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TITLE: LOW GOLIMUMAB TROUGH LEVELS AT WEEK 6 ARE ASSOCIATED WITH POOR CLINICAL, ENDOSCOPIC AND HISTOLOGICAL OUTCOMES IN ULCERATIVE COLITIS PATIENTS: PHARMACOKINETIC AND PHARMACODYNAMIC SUB-ANALYSIS OF THE EVOLUTION STUDY

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ABSTRACT

Background and Aims: Golimumab has an established exposure-response relationship in patients with ulcerative colitis (UC). However, the association of serum golimumab trough levels (TL) with objective markers of disease activity, such as endoscopic and histologic activity scores and concentration of biomarkers, remains less understood. This report describes the relationship of serum golimumab TL at the end of induction period (week 6) with clinical, endoscopic, histologic and biomarker parameters. **Methods:** This was an open-label, uncontrolled, prospective and interventional study. Moderate to severely active UC patients naïve to biological therapy were treated with golimumab. Serum golimumab TL and faecal calprotectin levels were measured at baseline (week 0 of induction) and week 6.

Results: Thirty-four patients completed the induction phase (week 6) and were included in this analysis. Overall, 47.1% and 14.7% of patients achieved clinical response and remission with significantly higher serum golimumab TL in patients with early response or remission (3.7 µg/mL vs. 1.3 µg/mL, p=0.0013; and 3.1 µg/mL vs. 1.7 µg/mL, p=0.0164, respectively). In addition, golimumab TL were significantly higher in patients achieving histological remission (4.2 µg/mL vs. 1.7 µg/mL, p= 0.0049). Week 6 golimumab TL were inversely correlated with the total Mayo score (rs = -0.546; p=0.0008), the Mayo endoscopic subscore (rs = -0.381; p=0.0262), the Geboes histological activity score (rs = -0.464; p=0.0057) and faecal calprotectin levels (rs= -0.497; p=0.0044).

Conclusions: A higher early exposure to golimumab is associated with a better objective response in active UC patients and appears to drive the outcome at week 6.

Clinical Trial Identification: EudraCT 2014–003262–25

Keywords: golimumab, trough levels, ulcerative colitis

INTRODUCTION

Golimumab is a subcutaneously administered fully human anti-tumour necrosis factor (TNF) antibody approved for the treatment of patients with moderate to severely active ulcerative colitis (UC). In the PURSUIT subcutaneous (sc) phase III induction trial[1], patients were randomized to receive either 400/200 (n=258), 200/100 (n=258) mg sc golimumab or placebo (n=258) at week 0 and 2, respectively. After 200/100 mg induction, at week 6, clinical response (assessed by total Mayo score) was observed in 51% of patients and the median golimumab serum concentration or trough levels (TL) were 1.9 µg/mL. A significant exposure-response relationship was detected, with a response rate of 60% in patients within the third (1.72 to 3.82 µg/mL) and fourth (≥ 3.82 µg/mL) quartiles of serum golimumab TL. These results were similar to those obtained in the PURSUIT Maintenance trial, with increasing rates of continuous clinical response to golimumab through week 54 from the first to the fourth quartile of serum golimumab TL.[2] Moreover, the median serum golimumab TL at week 6 were significantly higher in patients who achieved clinical response compared to non-responders (2.96 *vs.* 1.55 µg/mL), and in patients who achieved clinical remission vs those who did not (3.14 *vs.* 2.13 µg/mL).[3] Taken together, the pharmacokinetic (PK) data from golimumab demonstrate that adequate exposure drives clinical efficacy.

Although the exposure-response relationship of golimumab in UC is well established in what concerns clinical parameters, the association of serum golimumab TL with objective markers of UC disease activity - such as endoscopic/histologic activity scores and established biomarkers such as serum C-reactive protein [CRP] and faecal calprotectin - is less understood. A better knowledge of such relationships is needed to answer the question whether therapeutic drug

monitoring with golimumab in UC may improve treatment outcomes and deserves a role in clinical practice. This article reports on the relationship of serum golimumab TL at week 6 with clinical, endoscopic, histologic and biomarker parameters investigated in the EVOLUTION study (NCT02318667).

