Research Project GO-REAL

# 1 Project Title

GO-REAL - Real-life effectiveness of golimumab in biologic-naïve patients with rheumatoid arthritis – data from Reuma.pt, a Portuguese registry.

# 2 Introduction

## 2.1 Background

The use of tumor necrosis factor (TNF) antagonists has dramatically changed the rheumatology practice and transformed rheumatoid arthritis (RA) treatment. Although relatively expensive in short term, the direct costs of these biologics may be offset by slowed disease progression and significant improvements in RA symptoms, physical function and quality of life [1].

The relative benefits of using these agents earlier in the disease are recognized [2] and, to a certain extent, guidelines and practice have been adjusted following emerging evidence [3,4]. With the availability of new anti-TNFs such as golimumab (GLM) and other biologic agents, it can be expected that both the treatment of RA with biologic agents and the patients who are considered for treatment will continue to evolve. As these new agents, upon introduction in the market, have usually been studied only in a limited number of highly selected patient populations, it is important to continue to investigate and document their effectiveness in real life practice, outside of the clinical trial setting. We propose this innovative study, focusing not only in clinical outcomes but also in functional ability, quality of life and employment situation of the patients with RA that are treated with GLM.

## 2.2 Rationale

RA is a chronic inflammatory autoimmune disease manifested as joint pain, stiffness and swelling, which results in progressive destruction of cartilage and bone in multiple joints. If inadequately treated, RA can lead to permanent joint damage and deformity. Overall, the disease is associated with substantial disability, reduced life expectancy, quality of life impairment, and loss of work capacity. Thus, RA places a significant burden on patients and healthcare systems.

Remission is a realistic and a major therapeutic goal in RA patients. Evidence suggests that although biologics are costly, they remain cost-effective because of the major clinical benefits patients may experience.

In light of the relatively little information that currently exists and the broader use of GLM once it becomes available on the markets, this study aims at increasing the knowledge base of GLM in the real-life clinical practice.

# 3 Study Objectives

To assess the effectiveness of SC GLM 50 MG combined with MTX in biologic-naïve patients with active RA, administered by autoinjection once monthly

### 3.1 Primary Objective

To investigate the proportion of biologic-naïve patients with active RA achieving clinical remission (DAS28-ESR < 2.6) with SC GLM + MTX through 52 weeks of treatment.

### 3.2 Secondary Objectives

1. To evaluate SC GLM + MTX treatment persistence through the follow-up period of 52 weeks in biologic-naïve patients with active RA and its determinants, such as: age, disease duration, baseline DAS28, etc…
2. To investigate the proportion of biologic-naïve patients with active RA achieving functional response (ΔHAQ> 0.22) with SC GLM + MTX through 52 weeks of treatment.
3. To evaluate the effect of SC GLM + MTX on some of the DAS28 individual components - number of swollen joints (SJC) and of tender joints (TJC), Patient Global Disease Activity (PGDA) and erythrocyte sedimentation rate - in biologic-naïve patients with active RA through 52 weeks of treatment versus baseline.

### 3.3 Exploratory objectives

1. To evaluate QoL (using EQ-5D questionnaire) in biologic-naïve patients with active RA at 52 weeks of treatment with SC GLM + MTX.
2. To investigate the QALY of biologic-naïve patients with active RA at the first and second years after SC GLM + MTX initiation.
3. To investigate the association of the clinical outcomes (clinical remission, medication persistence, functional response) with covariates of interest.
4. To evaluate biologic-naïve patients' employment situation at 52 weeks of treatment with SC GLM + MTX versus baseline.

## 4 Methodology

### 4.1 Study design

This retrospective non-interventional study is designed to be based on the Portuguese registry database of rheumatic diseases, the Reuma.pt, and to describe the impact of SC GLM + MTX in patients with active RA treated in daily rheumatology practice. Data collection from Reuma.pt assures a real-life scenario, data quality and fast data collection. The accrual period will be from 1$^{st}$ of March 2011 to the date of study initiation.

### 4.2 Study Population

The GO-REAL study will be conducted in a cohort of patients aged 18+ diagnosed with active RA, treated with SC GLM 50 mg once monthly, in combination with MTX, despite previous treatment with conventional DMARDS, including MTX (biologic-naïve patients).

