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ORIGINAL RESEARCH

Improvement of HbA1c in Patients with Type 2 Diabetes Mellitus and Rheumatoid Arthritis Treated with bDMARDs

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Objective: The aim of our study was to evaluate the possible role of biological treatments for rheumatoid arthritis (RA) in improving the glycemic profile in patients affected not only by RA but also by type 2 diabetes mellitus (2TDM).

Methods: An observational retrospective study was conducted using data from patients referred to our Rheumatology Unit. Patients with active RA despite standard DMARDs therapy and concomitant 2TDM were selected into one of five exposure groups to first-line bDMARDs (adalimumab, golimumab, etanercept, tocilizumab, sarilumab) and observed for the outcome of CRP, ESR, DAS28CRP and glycated hemoglobin (HbA1c) variations.

Results: After the start of treatment, there was a significant reduction in the values of acute phase reactants ESR and CRP ($p<0.01$), DAS28-CRP ($p<0.01$) and HbA1C ($p<0.05$), in the absence of any confounding factors such as a reduction in BMI or a change in steroid doses. There was no statistically significant difference between the various treatments. Anti-IL6 drugs appear to be associated with a slightly greater reduction in HbA1c values, bordering on statistical significance ($p=0.047$).

Conclusion: Initiation of a bDMARD appears to be associated with an improvement in concomitant 2TDM in patients with active RA, which, in the first hypothesis, is linked with a reduction of the inflammatory milieu.

Keywords: diabetes mellitus, rheumatoid arthritis, bDMARDs

Background

In the literature there are various studies that suggest that patients with rheumatoid arthritis (RA) have a higher risk of developing diabetes (DM). It's also well known that insulin resistance is an independent risk factor for cardiovascular diseases (CVD).[1–5]

Moreover, patients with rheumatoid arthritis (RA) have an increased cardiovascular risk, estimated to be about 50% greater when compared to the general population and a correlation between insulin resistance, type II diabetes mellitus (2TDM) and RA is described in the literature.

The pro-inflammatory milieu that characterizes active RA (for example, high levels of cytokines such as IL1, IL6 and TNFalpha) may have a relationship with altered insulin production and therefore insulin resistance, as described by Esser and Wu, among others.[6,7] Although the potential link between pro-inflammatory milieu and insulin resistance is intriguing, to date few studies have assessed a possible relationship between disease activity (eg using a composite index such as DAS28-CRP or SDAI) and a DM marker such as as glycated haemoglobin.[8,9]

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Recently, the therapeutic arsenal against RA has been enriched by various agents such as antiTNF (etanercept, adalimumab, golimumab, infliximab), anti CD20 (rituximab), anti IL6 (tocilizumab, sarilumab) and fusion protein with CTLA4-Immunoglobulin (abatacept), which is designed to modulate the T cell co-stimulatory signal mediated through the CD28–CD80/86 pathway (bDMARDs).

In this study, we test the possible role of some bDMARDs in improving a concomitant 2TDM in patients with RA, evaluating periodically over 6 months the HbA1c values in parallel with DAS28-CRP, based on the hypothesis that a reduction of disease activity can lead to a better balance of glucidic metabolism.

Methods

Study Design

This study has been designed as an observational retrospective study. Clinical data were collected from patients with RA and 2TDM who started a first line of therapy with bDMARDs between October 2019 and December 2020.

Inclusion criteria were predefined as follows: moderate to severe disease activity as defined by DAS28-CRP despite treatment with standard disease-modifying anti-rheumatic drugs (DMARDs), stable treatment with methotrexate or other DMARDs. Concomitant 2TDM was treated with a stable dose of an insulin-sensitizing agent, such as metformin. Exclusion criteria were: infectious, neoplastic diseases, recent changes in dose of oral steroids and a daily steroid dose higher than 10mg/die of prednisone.

Given the observational design of the study, patients were eligible for treatment with biotechnological drugs (bDMARDs) if they were non-responders to standard DMARDS. Baseline data comprised anthropometric measurements (height, weight and body mass index), disease activity assessment based on DAS28-CRP calculation and lab test evaluations of ESR, CRP, glycemia and glycated hemoglobin. Patients were subsequently treated with a bDMARD according to the established procedures. After 3 and 6 months of treatment, patients were reassessed with the same schedule. The choice of bDMARD was made by a rheumatology expert in the use of these drugs, in accordance with the peculiar characteristics of the individual patient. This study was conducted in accordance with the ethics principles of the Declaration of Helsinki and was approved by the local research ethics committees.