MATERIALS AND METHODS

The EVOLUTION trial was an open-label, uncontrolled, prospective and interventional study including UC patients with an inadequate response to conventional therapy (including corticosteroids and 6-mercaptopurine or azathioprine), or who were intolerant to or had medical contraindications for such therapies. This paper presents an exploratory, pre-specified sub-analysis of the EVOLUTION trial aimed at assessing the relationship between serum golimumab TL levels at week 6 and disease outcomes.

The main inclusion criteria were: (a) a diagnosis of moderate to severe UC (Mayo score ≥6), including a Mayo endoscopy score ≥2 and corticosteroid-dependent patients intolerant or refractory to immunomodulators (b) naïve to biological therapy; (c) eligible to start golimumab according to its approved dosing regimen: induction with 200 mg golimumab at week 0 and 100 mg at week 2, followed by 50 mg every 4 weeks in patients with body weight (BW) <80 kg or 100 mg every 4 week in patients with BW ≥ 80 kg. The main exclusion criteria were: (a) any contraindication specified in golimumab's product monograph; b) evidence of severe extensive colitis; (c) presence of symptomatic colonic or small bowel obstruction, (d) history of colonic mucosal dysplasia; (e) concomitant or previous treatment with biologic therapy targeted at

TNFα, or integrins 12 months prior to inclusion, or other agents that deplete B or T cells 12 months prior to inclusion or continuing to manifest depletion; (f) rectal corticosteroids or 5–ASA compounds administered to the rectum or sigmoid colon within 2 weeks prior to study inclusion; (g) infection or predisposition to infections; (h) malignancy; (i) other relevant medical conditions. CRP level was not considered as a criterion of inclusion or exclusion. Patients were treated with golimumab 200mg (visit 1), 100mg after 2 weeks and 50mg or 100mg every 4 weeks thereafter. After the second dose of Golimumab, the study protocol recommended a corticosteroid taper schedule of 5mg per week.

The study was performed at nine centres in Portugal between February 2015 and September 2017 and included a screening visit, and visits at baseline (week 0), week 6 (end of induction) and week 16 (short-term maintenance).

All the patients enrolled in this study did so voluntarily and signed a written informed consent. The study was approved by the ethics committees of all hospitals involved and by the Portuguese Data Protection Authority. The national coordinator of the Portuguese IBD group [GEDII] monitored the study.

Physician assessments

Disease extent and severity at baseline were classified according to the Montreal criteria.[4] Clinical response was assessed by the Mayo score[5], and defined as a reduction of at least three points and 30% from the baseline score, accompanied by a decrease of at least one point in the rectal bleeding score or a rectal bleeding score of zero. Clinical remission was defined as Mayo score ≤ 2, with no individual subscore exceeding 1. Endoscopies were performed at screening

and at week 6 (end of induction): endoscopic activity was assessed with the Ulcerative Colitis Endoscopic Index of Severity (UCEIS)[6] and the Mayo endoscopy subscore. Active endoscopic disease was defined as endoscopic Mayo score subscore ≥2. Histologic activity was assessed by two independent pathologists on biopsies collected at screening and at week 6 using the Geboes histology activity score.[7] Active histologic disease was defined as a Geboes score ≥3.[7]

Laboratory measurements

Faecal calprotectin was measured at baseline and week 6 using the Quantum Blue® Calprotectin assay (Quantitative Lateral Flow Assay, Bühlmann, Switzerland), according to the manufacturers' instructions. Stool samples were collected and kept at 4°C (for a maximum of 48 h) until shipment to the central laboratory (Department of Biomedicine, Unity of Pharmacology and Therapeutics, Faculty of Medicine of University of Porto, Portugal). Faecal calprotectin was extracted from stools within a maximum of seven days after collection using the 'faecal sample preparation kit' (Roche Diagnostics, Germany), according to the instructions provided by the manufacturers, and stored at −80°C until quantification.

