greater functional activity (FFbH 56.7 *vs*. 51.9), fewer involved joints, and lower levels of inflammatory markers (data not shown).

Stepwise and backward regression analyses were used to explore the impact of prior biologic therapy on treatment response as evaluated by improvement criteria. Prior biologic therapy was associated with a statistically significant reduction ($p<0.001$) in the likelihood of obtaining a EULAR response (good

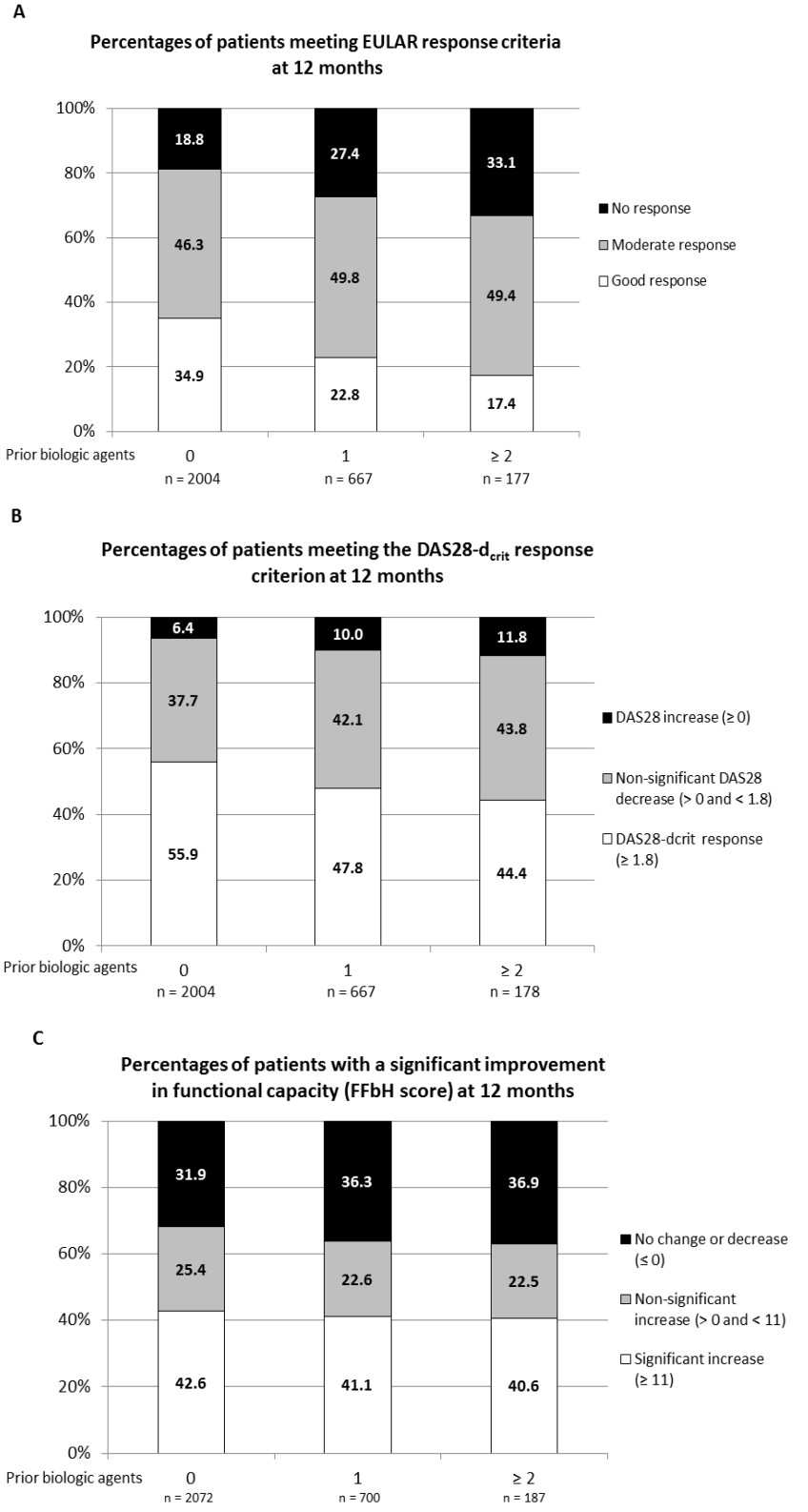

Fig. 1. Therapeutic response after 12 months of adalimumab therapy as assessed by (A) EULAR response criteria; (B) the DAS28-d_{crit} response criterion; or (C) significant improvement in functional capacity (FFbH score). Data are presented for patients with values for the indicated parameter at baseline and month 12. A good EULAR response requires a DAS28 decrease of >1.2 points and a current DAS28 state of ≤3.2. A moderate EULAR response requires a DAS28 decrease of >0.6 and current state ≤5.1 (17). The DAS28-d_{crit} response requires a decrease of ≥1.8 points from the baseline DAS28 score (19). A significant improvement in functional capacity requires an increase in FFbH of ≥11 points (15). Columns may not total 100% due to rounding.