## 4.3 Outcomes and covariates

### 4.3.1 Primary outcome

1. Percentage of patients achieving clinical remission defined by having DAS28-ESR < 2.6 through 52 weeks.

### 4.3.2 Secondary outcomes

1. Medication persistence evaluated as time from SC GLM + MTX initiation to discontinuation. By definition, persistence is reported as a continuous variable in terms of days for which therapy was administered [5]. Treatment discontinuation is defined as the first occurrence of either one of the following events:
    - End of treatment - 90-day continuous gap of treatment without a posterior biological treatment;
    - Switch of treatment - first occurrence of any switch to another biological agent within 90 days of the end of treatment of the index biological (SC GLM + MTX).

    Temporary stops of < 90 days (e.g elective surgery, adverse events,…), after which the treatment with SC GLM + MTX is resumed, are counted as continuous use of the drug [6].

    The 90-day cut-off to define treatment persistence is also used in the methodology applied to other registries, such as the British Society of Rheumatology Biologics Registry. Patients are censored at the last data collection date or the last date in current Reuma.pt dataset, whichever came first.
2. Percentage of patients achieving functional response (ΔHAQ = HAQbaseline – HAQweek > 0.22) at weeks 52.
3. Difference versus baseline of the number of SJC, TJC and PGDA and erythrocyte sedimentation rate at 12, 24 and 52 weeks.

### 4.3.3 Exploratory outcomes

1. EQ-5D QoL score at 52 weeks.
2. QALY at the first and second year after SC GLM + MTX initiation.
3. Clinical outcomes (clinical remission, medication persistence, functional response) association with covariates of interest (listed in section 4.3.4).
4. Employment status at 52 weeks versus just before (baseline) treatment with SC GLM + MTX, classified as: full-time worker, partial-time worker, homeworker, temporary medical absenteeism higher than 1 month, unemployed, retired (due to RA disability).

### 4.3.4 Covariates

Covariates included in the study will be used for descriptive and stratified analyses.

Covariates included in this study are: Age at disease onset, gender, smoker status, disease duration, concomitant use of NSAIDs and corticosteroids, positive for for ACPA, positive RF, comorbidities and number of surgeries since RA diagnosis

### 4.3.5 Variable collected from Reuma.pt

Patient characteristics: Gender, Date of birth, Date of diagnosis of RA.

Baseline characteristics (last evaluation before SC GLM + MTX initiation): ACPA, RF, DAS28-ESR, SDAI, HAQ, SJC, TJC, PGDA, ESR, employment status, smoker status, comorbidities, and previous RA therapies (including conventional DMARDs, NSAIDs and Corticosteroids).

Data collection during SC GLM + MTX treatment: Starting date of SC GLM + MTX treatment, doses of SC GLM used and date of modification, frequency of administration of SC GLM and date of modification, discontinuation date of SC GLM + MTX treatment, reason for discontinuation of SC GLM + MTX treatment, conventional DMARDs utilization (drug and date of initiation and discontinuation), NSAIDs and corticosteroids utilization (drug and date of initiation and discontinuation), DAS28-ESR (date of evaluation and result), SDAI (date of evaluation and result), HAQ (date of evaluation and result), SJC (date of evaluation and result), TJC (date of evaluation and result), PGDA (date of evaluation and result), ESR (date of evaluation and result), employment status (date of data collection and status), surgery since RA diagnosis (dates).

## 4.4 Statistical Analysis Plan

### 4.4.1 Statistical Methods

**Descriptive analysis**

Baseline characteristics will be reported using descriptive statistics. The following parameters will be presented:

- For qualitative data, absolute and relative frequencies. Percentages will be based on the total number of subjects with non-missing values unless specified otherwise. Counts for missing values will be also tabulated, but missing values will not be considered in the percentages.
- In case of quantitative data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum and number of non-missing cases (95% confidence intervals for parameters of interest).

**Statistical Models**

Unadjusted estimates and, if applicable, adjusted estimates and their precision (e.g., 95% CI) will be present for the statistical models.

In this study, a given patient may contribute different amounts of person-time to each separate analysis of a health outcome of interest, depending on whether or not he/she experiences one of the health outcomes of interest.

