Optimal concentration range of golimumab in patients with axial spondyloarthritis

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Abstract

Objective

To investigate the association between serum golimumab (GLM) trough levels, clinical disease activity and treatment response during the first year of therapy in patients with axial spondyloarthritis (axSpA), as well as determining an optimal concentration range of GLM in axSpA.

Methods

This was an observational prospective study including 49 patients with axSpA monitored during 52 weeks (W52). Serum GLM trough levels were measured by capture ELISA and antidrug antibodies by bridging ELISA at baseline, W24 and W52. Disease activity was assessed by the Ankylosing Spondylitis Disease Activity Score (ASDAS) and clinical improvement by ΔASDAS. The association between serum GLM trough levels and disease activity was assessed using univariable and multivariable regression. In case of drop-out or missing data before W52, the last observation carried forward (LOCF) was performed. ASDAS values and GLM levels at W24 were available for 42 patients and 38 patients at W52.

Results

In the univariable analyses, serum GLM trough levels were inversely associated with ASDAS at W24 (n=42, r =-0.445; p<0.01), at W52 (n=38, r=-0.330; p<0.05) and W52LOCF (n=49, r=-0.309; p<0.05). In the multivariable analysis, this significant association remained. Serum trough GLM levels above the 0.7-1.4mg/L range did not contribute to additional clinical improvement.

Conclusion

In patients with axSpA, serum GLM trough levels are associated with disease activity during the first year of treatment. A concentration range of 0.7–1.4mg/L appears to be useful to achieve clinical response to GLM.

Key words

spondyloarthritis, golimumab, clinical outcomes, therapeutic drug monitoring

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Introduction

Tumour necrosis factor inhibitors (TNFi) are effective in reducing clinical symptoms in patients with axial spondyloarthritis (axSpA) (1-3). However, this clinical response is not achieved by all patients. Among the possibilities, the presence of low serum drug levels due to immunogenicity may be relevant (1-3). An association between serum golimumab (GLM) trough levels and disease activity in patients with rheumatoid arthritis (RA) has been reported (4-5). Nevertheless, in patients with axSpA there is scarce evidence regarding this association. Only one publication in a small cohort of patients found a correlation between drug levels and therapeutic response (5).

Furthermore, determining a concentration range of serum drug trough levels associated with clinical efficacy would be very useful. Several publications have provided optimal therapeutic ranges for TNFi and inflammatory diseases but no data have been published for patients with axSpA treated with GLM (6-8).

The objective of this study was twofold: first, analyse the association between serum GLM levels and treatment response in patients with axSpA during the first year of therapy and second, to establish an optimal concentration range of serum GLM levels in patients with axSpA treated on standard dose.

Methods

Study design and patients

Forty-nine patients (43 from Spain and 6 from the Netherlands) from a prospective biological registry with axSpA (fulfilling ASAS criteria) (9) starting treatment with GLM were included. All included patients had predominant axial involvement and 16 patients (33%) also had peripheral involvement. The diagnosis was 35 ankylosing spondylitis (AS) patients, 6 non-radiographic axSpA patients, 5 psoriatic SpA (PSpA) patients and 4 SpA associated with inflammatory bowel disease patients. All patients received a standard dose of GLM (50 mg subcutaneously/monthly).The study was approved by the Medical Ethics Committees of La Paz University Hospital (PI no. 1155) and Reade Center (METC no. 1166) and all patients signed an informed consent form.

Clinical disease activity and treatment response

Disease activity was assessed by the Ankylosing Spondylitis Disease Activity Score (ASDAS) at baseline, week 24 (W24) and week 52 (W52) (10) after treatment initiation and data were available in all patients (n=49). According to the disease activity by ASDAS, patients were divided in two groups: group 1 with ASDAS<2.1 and group 2 with ASDAS ≥2.1. Clinical response at W24 and W52 was defined using the ΔASDAS value ≥1.1 for clinically important improvement and ≥2.0 for major improvement and we have one missing data of ΔASDAS (n=48)

Measurements of serum GLM levels

Blood samples were collected a maximum of 24 h before GLM administration and serum GLM trough levels were analysed at baseline, W24 and W52 by an enzyme-linked immunosorbent assay (ELISA) with the commercial kit Promonitor-GLM and Anti-GLM antibodies by the kit anti-GLM (Progenika, Biopharma SA, Derio, Spain) (11).

