Influence of Body Mass Index in Response to Biologic therapy in Rheumatoid Arthritis

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects both joints and extraarticular tissues[1]. The persistent systemic inflammatory state confers substantially increased of morbidity and mortality mostly due to the higher cardiovascular risk [2,3,4]. Obesity is a traditional cardiovascular risk factor that affects one third of rheumatoid arthritis patients [5]. However, the importance of obesity in RA activity is still unclear [6].

Adipose tissue is currently understood to be a metabolically and endocrinologically active organ, capable of modulating inflammation through the release of inflammatory cytokines (including tumor necrosis factor alpha, TNF-α and interleukin-6, IL-6) and of both pro-inflammatory (leptin, resistin and visfatin) and anti-inflammatory (adiponectin) adipokines, with the overall balance tending towards a chronic inflammatory response[7,8]. The influence of obesity in RA has paradoxical results. In fact, the distribution of total and regional body fat in patients with RA has been shown to correlate with markers of inflammation (CRP and IL-6) in women, with truncal fat presenting the strongest association[9]. On the other hand, it seems that obesity appears to protect against radiographic joint damage[10] and is associated to lower prevalence of mortality[11]. Nevertheless, obesity is associated with increased comorbidity, including pain and the need for total joint replacement in RA[12].

Biologic response modifier (BRM) drugs improve on the response achieved by methotrexate and classic RA disease-modifying antirheumatic drugs (DMARDs) by directly targeting pro-inflammatory cytokines or cells involved in the arthritic cascade[13]. The first BRM developed for RA targeted TNF-α, one of the cytokines released by adipose tissue. An increase in body fat with a resulting increased production of TNF-α would be expected to buffer the response to BRMs and, in fact, it has recently been demonstrated that an increasing body mass index is associated with worse remission rates and increased disease activity scores (DAS28) in RA patients treated with TNF inhibitors (TNFi)[14].

Aims of the proposed study

This study aims to determine the influence of obesity on treatment response to BRM evaluated by DAS28 at six months, in patients with RA, regardless of the targeted cytokine or cell, by analyzing a cohort of patients treated with anti-IL-6, anti-TNF-α or anti-CD20 drugs.

Primary aim: determine the influence of obesity on treatment response to BRM, in patients with RA first biologic users, using Disease activity Index (DAS28) at 6 months as the outcome.

Secondary aims:

1) Determine the influence of obesity on remission to BRM at 6 months, in patients with RA first biologic users using the following outcome measurements:

- European League Against Rheumatism (EULAR) Response (good response vs others)
- DAS28 remission (DAS<2.6)- (Yes/no)
- CDAI≤2.8 (yes/no)

- SDAI≤3.3 (yes/no)

2) Determine the influence of obesity on the different components of DAS28 (patients general health (GH), tender joint count pain (TJC), swollen joint count (SWJ) and c-reactive protein serum levels(CRP) and on pain evaluated by visual analogic scale (VAS pain) after 6 months of BRM in patients with RA first biologic users.

Detailed description

Patients and Methods

Database
Data will be collected from the Rheumatic Diseases Portuguese Registry (Reuma.pt). The Reuma.pt registry is a national based prospective longitudinal multicenter cohort initiated in 2006. It is a centralized clinical dataset from the Portuguese Society of Rheumatology (SPR) that captures more than 90% of patients treated with biologic therapies managed in rheumatology departments across Portugal. All biologic drugs are reimbursed by the Portuguese National Health Service. The decision to initiate and maintain the treatment is guided by the SPR's recommendations [15]. There is no guidance on which biologic agent should be used first with the exception of Rituximab (anti-CD20) is approved only when inadequate response to at least one TNF inhibitor.

Study population
Patients will be included if they met the American College of Rheumatology 1987 revised criteria for Rheumatoid Arthritis (AR), with at least 6 months of follow up after starting their first biologic therapy (TNF i, IL6 i and anti-CD20), with available data on weight and height data at baseline. Patients starting abatacept will not be included due to the low number available on the database.
Exclusion criteria will be the following: patients previously or currently treated with other biological therapies; patients under other DMARD than methotrexate or patients under prednisolone over 10mg/day or an equivalent dose of corticosteroid.