All golimumab PK samples were collected at baseline and week 6. Golimumab levels were quantified according to the instructions provided by the manufacturers using the commercial IDKmonitor® Golimumab drug level ELISA (Immundiagnostik AG, Germany).

Antibodies to golimumab were quantified according to the instructions provided by the manufacturers using the commercial IDKmonitor® Golimumab free ADA ELISA (Immundiagnostik AG, Germany). This assay is a drug-sensitive assay (*i.e.*, does not allow the detection of anti-drug antibodies in presence of golimumab).

Statistics

This was a pre-specified, exploratory analysis of the EVOLUTION trial with no formal hypothesis testing. For this sub-analysis, all endpoints were treated as exploratory, with no primary of secondary endpoints specified in the protocol. P-values are nominal.

Analyses were based on the Full Analysis Set (FAS), defined as all subjects who had received study medication and had at least one valid post-baseline assessment for the outcome variables of interest at week 6. Independent groups were compared by t-test or Mann-Whitney non-parametric test, for continuous variables. Comparison of changes within group was performed by paired t-test or non-parametric tests (signed rank and Wilcoxon signed rank-sum test). Categorical data were compared with Chi-square tests or Cochran-Armitage test (for ordered categorical data). Correlations between variables were calculated with the Spearman correlation coefficient ($r_{s.}$). Comparison of disease outcomes by tertile of golimumab TL was performed through Cochran-Armitage test for trend. Statistical analyses assumed a significance level of 0.05 and were performed with SAS® (version 9.4, SAS Institute Inc., Cary, North Carolina, USA).

RESULTS

Patients

A total of 38 patients started golimumab therapy. Thirty-four completed the induction phase (week 6) and 29 completed the maintenance phase (week 16). Reasons for discontinuation

throughout the study were: adverse event (n=1), lack of efficacy (n=6) and protocol violation (n=2). Patient demographics and baseline characteristics are shown in Table 1. Mean age was 34.6 years and 55.9% of patients were female. At baseline, 15 (44.1%) patients had left-sided colitis (Montreal classification E2) and 18 (52.9%) had extensive colitis (Montreal classification E3). Baseline disease severity was mild in 4 patients (Montreal classification S1, 11.8%), moderate in 24 (Montreal classification S2, 70.6%), and severe in 6 (Montreal classification S3, 17.6%). Seven (20.6%) patients were using glucocorticoids and 27 (79.4%) were on an immunosuppressive drug as concomitant medication.

Clinical activity

The mean (SD) total Mayo score was 8.2 (1.41) at baseline and significantly decreased to 5.7 (3.20) after golimumab induction, p<0.0001 (Table 2). The mean (SD) partial Mayo score decreased from 5.8 (1.26) to 3.9 (2.50) (p<0.0001). Overall, 16 (47.1%) and 5 (14.7%) patients achieved clinical response and remission by the end of golimumab induction, respectively. Table 3 presents a comparison of demographic and clinical characteristics according to clinical response at week 6. Golimumab TL levels were significantly higher (p=0.0006) among responders compared to non-responders at week 6. For the remaining variables there were no statistically significant differences between responders and non-responders at week 6.

Endoscopic and Histological activity

The mean (SD) UCEIS score significantly decreased from 7.6 (1.35) at screening to 6.4 (2.03) at week 6, p=0.0020 (Table 2). There was a strong correlation between the UCEIS and the Mayo endoscopy score (r_s= 0.830; p<0.0001). As for histologic activity, 32 patients (97.0%) at baseline

and 27 patients (79.4%) at week 6 had active disease (Geboes index >3.0). Following induction, the mean (SD) Geboes index significantly decreased from 4.7 (0.80) to 4.1 (1.72), p=0.0273.