Statistical analysis

Descriptive statistics were reported as median and interquartile range (IQR) or as absolute number and relative frequencies. The association between serum GLM levels and ASDAS was assessed using univariable and multivariable linear regression models. Age, sex, HLA-B27, DMARDs and ASDAS at baseline were included as independent variables in the multivariable analyses. In case of drop-out or missing data before W52, the last observation carried forward (LOCF) was performed.

Clinical parameters and serum drug levels were available in 49 patients: 31 patients have data at 2 visits (W24 and W52) and 18 patients only have data at 1 visit (11 patients at W24, and 7 patients at W52).

Serum GLM trough levels were categorised according to the tercile cut-off points. The concentration-effect curve at W52LOCF was built sorting the serum GLM trough concentration with

Table I. Baseline demographics and clinical characteristics for the total population*

Total no. patients, n=49	
Demographics	
Age at study entry, years	47.5 (36.75-55)
Men (%)	36 (73%)
BMI	26.06 (22.25-28.14)
Disease	
Ankylosing Spondylitis, n	35 (71%)
Non-radiographic axial SpA , n	6 (12%)
Psoriatic SpA, n	5 (10%)
Spondyoarthropathy with inflammatory bowel disease, n	4 (8%)
Disease status	
Disease duration, years	10.5 (5.25-19)
HLA-B27 positive, n (%)	34 (69%)
CRP, mg/l,	9.47 (4-20.8)
Baseline ASDAS	3.5 (2.87-4.19)
¥ASDAS week52LOCF, n	
Inactive (n=15)	0.93 (0.721.1)
Moderate (n=18)	1.7 (1.5-2)
High (n=16)	2.7 (2.3-3.2)
Prior Biologic use, n (%)	20 (41%)
Concomitant medications	
Monotherapy, n (%)	18 (37%)
‡MTX, n (%)	8 (16%)
MTX+SSZ, n (%)	8 (16%)
¶ SSZ, n (%)	15 (31%)

*Median (IQR) or numbers (percentages) are shown. ¥Disease activity was defined as Inactive (ASDAS <1.3); Moderate (ASDAS 1.3–2.1) and high (ASDAS ≥2.1). ‡Methotrexate (MTX), ¶Sulfasalazine (SSZ).

the ASDAS or ΔASDAS values at the same visit. The percentage of patients according with clinical activity (n=49) and proportion of patients achieving no treatment response (ΔASDAS<1.1), clinically important (ΔASDAS≥1.1) or major (ΔASDAS≥2.0) improvement at W52LOCF (n=48) was compared between the three possible concentration ranges using a chi-square test.

All analysis were performed with GraphPad Prism 6 (San Diego, CA, USA) and SPSS 21.0 software, significant *p*-values: <0.05.

Results

Patient characteristics

Demographic and clinical characteristics of patients are shown in Table I. A total of 49 patients with axSpA were enrolled in the study, including 36 (73%) men, and 34 HLA B27+ (69%). At W52, 44 (89%) patients were still on GLM treatment.

Association between serum GLM trough levels and clinical disease activity

ASDAS values and serum GLM trough levels were available for 42 patients at W24, 38 patients at W52 and all patients (49) at W52LOCF. Thirty-three (67%) patients were in group 1 and 16 (33%) were in group 2 at W52LOCF. Patients in group 1 had higher serum GLM trough levels than patients in group 2 at W52LOCF [1.07 (0.7–1.9) *vs*. 0.6 (0.1–1.4); $p<0.01$, respectively]. An inverse correlation between serum GLM trough levels and ASDAS was found using the univariable analysis: W24 (n=42, r =-0.445; $p<0.01$), W52 (n=38, r=-0.330; $p<0.05$) and W52LOCF (n=49, r=-0.309; $p<0.05$) (Fig. 1). In the multivariable analysis, serum GLM trough levels remained significantly associated with ASDAS at W24 and nearly to significance at W52 and W52LOCF adjusting for possible confounders (Table II).

