Association of Golimumab Trough Levels With Endoscopic and Histologic Healing in Patients With Ulcerative Colitis

(GLMLEVEL)

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Version 2

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1. IDENTIFICATION OF THE PROTOCOL

Protocol code: CTS-GOL-2018-01

Acronym: GLMLEVEL

Version 2: November 15th, 2018

2. TITLE

Association of Golimumab Trough Levels With Endoscopic and Histologic Healing in Patients With Ulcerative Colitis

3. IDENTIFICATION OF THE SPONSOR

Inflammatory Bowel Disease (IBD) Unit of the Hospital Clinico San Carlos.

4. RELEVANT ASPECTS ON THE FUNDING OF THE STUDY

The study will be carry out with the funds of the IBD Unit dedicated to research. There is no compensation planned for researchers or for patients.

5. MAIN RESEARCHERS

Hidden

6. REFERENCE IRB/ETHICS COMMITTEE

The IRB that will act as reference will be the Hospital Clínico San Carlos Ethics Committee.

7. SITES WHERE THE STUDY WILL BE CARRIED OUT

Hospital Clínico San Carlos, Madrid; Hospital Ramón y Cajal, Madrid; Hospital Gregorio Marañón, Madrid; Hospital 12 de Octubre, Madrid; Hospital Puerta de Hierro, Madrid; Hospital La Paz, Madrid; Hospital Universitario de Fuenlabrada, Madrid; Hospital Fundación Alcorcón, Madrid; Hospital Infanta Sofía, Madrid; Hospital La Fe, Valencia; Hospital Clínico Valencia, Valencia; Hospital Complejo Universitario de Navarra, Navarra

8. JUSTIFICATION AND OBJECTIVES OF THE STUDY

8.1 BACKGROUND

Antagonists of tumor necrosis factor (anti-TNF) -α have changed the treatment of ulcerative colitis (UC) in order to prevent the progression of the disease instead of simply controlling the symptoms. Anti-TNF agents have demonstrated the ability to achieve clinical remission and mucosal healing in UC [1-3]. However, histologic remission represents a different objective of endoscopic healing in UC and seems to be a better predictor of clinical outcomes [4-6]. In addition, histologic remission and not mucosal healing has been associated with a lower risk of colorectal cancer in patients with UC [7-9]. It has been reported that infliximab, an anti-TNF, induces histological remission in a significant proportion of patients with UC [10,11]. More recently, adalimumab achieved histologic remission in almost one third of patients who had not received prior treatment with another anti-TNF and who had moderate to severe active UC [12].

8.2 JUSTIFICATION

The therapeutic monitoring of anti-TNF agents can help to identify mechanisms for the loss of response and find an optimal and individualized treatment, and has also proved to be cost-effective compared to the empirical intensification of doses [13,14]. Proactive drug monitoring showed that trough anti-TNF levels correlate with clinical response, clinical remission and mucosal healing in patients with inflammatory bowel disease (IBD) [15-19]. In contrast, inadequate concentrations of trough drug and anti-drug antibodies are associated with poorer clinical outcomes [20,21]. Recently, a study in patients with UC correlates the concentrations of infliximab needed during maintenance therapy with endoscopic and histological healing [22].

Golimumab, a fully humanized TNF antibody administered subcutaneously, induces response and clinical remission in patients with active UC of moderate to severe [3]. In patients who responded to induction therapy, the doses of golimumab administered every 4 weeks as a maintenance regimen were effective in maintaining the clinical response for 1 year [23]. The available data on golimumab monitoring and the exposure-response relationship in patients with UC come from the PURSUIT trials [24]. A positive association between golimumab levels and efficacy results, including mucosal healing, is confirmed during the induction and maintenance phases of the PURSUIT studies.

A real-life study demonstrates the effectiveness and safety of golimumab in patients with UC [25]. However, we do not have sufficient data in real life about golimumab valley concentrations in patients in maintenance with this drug, and its correlation with clinical results. The available data come from an observational study with a limited number of patients [26]. In addition, there are no published

data on the ability of golimumab to achieve histological remission in patients with UC.