Biomarkers

Median CRP values did not significantly decrease from baseline (3.9 mg/L) to week 6 (2.5 mg/L), p=0.0666 (Table 2). Sixteen (50.0%) and 19 (57.6%) patients at baseline and week 6, respectively, had CRP values within the normal range (cut-off values for normal CRP defined by each laboratory). Median (range) faecal calprotectin levels were 802.5 µg/g (126-10,000) at baseline and 816.0 µg/g (30-6150) at week 6, p=0.8249.

Pharmacokinetics

The median (range) serum golimumab TL at week 6 was 2.0 µg/mL (0.3-6.4). Figure 1 depicts golimumab serum TL levels stratified by clinical response, clinical remission, endoscopic activity and histologic activity: values were significantly higher among clinical responders (3.7 µg/mL *vs.* 1.3 µg/mL, p=0.0013), patients with endoscopically-inactive disease (3.1 µg/mL *vs.* 1.7 µg/mL, p=0.0164), and patients with histologically-inactive disease (4.2 µg/mL *vs.* 1.7 µg/mL, p= 0.0049). Of note, the clinical response rates increased with the tertile of serum golimumab TL: 18.2% for TL<1.6 µg/mL; 45.5% for 1.6≤TL<2.9 µg/mL; and 75.0% for TL≥2.9 µg/mL (p=0.0032). The same trend was observed with clinical remission, but it was not statistically significant (p=0.1375). Contrarily, endoscopic and histological activity rates decreased with the tertile of golimumab TL with fewer patients with active disease in the higher tertile. For endoscopic activity: 81.8% for TL<1.6 µg/mL; 63.6% for 1.6≤TL<2.9 µg/mL; and 33.3% for TL≥2.9 µg/mL

(p=0.0089); and for histological activity: 100% for TL<1.6 µg/mL; 90.9% for 1.6≤TL<2.9 µg/mL; and 50.0% for TL≥2.9 µg/mL (p=0.0014) (Figure 2).

Moreover, as shown in Table 3, serum golimumab TL were inversely correlated with the total Mayo score, the Mayo endoscopic subscore, the UCEIS, the histological activity score and the faecal calprotectin levels. The correlation between golimumab TL at week 6 and CRP and faecal calprotectin levels at baseline (to assess the impact of inflammatory burden on TL) was not significant (r_s= -0.046, p=0.7989; r_s= -0.199, p=0.2738, respectively). When stratified by body weight, patients with BW ≥80 Kg (9/33 patients) had numerically lower median TL than patients <80 Kg (1.70 *vs.* 2.30 ug/ml) but this difference was not significant (p=0.4301). No patient tested positive for antibodies to golimumab above the assay threshold of >10 AU/mL. All samples had detectable levels of golimumab.

Table 5 shows the correlation between golimumab TL at week 6 and outcomes/biomarkers of interest in the maintenance phase, at week 16. Overall, golimumab TL at week 6 were not significantly correlated with any outcome of interest in the maintenance phase at week 16.

DISCUSSION

This is the first comprehensive analysis of the relationship between early golimumab exposure and clinical, endoscopic, histologic and biomarker outcomes in patients with moderate to severely active UC. Our results show an association between week 6 serum golimumab TL and clinical response, endoscopic activity, histological activity, and biomarker concentration.

Our results confirm the early exposure-response relationship reported in the PURSUIT sc golimumab induction trial[1]. In fact, the median serum golimumab TL observed in our study were significantly higher in week 6 responders (3.7 µg/mL) compared to non-responders (1.3 µg/mL) (p=0.0213). In PURSUIT sc induction trial, the week 6 serum golimumab TL was 2.96 µg/mL *vs.* 1.55 µg/mL in responders and non-responders, respectively (p<0.001)[3]. Additionally, the difference found at week 6 between golimumab TL of endoscopically-inactive and active patients (3.1 µg/mL vs 1.7 µg/mL) was remarkably similar to that found in the PURSUIT trial between patients in the same patient populations (3.14 µg/mL *vs.* 1.70 µg/mL).[3] Of note, the responder week 6 median golimumab TL reported in our study (3.7 µg/mL) falls within the third quartile of exposure (2.40 to 4.27 µg/mL) of the PURSUIT patients.[1] Still, and although there may be numerical differences in absolute TL values (probably related with the utilization of different quantification assays), we feel confident that the week 6 golimumab exposure experienced by the patients in our study is comparable to that experienced by the patients involved in the PURSUIT sc induction trial.