Furthermore, patients were stratified according to serum GLM trough levels at W52LOCF and divided into terciles. The highest tercile included GLM levels >1.4 mg/L, the medium tercile included 0.7 ≤GLM levels ≤1.4 mg/L and the lowest tercile included GLM levels <0.7 mg/L.

No patients had undetectable serum GLM trough levels or presence of anti-GLM antibodies during the whole study period.

Concentration-effect curve of GLM

To establish a concentration-effect curve at W52LOCF, serum trough GLM concentrations were plotted versus ASDAS values (Fig. 2A) and ΔASDAS (Fig. 2B). Discontinuous lines mark the medium tercile (0.7–1.4 mg/L) showing that drug levels included in this range appear to be sufficient to reach the therapeutic aim and higher GLM levels do not contribute to more clinical improvement.

Association between serum GLM trough levels and clinical activity

Most patients with serum GLM trough levels >0.7 mg/L were classified in

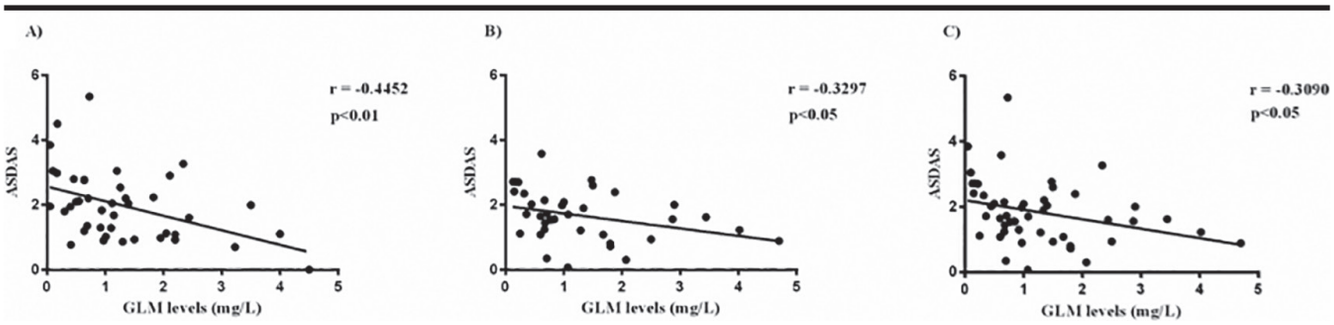

Fig 1. Univariable Spearman correlation between ASDAS and serum golimumab (GLM) trough levels at **A**) 6 months; **B**) one year and **C**) one year performing the last observation carried forward (LOCF) of treatment.

Table II. Multivariable regression analyses for the association between serum GLM trough levels and clinical activity (ASDAS)*.

	Number of patients	Standardised coefficient, (beta)	*p*-value	95% IC
Serum GLM trough levels at W24	42	-0.445	<0.01	-0.769 to -0.121
Serum GLM trough levels at W52	38	-0.247	0.06	-0.510 to 0.016
Serum GLM trough levels at W52LOCF	49	-0.289	0.06	-0.591 to 0.13

*Analysis adjusted for age, sex, HLA-B27 status, concomitant DMARDs and ASDAS at baseline as possible confounders at W24, W52 and W52LOCF.

group 1 (81%). However, patients with serum GLM trough levels <0.7 mg/L were more frequently in group 2 (63%) (<0.7 mg/L: 37% patients in group 1 *vs*. 63 % patients in group 2; 0.7–1.4 mg/L: 88% patients in group 1 *vs*. 12% patients in group 2; >1.4 mg/L: 75% patients in group 1 *vs*. 25% patients in group 2). Figure 3A shows the clinical activity by ASDAS according to GLM concentration terciles. Differences in clinical activity were statistically significant between the lowest (GLM <0.7 mg/L) and the medium tercile (0.7≤GLM≤1.4 mg/L); (Chi square test p=0.002) and between the lowest and highest tercile (GLM>1.4 mg/L); (Chi square test p=0.03). However, no statistical differences between medium and highest terciles were found (Chi square test p=0.3).

