

Concise report

Effects of subcutaneous and intravenous golimumab on inflammatory biomarkers in patients with rheumatoid arthritis: results of a phase 1, randomized, open-label trial

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Abstract

Objective. To evaluate the effects of the anti-TNF- α monoclonal antibody golimumab, administered by s.c. injection or i.v. infusion, on markers of inflammation in patients with RA.**Methods.** In this phase 1, open-label study, patients with active RA were randomized to receive s.c. golimumab 100 mg at baseline and every 4 weeks through week 20 ($n=33$; group 1) or i.v. golimumab 2 mg/kg at baseline and week 12 ($n=16$; group 2). Serum levels of CRP, IL-6, serum amyloid A (SAA), TNF receptor II (TNFRII), MMP-3, hyaluronic acid, haptoglobin, ferritin and haemoglobin and serum/urine hepcidin were measured at various time points. Associations between the biomarkers were assessed with Spearman's correlations.**Results.** In both groups 1 and 2, decreases in mean serum levels of CRP, IL-6, SAA, TNFRII, MMP-3, haptoglobin, ferritin and hepcidin, and mean urine levels of hepcidin occurred within 1 week and were sustained through week 8. Decreases in concentrations of serum CRP, IL-6, SAA, MMP-3, hepcidin, ferritin and haptoglobin and urine hepcidin were maintained through week 24 in group 1, but began to reverse after week 8 in group 2. Among all patients, decreases in serum hepcidin correlated significantly with decreases in serum CRP and ferritin.**Conclusion.** Decreases in serum and urine concentrations of markers of inflammation occurred as early as 24 h after treatment with golimumab, and most of these improvements were sustained through week 24 in group 1.**Key words:** golimumab, rheumatoid arthritis, biological markers, hepcidin, pharmacodynamics.**Trial registration:** ClinicalTrials.gov, <http://clinicaltrials.gov/>, NCT01362153.

Introduction

The prolonged inflammation of RA results from dysregulation of the immune system. Increased levels of the

pro-inflammatory cytokines TNF- α and IL-6 have been associated with active RA [1]. Serum amyloid A (SAA) [2], MMP-3 [3], CRP [4] and ferritin [5] are acute-phase proteins that may be useful as markers to monitor inflammation in RA patients.

Anaemia of inflammation is a common complication of RA and is associated with physical disability [6] and increased mortality [7]. Although the exact mechanism of anaemia of inflammation is unknown, IL-6 has been shown to induce expression of the acute-phase protein hepcidin [8], which inhibits iron absorption in the duodenum [9] and release of iron from macrophages and hepatocytes [10].

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In large, phase 3 trials of s.c. and i.v. golimumab, a human anti-TNF- α monoclonal antibody, RA patients treated with golimumab $\pm$ MTX had significant improvements in disease signs and symptoms than did patients who received MTX monotherapy or placebo [11–16]. In one of these trials, treatment with golimumab modulated some inflammatory markers (e.g. CRP, IL-6, MMP-3) at week 4, with a more pronounced effect observed among responders to golimumab [17]. As part of a phase 1 trial performed primarily to analyse the pharmacokinetics and pharmacodynamics of s.c. and i.v. golimumab, an exploratory analysis assessed the onset of action of golimumab by evaluating changes in markers of anaemia and inflammation at early time points (e.g. 24 and 48 h). Pharmacokinetic data were previously reported [18]. Here we report the effects of s.c. and i.v. golimumab on markers of inflammation and anaemia in patients with RA.

Patients and methods

Patients and study design

As previously described [18], eligible patients were ≥ 18 years of age and had a diagnosis of RA [19] for ≥ 3 months. Additionally, patients had to have a baseline haemoglobin level ≥ 8.0 g/dl. Patients receiving DMARDs were required to have been on stable doses of no more than three DMARDs for ≥ 3 months before screening. MTX doses could not exceed 25 mg/week. Stable doses of NSAIDs, other analgesics for RA or oral CSs (≤ 10 mg prednisone/day) were permitted.

In this phase 1, open-label trial, patients were randomized (2:1) to receive s.c. injections of golimumab 100 mg at baseline and every 4 weeks thereafter through week 20 (group 1) or i.v. infusions of golimumab 2 mg/kg at baseline and week 12 (group 2). Patients were monitored for adverse events (AEs) through week 30 in group 1 and week 24 in group 2.

This study was conducted in accordance with the Declaration of Helsinki. Coast IRB, LLC (Colorado Springs, CO, USA) approved the protocol and informed consent for the entire trial. All patients provided written informed consent before undergoing study-related procedures.