For the analysis of each health outcome of interest (clinical remission, medication persistence, functional remission, minimal function remission), exact mid-probability confidence intervals will be calculated based on person-time at risk [7] and the Poisson distribution. The statistical analysis will only consider the first event occurrence of a given type. The incidence rate will be calculated as the number of first occurrences of each type of health outcome of interest divided by the total aggregate person-time accrued by all patients in the Reuma.pt dataset.

Accrued person-time for patients that experience an event is calculated as the total number of days accrued between the date of the first prescription of SC GLM + MTX following cohort entry (zero time) until the date of the event; whereas, accrued person-time for patients that do not experience an event (censored observation) is calculated as the total number of days accrued between the first prescription date until the last data collection date or the last date in current Reuma.pt dataset, whichever occurred first.

The cumulative incidence on an event will be calculated based on the Kaplan-Meier (KM) method [8]. This approach involves conditional probabilities, i.e, the estimation is conditioned on being at risk (alive or no censored) at each time event. The censored observations are counted only in the denominator for the calculation of the conditional probabilities corresponding to events occurring up to the time when the censoring occurs [9].

Patients who undergo surgical procedures during the study period will be treated as a co-morbid condition and adjusted for in the analysis.

The following general topics will be considered in the statistical analysis of this project:

- Missing data will not be imputed;
- The baseline characteristics for those with adequate follow-up will be compared with the baseline characteristics for those lost to follow-up due to incomplete data at specific time points, namely, at 12, 24 and 52 weeks.
- In case of the Cox proportional hazard model the underlying assumptions will be checked. In case of severe violations of assumptions, alternative models will be adopted instead;
- Exploratory post-hoc subgroup analyses may be performed, if appropriate;
- All statistical tests will be two-sided considering a significance level of 5%. When multiple tests occur, a Bonferroni correction of the level of significance will be applied (0.05/(k-1) where k-1 is the number of tests)
- Whenever it is necessary (due to small numbers or zero counts), categorical variables will be re-categorized collapsing original categories (or consecutive categories in case of ordinal data).
- Continuous variable can be categorized whenever the grouping makes sense for separate group risk analysis or when a very small of discrete values is observed.

**Primary Objective**

1. To take into account that patients will have different treatment exposures (person-times) and that censored observation can also occur (patients that will not experience the remission during the study), the proportion (incidence) of biologic-naïve patients with active RA achieving clinical remission will be analyzed using a survival analysis framework. Through Kaplan-Meier estimates, the cumulative incidence of achieving clinical remission at 12, 24 and 52 weeks will be calculated. With censored observations, the result translates the expected proportion of patients under study that have achieved remission in those weeks or less.

**Secondary objectives**

1. The SC GLM + MTX persistence will be first analyzed by the KM estimator. Survival curve will be presented together with 95% CI. Median survival time and its 95%CI will also be calculated. Hypothesis test, such as Log rank and Peto test will be used to evaluate difference of the survival curves stratified by covariates of interest. Survival analysis based on the Cox proportional hazard model approach will be used to evaluate medication persistence adjusted by baseline patient characteristics. These statistical models will allow the estimation of the median time of treatment persistence and the respective hazard ratio according to particular value of baseline characteristics which can be useful in advising the patient about their prognosis. The hazard ratio of a covariate will be calculated by the exponential of the respectively estimated Cox proportional hazard regression coefficient. The median time of treatment persistence adjusted by covariates will be estimated as the shortest time at which the estimated survival function is $\leq$ 0.5. The estimated survival function is defined by the survival function at baseline to the power of the exponential of linear predictor of the Cox proportional hazard model. All the covariates included in the model are time-fixed at baseline. Several studies recently published, including studies from other national registries, have also used KM estimator to analyze persistence on treatment [10-13].
2. For the proportion (incidence) of biologic-naïve patients with active RA achieving functional response will be estimated using Kaplan-Meier estimates as described for the primary objective.
3. Descriptive statistics (mean, standard deviation, median, $25^{th}$ and $75^{th}$ percentiles, minimum, and maximum and number of non-missing cases) will be present for number of SJC and TJC, PGDA and ESR. Stratified analysis according to covariates of interest (section 4.3.4) will be based on the hypothesis test of no difference between covariate strata: t-test and analysis of variance for normally distributed continuous variable and Mann-Whitney and Kruskal-Wallis tests to non-normal distributed variable. When the before mentioned tests reject the null hypothesis of no difference among strata, appropriate multiple comparison test will be conducted, such as Tukey test.