Statistical Analysis

Data are expressed as mean standard deviation (SD), median (25th–75th percentile) or number (percentage), as appropriate. Continuous variables that were not normally distributed were ln-transformed before analysis. Paired samples student's *t*-test or ANOVA have been used, where appropriate, to compare means. The Pearson product–moment correlation coefficient was used to evaluate correlations between variables.

A p-value<0.05 was considered statistically significant. All tests were two-tailed. The Statistical Package for Social Sciences (SPSS for Windows, version 20.0, SPSS Inc., Chicago, IL) was used for all analyses.

Clinical Outcomes

Data relating to 67 patients with active RA (DAS28-CRP >3.2) despite treatment with MTX and T2DM were collected from 3 months before (t-3) the start of bDMARD (T0) treatment up to 6 months after, every 3 months (T3, T6). Fourteen were treated with adalimumab, 23 with etanercept, 15 with golimumab, 6 with sarilumab and 9 with tocilizumab. Anthropometric data are shown in Table 1.

Results

DAS28-CRP/HbA1c mean values (±SD) at T-3 and T0 were 5.15 (±0.37)/46.7 (±6.6) mmol/l and 5.25 (±0.39)/48.9 (±7.8), respectively. After the therapy with bDMARDs was started, a significant lowering in ESR, CRP, DAS28-CRP and HbA1c values was observed (Figures 1 and 2 show DAS28-CRP and HbA1c) at 3 months and 6 months (p<0.01). The ANOVA test did not showe a significant difference between the bDMARD treatments; rather, it showed only a statistical trend towards treatment with tocilizumab and sarilumab vs anti TNF (p=0.047). No significant variation in anthropometric values was observed (p>0.5) (Table 2).

Table 1 Demographic Data of the Whole Population

	Whole Population (N=67)
Males n (%)	28 (41.7%)
Age, years (±SD)	57.8±4.5
RA duration, years	2.8±1.8
Weight, kg (±SD)	84±8.5
Height, m (±SD)	1.69±0.02
BMI, Kg/m2 (±SD)	28.1±3.6

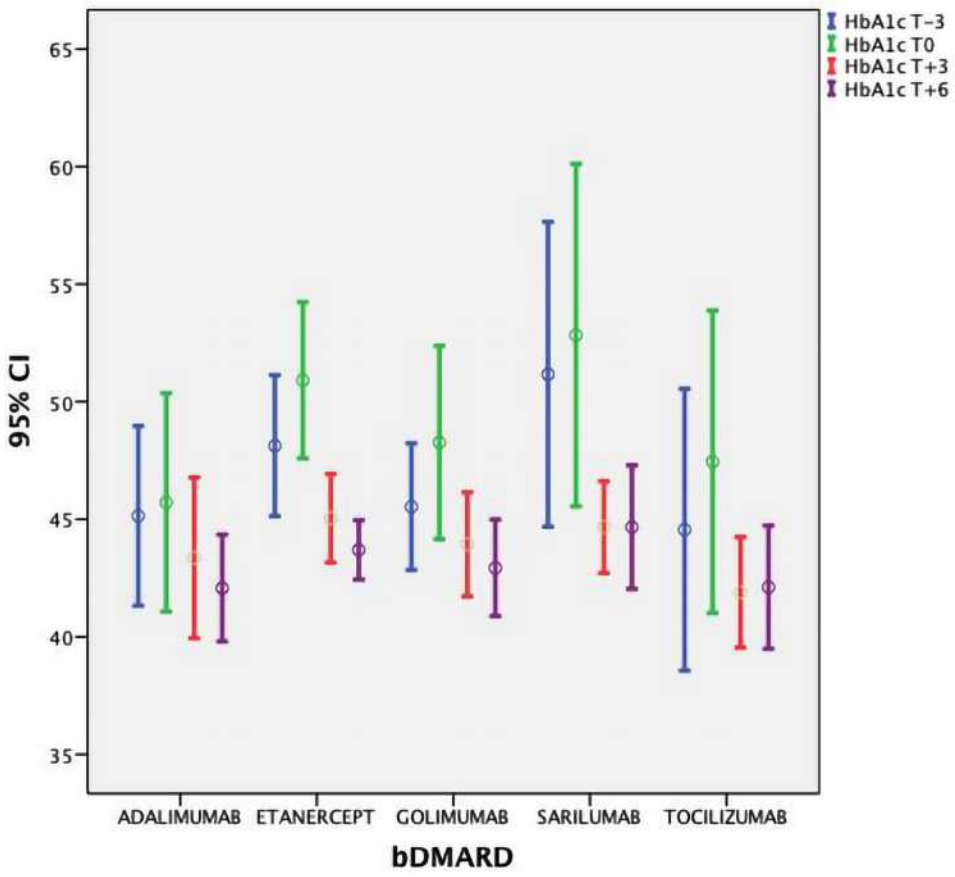

Figure 1 DAS28-CRP values during the study from 3 months before to 6 months after the start of therapy with bDMARDs.