8.3 HYPOTHESIS

Several exposure-response studies have shown that trough concentrations of adequate anti-TNF drugs are associated with better clinical outcomes in IBD. Drug levels and anti-drug antibodies are very relevant to our understanding of the mechanisms of primary or secondary loss of response to anti-TNF agents, and can help to guide therapeutic decisions. In this regard, determining golimumab levels during maintenance treatment may be clinically relevant in order to predict the efficacy of golimumab.

8.4 OBJECTIVES

The objective of this study is to investigate in clinical practice the association of trough concentrations of golimumab during maintenance treatment in patients with UC, with outcomes that include clinical and biological response, mucosal healing and histological remission.

9. DESCRIPTION AND DESIGN OF THE STUDY

9.1 Study design.

Multicenter, non-interventional, cross-sectional study.

Target population: Eligible patients will include patients of at least 18 years old with moderate to severe UC who are previously in maintenance therapy with golimumab according to usual clinical practice and have received the induction regimen with the drug according to the guidelines accepted in the technical file, followed by maintenance treatment for at least 6 months from the first dose of the drug.

The study population will include all consecutive patients who meet these criteria and in whom a scheduled colonoscopy is performed according to clinical practice and at the discretion of the responsible physician for one of the following reasons:

1. UC flare requiring endoscopic evaluation

2. To evaluate the effects of the drug on the target mucous healing, in a treat-to-target strategy

3. In case of long-term remission with intention to discontinue the drug

4. Screening for prevention of colorectal cancer according to protocol (> 8 years of illness)

9.2 Procedures

If they agree to participate, patients will sign an informed consent and a scheduled colonoscopy will be performed, and the following procedures will be carried out:

1. The demographic and clinical characteristics, the concomitant treatment and the dosage of golimumab will be recorded in the corresponding Case Report Form (CRF).

2. Samples will be taken for valley trough levels immediately before the administration of the subcutaneous dose of golimumab closest to the colonoscopy. Venous blood samples will be taken in BD Vacutainer trough tubes, and will be processed immediately or within 4 hours after extraction. Serum samples will be obtained after centrifugation at 2330 g for 10 minutes at room temperature, and finally 4 separate aliquots will be frozen at -20 °C. Golimumab concentrations will be determined centrally in the main center using commercially available drug-sensitive enzyme-linked immunosorbent assays (ELISA) kits: Promonitor (Progenika Biopharma, Spain) and Lisa-Tracker Anti-Infliximab (Theradiag, France). Twp aliquots will be reserved to give the opportunity to perform a sensitivity analysis using another tests, if necessary.

3. Anti-golimumab antibodies will be evaluated by a drug-sensitive enzyme-linked immunosorbent assay (ELISA) by kits from the same manufactures.

4. The 9-point partial Mayo score, which uses the results reported by patients in addition to the Physician Global assessment (PGA), will be recorded by the responsible physician on the day of extraction of the levels.

5. Quality of life is assessed through SIBDQ-9 questionnaire on the day of extraction of the levels.

7. Samples of C-reactive protein and fecal calprotectin will be obtained on the day of extraction of the levels.

8. Colonoscopy with local reading (to evaluate the endoscopic activity by a Mayo endoscopic subscore) sub-score will be performed between 15 days before and 15 days after the extraction of trough levels and other procedures of the study.

9. Histology: during colonoscopy, two rectal biopsies (called R-biopsy) and two sigmoid biopsies (called S-biopsy) will be taken for histological examination. In patients who have maximum endoscopic activity beyond sigma, two additional biopsies of this area will be taken. In order not to break the blind of pathologists, in these patients only biopsies of the rectum (called R-biopsy) and biopsies of the area with the highest endoscopic involvement (called S-Biopsy -replace sigma biopsy-) were remitted for histological evaluation.

