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Serum golimumab concentration and anti-drug antibodies are associated with treatment response and drug survival in patients with inflammatory joint diseases: data from the NOR-DMARD study

JE Gehin1,2, DJ Warren1, SW Syversen3, E Lie3,4, J Sexton3, L Loli5, A Wierød6, T Bjørn1,2, TK Kvien2,3, N Bolstad1, GL Goll3

1Department of Medical Biochemistry, Oslo University Hospital-Radiumhospitalen, Oslo, Norway
2Faculty of Medicine, University of Oslo, Oslo, Norway
3Division of Rheumatology and Research, Diakonhjemmet Hospital, Oslo, Norway
4Department of Cardiology, Oslo University Hospital-Ulløvål, Oslo, Norway
5Department of Rheumatology, Lillehammer Hospital for Rheumatic Diseases, Lillehammer, Norway
6Department of Rheumatology, Vestre Viken Hospital Trust, Drammen, Norway

Objectives: This study aimed to identify the therapeutic target concentration and frequency of anti-drug antibodies (ADAbs) in golimumab-treated patients with inflammatory joint disease (IJD).

Method: Associations between golimumab concentration, ADAbs, and treatment response were examined in 91 patients with IJD (41 axial spondyloarthritis (axSpA), 20 rheumatoid arthritis (RA), and 30 psoriatic arthritis (PsA)) included in the NOR-DMARD study. Treatment response was defined by Ankylosing Spondylitis Disease Activity Score (ASDAS) clinically important improvement in axSpA, European League Against Rheumatism (EULAR) good/moderate response in RA, and improvement of ≥50% in modified Disease Activity index for Psoriatic Arthritis (DAPSA) (28 swollen/tender joint counts) in PsA. Serum drug concentrations and ADAbs were analysed using automated in-house assays.

Results: At inclusion, 42% were biological disease-modifying anti-rheumatic drug naïve and 42% used concomitant synthetic disease-modifying anti-rheumatic drug. The median golimumab concentration was 2.2 (interquartile range 1.0–3.5) mg/L. The proportions of responders after 3 months among patients with golimumab concentration < 1.0, 1.0–3.9, and ≥ 4.0 mg/L were 19%, 49%, and 74%, respectively. A higher rate of treatment discontinuation was seen in patients with serum golimumab concentration < 1.0 compared to ≥ 1.0 mg/L (hazard ratio 3.3, 95% confidence interval 1.8–6.0, p < 0.05). ADAbs were detected in 6%, and were associated with lower drug concentrations and both reduced treatment response and drug survival.

Conclusions: Golimumab concentrations ≥ 1.0 mg/L were associated with improved treatment response and better drug survival, although some patients may benefit from higher concentrations. This study suggests a rationale for dosing guided by therapeutic drug monitoring in golimumab-treated patients with IJD. The results should be confirmed in larger studies including trough samples, and the efficacy of such a strategy must be examined in randomized controlled trials.

Golimumab, a human immunoglobulin G1-kappa (IgG1-κ) monoclonal antibody against tumour necrosis factor-alpha (TNF-α), has proven efficacious in the treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA), and axial spondyloarthritis (axSpA) (1–3). However, not all patients respond adequately to treatment. Lack or loss of response to TNF inhibitors (TNFi) can be caused by subtherapeutic drug concentrations (pharmacokinetic failure), sometimes associated with the formation of anti-drug antibodies (ADAb), or a mismatch between drug target and key disease mediators (pharmacodynamic failure) (4–12).

As a supplement to standard clinical care, therapeutic drug monitoring (TDM) has the potential to improve the effectiveness, safety, and cost-effectiveness of treatment with biological drugs in rheumatology (13–15). For TDM to be validated as a clinical tool in golimumab-treated patients with inflammatory joint disease (IJD), the therapeutic target concentration must be identified. Associations between serum golimumab concentrations and treatment responses have been suggested in relatively small observational studies on patients with RA.
and axSpA (3, 16–18). The occurrence of ADAbs against golimumab varies between 0% and 15% (16, 18, 19).

A therapeutic target concentration of 0.7–1.4 mg/L for golimumab has been suggested in axSpA (17). Therapeutic target concentrations for treatment of RA and PsA remain to be identified, and the suggested target concentration in axSpA should be confirmed. Furthermore, there are few reports on the clinical relevance of ADAbs against golimumab in IJD patients (16, 18).