Discussion

Rheumatoid arthritis is characterized by an increased cardiovascular risk comparable to that posed by type 2 diabetes mellitus.[11,12] This attribute can be explained as a combination of traditional risk factors, such as hypertension and dyslipidemia, with the inflammatory milieu present in RA uncontrolled by drugs.[10,13,14]

The importance of recognizing and managing cardiovascular disease risk in RA patients was emphasized in the European League Against Rheumatism (EULAR) 2010 recommendations.[15]

In this preliminary study, we showed that treatment of active RA using a bDMARD improves concomitant 2TDM. The observed improvement was not due to a significant loss of weight or BMI variation (stable at each timepoint, T-3, T0, T3 and T6, $p>0.5$) nor to a reduction in steroid doses; rather, it was the result of a lowering in inflammation, as demonstrated by decreased CRP and ESR values. Overall, the findings support the hypothesis that systemic inflammation as observed in active RA promotes insulin resistance; support efforts to prevent diabetes through optimal control of disease activity; and are intriguing regarding the role of each cytokine in determining the risk of developing diabetes.

Preclinical evidence can help us to hypothesize about the possible mechanisms behind this novel effect of bDMARDs. Immune cells, in particular macrophages and T cells, are nowadays recognized as important players in the pathogenesis of adipose tissue inflammation and, consequently, 2TDM.[16]

Fujii et al recently demonstrated that abatacept improved insulin resistance in a mouse model of diet-induced obesity, mainly through polarization of adipose tissue macrophages from the pro-inflammatory M1 to the anti-inflammatory M2 phenotype.[17] IL-6 was also demonstrated to be independently associated with incident diabetes, as has been shown in other populations.[18,19] It has been suggested that IL-6 is involved in the development of obesity-related and T2DM-related insulin resistance. Experimental and clinical studies now converge to show that several ILs, and primarily IL6, contribute to the