The specimens will be fixed in neutrally buffered formalin [4%] and will be mailed to the central pathologist (Hospital Clinico San Carlos) blinded for patient disease status and endoscopic score. Biopsies were centrally evaluated by two independent gastrointestinal pathologist using the Geboes index. In case of

disagreement between pathologists biopsies were evaluated by a third senior specialized gastrointestinal pathologist. The biopsy with the maximum histological activity will be selected for the analysis of the histological score.

The Geboes index is composed by six grades (each with subgrade), which corresponds to an increase in the degrees of inflammation in the mucosa. Grade 0 indicates structural (architectural) change, grade 1 chronic inflammatory infiltrate, degree infiltrated in eosinophil lamina (2A) or neutrophils (2B), grade 3 neutrophils in epithelium, grade 4 destruction of crypts, and grade 5 erosions or ulcers. Within each grade, the highest subgrade scores reflect a more severe histological alteration.

9.2 Duration of the study

One year is estimated for the inclusion of the total number of patients.

9.3 Outcomes

9.3.1 Primary

1- Correlation between Golimumab trough levels and Endoscopic remission: defined as an endoscopic Mayo sub-score of 0.

2- Correlation between Golimumab trough levels and Endoscopic healing: defined as an endoscopic Mayo sub-score of 0 or 1.

3- Correlation between Golimumab trough levels and Histological remission: defined as a Geboes index ≤3.0.

9.3.2 Secondary

4- Correlation between Golimumab trough levels and Clinical remission: defined as a total Mayo score of ≤2 without any individual sub-score greater than 1 point.

5- Correlation between Golimumab trough levels and Clinical response: defined as a decrease from the beginning to the evaluation point of at least 3 points in the total Mayo score (only if baseline endoscopy is available before induction).

6. Thresholds of golimumab trough levels for outcomes 1 to 5 will be determined using the receiver-operating-characteristic curve [ROC] analysis.

7. Correlation between Golimumab trough levels with C-reactive protein and fecal calprotectin.

8. Proportion of patients with Histological remission defined as a Geboes index ≤3.0.

9.4 Treatment

The study is observational, does not prefix the start of the treatment or its maintenance.

We believe that the study does not induce prescription because patients are already receiving the drug.

The treatment will be discontinued according to the investigator's criteria due to adverse effect or loss of secondary response.

10. SELECTION OF PATIENTS

10.1 Criteria for the inclusion of patients

- Age greater than or equal to 18 years.
- Patients with a diagnosis of ulcerative colitis at least 12 months prior to the start of the study.
- Patients who have previously been treated with golimumab for ulcerative colitis, prescribed according to the usual clinical practice of each center, and who have received at least 5 maintenance doses according to the guidelines accepted in the technical file.
- Sign of informed consent.

10.2 Exclusion criteria

- Patients with Crohn's disease or colitis pending classification
- Alterations in the coagulation that contraindicate the taking of biopsies
- Patients with moderate-severe heart failure (grades III / IV NYHA)
- Patients with tuberculosis or other serious infections such as septicemia, abscesses and opportunistic infections
- Psychiatric illness that discourages participation in the study
- Patients with a history of hypersensitivity to golimumab, to other murine proteins or to any of the excipients included in the golimumab data sheet
- Withdrawal of the informed consent by the patient
- Any other condition that in the opinion of the investigator discourages the participation of the subject in the study.

10.3 Sample size

Since this is a pilot study, no hypothesis will be established about the results to be obtained and, therefore, no statistical estimation of the sample size will be

made, which will be established in 100 patients with UC considering it as a realistic number, suitable to draw conclusions from the results.

10.4 Recruitment period

Start, January 2019. End, October 2019.

4. DATA COLLECTION.

The Case Report Form (annex 9.1) will include all the variables of interest. It will be prepared in paper format, and once all the variables have been agreed, an encrypted computer application (Excel) with limited access will be designed as an alternative, in which the patient data will be collected.