Figure 3B shows the clinical improvement of patients according to GLM concentrations terciles. In the lowest tercile group (GLM <0.7 mg/L), only one patient (7%) reached major improvement. However, most patients with serum levels in the medium (0.7≤GLM≤1.4 mg/L) or highest (GLM>1.4 mg/L) tercile had clinically important or major improvement (59% and 62.5%, respectively), with no statistical differences between both groups (Chi square test p>0.05). Moreover, statistically significant differences in clinical improvement between patients in the lowest tercile (GLM<0.7 mg/L) and patients in the medium or highest tercile (0.7≤GLM≤1.4 mg/L levels and GLM>1.4 mg/L) were observed (Chi square test p<0.01 in both cases).

Discussion

To our knowledge, the present study is the first one showing a short- and long-term association between serum GLM trough levels and clinical disease activity in patients with axSpA during the first year of therapy. In addition, an optimal concentration range of serum GLM trough levels has been described. In our cohort, the proportion of patients with a better clinical activity at W52 LOCF was relatively high (almost 70%). Furthermore, most of them had serum GLM trough levels higher than patients with poorer clinical control. Chen *et al*. (5) observed an association between treatment response and serum GLM trough levels after 6 months of therapy in 43 AS patients treated with standard dose of GLM. Another study in RA patients found higher GLM trough levels in responders at 1 year of treatment and, moreover, they obtained serum golimumab ranges which are quite similar to our results (4).

Nowadays, there is a growing interest to define a range of circulating drug in serum associated with clinical efectiveness (7, 8). Pouw *et al*. (7) identified a therapeutic range of 5–8 mg/L of serum Adalimumab levels associated with optimal clinical effect in 221 patients with RA. Kneepkens *et al*. (8) did not find an optimal range in 162 AS patients treated with etanercept. In our study, the concentration-effect curve showed an optimal range of 0.7–1.4 mg/L serum GLM trough levels to achieve clinical response and improvement in axSpA patients. This indicates that 0.7–1.4 mg/L serum GLM trough levels are enough to control disease activity in patients with axSpA and higher amount of circulating drug does not result in a major benefit.

A reason for non-response to TNFi treatment is ADA formation (12). In previous studies the frequency of ADA detection in patients with RA treated with GLM varied between 2.1% and 13%, being around 4% in AS (13). In our cohort, no patient had detectable antibodies to golimumab during the first year of therapy. A feasible explanation might be that the GLM molecule, developed in the human immunoglobulin locus of transgenic mice, has proved to