or moderate), DAS28-d_{crit} response, or remission. For all three outcomes, the odds ratio for the number of previous biologic therapies ranged between 0.60 and 0.69 in stepwise regression analyses, indicating that each prior biologic therapy was associated with an approximately 30% to 40% reduction in the likelihood of achieving these improvement criteria. Backward regression analyses produced similar results.

Response by agent and reason for discontinuation

Therapeutic response was also evaluated on the basis of the last previous biologic agent (infliximab or etanercept; there were too few patients receiving prior treatment with other biologic agents to provide meaningful results) and on the basis of primary reason for discontinuing the last previous biologic (lack of efficacy, lack of tolerance, or both). These analyses were conducted in patients who had data at baseline and month 12 and had received only one prior biologic agent so that the results would not be confounded by the effects of multiple biologic agents on therapeutic response. Therapeutic response to adalimumab appeared to be generally comparable in patients who had previously received infliximab or etanercept (Fig. 2A) and did not appear to be significantly affected by the reason for discontinuation of the prior biologic agent (lack of efficacy *vs*. lack of tolerance; Fig. 2B).

Discussion

Large observational, non-interventional studies are well-suited to exploring therapeutic effectiveness under conditions of "real world" clinical practice (12). We utilised data from a cohort of 4700 patients with RA to examine therapeutic response to adalimumab in patients receiving previous treatment with 0, 1, or ≥2 biologic therapies, primarily infliximab and etanercept. Although all of the patient groups showed a therapeutic response to adalimumab at 12 months, patients who had not received previous treatment with biologic agents showed the best response by both objective and subjective criteria, while those who were treated with

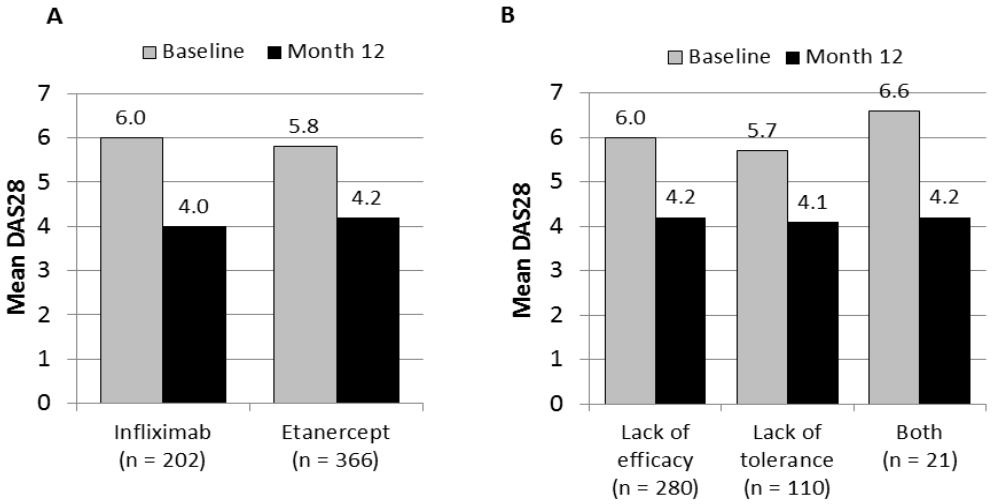

Fig. 2. Mean DAS 28 values in patients with data at baseline and month 12 who had received one previous biologic agent by (**A**) previous biologic and (**B**) reason for discontinuation of previous biologic.

≥2 prior biologic agents had the lowest response. Analyses of improvement criteria identified a similar pattern. Regression analyses confirmed the finding reported by Kleinert *et al*. (13) that prior biologic treatment was a significant negative predictor for improvement in DAS28 or FFbH, and further found that prior biologic treatment was significantly associated with a reduced likelihood of achieving a EULAR response, a DAS28-d_{crit} response, or remission. These data thus suggest that patients previously treated with ≥2 prior biologic agents are the most difficult to treat and may be refractory to further treatment. Nevertheless, a substantial proportion of patients in the group previously treated with ≥2 biologic agents experienced considerable benefit from adalimumab therapy at 12 months as assessed by therapeutic response and functional criteria. TNF-α inhibitors (etanercept and infliximab) accounted for the vast majority of previous biologic agents in our study, so our findings suggest that even a third TNF-α inhibitor can result in noticeable clinical improvements for many patients.