Pharmacodynamics

Serum levels of CRP, IL-6, SAA, TNF receptor II (TNFRII), MMP-3, hyaluronic acid (HA), haptoglobin and hepcidin were assessed at baseline, 24, 48, and 72 h, and at weeks 1, 2, 4, 8, 12 (group 2 only), 20 and 24. Serum levels of haemoglobin, transferrin receptor, ferritin, erythropoietin, reticulocyte count, total iron-binding capacity, and total iron and urine hepcidin levels were measured at baseline, 48 h, and at weeks 2, 4, 8, 12 (group 2 only), 20 and 24. On days when study agent was administered, blood samples were drawn before treatment administration. The follow-up periods and sample collection time points for the two groups varied because of the differences in dosing schedules and the predicted half-lives of the two administration methods. Pharmacodynamic

assessments were also performed for patients with anaemia at baseline (haemoglobin < 12 g/dl for females; < 13 g/dl for males).

Efficacy assessments

The proportions of patients achieving ≥ 20 , 50 or 70% improvement in ACR criteria (ACR20, ACR50 and ACR70, respectively) were determined at weeks 2, 4, 8, 20 and 24. Individual ACR components were evaluated: swollen joint count (SJC), tender joint count (TJC), patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, physical function [HAQ-Disability Index (HAQ-DI)] and CRP level. Clinical response was also assessed with the 28-joint DAS using CRP (DAS28-CRP). The proportions of patients achieving a moderate or good DAS28-CRP response [20] or DAS28-CRP remission (score < 2.6) were determined. Fatigue was assessed using the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) score.

Statistical analysis

Descriptive statistics are reported. Biomarker concentrations below the lower limit of quantification were assigned a value of 0. Spearman's correlations were performed for serum and urine hepcidin levels at each time point. A *post hoc* Spearman's analysis was performed for correlations between changes from baseline in hepcidin (serum and urine) and changes from baseline in CRP and ferritin levels. *Post hoc* Spearman's correlations between baseline biomarker levels and SJC, TJC and DAS28-CRP score at week 24 and between changes in biomarker levels (evaluated at days 2, 3 and 4, and weeks 1, 2, 4 and 8) and changes in efficacy measures (per cent improvements in SJC and TJC, change in DAS28-CRP score) at week 24 were performed with patients stratified by baseline CRP level ($<$ or ≥ 1.0 mg/dl). Only patients with evaluable data at both time points were included in the model. Pearson's correlations were performed between change from baseline in serum/urine hepcidin and serum IL-6 over time. In the correlation analyses, false discovery rate (FDR) corrections were made to *P*-values due to multiple testing. Because of the small sample size, no formal statistical comparisons between the two treatment arms were performed.

Results

Baseline demographics and disease characteristics

Fifty-one patients were initially randomized, and two withdrew before the first study agent administration [18]; 49 patients received s.c. ($n = 33$) or i.v. ($n = 16$) golimumab. Four patients (all in group 1) discontinued before week 24. Baseline demographic and disease characteristics were similar between treatment groups (supplementary Table S1, available as supplementary data at *Rheumatology* Online). Of note, patients generally had low CRP levels and normal haemoglobin levels.

Changes in biomarker levels

In both groups, mean serum concentrations of CRP, IL-6, SAA, TNFR II, MMP-3, ferritin, haptoglobin and serum/urine hepcidin levels generally decreased from baseline through week 8 (Fig. 1). Overall, these decreases occurred within 24 h, and were sustained up to week 8. Decreases in MMP-3 and haptoglobin were evident within 1 week. Generally there were no apparent differences between the treatment groups in the first 24 h. In group 1, decreases in mean serum CRP, IL-6, SAA, MMP-3, hepcidin, ferritin and haptoglobin levels and in mean urine hepcidin levels persisted through week 24; however, in group 2, serum CRP, IL-6, TNFR II, MMP-3, haptoglobin and SAA, and serum/urine hepcidin approached baseline levels by week 24. Serum HA levels increased in the first 24 h, decreasing to baseline levels in group 1; no trend was observed in group 2 (data not shown).

Serum and urine levels of hepcidin were normal at baseline and correlated significantly with each other at all time points in both groups (data not shown). Among all patients, decreases in serum hepcidin levels significantly correlated with decreases in serum CRP and ferritin at nearly all time points (Table 1). Serum hepcidin was inversely correlated with serum IL-6 in group 2 only; no trends were observed between urine hepcidin and serum IL-6 (data not shown).