**Exploratory objectives**

1. To evaluate QoL, the EQ-5D utility values from the RA patients will be derived from HAQ scores using the relation function as reported by Carreño et al (2011) [14]. These authors developed linear regression models converting HAQ scores into EQ-5D utility values by the following expression:

   $$EQ\text{-}5D = 0.9567 - (0.306 \times HAQ)$$

   After predicting EQ-5D values, descriptive statistics (mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum and number of non-missing cases) will be computed.
2. QALY will be defined as quality adjusted follow-up time. QALY values will be calculated through the sum of each patient EQ-5D profile (derived from HAQ) multiplied by the corresponding follow-up time [15]. The average utility values will also be reported by the ratio of QALY and aggregate follow-up time in each year, as show in the table below:

| | QALY | Aggregate follow-up time (person-time, PT) | Average utility values | Number of patients |
|---|---|---|---|---|
| 1st year (1y) | $QALY^{(1y)} = \sum_i^m QALY_i^{(1y)}$ | $PT^{(1y)} = \sum_i^m PT_i^{(1y)}$ | $\frac{QALY^{(1y)}}{PT^{(1y)}}$ | $m$ |
| 2nd year (2y) | $QALY^{(2y)} = \sum_i^m QALY_i^{(2y)}$ | $PT^{(2y)} = \sum_i^q PT_i^{(2y)}$ | $\frac{QALY^{(2y)}}{PT^{(2y)}}$ | $q$ |

For each patient in each year, $QALY_i$ is defined by the sum of EQ-5D values multiplied by the corresponding follow-up time (time interval between EQ-5D measurements; the first interval being defined as the interval between start of SC GLM + MTX and the first measurement). The first year estimation comprehends EQ-5D values derived during the first 52 weeks from the start of SC GLM + MTX. The second year includes EQ-5D values derived from week 53 to week 104.

3. The association of the clinical remission and functional response with covariates of interest (listed in section 4.3.4) will be addressed via hypothesis test. Log rank and Peto test will be used to evaluate difference of the cumulative incidence curves stratified by covariates of interest (section 4.3.4). Cox proportional hazard model will be used to investigate the association between medication persistence and covariates of interest which will be time-fixed at baseline or cohort entry (listed in section 4.2) (see the SAP for the second secondary objective).
4. Test for marginal homogeneity of matched pairs with multinomial response are suitable candidates to analyze the employment status change from baseline to 52 weeks. To test the change for a given employment status comparing the marginal proportion before treatment and after 52 weeks, the McNemar test will be applied collapsing the other categories and adjusting the level of significance due to multiple testing [16]. In this analysis, only the subgroup of patients observed at 52 weeks will be considered.

### 4.4.2 Sample Size and Power Calculations

This study will include all the patients registered in Reuma.pt database who fill the eligibility criteria defined for this study (section 4.2).

Notwithstanding and aware of the limitation of the final sample size, we will present a simulation exercise for the primary endpoint. The table 1 presents the statistical power reported by the analysis of the confidence interval at 5% significance [17-19] level assuming several scenarios.

Additionally, it was assumed in this simulation exercise that the occurrence of the event (primary outcome) and the losses to follow-up happened uniformly every 3 months. The parameters values and the assumptions of this exercise are consistent with the principal investigator definition of plausible scenarios, taking into account all the effort that will be placed by Reuma.pt team in order to complete missing data. The 95% CI were estimated using Greenwood's formula [20].