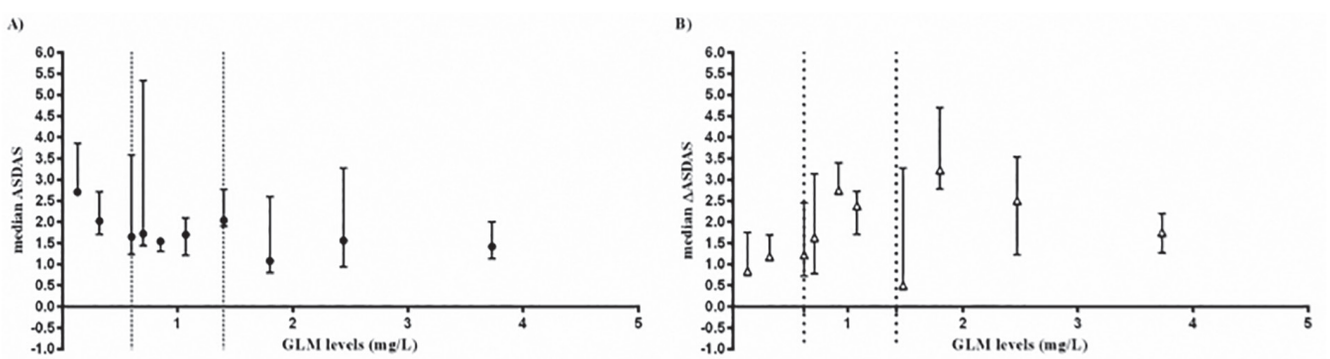

Fig. 2. Concentration-effect curve : Relationship between serum Golimumab trough levels and **A**) ASDAS (clinical activity); each dot represents 5 patients except the last one which represents 4 patients; and **B**) ΔASDAS (clinical improvement); each dot represents 5 patients except the last two that represent 4 patients in patients with axial spondyloarthropathy at week 52 of treatment, performing LOCF.

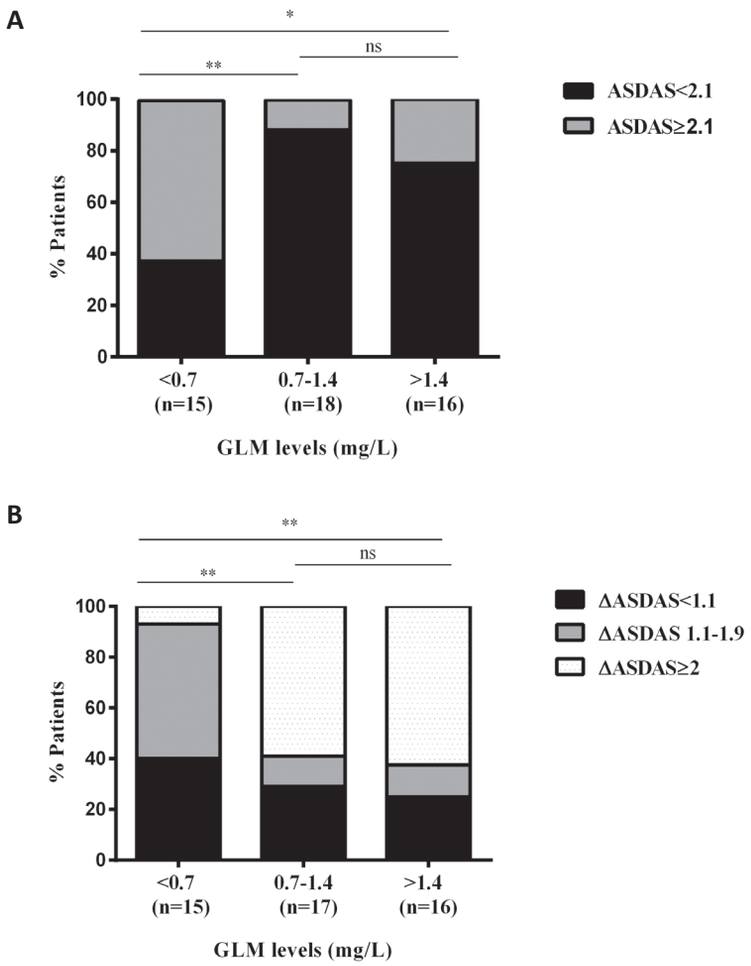

Fig. 3A. Percentage of patients according to serum golimumab trough levels and clinical activity and **B**) Percentage of patients achieving clinical improvement according to serum golimumab trough levels, at week 52LOCF of treatment. ΔASDAS <1.1 (patients with no clinical improvement), ΔASDAS 1.1–1.9 1.1 (patients with clinical improvement), ΔASDAS ≥2 (patients with major clinical improvement). *Chi square test $p<0.05$; **Chi square test $p<0.01$.

be less immunogenic than other TNFi (14). Another reason is the underestimation of ADA in the presence of drug when the antibodies are assayed by the bridging ELISA (15).

The main limitation of our study is the relatively low number of patients. On our behalf, the studied cohort includes SpA patients with axial involvement in which clinical disease activity and improvement were assessed by ASDAS, a validated index combining not only the patient reported outcomes but also the CRP (16).