5. STATISTICAL ANALYSIS.

The results of golimumab levels will be summarized as median and interquartile range (IQR) and the qualitative data will be shown as numbers and percentages. The trough concentrations of golimumab in serum will also be classified in quartiles. Golimumab levels will be compared between patients who achieve or do not the specified efficacy results, using a two-sided Wilcoxon-Mann-Whitney test. Endoscopic and histologic healing / remission rates will be compared in golimumab concentration quartiles using a chi-square test (linear-linear association). The associations between golimumab levels and efficacy outcomes, including patient characteristics, will be evaluated using the multivariable logistic regression model. The thresholds of golimumab levels for efficacy results will be determined using the receiver-operating-characteristic curve [ROC] analysis.

6. ADVERSE EVENTS

The research team will monitor the possible adverse effects that may arise throughout the study, including the time of appearance, duration, intensity, course, outcome and causality.

According to the ICH guideline E2A "Clinical Safety Data Management; Definitions and Standards for Expedited Reporting" of 04.10.99, an adverse event is defined as any unwanted medical event that occurs to a patient or research subject to which a pharmaceutical product is being administered and that does not necessarily have to be related to the product administered. The administration of any drug during the study is not predetermined.

In accordance with order SAS/3470/2009 concerning the guidelines on observational post-authorization studies carried out with medicinal products for human use, the suspicion of serious adverse reactions detected during the course of the study will be notified to the contact point designated by the

competent body in the field of pharmacovigilance of the Autonomous Community where the health professional who reports the case performs its activity, within a maximum period of 15 calendar days since the suspected adverse reaction was known through the submission of a yellow card to the corresponding regional pharmacovigilance center, indicating in observations, the name and code of the study from which the AEMPS already comes, using the "on-line" upload through the SINAEM portal of the AEMPS, following the instructions published by the AEMPS.

7. ETHICAL ASPECTS.

7.1. Declaration of Helsinki.

The study will be carried out strictly following the international ethical recommendations for research and clinical trials in humans included in the Declaration of Helsinki of 1964 and its successive updates.

7.2 Information to the patient and obtaining consent.

It is the responsibility of the researcher to explain to the patients, verbally and in writing in an intelligible language, the objectives and requirements of the study. These explanations will include complete information about the nature, objective, possible risks and benefits of the study. You will be allowed to ask the questions that you consider appropriate and you will be given some time to consider your decision. Patients must be explicitly informed of their complete freedom to withdraw at any time during the study. The researcher must obtain written or verbal informed consent from each of the participants before a witness, before its inclusion.

The Patient Information and Informed Consent models are included in Annex 9.3. Each patient will keep a copy of both documents.

The forms with the Informed Consent will be kept by the researcher in the study file. If modifications are made according to local requirements, the new version must be approved by the study Sponsor and by the Hospital Ethics Committee.

8. REFERENCES

1- Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005;353:2462–2476.

2- Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2012;142:257–265.

3- Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2014;146:85-95.

4- Rosenberg L, Nanda KS, Zenlea T, et al. Histologic markers of inflammation in patients with ulcerative colitis in clinical remission. Clin Gastroenterol Hepatol. 2013;11:991-996.

5- Zenlea T, Yee EU, Rosenberg L, et al. Histology Grade Is Independently Associated With Relapse Risk in Patients With Ulcerative Colitis in Clinical Remission: A Prospective Study. Am J Gastroenterol. 2016;111:685-690.

6- Bryant RV, Burger DC, Delo J, et al. Beyond endoscopic mucosal healing in UC: histological remission better predicts corticosteroid use and hospitalisation over 6 years of follow-up. Gut. 2016;65:408-414.

7- Rutter M, Saunders B, Wilkinson K, et al. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. Gastroenterology. 2004; 126:451-459.

8- Gupta RB, Harpaz N, Itzkowitz S, et al. Histologic inflammation is a risk factor for progression to colorectal neoplasia in ulcerative colitis: a cohort study. Gastroenterology. 2007;133:1099-1105.