Besides supporting the PURSUIT trial results, this was the first prospective study that explored the relationship between golimumab exposure and UC histological activity. Our results show a negative correlation between golimumab TL and the UC histologic activity score at the end of the induction phase. Accordingly, patients in histological remission were shown to have significantly higher TL of golimumab at week 6, when compared to those with persistent histologic activity. Histological activity is defined by the presence of epithelial neutrophils with or without crypt destruction or erosions (Geboes ≥3.1)[7], and by the end of the induction phase 79.4% of all patients still fell into this category. Of note, this percentage is larger than that

pertaining patients with active disease according to the endoscopic Mayo score (endoscopic Mayo score ≥ 2): 58.8%. However, such a difference is to be expected, as the cellular dynamics and microscopic appearance of the healing process of the colonic mucosa may be quite different from the endoscopic visual appearance. In fact, histologic changes have been shown to lag behind clinical response and/or remission after starting UC treatment.[8] We thus conclude that clinical response by Mayo score (including endoscopy) may not reveal the presence (or absence) of tissue healing in UC after golimumab induction. This raises the question whether histological healing needs to be a treatment target in UC. Although histological studies are informative, the STRIDE consensus has not recommended histological healing as a treatment target in UC .[10]

Although histological activity is not strongly associated with endoscopic findings at week 6, it correlates well with elevated median faecal calprotectin values. This may be explained by the fact that histological activity is partly defined by epithelial neutrophils, which are the local source of faecal calprotectin.[9]

Our study had a prospective nature and involved clinical, endoscopic, histologic and biomarker data, which should be regarded as strengths. Nonetheless, it did have several limitations that we hereafter acknowledge: first, this was a small open-label and uncontrolled study. The use of immunosuppressive treatment has the potential to introduce bias, and therefore we conducted an analysis in which patients were stratified according to the use of immunosuppressive concomitant medication, as well as stratified according to the use of glucocorticoids. We found no significant differences between groups, but these analyses have limited statistical power due

to the reduced sample size. Moreover, we were unable to investigate the possible effect of anti-drug antibodies (ADA) since all samples were negative for anti-golimumab antibodies. We used a drug-sensitive assay, which can explain these results since all samples had detectable levels of golimumab, potentially impairing the ability of the assay to detect anti-drug antibodies. Contrasting with our results, Detrez *et al.* used a drug-tolerant assay and detected ADA in four (out of 21) UC patients treated with golimumab; interestingly, three of these patients actually achieved a partial clinical response to golimumab.[11] The clinical significance of golimumab ADA in the presence of a measurable golimumab TL remains uncertain. Additionally, the dose regimen used was according to the old golimumab label, without dose optimization. Very recently, a new golimumab posology has been approved by EMA allowing patients with BW <80kg who have an inadequate response to benefit from continuing with 100 mg at week 6 and every 4 weeks thereafter, instead of 50 mg (the dose taken by all patients <80 kg in the present analysis). The PK results of this study are supportive of this regulatory change, as higher early levels of golimumab were associated with better outcomes. Finally, this study included biological-naïve patients, contrary to most clinical trials assessing safety and efficacy of biological treatments in UC that include significant portions of biological-experienced patients. Golimumab, in particular, can be used in biological-naïve as well as biological-experienced patients, but given our patient population, these findings can only be generalized to biological-naïve patients.

In summary, week 6 golimumab TL are negatively correlated with the Mayo score, the Mayo endoscopic subscore, the UCEIS, the Geboes histology activity score, and faecal calprotectin levels. Low golimumab levels at the end of the induction phase are associated with poor

outcomes in terms of clinical response and endoscopic/histological disease activity. Therefore, adequate early exposure to golimumab appears to be needed to control the inflammatory burden in active UC, but further studies are needed to investigate the possible role of pro-active therapeutic drug monitoring of golimumab in UC.