The main objective of this study was to identify a therapeutic target concentration for non-trough serum samples in golimumab-treated patients with IJD by examining the association between golimumab concentrations and treatment response and drug survival. In addition, we wanted to assess the clinical significance of early ADAb development.

Method

The NOR-DMARD study and patient selection

The Norwegian DMARD study (NOR-DMARD; clinicaltrials.gov: NCT01581294) is a longitudinal observational study of adult IJD patients initiating treatment with a biological disease-modifying anti-rheumatic drug (bDMARD) (20). Clinical data are registered at baseline, 3, 6, 9, and 12 months, and every 6 months thereafter. Biobank samples are collected at baseline and at the 3 month follow-up visit.

For the current analyses, we included consecutive patients enrolled in the study between January 2013 and June 2017, with a clinical diagnosis of axSpA, RA, or PsA, who had started golimumab treatment and had available biobank samples from the 3 month visit. Serum samples analysed in this study were non-trough samples, collected at the 3 month visit and stored at −80°C. Clinical data from baseline and the 3 and 6 month follow-up visits were used in the analyses.

The study was approved by the Regional Ethics Committee of Eastern Norway (ref. 2011/1339). All patients provided written, informed consent before inclusion.

Clinical response

The disease activity measures used in this study were the Ankylosing Spondylitis Disease Activity Score–C-reactive protein (ASDAS-CRP) for axSpA (21), the 28-joint Disease Activity Score–erythrocyte sedimentation rate (DAS28-ESR) (22) for RA, and a modified version of the Disease Activity index for Psoriatic Arthritis, using 28 swollen/tender joint counts (DAPSA28) for PsA (23–25). Modified DAPSA28 was calculated as DAPSA28 = (28TJC × 1.6) + (28SJC × 1.6) + Patient global (0–10VAS) + Pain (0–10VAS) + CRP (mg/dL) (23). Treatment response was defined by ASDAS Clinically important improvement (CII) (an ASDAS-CRP reduction of ≥ 1.1 units) in axSpA (21), European League Against Rheumatism (EULAR) good or moderate response in RA (26), and DAPSA28 improvement ≥ 50% in PsA (24). Sensitivity analyses, using DAPSA32 (27) improvement ≥ 50% and DAS28 improvement of ≥ 0.6 (28) to define treatment response, were performed in PsA.

Measurement of golimumab drug concentrations and ADAbs

Drug concentrations were measured using an in-house, European In-Vitro Diagnostic Devices Directive-compliant, time-resolved fluorometric assay automated on the AutoDELFIA (PerkinElmer, Waltham, MA, USA) immunoassay platform. The assay is a minor modification of our previously described method for serum belatacept (29) and uses human recombinant TNF-α as the capture reagent. Golimumab binding to the TNF-α solid phase is detected using a europium-labelled protein-A tracer reagent (29–31). ADAbs were detected by an in-house assay measuring neutralizing ADAb. In this assay, the amount of Eu-labelled golimumab (Fab’)2 binding to the TNF-α solid phase is inversely proportional to the amount of ADAb present in the sample. As are most ADAb assays, our assay is drug sensitive. In brief, europium-labelled golimumab (Fab’)2 was dispensed into streptavidin-coated 96-well plates, followed by patient serum. After 1 h incubation, biotinylated recombinant TNF-α was added to the wells. After 30 min incubation, the plates were washed and time-resolved fluorescence was measured. The calibrator in our ADAb assay, which was developed in house, was a high-affinity murine anti-idiotypic IgG1 monoclonal antibody (mAb), S17.1, against golimumab. Blank serum was used to prepare a blank calibrator and dilutions of purified mAb, S17.1, to 15, 30, 50, 80, and 100 µg/L. Samples were defined as positive if the ADAb level was ≥ 20 µg/L in combination with golimumab concentration < 5.0 mg/L. All samples were also tested for ADAbs using a more drug-tolerant pH-shift assay, which dissociates complexes of ADAb bound to golimumab. The pH-shift assay was equivalent to the main (drug-sensitive) ADAb assay, but included a predilution of the serum samples in 0.05 M glycine–HCl buffer to pH 2.4 to dissociate the ADAb–drug complexes. Europium labelled golimumab (Fab’)2 in 0.4 M Tris buffer (pH 7.8), was dispensed onto streptavidin-coated wells before adding the prediluted serum samples (pH 7.0). After incubation, biotinylated TNF-α in 0.4 M Tris buffer was added (pH 7.4).