Patients with anaemia at baseline

Most patients were iron replete at baseline, with a mean baseline ferritin level of 97.4 ng/ml, although it should be noted that patients with a baseline haemoglobin level <8.0 g/dl were excluded from the trial. Five patients (group 1) had anaemia at baseline; two withdrew early due to AEs. Among the five patients with anaemia, serum CRP and urine hepcidin levels decreased rapidly (often within 24 h), and haemoglobin increased within 2 weeks (data not shown).

Efficacy

At week 24, 62.1% of patients in group 1 and 56.3% in group 2 achieved an ACR20 response, 31.0 and 25.0%, respectively, achieved an ACR50, and 20.7 and 18.8%, respectively, achieved an ACR70 (supplementary Table S2, available as supplementary data at *Rheumatology* Online). Improvements in DAS28-CRP scores, patient's assessment of pain, physician's global assessment, patient's global assessment, TJC, SJC, HAQ-DI scores and FACIT-F scores were observed at week 24 in both groups.

Correlations between biomarker levels and clinical response at week 24

Correlation analyses did not reveal consistent or clinically relevant correlations between baseline levels of

Fig. 1 Mean biomarker levels over time.

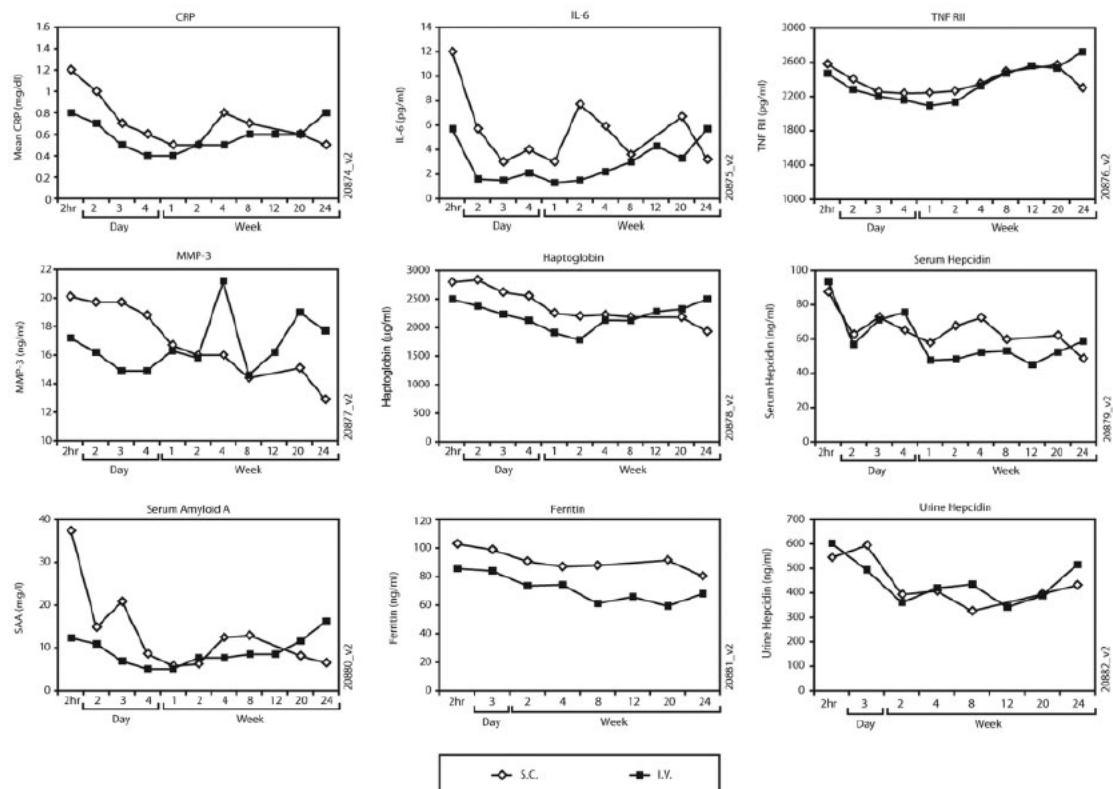


TABLE 1 Spearman's correlation of changes in serum hepcidin with changes in serum ferritin and changes in CRP for all patients