FIGURE LEGENDS

Figure 1. Median serum golimumab trough levels (TL) at week 6. EA: Endoscopic Activity; HA: Histologic Activity.

Figure 2. Proportion of patients in clinical response, clinical remission, with endoscopic activity and histologic activity according to serum GLM trough levels (TL) tertiles, at week 6.

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Table 1. Patient demographics and baseline characteristics.

	Baseline n= 34
Age (years)	
Mean (SD)	34.6 (12.63)
Median [Q1-Q3]	33.5 [23.0-42.0]
Minimum	19
Maximum	65
Gender, n (%)	
Female	19 (55.9)
Male	15 (44.1)
Time since UC diagnosis (years)	
Mean (SD)	6.8 (6.01)
Median [Q1-Q3]	5.0 [2.0-10.0]
Minimum	1
Maximum	23
UC Montreal classification	
Extension, n (%)	
E1	1 (2.9)
E2	15 (44.1)
E3	18 (52.9)
Severity, n (%)	
S0	0 (0.0)
S1	4 (11.8)
S2	24 (70.6)
S3	6 (17.6)
Ongoing Medication, n (%)	
Glucocorticoids	7 (20.6)
Other immunosuppressants	27 (79.4)

E1, ulcerative proctitis; E2, left-sided UC; E3, extensive UC; S0, clinical remission; S1, mild UC; S2, moderate UC; S3, severe UC.

Table 2. Clinical, endoscopic and histologic scores and biomarkers at screening or baseline visits and after induction, at week 6.

Outcome (N=34)	Screening[1] or baseline[2]	Week 6	p-value
Total Mayo Score			TT: <0.0001
[mean (SD)]	8.2 (1.41)[2]	5.7 (3.20)	
[median (range)]	8.0 (6-11)[2]	6.0 (0-11)	
Partial Mayo Score			WC: <0.0001
[mean (SD)]	5.8 (1.26)[2]	3.9 (2.50)	
[median (range)]	6.0 (3-8)[2]	4.0 (0-8)	
Mayo endoscopic score			
[mean (SD)]	2.4 (0.5)	1.8 (1.0)	WC: 0.0004
[median (range)]	2.0 (2-3)	2.0 (0-3)	
UCEIS			WC: 0.0020
[mean (SD)]	7.6 (1.35)[1]	6.4 (2.03)	
[median (range)]	7.5 (4-10)[1]	7.0 (3-10)	
Geboes index			WC: 0.0273
[mean (SD)]	4.7 (0.80)[1]	4.1 (1.72)	
[median (range)]	5.0 (1-5)[1]	5.0 (0-5)	
Calprotectin [median µg/g (range)]	802.5 (126-10,000)[2]	816.0 (30-6150)	WC: 0.8249
CRP [median mg/dL (range)]	3.9 (0.4-76)[2]	2.5 (0.2-36.4)	WC: 0.0666

TT: Comparison performed by paired T-test. WC: Comparison performed by Wilcoxon signed rank-sum test.

Table 3. Comparison of demographic and clinical characteristics, according to clinical response at week 6.

	Clinical response at week 6 (n=16)	No clinical response at week 6 (n=18)	p-value
Golimumab levels at week 6, mean (SD)	3.47 (1.71)	1.56 (0.95)	TT: 0.0006
Baseline variables			
Age, mean (SD)	35.81 (12.63)	33.44 (12.89)	TT: 0.5932
Female	10 (62.5%)	9 (50.0%)	CS: 0.4637
Weight, mean (SD)	67.21 (14.18)	65.20 (12.45)	TT: 0.4445
Total Mayo score, mean (SD)	7.81 (1.47)	8.56 (1.29)	TT: 0.4445
Endoscopic Mayo subscore, median (range)	2.00 (2-3)	2.50 (2-3)	MW: 0.4828
Fecal calprotectin, median (range)	836.50 (139-4530)	794.00 (126-10000)	MW: 0.9848
CRP, median (range)	2.80 (0.5-76)	4.10 (0.4-41.6)	MW: 0.4847
Albumin, mean (SD)	4.19 (0.35)	4.12 (0.27)	TT: 0.5416

SD: standard deviation; TT: Independent T-Test; CS: Chi-square test; MW: Mann-Whitney test.