Statistical analyses

For differences in baseline characteristics, independent samples t-test, Mann–Whitney U test, or chi-squared tests were used. Statistical tests were two sided with the level of significance set at 0.05. Associations between golimumab concentrations and response were assessed by multivariate logistic regression, adjusting for age, gender, and prior use...
of bDMARDs (Yes/No). For missing 3 and 6 month disease activity data, the next observation carried backwards or last observation carried forward approach was used, respectively (Figure 1).

Drug survival was assessed with Kaplan–Meier curves and Cox proportional hazard regression analysis, adjusting for age, gender, and prior use of bDMARD (Yes/No). Patients without data on discontinuation and those who discontinued treatment owing to pregnancy or remission, were censored at the last registered visit. Statistical analyses were performed using IBM SPSS Statistics, version 25 (IBM Corp, Armonk, NY, USA).

Results

Study population and baseline characteristics
An overview of the study population is shown in Figure 1. Baseline characteristics stratified for diagnosis and golimumab serum concentration < 1.0 mg/L versus ≥ 1.0 mg/L in the 3 month sample are shown in Table 1. Among RA patients, those with golimumab concentration < 1.0 mg/L had a significantly lower mean age at inclusion compared to patients with golimumab concentration ≥ 1.0 mg/L. Other baseline characteristics did not differ significantly between patients with golimumab concentration < 1.0 vs ≥ 1.0 mg/L.

Distribution of golimumab serum concentrations
Golimumab concentrations in the 3 month samples varied from 0.0 to 8.2 mg/L (Figure 2). For the total IJD population, median [interquartile range (IQR)] golimumab concentration was 2.2 (1.0–3.5) mg/L (coefficient of variation 76%). For individual diagnoses, the median (IQR) concentrations were 2.7 (1.2–4.8) in axSpA, 1.6 (0.5–2.8) in RA, and 2.3 (1.2–3.2) mg/L in PsA. The golimumab concentrations were < 1 mg/L in 24 patients. Among these, the concentrations varied from 0.0 to 0.9 mg/L, median (IQR) 0.3 (0.0–0.6) mg/L. Seven patients had undetectable levels.

Most patients were being given the standard dose, 50 mg every fourth week, at the 3 month visit. Among the three patients who were not being given the standard dose at 3 months, two patients received 100 mg every fourth week and one patient on the standard dose had paused treatment at the 3 month visit.

Association between golimumab concentrations and treatment response
The associations between serum golimumab concentration and treatment response, defined as ASDAS CII in axSpA, EULAR good/moderate response in RA, and improvement of ≥ 50% in DAPSA28 score in PsA,
Table 1. Comparison of baseline characteristics in patients with golimumab serum concentration < 1.0 mg/L vs ≥ 1.0 mg/L at 3 month follow-up.