**TABLE 1 - STATISTICAL POWER SIMULATION EXERCISE FOR THE PRIMARY OUTCOME**

| | | | Patients at $t_0$ N = 80 | | | | Patients at $t_0$ N = 90 | | | | Patients at $t_0$ N = 100 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 10% of events | | 15% of events | | 10% of events | | 15% of events | | 10% of events | | 15% of events | |
| | | | Loss to follow-up | | | | Loss to follow-up | | | | Loss to follow-up | | | |
| | | | 5% | 10% | 5% | 10% | 5% | 10% | 5% | 10% | 5% | 10% | 5% | 10% |
| weeks | 12 | Estimate | 0.10 | 0.10 | 0.15 | 0.15 | 0.10 | 0.10 | 0.16 | 0.16 | 0.10 | 0.10 | 0.15 | 0.15 |
| | | 95% IC | 0.05 0.19 | 0.05 0.19 | 0.09 0.25 | 0.09 0.25 | 0.05 0.18 | 0.05 0.18 | 0.10 0.25 | 0.10 0.25 | 0.06 0.18 | 0.06 0.18 | 0.09 0.24 | 0.09 0.24 |
| | 24 | Estimate | 0.19 | 0.20 | 0.28 | 0.29 | 0.19 | 0.20 | 0.28 | 0.29 | 0.19 | 0.20 | 0.29 | 0.28 |
| | | 95% IC | 0.12 0.30 | 0.12 0.31 | 0.19 0.39 | 0.20 0.40 | 0.12 0.29 | 0.13 0.30 | 0.20 0.39 | 0.21 0.40 | 0.13 0.29 | 0.13 0.30 | 0.21 0.39 | 0.20 0.38 |
| | 52 | Estimate | 0.39 | 0.41 | 0.52 | 0.54 | 0.38 | 0.39 | 0.52 | 0.53 | 0.38 | 0.40 | 0.52 | 0.52 |
| | | 95% IC | 0.29 0.51 | 0.30 0.54 | 0.41 0.64 | 0.43 0.67 | 0.29 0.50 | 0.29 0.51 | 0.42 0.63 | 0.42 0.65 | 0.29 0.49 | 0.30 0.51 | 0.43 0.63 | 0.41 0.63 |

# 5 Limitations

This study might have some characteristic limitations of non-interventional studies, such as: selection bias (both patient and treatment selection bias), information bias, confounding (absence of data on potential confounding factors if the data was not recorded in the past), ascertainment / enrollment bias, lost to follow-up and censored observations.

A specific limitation of this study will be the lack of a control group and its small sample size (since GLM entered the Portuguese market in early 2011). Other specific limitation of this study might be the heterogeneity between the participants selected due to the utilization of:

- different treatment guidelines according to the date the participant has initiated treatment with conventional DMARDs, NSAIDs or corticosteroids;
- different definition of co-morbidities over time (for example, the cut-offs for the definition of hypertension or diabetes have been changing over time);
- different methods to evaluate the outcomes defined for this study.

Another possible limitation of the study is the fact that Reuma.pt only captures a subset of RA patients that are treated in public hospitals and private clinics, the patients seen in primary care are not included in the database. However, the patients being followed in primary care centers are likely to have milder disease than those identified in the database, so they would not be eligible to enter the study.

# 6 Project Activities and Timelines

The project will encompass the following activities performed by Sociedade Portuguesa de Reumatologia:

- Variables selection and database preparation for exporting data
- Global data evaluation after export
- Database cleaning
- Data quality evaluation
- Statistical analysis
- Final report

| Activity | months | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 |
| Variables Selection and Extraction | | | | | | |
| Database Cleaning | | | | | | |
| Statistical Analysis | | | | | | |
| Clinical Study Report | | | | | | |

## 7 Study Team

Dr Ana Filipa Mourão
Prof Dr Helena Canhão

## 8 Budget and Payment scheduled

This study will be sponsored by Merck Sharp & Dohme, Lda and developed by SPR.