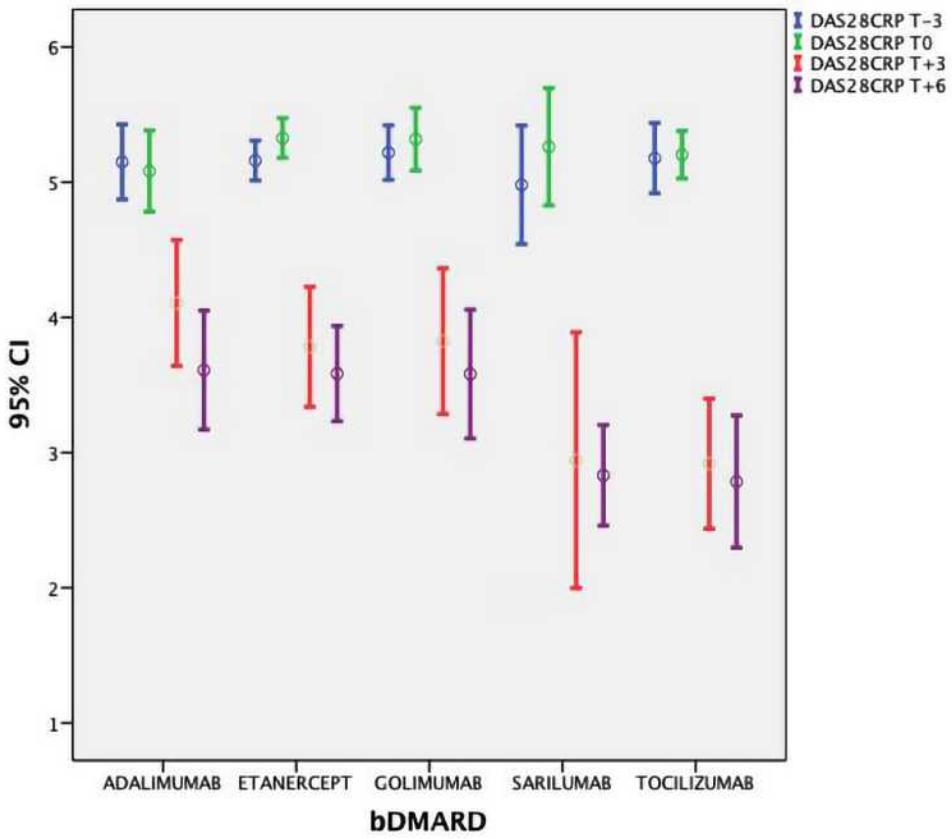

Figure 2 HbA1c values during the study from 3 months before to 6 months after the start of therapy with bDMARDs.

pathology and physiology of T2DM through their interaction with insulin signaling pathways and beta-cell function.[20,21]

In our study, the use of anti-IL6 drugs (tocilizumab and sarilumab) has been shown to lead to a further improvement in glycated hemoglobin values compared to the use of other classes of bDMARD. However, the small size of the sample in question prevents us from reaching definitive conclusions (p=0.047). Further study with longitudinal IL-6 measurement is needed in order to determine if IL-6 is in the causal pathway

Table 2 Data on DAS28CRP, HbA1c and BMI for Each bDMARD Used, During All Observation Periods

	bDMARD									
	Adalimumab		Etanercept		Golimumab		Sarilumab		Tocilizumab	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
DAS28CRP T-3	5.15	0.48	5.16	0.34	5.22	0.36	4.98	0.42	5.18	0.34
DAS28CRP T0	5.08	0.52	5.33	0.34	5.32	0.42	5.26	0.41	5.20	0.23
DAS28CRP T+3	4.11	0.81	3.78	1.03	3.82	0.97	2.94	0.90	2.92	0.63
DAS28CRP T+6	3.61	0.76	3.58	0.81	3.58	0.86	2.83	0.35	2.79	0.64
HbA1c T-3	45.1	6.6	48.1	6.9	45.5	4.9	51.2	6.2	44.6	7.8
HbA1c T0	46	8	51	8	48	7	53	7	47	8
HbA1c T+3	43	6	45	4	44	4	45	2	42	3
HbA1c T+6	42	4	44	3	43	4	45	3	42	3
BMI T-3	27.69	1.21	27.82	1.43	27.85	1.29	28.55	1.42	28.14	0.86
BMI T0	29.33	1.33	28.30	1.35	28.52	1.33	29.39	1.29	28.70	1.17
BMI T+3	28.44	1.45	27.52	1.29	27.89	1.44	28.01	1.45	28.57	1.27
BMI T+6	28.00	0.99	28.26	1.05	28.68	1.11	27.99	0.85	28.92	1.03

leading from obesity to diabetes. It therefore remains unknown whether blocking IL-6 might prevent the onset of DM in the general population and in patients with RA. In conclusion, our study, although with evident limitations (observational design, low number of patients, lack of a control group), provides preliminary evidence of a potential insulin-sensitizing effect of bDMARDs resulting from an anti-inflammatory effect, demonstrated by the significant reduction in the values of acute phase reactants. Obviously, our data need to be confirmed by more rigorous studies, including a control group, and at least direct measurements of insulin sensitivity. Our finding, if confirmed, could improve the management of comorbidity in RA patients. Cardiometabolic risk management, according to the EULAR recommendations, should be one of the biggest focuses for clinicians dealing with RA patients because greater disease activity in RA is associated with a greater risk of diabetes.

Article Summary

Strengths

1. Patients with rheumatoid arthritis often present with diabetes mellitus. The present study evaluates the effect of rheumatological therapies on the progress of diabetes.
2. The data collected show an improvement in diabetes resulting from effective treatment of rheumatoid arthritis.

Limitations

1. The sample size is very small and the observation period is limited. This led to not being able to assess the possible differences between the various treatments used.

Key Messages

1. Diabetes mellitus and rheumatoid arthritis increase cardiovascular risk.

2. High levels of pro-inflammatory cytokines, as in uncontrolled rheumatoid arthritis, are correlated with poorer glucose balance in diabetes.

3. Better control of arthritis leads to better control of concomitant diabetes.

Patient and Public Involvement

Not applicable. It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Data Sharing Statement

Data are available upon request as Spss files or Excel files.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

None of the authors have relevant conflicts of interest.

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