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Golimumab &lt; 1.0 mg/L</th>
<th>Golimumab ≥ 1.0 mg/L</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial spondyloarthritis</td>
<td>(n = 47)</td>
<td>(n = 8)</td>
<td>(n = 39)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>40 ± 11</td>
<td>41 ± 12</td>
<td>40 ± 12</td>
<td>0.81</td>
</tr>
<tr>
<td>Female</td>
<td>24 (51)</td>
<td>4 (50)</td>
<td>20 (51)</td>
<td>0.95</td>
</tr>
<tr>
<td>Disease duration (years)*</td>
<td>2.2 (0.5–8.9)</td>
<td>0.7 (0.4–5.6)</td>
<td>2.7 (1.0–20.9)</td>
<td>0.29</td>
</tr>
<tr>
<td>ASDAS-CRP</td>
<td>2.7 ± 1.0</td>
<td>2.4 ± 0.5</td>
<td>2.7 ± 1.1</td>
<td>0.41</td>
</tr>
<tr>
<td>HLA-B27 positive†</td>
<td>35 (88)</td>
<td>6 (75)</td>
<td>29 (91)</td>
<td>0.23</td>
</tr>
<tr>
<td>Prior use of bDMARD</td>
<td>26 (55)</td>
<td>5 (63)</td>
<td>21 (54)</td>
<td>0.65</td>
</tr>
<tr>
<td>Concomitant csDMARD</td>
<td>4 (9)</td>
<td>1 (13)</td>
<td>3 (8)</td>
<td>0.66</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>(n = 25)</td>
<td>(n = 10)</td>
<td>(n = 15)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>52 ± 16</td>
<td>41 ± 18</td>
<td>59 ± 11</td>
<td>0.02</td>
</tr>
<tr>
<td>Female</td>
<td>22 (88)</td>
<td>9 (90)</td>
<td>13 (87)</td>
<td>0.80</td>
</tr>
<tr>
<td>Disease duration (years)‡</td>
<td>12.2 (4.9–25.6)</td>
<td>7.7 (3.8–25.8)</td>
<td>14.0 (5.3–25.5)</td>
<td>0.75</td>
</tr>
<tr>
<td>DAS28</td>
<td>4.6 ± 1.7</td>
<td>4.8 ± 1.6</td>
<td>4.4 ± 1.8</td>
<td>0.57</td>
</tr>
<tr>
<td>RF-positive§</td>
<td>13 (62)</td>
<td>7 (78)</td>
<td>6 (50)</td>
<td>0.20</td>
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<tr>
<td>Anti-CCP positive‖</td>
<td>14 (67)</td>
<td>8 (89)</td>
<td>6 (50)</td>
<td>0.06</td>
</tr>
<tr>
<td>Prior use of bDMARD</td>
<td>20 (80)</td>
<td>9 (80)</td>
<td>12 (80)</td>
<td>1.00</td>
</tr>
<tr>
<td>Concomitant csDMARD</td>
<td>19 (70)</td>
<td>7 (70)</td>
<td>12 (80)</td>
<td>0.57</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>(n = 35)</td>
<td>(n = 6)</td>
<td>(n = 29)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>48 ± 12</td>
<td>50 ± 13</td>
<td>47 ± 13</td>
<td>0.33</td>
</tr>
<tr>
<td>Female</td>
<td>18 (51)</td>
<td>3 (50)</td>
<td>15 (52)</td>
<td>0.94</td>
</tr>
<tr>
<td>Disease duration (years)¶</td>
<td>5.0 (0.4–10.4)</td>
<td>7.4** (3.4–7.6)</td>
<td>4.9 (0.4–11.3)</td>
<td>0.81</td>
</tr>
<tr>
<td>DAPSA28</td>
<td>13.4 (9.5–16.6)</td>
<td>15.3 (10.1–19.5)</td>
<td>13.0 (8.5–15.7)</td>
<td>0.52</td>
</tr>
<tr>
<td>Prior use of bDMARD</td>
<td>16 (47)</td>
<td>2 (33)</td>
<td>14 (50)</td>
<td>0.46</td>
</tr>
<tr>
<td>Concomitant csDMARD</td>
<td>22 (65)</td>
<td>3 (50)</td>
<td>19 (68)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Data are shown as mean ± sd, n (%), or median (interquartile range). Data available in n = **28, 140, 14, 521, ||21, and P22 patients.

**Interquartile range not applicable, data available in n = 3 patients.

ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score; C-reactive protein; HLA, human leucocyte antigen; bDMARD, biological disease-modifying anti-rheumatic drug; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; DAS28, 28-joint Disease Activity Score; RF, rheumatoid factor; anti-CCP, anti-cyclic citrullinated peptide; DAPSA28, 28-joint Disease Activity Index for Psoriatic Arthritis.

were examined. The proportions of responders after 3 and 6 months, stratified by golimumab serum concentration at 3 months, for the total IJD population and for axSpA, RA, and PsA separately, are shown in Table 2 and Figure 3A–Figure 3D. Based on the explorative concentration–effect analyses (depicted in Figure 3), we wanted to assess the association between golimumab concentration ≥ 1.0 mg/L and treatment response. To this end, we compared responses among patients with golimumab ≥ 1.0 versus < 1.0 mg/L. Furthermore, the concentration–effect analyses suggested an additional effect of having a golimumab concentration ≥ 4.0 mg/L; hence, we compared responses among patients with golimumab ≥ 4.0 versus 1.0–3.9 mg/L. For the total population of IJD, the likelihood of response after 3 months of treatment was significantly higher in patients with serum golimumab concentrations ≥ 1.0 mg/L than in those with golimumab < 1.0 mg/L [odds ratio (OR) 5.8, 95% confidence interval (CI) 1.7–19.7, p = 0.005]. The association between serum golimumab concentration ≥ 1 mg/L and response after 6 months showed a similar tendency but was not statistically significant (OR 2.7, 95% CI 0.9–7.8, p = 0.08). Across the total IJD population, the proportion of responders was highest among patients with golimumab concentration ≥ 4.0 mg/L (Figure 3A–Figure 3D), although the difference in response between the group with golimumab concentration ≥ 4.0 mg/L compared to 1.0–4.0 mg/L was not statistically significant (ORs for response for golimumab concentration ≥ 4.0 mg/L vs 1.0–4.0 mg/L at 3 and 6 months: OR 2.1, 95% CI 0.6–7.1, p = 0.24, and OR 1.5, 95% CI 0.4–5.1, p = 0.54, respectively). The results were confirmed by sensitivity analyses using ≥ 50% improvement in DAPSA32 and improvement of ≥ 0.6 in DAS28 as response criteria in PsA (results not shown).