# 9 References


1. Curtis JR, Singh JA.Use of biologics in rheumatoid arthritis: current and emerging paradigms of care. Clin Ther 2011; 33 (6): 679-707.
2. van der Kooij SM, le Cessie S, Goekoop-Ruiterman YP, De Vries-Bouwstra JK, van Zeben D, Kerstens PJ, et al. Clinical and radiological efficacy of initial versus delayed treatment with infliximab plus methotrexate in patients with early rheumatoid arthritis. Ann Rheum Dis published online 17 Oct 2008; doi:10.1136/ard.2008.093294.
3. Hetland HM, Lindegaard HM, Hansen A, Pøndenfant J, Unkerskov, Ringsdal VS, et al. Do changes in prescription practice in patients with rheumatoid arthritis treated with biological agents affect treatment response and adherence to therapy? Results from the nationwide Danish DANBIO Registry. Ann Rheum Dis 2008; 67 (7): 1023-26.
4. Ledingham J, Deighton C. Update on the British Society for Rheumatology guidelines for prescribing TNF-blockers in adults with rheumatoid arthritis (update of previous guidelines of April 2001). Rheumatology (Oxford) 2005; 44: 157-63.
5. Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA, Wong PK. Medication compliance and persistence: terminology and definitions. Value Health. 2008 Jan-Feb;11(1):44-7
6. Saad AA, Ashcroft DM, Watson KD, et al. Persistence with anti-tumour necrosis factor therapies in patients with psoriatic arthritis: observational study from the British Society of Rheumatology Biologics Register. Arthritis Res Ther 2009; 11: R52.
7. Rothman, K.J., Greenland, S., & Lash, T.L. Modern Epidemiology, 3rd Edition. Philadelphia, PA: Lippincott, Williams & Wilkins, 2008.
8. Sklo M and Nieto FJ. Epidemiology: Beyond the Basics, Second Edition. Jones and Bartlett Publishers, 2007.
9. Kaplan EL, Meier P.Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-81.
10. Hetland ML, Christensen IJ, Tarp U, Dreyer L, Hansen A, Hansen IT, Kollerup G, Linde L, Lindegaard HM, POulsen UE, Schlemmer A, Jensen DV, Jensen S, Hostenkamp G, Ostergaard M, on behalf of All Departments of Rheumatology in Denmark. Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab. Arthritis & Rheumatism: results from eight years of surveillance of clinical practice in the nationwide Danish DANBIO registry. 2010; 62 (1): 22-32.
11. Markenson JA, Gibofsky A, Palmer WR, Keyestone EC, Schiff MH, Feng J, Baumgartner SW. Persistence with anti-tumor necrosis factor therapies in patients with rheumatoid arthritis: observations from the RADIUS registry. J Rheumatol 2011; 38 (7): 1273-81.
12. Ogale S, Hitraya E, Henk HJ. Patterns of biologic agent utilization among patients with rheumatoid arthritis: a retrospective cohort study. BMC Musculoskeletal Disorders 2011; 12: 204-14.
13. Senabre-Gallego JM, de Salazar JR-G, Santos-Soler G, Santos-Ramírez C, Sánchez-Barrioluengo M, Salas-Heredia E, Barber-Vallés X, Cano-Pérez C, Llahí-Vidal N, Riestra-Juán R. Duration of treatment with etanercept and motives for discontinuation in a cohort of patients with rheumatic disease. Reumatol Clin 2011; 7 (6): 385-8.
14. Carreño A, Fernández I, Badia X, Varela C, Roset M. Using HAQ-DI to estimate HUI-3 and EQ-5D utility values for patients with rheumatoid arthritis in Spain. Value in Health 2011; 14: 192-200.
15. Badia X, Roset M, Herdman M, Kind P. A comparison of United Kingdom and Spanish general population time trade-off values for EQ-5D health states. Med Decis Making. 2001 Jan-Feb;21(1):7-16.
16. Agresti A. Categorical data analysis. New York: Wiley, 2002.
17. O'Keefe DJ. Post Hoc Power, Observed Power, A Priori Power, Retrospective Power, Prospective Power, Achieved Power: Sorting Out Appropriate Uses of Statistical Power Analyses. Communication Methods and Measures 2007, 1(4);291-299.
18. Smith AH, Bates MN. Confidence limit analyses should replace power calculations in the interpretation of epidemiologic studies. Epidemiology 1992: 3(5); 449-52.
19. Hoenig, JM and Heisey, DM. The Abuse of Power: The Pervasive Fallacy of Power Calculations for Data Analysis. The American Statistician, February 2001, Vol. 55, No. 1
20. Collett, D. Modelling Survival Data in Medical Research. Second Edition. Champman & Hall/CRC, 2003.