In conclusion, monitoring of GLM treatment in axSpA patients considering the circulating GLM levels is an valuable tool for the optimal management of patients. This might guide clinicians to lower the drug dose, avoiding side effects and increasing cost-effectiveness. Further studies on GLM pharmacokinetics, concomitant DMARDs use and patient-related factors might be useful to identify non-responder patients to GLM.

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References

1. BARTELDS GM, KRIECKAERT CLM, NURMOHAMED MT *et al*.: Development of antidrug antibodies against adalimumab and association with disease activity and treatment failure during long-term follow-up. *JAMA* 2011; 305: 1460-8.
2. PLASENCIA C, PASCUAL-SALCEDO DF, NUNO LF *et al*.: Influence of immunogenicity on the efficacy of longterm treatment of spondyloarthritis with infliximab. *Ann Rheum Dis* 2012; 71: 1955-60.
3. PAPAGORAS C, VOULGARI PV, DROSOS AA: Golimumab, the newest TNF-alpha blocker, comes of age. *Clin Exp Rheumatol* 2015; 33: 570-7.
4. KNEEPKENS EL, PLASENCIA C, KRIECKAERT CL *et al*.: Golimumab trough levels, antidrug antibodies and clinical response in patients with rheumatoid arthritis treated in daily clinical practice. *Ann Rheum Dis* 2014; 73: 2217-9.
5. CHEN DY, CHEN YM, HUNG WT *et al*.: Immunogenicity, drug trough levels and therapeutic response in patients with rheumatoid arthritis or ankylosing spondylitis after 24-week golimumab treatment. *Ann Rheum Dis* 2015; 74: 2261-4.
6. VANDE CN, FERRANTE M, VAN AG *et al*.: Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. *Gastroenterology* 2015; 148: 1320-9.
7. POUW MF, KRIECKAERT CL, NURMOHAMED MT *et al*.: Key findings towards optimising adalimumab treatment: the concentration-effect curve. *Ann Rheum Dis* 2015; 74: 513-8.
8. KNEEPKENS EL, KRIECKAERT CL, VAN DER KLEIJ D *et al*.: Lower etanercept levels are associated with high disease activity in ankylosing spondylitis patients at 24 weeks of follow-up. *Ann Rheum Dis* 2015; 74: 1825-9.
9. RUDWALEIT M, VAN DER HEIJDE D, LANDEWÉ R *et al*.: The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009; 68: 777-83.
10. MACHADO P, LANDEWÉ R, LIE E *et al*.: Ankylosing Spondylitis Disease Activity Score (ASDAS): defining cut-off values for disease activity states and improvement scores. *Ann Rheum Dis* 2011; 70: 47-53.
11. MARTIN S, DEL AGUA AR, TORRES N *et al*.: Comparison study of two commercially available methods for the determination of golimumab and anti-golimumab antibody levels in patients with rheumatic diseases. *Clin Chem Lab Med* 2015; 53: e297-e299.
12. ARENDS S, LEBBINK HR, SPOORENBERG A *et al*.: The formation of autoantibodies and antibodies to TNF-alpha blocking agents in relation to clinical response in patients with ankylosing spondylitis. *Clin Exp Rheumatol* 2010; 28: 661-8.
13. BRAUN J, DEODHAR A, INMAN RD *et al*.: Golimumab administered subcutaneously every 4 weeks in ankylosing spondylitis: 104-week results of the GO-RAISE study. *Ann Rheum Dis* 2012; 71: 661-7.
14. ISAACS JD: Antibody engineering to develop new antirheumatic therapies. *Arthritis Res Ther* 2009; 11: 225.
15. BLOEM K, VAN LA, VERBEEK G *et al*.: Systematic comparison of drug-tolerant assays for anti-drug antibodies in a cohort of adalimumab-treated rheumatoid arthritis patients. *J Immunol Methods* 2015 27; 418: 29-38.
16. LUKAS C, LANDEWÉ R, SIEPER J *et al*.: Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. *Ann Rheum Dis* 2009; 68: 18-24.