As shown in Table 2, the association between concentration and response was strongest in bDMARD-naïve patients [OR 21.6, 95% CI 2.0–233.5, p = 0.01 for response among patients with golimumab ≥ 1.0 mg/L compared to golimumab < 1.0 mg/L (all diagnoses)]. bDMARD-naïve
Golimumab levels and immunogenicity

Figure 2. Distribution of golimumab serum concentrations in mg/L at 3 months (total inflammatory joint disease population). Median (interquartile range) = 2.2 (1.0–3.5) mg/L.

patients were responders after 3 months in 60% of cases, compared to 38% among those with prior use of bDMARD (p = 0.04). The results were consistent after 6 months. The median (IQR) golimumab serum concentration was similar in patients with prior use of bDMARD, compared to bDMARD-naïve, 2.1 (1.0–3.0) mg/L versus 2.8 (1.7–4.5) mg/L, respectively (p = 0.06). However, the proportion of patients with high golimumab concentrations, ≥ 4 mg/L, was higher among bDMARD-naïve patients than those with prior use of bDMARDs, 14 (32%) versus eight (13%), respectively (p = 0.02).

Drug survival

Data for discontinuation were registered in 61 of 107 patients within the first 36 months of golimumab treatment. The discontinuation rates differed between groups stratified by golimumab concentration (Figure 4). The hazard ratio (HR) for discontinuation was 3.3 (95% CI 1.8–6.0) (p < 0.001), for patients with golimumab concentration < 1.0 mg/L versus ≥ 1.0 mg/L. We found a trend, although not statistically significant, towards a higher discontinuation rate in the 1.0–3.9 mg/L group compared to the ≥ 4.0 mg/L group (HR 1.5, 95% CI 0.7–3.3, p = 0.32).

Among patients with golimumab concentration < 1.0 mg/L, 20 of 24 (83%) discontinued within 36 months of treatment initiation, compared to 32 of 61 (53%) of those with golimumab concentration 1.0–3.9 mg/L and nine of 22 (41%) with ≥ 4.0 mg/L.

Reasons for discontinuation were lack of efficacy (LOE) in 37 patients (61%), adverse events (AEs) in 16 (26%), remission in one (2%), pregnancy in three (5%),

Table 2. Response* (%) at 3 and 6 months, stratified by golimumab concentration at 3 months.

| Responders* after 3 months | Overall | Golimumab < 1.0 mg/L§ | Golimumab 1.0–3.9 mg/L|| Golimumab ≥ 4.0 mg/L¶ | OR† (95% CI) response in golimumab ≥ 1.0 vs < 1.0 mg/L | p | OR† (95% CI) response in golimumab ≥ 4.0 vs 1.0–3.9 mg/L | p |
|----------------------------|---------|------------------------|-------------------------|---------------------------|---------------------------------|------------|---------------------------------|------------|
| All patients (n = 90)      |         |                        |                         |                           |                                 |           |                                 |           |
| axSpA (n = 41)             | 47%     | 19%                    | 49%                     | 74%                       | 5.8 (1.7–19.7)                  | 0.005     | 2.1 (0.6–7.1)                   | 0.24       |
| RA (n = 20)                | 55%     | 22%                    | 78%                     | 100% (n = 2)              | 26.5 (1.2–607.7)               | 0.04      | NA**                           |           |
| PsA (n = 30)               | 37%     | 20%                    | 37%                     | 50%                       | 2.8 (0.2–31.8)                 | 0.40      | 1.3 (0.2–10.6)                 | 0.83       |
| bDMARD naïve (n = 40)      | 60%     | 13%                    | 63%                     | 85%                       | 21.6 (2.0–233.5)               | 0.01      | 5.4 (1.0–30.4)                 | 0.05       |