Time point	Changes in ferritin			Changes in CRP		
	Spearman's coefficient	P-value	FDR-adjusted P-value	Spearman's coefficient	P-value	FDR-adjusted P-value
Day 2	ND	ND	ND	0.162	0.2768	0.2941
Day 3	0.132	0.3722	0.3722	0.529	0.0001	0.0009
Day 4	ND	ND	ND	0.371	0.0094	0.0145
Week 1	ND	ND	ND	0.651	<0.0001	0.0009
Week 2	0.431	0.0028	0.0068	0.342	0.0198	0.0281
Week 4	0.487	0.0006	0.0020	0.490	0.0005	0.0020
Week 8	0.385	0.0083	0.0141	0.389	0.0075	0.0141
Week 12	0.514	0.0498	0.0564	0.570	0.0266	0.0348
Week 20	0.320	0.0323	0.0392	0.402	0.0069	0.0141
Week 24	0.536	0.0002	0.0011	0.488	0.0008	0.0023

ND: not determined.

inflammatory biomarkers (including CRP) and improvements in SJC, TJC, or DAS28-CRP scores at week 24 (data not shown).

Correlations between baseline biomarker levels and week 24 efficacy measures (TJC, SJC and DAS28-CRP score) were also evaluated and stratified by baseline CRP level ($<$ or ≥ 1.0 mg/dl) (data not shown). Among patients with baseline CRP <1.0 mg/dl ($n=31$), patients with low levels of HA at baseline were more likely to have increases in week 24 TJC and DAS28-CRP scores, while low levels of urine hepcidin at baseline correlated with decreases in SJC, and low baseline levels of serum hepcidin and iron correlated with decreases in TJC. Among patients with baseline CRP ≥ 1.0 mg/dl ($n=13$), high baseline ferritin levels correlated with decreases in TJC.

A similar analysis explored changes from baseline to week 24 in efficacy measures and changes in biomarker levels at week 24. Among patients with CRP <1.0 mg/dl, increases in erythropoietin were associated with improvements in DAS28-CRP scores, decreases in serum hepcidin were associated with improvements in TJC score and decreases in total iron were associated with improvements in SJC. Among patients with CRP ≥ 1.0 mg/dl, increases in serum hepcidin were associated with improvements in TJC score.

Safety

Golimumab was generally well tolerated. Twenty-five patients (75.8%) in group 1 and 12 patients (75.0%) in group 2 reported AEs; the majority were mild [18]. Infections were the most common type of AE. No deaths were reported.

Discussion

The population size in this small, phase 1 study was adequate for pharmacokinetic analyses; however, it was not optimal for assessing pharmacodynamic effects, given the

minimally active disease, as indicated by low CRP levels and a low rate of anaemia. Overall, serum levels of CRP, IL-6, SAA, TNFR1I, MMP-3, hepcidin, ferritin and haptoglobin and urine hepcidin decreased within 1 week of initiation of therapy, and generally remained below baseline levels up to week 8. In addition, the decreases in serum CRP, IL-6, SAA, MMP-3, haptoglobin, hepcidin and ferritin levels, as well as urine hepcidin levels, were maintained through week 24 in group 1 (s.c. monthly dosing). However, in group 2 (i.v. dosing at baseline and week 12), serum levels of CRP, IL-6, MMP-3, haptoglobin, SAA, ferritin and TNFR1I and urine hepcidin levels began to rise at week 8 and continued to gradually increase through week 24, even after the second dose at week 12. This indicates that the dosing regimen in group 2 is not ideal for RA patients. This is consistent with a phase 3 study in which trough golimumab levels were lower than expected with every 12-week dosing [21].

Although serum and urine hepcidin levels were not elevated above normal ranges [22], the decreases that were observed following golimumab treatment are notable because of the role of hepcidin in anaemia of inflammation and as an acute-phase reactant in RA patients. A lower hepcidin concentration within the normal range after golimumab treatment is consistent with reduced inflammation. It would be predicted to enhance iron absorption from the diet, iron recycling by macrophages, haemoglobin production and erythropoiesis in these patients.

Within the limitations of the small patient numbers in this study, some exploratory correlations and predictive modelling was done. Clinical improvements were generally associated with appropriate shifts in anaemia-related biomarkers. Decreased hepcidin and increased erythropoietin and possibly increased iron utilization (decreases in iron concentration) were associated with improved clinical signs and symptoms. Likewise, decreases in serum hepcidin significantly corresponded with decreases in

CRP and ferritin, indicating control of inflammation. These results were not as clear as those observed in previous studies [23, 24] and were limited by the small population size and the relatively less severe, baseline disease activity. While highly speculative, these results can be tested in future trials.