Our major analyses utilised patients with data at both baseline and 12 months, as our primary goal was to examine the impact of prior biologic therapy on subsequent treatment responses over a one-year period. This restriction did not alter the basic finding since the analyses were also confirmed in LOCF analyses of the full patient cohort.

In this observational cohort of RA patients, 53.6% were treated with concomitant MTX. This is somewhat low, given the known therapeutic benefit of MTX in combination with biologics and specifically with adalimumab (3). However, approximately 20% of patients received concomitant leflunomide at baseline, and only 26.8% were on adalimumab monotherapy, which is in good agreement with the approximately 30% of RA patients on biologic monotherapy reported in biologic registries and claims databases (22). Overall, 82.6% of patients reported having received MTX at some point during their RA therapy in agreement with recommendations. The concomitant use of MTX resulted in greater reductions in disease activity in all three patient groups compared with adalimumab monotherapy, but did not change the pattern of response: with or without MTX, the best response was observed in patients with 0 prior biologic therapies and the lowest response was observed in patients with ≥2 prior biologic therapies.

Our findings support and extend observations from a 12-week open-label study of adalimumab therapy, the multinational Research in Active Rheumatoid Arthritis Trial (ReAct), which found that response rates were higher in patients who had not received prior treatment with an anti-TNF-α agent (n=5711) than in patients with prior anti-TNF-α experience (n=899; EULAR good response rates of 35% *vs*. 23%) (23). This finding is not unique to adalimumab: other studies have observed a reduced therapeutic response to anti-TNF-α agents (24-26), including a systematic review of 28 studies on this topic (27), and to other biologic agents (tocilizumab [28] or rituximab [29]) following multiple biologic agents. However, most of these studies have been limited by small patient numbers, particularly in the cohort of patients previously treated with multiple biologic agents.

An assessment of the characteristics of patients who had been treated with ≥2 prior biologic agents and achieved remission provided some interesting insights into this subgroup, although the numbers were small (16 patients achieved remission at month 3). Compared with patients who received ≥2 prior biologic agents and did not achieve remission, patients in remission had lower disease activity at baseline and were more likely to be male. Patients in remission were also younger, both at disease onset and study initiation, but had a similar mean duration of RA.

For RA patients who have failed a therapy, associations between the specific agent or reason for discontinuation and the likelihood of responding to the next therapy are important issues, as these factors have the potential to guide clinicians and patients in selecting subsequent therapies. In our study, neither the previous biologic agent (infliximab or etanercept) nor the reason for discontinuation (lack of response or lack of tolerance) exerted strong influences on therapeutic response to adalimumab in patients with only one prior biologic agent. There is some disagreement in the literature concerning the effect of reasons for discontinuing a prior anti-

TNF-α agent on subsequent response to a different TNF-α inhibitor. Data from a registry in Spain indicate that drug survival of a second TNF-α inhibitor is improved in patients who discontinued the previous agent due to adverse events compared with those who discontinued due to other reasons, including lack of response (30). In contrast, Caporali *et al*. found that patients who switched anti-TNF-α agents due to lack of response had improved EULAR response rates compared to those who switched due to adverse events (30). Our study does not support either conclusion. Instead, we found similar DAS28 scores in patients at month 12 regardless of the reason for discontinuing the previous anti-TNF-α agent.

A limitation of our study is that the groups were not prospectively randomised on the basis of characteristics likely to impact therapeutic effectiveness, such as age and baseline disease activity. In addition, some subgroups, such as the number of patients with ≥2 prior biologic agents who achieved remission, included a low number of patients. These issues, although unavoidable in non-interventional studies, limit interpretations of between-group comparisons. For this reason, we used regression analyses, which are not affected by confounding factors, to confirm the negative influence of prior biologic therapy on therapeutic response.

Conclusion

On the basis of data from this non-interventional study, we conclude that therapy with adalimumab confers substantial benefit to patients in daily clinical practice. Patients who had not been previously treated with biologic agents were most likely to experience a clinically significant improvement: the use of adalimumab as a third or subsequent biologic agent was associated with a lower therapeutic response than the use of this agent as a first or second biologic agent. It is notable, however, that more than 40% of patients treated with multiple previous biologic therapies achieved clinically significant improvements in DAS28 and functional capacity during adalimumab treatment. Adalimumab thus remains an important therapeutic option for both treatment-naïve patients and those who have failed treatment with other biologic agents.

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