| Responders* after 6 months | Overall | Golimumab < 1.0 mg/L§ | Golimumab 1.0–3.9 mg/L|| Golimumab ≥ 4.0 mg/L¶ | OR† (95% CI) response in golimumab ≥ 1.0 vs < 1.0 mg/L | p | OR† (95% CI) response in golimumab ≥ 4.0 vs 1.0–3.9 mg/L | p |
|----------------------------|---------|------------------------|-------------------------|---------------------------|---------------------------------|------------|---------------------------------|------------|
| All patients (n = 90)      |         |                        |                         |                           |                                 |           |                                 |           |
| axSpA (n = 41)             | 48%     | 33%                    | 47%                     | 68%                       | 2.7 (0.9–7.8)                  | 0.08      | 1.5 (0.4–5.1)                   | 0.54       |
| RA (n = 20)                | 56%     | 29%                    | 52%                     | 82%                       | 3.9 (0.6–26.9)                 | 0.17      | 2.5 (0.3–25.0)                 | 0.42       |
| PsA (n = 30)               | 37%     | 20%                    | 37%                     | 50%                       | 2.6 (0.2–30.2)                 | 0.45      | 1.2 (0.1–11.8)                 | 0.86       |
| bDMARD naïve (n = 40)      | 60%     | 13%                    | 63%                     | 85%                       | 26.4 (2.0–341.1)               | 0.01      | 5.6 (0.9–34.3)                 | 0.06       |

*Response in axial spondyloarthritis (axSpA) was defined by clinically important improvement in the Ankylosing Spondylitis Disease Activity Score, in rheumatoid arthritis (RA) as European League Against Rheumatism good/moderate response, and in psoriatic arthritis (PsA) as improvement of ≥ 50% in the 28-joint Disease Activity Index for PSoriatic Arthritis (DAPSA28).

†/‡ Multivariable logistic regression comparing response in patients with golimumab ≥ 1.0 mg/L and ≥ 4.0 mg/L, adjusting for age, gender, and prior biological disease-modifying anti-rheumatic drug (bDMARD) use (Yes/No).

§n = 21 overall, 7 axSpA, 9 RA, 5 PsA, and 8 bDMARD naïve; ||n = 51 overall, 23 axSpA, 9 RA, 19 PsA, and 19 bDMARD naïve; ¶n = 19 overall, 11 axSpA, 2 RA, 6 PsA, and 13 bDMARD naïve.

**Odds ratio not applicable, data available in n = 2 patients.

OR, odds ratio; CI, confidence interval.
Figure 3. Proportion of responders at 3 months, stratified by golimumab concentration (mg/L). (A) Total inflammatory joint disease population; (B) Ankylosing Spondylitis Disease Activity Score (ASDAS) clinically important improvement (CII) responders in axial spondyloarthritis (AxSpA); (C) European League Against Rheumatism (EULAR) good/moderate response in rheumatoid arthritis (RA); (D) 28-joint Disease Activity Index for Psoriatic Arthritis (DAPSA28) ≥ 50% improvement in psoriatic arthritis (PsA).

other reasons in three patients (5%), and unknown in one patient (2%). Stratified by golimumab concentration, LOE was the discontinuation cause in 10 of 24 (42%), 22 of 61 (36%), and five of 22 (23%), and AEs were the cause in seven of 24 (29%), seven of 61 (12%), and two of 22 patients (9%) among patients with golimumab concentrations of < 1 mg/L, 1–3.9 mg/L, and ≥ 4 mg/L, respectively.

Frequency and clinical significance of ADAbs at 3 month sampling

Out of 107 patients, six (6%) had developed ADAbs after 3 months of treatment (two AxSpA, two RA, and two PsA). Golimumab serum concentrations were significantly lower in ADAb-positive patients compared to ADAb-negative individuals [median 0.1 (IQR 0.0–1.0) mg/L vs 2.4 (1.2–3.6) mg/L, p = 0.001].

Out of 91 patients with available response data, only one out of five ADAb-positive patients was a responder at 3 and 6 months. Conversely, 42 and 43 out of 86 ADAb-negative patients were responders after 3 and 6 months, respectively. Using the pH-shift assay, an additional two samples (both PsA) were ADAb positive. Of these, one was a responder at 3 months while neither was a responder at 6 months.

Out of the six ADAb-positive patients, four discontinued treatment owing to LOE and one to AEs within

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the first 14 months. One patient discontinued after 5 months because of pregnancy.