Following treatment with i.v. or s.c. golimumab, decreases in several inflammatory markers were observed. These decreases were rapid, often within 24 h, and were maintained through week 24 in group 1. This analysis also demonstrated that serum and urine hepcidin levels have potential as biomarkers when evaluating inflammation in RA patients. Although there were too few patients with anaemia to fully evaluate the effects of golimumab on anaemia of inflammation, the decreases in hepcidin, CRP, IL-6 and ferritin are notable.

Further evaluation of the effect of golimumab on anaemia is currently under way in RA patients. Larger studies in the future that include measurements of hepcidin may help elucidate its role as a biomarker in anaemia of inflammation.

Rheumatology key messages

- Early decreases in hepcidin were observed with s.c. and i.v. golimumab in RA patients.
- Inflammatory biomarkers decreased through 24 weeks in RA patients receiving s.c. golimumab every 4 weeks.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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Supplemental Table 1. Baseline patient demographics, disease characteristics, and biomarker levels.

	Group 1 (n = 33)	Group 2 (n = 16)
Demographics		
Age, y	55.1 (13.0)	57.3 (9.9)
	59.0 [19.0, 74.0]	56.5 [39.0, 76.0]
Female, n (%)	25 (75.8)	12 (75.0)
Race, n (%)		
Caucasian	26 (78.8)	15 (93.8)
Black	5 (15.2)	1 (6.3)
Asian	1 (3.0)	0 (0)
Other	1 (3.0)	0 (0)
Disease characteristics		
Disease duration, y	8.9 (8.3)	10.3 (8.0)
	5.5 [0.3, 28.2]	9.6 [0.5, 23.4]
DAS28-CRP	5.3 (1.0)	5.1 (1.2)
	5.3 [4.5, 5.9]	4.9 [4.4, 6.0]
TJC	22.1 (17.0)	23.5 (19.6)
	17.0 [3.0, 68.0]	17.0 [4.0, 66.0]
SJC	19.1 (16.8)	18.4 (14.6)
	12.0 [2.1, 64.0]	14.5 [0.0, 62.0]
HAQ-DI	1.3 (0.6)	1.1 (0.5)
	1.5 [0.0, 2.4]	1.3 [0.0, 1.9]
FACIT-F	29.4 (10.0)	36.1 (11.5)
	30.0 [12.0, 48.0]	35.5 [14.0, 51.0]
CRP, mg/dL	1.2 (1.4)	0.8 (1.0)
	0.6 [0.3, 6.1]	0.3 [0.3, 4.0]
Hemoglobin, g/dL	13.2 (1.6)	13.3 (1.2)
	13.3 [10.3, 17.2]	13.3 [11.2, 15.4]
Rheumatoid factor		
Positive, n (%)	21 (63.6)	11 (68.8)
Anti-CCP		
Positive, n (%)	21 (63.6)	11 (68.8)

Data presented as mean (standard deviation) and median [range] unless otherwise noted.

DAS28, 28-joint disease activity score; CRP, C-reactive protein; TJC, tender joint count; SJC, swollen joint count; HAQ-DI, health assessment questionnaire-disability index; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; CCP, cyclic citrullinated peptide

Supplemental Table 2. Efficacy results at week 24.

	Group 1	Group 2
Patients randomized, n	33	16
ACR 20	18 (62.1)	9 (56.3)
ACR 50	9 (31.0)	4 (25.0)
ACR 70	6 (20.7)	3 (18.8)
DAS28-CRP		
Good	11 (37.9)	5 (31.3)
Moderate	14 (48.3)	6 (37.5)
Remission	11 (33.3)	4 (25.0)
Mean (SD) improvement in patient's assessment of pain (VAS), %	49.5 (37.2)	28.8 (53.6)
Mean (SD) improvement in physician's global assessment (VAS), %	47.9 (57.0)	58.5 (28.8)
Mean (SD) improvement in patient's global assessment (VAS), %	43.4 (41.9)	36.6 (44.4)
Mean (SD) improvement in TJC, %	57.8 (41.8)	50.7 (42.7)
Mean (SD) improvement in SJC, %	72.3 (41.1)	75.7 (24.1)
Mean (SD) change in HAQ-DI	-0.40 (0.52)	-0.46 (0.66)
Mean (SD) change in FACIT-F	8.9 (11)	2.6 (10.2)

Data presented as n (%) unless otherwise noted.

SC, subcutaneous; IV, intravenous; ACR20/50/70, 20%/50%/70% improvement in the American College of Rheumatology criteria; DAS28-CRP, 28-joint disease activity score using C-reactive protein (CRP); TJC, tender joint count; SJC, swollen joint count; HAQ-DI, health assessment questionnaire-disability index; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue