Glucocorticoid Effect on Radiographic Progression in Placebo Arms of Rheumatoid Arthritis Biologics Trials

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ABSTRACT. ***Objective.*** To assess the effect of glucocorticoids (GC) on damage progression in placebo-biologic arms of rheumatoid arthritis (RA) biologics trials.

Methods. Posthoc metaanalysis of 2 infliximab (IFX) trials (established and early RA) and 1 tocilizumab (TCZ) trial (established RA).

Results. The proportion of patients receiving GC was 38%–64%, baseline damage was 11–82 Sharp/van der Heijde points, and progression in the placebo groups was 0.5–4.8 points in 6 months. In the pooled IFX studies, GC cotreatment reduced 6-month progression by 2.6 points (95% CI 0.6–4.5). In the TCZ study (progression rate 0.5 Genant points), no such difference was seen.

Conclusion. GC cotreatment may affect results in RA trials. (First Release April 1 2016; J Rheumatol 2016;43:1024–6; doi:10.3899/jrheum.150932)

Key Indexing Terms:
RHEUMATOID ARTHRITIS JOINT DAMAGE BIOLOGICS
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In most registration trials of antirheumatic agents, comedication with a stable low or medium dose of glucocorticoids (GC; usually up to 10 mg/d of prednisolone equivalents) is allowed. GC are known inhibitors of damage progression in rheumatoid arthritis (RA)[1], and yet in the analysis of trials, their contribution has been mostly ignored.

We compared the 6-month radiographic progression rates of patients with or without background GC comedication in the control (placebo-biologic) arms of biologics trials. We also analyzed results at 12 months and those of the active arms.

MATERIALS AND METHODS

Of the available trials, posthoc analyses were made available for 3 trials: the ATTRACT (Anti-Tumor necrosis factor Trial in Rheumatoid Arthritis with Concomitant Therapy)[2] and ASPIRE (Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset)[3] trials studying infliximab (IFX) in established and early RA, respectively, and the LITHE (Tocilizumab Safety and the Prevention of Structural Joint Damage) trial[4] studying tocilizumab (TCZ) in established RA. In the ATTRACT trial, 428 patients were randomized to methotrexate (MTX) background plus placebo infusions (n = 88) or 1 of 4 IFX strategies plus MTX. At 6 months, 50 placebo patients were available for analysis (30 with and 20 without GC). In the ASPIRE trial, 1049 patients with disease duration of at most 3 years were randomized to *de novo* MTX plus placebo infusions (n = 298) or 1 of 2 IFX plus MTX strategies. At 6 months, 205 placebo-biologic patients had radiograph scores available for analysis (67 with and 138 without GC). Neither of these trials had an escape option to IFX in case of nonresponse. Finally, in the LITHE trial, 1196 patients with established RA were randomized to background MTX plus placebo (n = 393) or 1 of 2 MTX plus TCZ strategies. At 6 months, 283 placebo-biologic patients were available for analysis (201 with and 82 without GC). In LITHE, 50% of placebo-biologic patients were offered escape TCZ for nonresponse after 16 weeks. In these, a radiograph taken within 60 days after the switch was used in the radiographic analyses. Changes in radiographic damage were expressed in Sharp/van der Heijde units (range 0–440) in ATTRACT and ASPIRE, and in Sharp-Genant scores (range 0–290) in the LITHE trial. Study results were weighted by inverse variance, standardized mean differences were calculated, and these were pooled in a fixed-effect model if homogeneous (I^2 statistic) with help of RevMan software v 5.3 (Cochrane collaboration).

RESULTS

Trial characteristics are shown in Table 1. The mean (SD or range) disease duration was 11 (8), 0.9 (0.7), and 9 (range 0.5–44) years; 64%, 38%, and 62% of patients were receiving GC; and baseline mean damage scores were 82 (77), 11 (16), and 28 (range 0–190) for the ATTRACT, ASPIRE, and LITHE trials, respectively. The mean 6-month progression in the current dataset of placebo-biologic groups was 4.8 (9.1), 2.4 (7.4), and 0.5 (1.3), respectively (Table 2).

Heterogeneity prevented overall pooling of the 3 studies (after multiplication of Genant results by 1.5 to create a common scale: chi-square = 6.7, p = 0.04, I^2 = 70%). The 2 IFX studies were homogeneous (I^2 = 0%): patients treated

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Table 1. Characteristics of included studies. Values are mean (SD) unless specified otherwise.