Table 4. Correlation coefficients between golimumab TL and outcomes/biomarkers at week 6.

Outcomes/biomarkers (n) – Week 6	**r_s**	**p-value**
Complete Mayo score (34)	-0.546	p=0.0008
Mayo endoscopic score (34)	-0.381	p=0.0262
UCEIS (34)	-0.390	p=0.0227
Geboes score (34)	-0.464	p=0.0057
Faecal calprotectin levels (31)	-0.497	p=0.0044
C-reactive Protein (33)	-0.519	P=0.0020

r_s = Spearman correlation coefficient. All outcomes/biomarkers measured at week 6.

Table 5. Correlation coefficients between golimumab TL at week 6 and outcomes/biomarkers at week 16.

Outcomes/biomarkers (n) – Week 16	**r_s**	**p-value**
Total Mayo score (29)	-0.249	0.1928
Mayo endoscopic score (29)	-0.173	0.3698
UCEIS (29)	-0.147	0.4477
Geboes score (29)	-0.329	0.0818
Faecal calprotectin levels (28)	-0.323	0.0937
C-reactive Protein (29)	-0.199	0.3014

r_s = Spearman correlation coefficient. All outcomes/biomarkers measured at week 16.

Figure 1

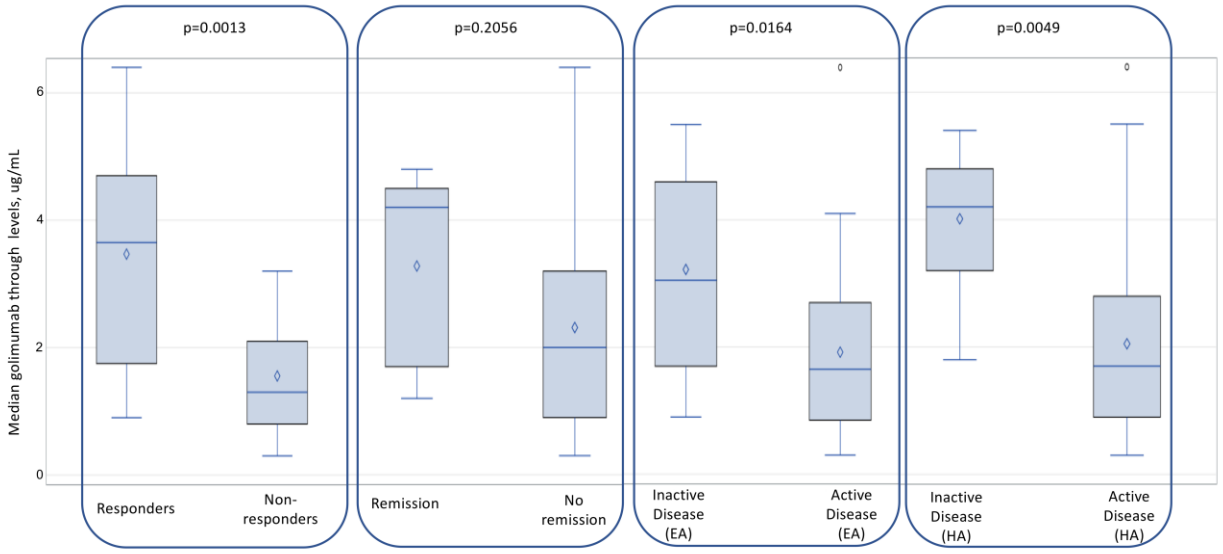

Figure 2