Mean drug survival time was 7 (95% CI 2–11) months in patients who were ADAb positive at 3 months, compared to 30 (95% CI 25–34) months in the ADAb-negative group. Both of the additional two patients who were positive in the pH-shift assay had discontinued treatment within 12 months.

Among ADAb-positive patients with data on the use of concomitant synthetic DMARDs, two out of five used a concomitant synthetic DMARD (methotrexate), and among ADAb-negative patients the proportion was 43 out of 101 (37 methotrexate, six other synthetic DMARDs).

Discussion
Our results demonstrate a concentration–effect relationship in non-trough samples from golimumab-treated patients with IJD. We found a higher proportion of responders among patients with serum concentration ≥ 1.0 mg/L compared to < 1.0 mg/L, across the total IJD population as well as for the individual diagnoses. Furthermore, drug survival was better among patients with serum concentration ≥ 1.0 mg/L. A trend towards even better response rates and drug survival in patients with drug concentrations ≥ 4.0 mg/L was found across all diagnoses.

Golimumab serum concentrations varied significantly between individuals, which might suggest both under-treatment and overtreatment. We aimed to identify a therapeutic target concentration applicable to clinical practice. Our results suggest that a non-trough golimumab concentration ≥ 1.0 mg/L increases the likelihood of achieving a response to golimumab treatment. This is supported by drug survival analyses and is consistent with previous results from small observational studies in RA and axSpA (16–18). We were not able to identify an upper limit of the target concentration and our results may suggest an additional benefit of higher drug concentrations (≥ 4.0 mg/L) in some patients. The authors of a previous dose-finding study did not find a clear difference in response between different dosing groups, although they did report a higher proportion of American College of Rheumatology 20% improvement responders in the group receiving 100 mg every 2 weeks (32). In a study on patients with RA, a better treatment response was found among patients with golimumab concentration ≥ 1.4 mg/L, compared to < 1.4 mg/L (18). A study on axSpA patients suggested 0.7–1.4 mg/L as the therapeutic range of golimumab trough concentrations (17). Response among patients with higher drug concentrations was not assessed in these studies, and results from these studies may not be directly comparable to our results owing to different sampling times. The discrepancy between the therapeutic levels suggested by these previous studies could be a consequence of different patient populations with regard to diagnosis, age, and gender, as well as differences in study design, disease-specific outcome measures, and assays to measure drug concentration.

The random timing of serum sampling during an injection cycle could contribute to the large variation in golimumab concentrations seen between individuals in this study and could potentially influence the results of the concentration–effect analyses. However, in clinical practice it is rarely feasible or cost-effective to measure trough concentration for TNFi that are subcutaneous and self-administered. Hence, knowledge about therapeutic concentrations for non-trough samples is clinically useful. By assessing samples collected at random times, we risk underestimating the incidence of low drug levels, but we expect the specificity of a low concentration to be high. Importantly, a low random-sampling drug measurement will alert the clinician to a patient who may benefit from specific evaluation of whether the golimumab dose may be adjusted. In that case, a trough sample may be taken from that one specific patient to ensure the best evaluation possible of eligible patients, without the challenging logistics of trough measurements in all patients. Previous studies have demonstrated a benefit of pharmacological testing of non-trough samples from patients treated with subcutaneous TNFi (9, 10, 33). In a pharmacokinetic study assessing golimumab serum concentrations at different time points during an injection cycle in PsA patients, a relatively small variation was illustrated in observed concentrations, on a group level, for patients treated with golimumab 50 mg every 4 weeks (34). Furthermore, pharmacokinetic testing and simulation for other subcutaneous TNFi have suggested that the intraindividual variation in serum concentrations is moderate between injections (35, 36).

The association between golimumab serum concentrations and response after 3 months was most consistent for axSpA and RA. Our study was not powered to evaluate axSpA, RA, and PsA separately, but we considered it relevant to assess whether there were considerable differences between individual diagnoses. Stratification of patients in groups based on drug concentrations was tailored to the individual diagnoses (Figure 3B–Figure 3D), based on differences in numbers of patients and the distribution of drug concentrations between diagnoses.