9- Korelitz BI, Sultan K, Kothari M, et al. Histological healing favors lower risk of colon carcinoma in extensive ulcerative colitis. World J Gastroenterol. 2014;20:4980-4986.

10-Wiernicka A, Szymanska S, Cielecka-Kuszyk J, et al. Histological healing after infliximab induction therapy in children with ulcerative colitis. World J Gastroenterol. 2015;21:10654-10661.

11-Magro F, Lopes SI, Lopes J, et al. Histological Outcomes and Predictive Value of Faecal Markers in Moderately to Severely Active Ulcerative Colitis Patients Receiving Infliximab. J Crohns Colitis. 2016;10:1407-1416.

12-Fernández-Blanco JI, Fernández-Díaz G, Cara C, Vera MI, Olivares D, Taxonera C. Adalimumab for Induction of Histological Remission in Moderately to Severely Active Ulcerative Colitis. Dig Dis Sci. 2018 Jan 25. doi: 10.1007/s10620-018-4935-5. [Epub ahead of print]

13-Steenholdt C, Brynskov J, Thomsen OØ, et al. Individualised therapy is more cost-effective than dose intensification in patients with Crohn's disease who lose response to anti-TNF treatment: a randomised, controlled trial. Gut. 2014;63:919–27.

14-Velayos FS, Kahn JG, Sandborn WJ, et al. A test-based strategy is more cost effective than empiric dose escalation for patients with Crohn's disease who lose responsiveness to infliximab. Clin Gastroenterol Hepatol. 2013;11:654-66.

15-Maser EA, Villela R, Silverberg MS, et al. Association of trough trough infliximab to clinical outcome after scheduled maintenance treatment for Crohn's disease. Clin Gastroenterol Hepatol. 2006;4:1248–54.

16-Seow CH, Newman A, Irwin SP, et al. Trough trough infliximab: a predictive factor of clinical outcome for infliximab treatment in acute ulcerative colitis. Gut. 2010;59:49–54.

17-Paul S, Del Tedesco E, Marotte H, et al. Therapeutic drug monitoring of infliximab and mucosal healing in inflammatory bowel disease: a prospective study. Inflamm Bowel Dis. 2013;19: 2568-76.

18-Vande Casteele N, Ferrante M, Van Assche G, et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. Gastroenterology. 2015;148:1320-9.

19-Cornillie F, Hanauer SB, Diamond RH, et al. Postinduction trough infliximab trough level and decrease of C-reactive protein level are associated with durable sustained response to infliximab: a retrospective analysis of the ACCENT I trial. Gut. 2014;63:1721–7.

20-Adedokun OJ, Sandborn WJ, Feagan BG, et al. Association between trough concentration of infliximab and efficacy in adult patients with ulcerative colitis. Gastroenterology. 2014;147:1296–307.

21-Vande Casteele N, Khanna R, Levesque BG, et al. The relationship between infliximab concentrations, antibodies to infliximab and disease activity in Crohn’s disease. Gut. 2015;64:1539–45.

22-Papamichael K, Rakowsky S, Rivera C, Cheifetz AS, Osterman MT. Infliximab trough concentrations during maintenance therapy are associated with endoscopic and histologic healing in ulcerative colitis. Aliment Pharmacol Ther. 2018;47:478-484.

23-Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2014;146:96-109.

24-Adedokun OJ, Xu Z, Marano CW, et al. Pharmacokinetics and Exposure-response Relationship of Golimumab in Patients with Moderately-to-Severely Active Ulcerative Colitis: Results from Phase 2/3 PURSUIT Induction and Maintenance Studies. J Crohns Colitis. 2017;11:35-46.

25-Detrez I, Dreesen E, Van Stappen T, et al. Variability in Golimumab Exposure: A 'Real-Life' Observational Study in Active Ulcerative Colitis. J Crohns Colitis. 2016;10:575-81.