Proof of Concept Group
RA patients who met the ACR 1987 revised criteria, with at least 6 months of follow up after starting their first non-biologic DMARD, with available data on weight and height data at baseline will be included as a proof of concept group. Our initial hypothesis is that obesity influence treatment response either to DMARD therapy as to biologic therapy since there is no evidence to suggest a specific effect of obesity on biologic treatment response.

Data collection
We identified patients in Reuma.pt registry with rheumatoid arthritis and obtained information on patient demographics (age, gender and race), education level (years), body mass index (BMI), present smoking status, disease duration (years), current steroid therapy (yes/no), baseline DAS28 and its componentsCRP, TJC, SJC, GH,baseline VAS pain erosive disease (yes/no), Rheumatoid factor status, anti-citrullinated protein antibody (anti-CCP) status, Health Assessment Questionnaire (HAQ) score, dose and type of biologic therapy (anti-TNF, anti-CD20, anti-IL6).
BMI was categorized in two classes: non-obese (BMI<30) and obese (BMI>=30Kg/m2)

Primary Outcomes: Disease activity Index (DAS28) at 6 months;

Secondary Outcomes:

Remission outcomes at 6months: EULAR Response (good response vs others); DAS28 remission (DAS28<2.6);CDAI≤2.8 (yes/no); SDAI≤3.3 (yes/no
DAS28 components at 6 months (GH, TJC, SJC, CRP)
VAS pain at 6 months
Exposure was defined as BMI >30kg/m2 at baseline.

Statistical analysis

Categorical covariates will be described by frequency distribution while continuous covariates will be expressed in terms of their mean and standard deviation or median and interquartile range as appropriate. Patients were divided according to the BMI groups (BMI<30 vs BMI≥30) and unadjusted comparisons between groups of the covariates and the outcomes are going to be evaluated using chi2 tests for categorical data, while for continuous data, we will use the student's t-test for normally distributed variables and the Kruskall-Wallis test for non-parametric data.
To determine the effect of obesity on the biologic treatment response at 6 months in patients with RA a multivariate analysis will be performed using a stepwise linear regression models. The response variable is defined as DAS28 after 6 months. The baseline variables taken into account will be demographic data, disease duration (years), methotrexate (yes/no), Current steroid therapy (yes/no), baseline DAS28, erosion disease (yes/no), RF positive (yes/no), anti-CCP (yes/no), HAQ score, present smoking (yes/no), education level (years). Biological therapy will also be included in the model as TNFi (yes/no).
To determine the effect of obesity on remission a multivariate analysis will performed using a stepwise logistic regression models. The response variables will be EULAR response ((good response vs others) Das 28 remission (DAS 28<2.6) after 6 months, CDAI≤2.8 (yes/no); SDAI≤3.3 (yes/no). The baseline variables taken into account will be the same as in the previous models.
Finally, we will also use stepwise linear regression models to determine the effect of obesity on DAS 28 components and on VAS pain at 6 month.
All the analysis will be performed using STATA, version 12.1 and P value <0.05 will be considered statistically significant.

Expected Results

Using a national based prospective longitudinal multicenter cohort – The Reuma.pt registry we expect to determine an association between obesity and treatment response (DAS 28) at 6 months in established RA patient's naïve to biologic treatment. We also expect to further understand this association by analyzing the relation between DAS 28 components and obesity in RA patients. Moreover, we also meant to find a negative association between obesity and remission.

Finally, we will also expect to find association between obesity and treatment response in a group of recently diagnosed RA patients starting methotrexate.

Study Limitations

The more important limitation of this project could be the missing data that could lead to bias. Reuma.pt has 4262 rheumatoid arthritis patients however, we expect to have a considering amount of missing data regarding weight and height. Although we think that there will not be any particular reason for that finding, these covariates are inclusion criteria and this could lead to an underpowered study.

Calendar

This project will start in January 2014 and finish in March 2014
Data will be provided by Coreuma.pt team data management in January 2014 and a team of 3 students of the program "Clinical Scholars Research Training (CSRT) II" from Harvard Medical School- Portugal Program will do the data analysis and do the manuscript writing. Mentors from Harvard school and from Portugal will review the manuscript. This project is one of the tasks proposed in the CSRT program.

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Budget

Considering that the data is going to be freely available and the statistical software was given to us by the CRSTII program we do not expect to have additional expenses.

Conflict of interests

This team has no conflicts of interest.

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