We found a relatively low proportion of responders among PsA patients in our cohort. This may be related to the response criteria used. PsA is a heterogeneous disease with diverse manifestations, making appropriate response measures a challenging issue. DAPSA28 was used as a disease activity measure in PsA because DAPSA based on the 28 swollen/tender joint count has been shown to be a valid disease activity measure in PsA, if the more extensive 66/68 joint count is not available (23). DAPSA reductions of 50/75/85% have
previously been validated as cut-off points for DAPSA response (24). Sensitivity analyses using improvement of ≥ 50% in DAPSA32 (27) and of ≥ 0.6 in DAS28 (28) as response criteria were performed in PsA and showed similar results (results not shown).

Our results demonstrated a higher rate of premature discontinuation of treatment in patients with serum golimumab concentration < 1.0 mg/L compared to ≥ 1.0 mg/L. Low serum concentrations of golimumab and ADAbs have been shown to be associated with LOE, and ADAbs may theoretically be a risk factor for AE (16–18, 37). Pregnancy and remission as reasons for discontinuation are unlikely to be associated with low drug concentration; thus, these patients were censored in the survival analyses.

The incidence of ADAbs against golimumab detected in our study is consistent with previous studies (16, 18, 19). ADAbs were associated with LOE in two small cohorts of golimumab-treated RA patients (16, 18). We found a lower proportion of responders and an increased incidence of premature treatment discontinuation among ADAb-positive patients, compared to ADAb-negative, although the number of ADAb-positive patients was relatively small. Detection of ADAbs early after treatment initiation is potentially clinically relevant, as anti-infliximab antibodies have been shown to appear early after treatment initiation and precede loss of response to treatment as well as hypersensitivity reactions (38). In line with these results, a study by Siljehult et al showed similar incidences of anti-infliximab antibodies at weeks 14 and 52 (11). We detected ADAbs in an additional two samples with the more drug-tolerant pH-shift assay. Acid pretreatment may improve detection of ADAbs, particularly in non-trough samples (39–41), but the clinical utility remains unclear (42, 43).

Our study shows associations between serum golimumab concentration, ADAbs, and clinical efficacy on a group level. The findings that some patients were responders despite low drug concentration, and others did not respond in the presence of high drug concentrations, may appear counterintuitive. However, these scenarios illustrate the potential utility of TDM. It is relevant to identify patients likely to be in spontaneous remission despite low or unmeasurable concentrations of active drug, as these patients may potentially taper or discontinue treatment without increasing the risk of a disease worsening (44). Conversely, non-response in the presence of high drug levels could indicate a pharmacodynamic failure and these patients could probably benefit from switching to a bDMARD with another mechanism of action or a targeted synthetic DMARD (14, 44). These strategies remain to be examined in randomized controlled strategy trials.

The main strength of this study is the applicability of the results to regular clinical care, including feasible sample collection. Data are from a real-life cohort using non-trough biobank samples collected at 3 months after treatment initiation. A clinical tool to aid in decision making at the 3 month evaluation of treatment efficacy is useful and in line with the early treat-to-target strategy recommended by EULAR and EULAR-ASAS (45–47).

Limitations of our study include the small sample sizes and subsequent lack of statistical power when studying individual diagnoses and higher drug concentrations across diagnoses. Patients with incomplete data on follow-up, and the subsequent use of imputation of data, could represent a bias. Furthermore, the lack of data regarding the timing of sample collection in relation to the last administered dose of golimumab is a weakness. These limitations should be kept in mind when interpreting the results of our study, and the results should be confirmed in larger studies including trough samples. The lack of more extensive joint counts (discussed above) and extra-articular manifestations in PsA patients is a weakness, as well as the lack of data for body weight or body mass index, which are relevant when assessing serum drug concentrations. These parameters were not recorded in the NOR-DMARD study. Our study included relatively few bDMARD-naive patients, especially among RA patients. Previous results from the NOR-DMARD cohort have shown similar drug survival, but better treatment responses, in bDMARD-naive compared to non-naive golimumab-treated patients with IJD (48).

Conclusion

Our results suggest that a golimumab serum concentration ≥ 1.0 mg/L increases the likelihood of achieving a clinical response in IJD, although we cannot exclude that higher concentrations are beneficial in subsets of patients or in certain clinical settings. A significant proportion of patients had already developed ADAbs after 3 months of treatment. These patients had lower drug concentrations, reduced response, and reduced drug survival rates compared to ADAb-negative patients. We observed large variations in golimumab concentrations between individuals on a standard dose, and consistent relationships between drug concentration and both effectiveness and drug survival. Taken together, our results suggest a rationale for personalized dosing guided by TDM in golimumab-treated patients with IJD, but the efficacy of such a strategy must be examined in randomized controlled trials.

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