Characteristics	ATTRACT		ASPIRE		LITHE	
Patients, n	428		1049		1196	
Placebo-biologic, n	88		298		393	
Disease duration, yrs, mean (SD)/mean (range)	11 (8)		0.9 (0.7)		9 (0.5–44)	
Glucocorticoid use	–	+	–	+	–	+
Patients analyzed, n	20	30	138	67	82	201
Baseline disease activity†						
DAS‡	N/A	N/A	6.2 (1.0)	6.3 (1.0)	6.5 (1.0)	6.5 (0.9)
SDAI‡	47.1 (14.4)	47.5 (15.5)	37.4 (10.9)	39.8 (13.1)	N/A	N/A
CRP, mg/ml	4.0 (3.8)	3.6 (3.4)	2.4 (2.6)	2.9 (3.5)	1.8 (2.1)	2.4 (2.6)

† Results for all randomized patients. ‡ DAS was not calculated in ATTRACT; SDAI was not calculated in LITHE. ATTRACT: Anti-Tumor necrosis factor Trial in Rheumatoid Arthritis with Concomitant Therapy; ASPIRE: Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset; LITHE: Tocilizumab Safety and the Prevention of Structural Joint Damage; DAS: Disease Activity Score; SDAI: Simplified Disease Activity Index; CRP: C-reactive protein; N/A: not available.

Table 2. Radiographic damage and 6-month progression in placebo groups of 3 biologics trials. Values are mean (SD) unless specified otherwise.

Variables	ATTRACT		ASPIRE		LITHE	
Baseline damage†, mean (SD)/mean (range)	82.0 (77.0)		11.3 (15.9)		28.5 (0–190.5)	
Progression						
1 yr, trial report	7.0 (10.3)		3.7 (9.6)		1.1‡	
6 mos, interpolated	3.5 (6.2)		1.8 (4.8)		0.6	
6 mos, current dataset	4.8 (9.1)		2.4 (7.4)		0.5 (1.3)	
Glucocorticoid use	–	+	–	+	–	+
Baseline damage	92.5 (80.6)	80.6 (80.9)	11.6 (15.7)	10.3 (16.3)	25.3 (29.0)	31.0 (33.9)
Progression	7.7 (13.1)	2.9 (4.9)	3.2 (7.9)	0.9 (6.4)	0.5 (1.4)	0.5 (1.3)

† ATTRACT and ASPIRE expressed in Sharp/van der Heijde points (range 0–440); LITHE expressed in Sharp-Genant points (range 0–290). ‡ SD not reported. ATTRACT: Anti-Tumor necrosis factor Trial in Rheumatoid Arthritis with Concomitant Therapy; ASPIRE: Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset; LITHE: Tocilizumab Safety and the Prevention of Structural Joint Damage.

with GC had 2.6 Sharp/van der Heijde points (95% CI 0.6–4.5) less progression at 6 months (Table 2). In the LITHE study, the advantage was absent (mean Genant points difference 0.0, 95% CI –0.3 to 0.4). The pattern was similar at 12 months (data not shown). As published[2,3,4], damage progression was greatly reduced in the active biologic treatment groups; here, despite similar proportions of patients receiving GC, no effect of GC on progression was seen (data not shown).

DISCUSSION

GC treatment was favorable in 2 out of 3 placebo-biologic arms of biologics trials. GC effects were not demonstrable in the active arms, most likely because of low progression rates. The effect in placebo-biologic groups is remarkable because GC treatment is preferentially given to patients with very active disease and unfavorable prognostic characteristics, potentially biasing against protective effects of GC in this observational study. We suggest that the lack of effect of GC in the LITHE trial may be because of the overall low progression rate, in turn explained by less severe disease. Compared with patients in the other 2 trials, LITHE patients had lower yearly progression rates before the trial and a lower C-reactive protein at baseline. Another possibility is the use of the Genant score with a lower maximum and a different handling of erosions. The data provided did not allow further study of effect modifiers such as dose and expected rate of progression, and confounders such as baseline damage and serological status. However, such confounding would also most likely bias against the protective effects of GC, as noted above. Nevertheless, limitations of our study include the modest size of the dataset because we were unable to obtain permission to use the data of other trials, and the number of missing observations in the primary data.

A recent metaanalysis has shown that the initial advantage in damage progression provided by biologics treatment is not present in patients treated with an initial GC course[5]. Our analysis suggests that the advantage is also attenuated in patients already receiving GC. Hence, for future trials we advise stratification for GC use in the design phase, and separate analyses of damage progression in patients treated with GC.

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