Diagnosis and treatment of rheumatoid arthritis in the Emilia Romagna region: a prospective population-based study

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Abstract

Objective

To perform a population-based study in rheumatoid arthritis (RA) patients, in order to evaluate the efficacy and safety of pharmacologic treatments.

Methods

1087 patients with RA were enrolled; inclusion criteria were: newly diagnosed RA, already diagnosed RA with high disease activity (HDA) (DAS28≥4.2) starting biologic DMARDs (bDMARDs), already diagnosed RA with HDA continuing with conventional DMARDs (cDMARDs). The following data were collected: demographics, clinical and laboratory features, imaging and prescribed drugs. All parameters except immunology and imaging (performed yearly) were repeated at each follow-up evaluations (after 3, 6 and 12 months, and thereafter every 12 months). In order to evaluate clinical response, the EULAR response criteria were used as the gold standard.

Results

414 (38.1%) newly diagnosed patients with RA, 477 (43.9%) RA patients who started bDMARDs and 196 (18.0%) RA patients who continued with cDMARDs were enrolled from April 2012 to March 2015 at 12 Rheumatology Centres in the Emilia Romagna Region. Statistical analyses showed a relative risk ratio (RRR) for moderate response of 1.65 in RA patients who started bDMARDs (p=0.16) and 2.49 for newly diagnosed RA (p=0.01). Sex, age and Health Assessment Questionnaire were not statistically significant. A RRR of 2.00 has been confirmed for RA patients who started bDMARDs (p<0.0005) for a good response as well as 2.20 for newly diagnosed RA (p<0.0005). An increase in adverse events among bDMARDs was found, but when looking at infections or neoplasia, no differences were highlighted between RA which started bDMARDs and RA who continued with cDMARDs.

Conclusion

Our results are in line with already published papers from British and Swedish Registries: a greater likelihood to have a good response is demonstrated for not longstanding RA starting cDMARDs or RA with HDA when a bDMARD is started. Also a good safety profile is demonstrated.

Key words

rheumatoid arthritis, biologic DMARDS, conventional DMARDS, efficacy, safety

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory arthropathy clinically characterised by joint pain and stiffness, often associated with swelling. RA causes articular functional impairment progressing to disability and is variably associated with a host of extra-articular manifestations which can cause additional morbidity and sometimes result in increased mortality (1-2). The most reliable estimates of incidence, prevalence, and mortality in chronic polyarthritis are those derived from population-based studies. The incidence and prevalence of RA generally rise with increasing age until about 70 years, then they decline. Around twice as many women as men are affected. The incidence of RA is 20–300 per 100,000 subjects per year. The prevalence of RA in most industrialised countries varies between 0.3% and 1% (3-4).

The goal of RA treatment is ideally to induce clinical remission and prevent joint damage and disability. To this end, a great number of conve tional pharmacological agents are in use, including non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (GC), as well as disease-modifying anti-rheumatic drugs (DMARDs), such as antimalarials, sulfasalazine, methotrexate, leflunomide and cyclosporine. However, a significant proportion of patients fail to adequately respond to these treatments (5-7).

Over the last few years, a growing number of biological agents have become available: there is mounting evidence supporting the effectiveness of biological DMARDs (bDMARDs), in controlling clinical manifestations and in preventing disease progression in both DMARD-naive patients and in those for whom previous DMARD therapy has proved unsuccessful. However, current evidence still leaves a number of important questions unanswered (8-9). In particular, the long-term efficacy and safety of biological drugs is still unclear, there is little knowledge regarding the parameters that may predict a favourable response in individual patients and the cost-effectiveness profile of these agents has been investigated in very few studies.

In order to obtain more information, some Rheumatology Societies, particularly in the United Kingdom and in Sweden, helped to create national registries that include patients treated with biological agents. These registries aim to collect sufficient data to evaluate the long-term efficacy and safety of biological treatments in patients drawn from nationwide clinical settings (10-13). They provide valuable contributions for both quality control and scientific purposes, being among the most important datasets used for longitudinal observational studies in rheumatic diseases. They are an essential complement to data obtained from randomised controlled trials, compared to which registries have a number of advantages related to real-life features. However, regarding safety registries, since the patients are not randomised, they have a selection bias because patients who were likely to have adverse events (AEs) on a particular biologic did not start the drug and probably did not have the AE.

In order to provide reliable data, registries must include clearly characterised patients. In particular, it is essential that the patients enrolled have a well-defined diagnosis. The 1987 American College of Rheumatology (ACR) criteria for RA, as well as the 2010 ACR/European League against Rheumatism (EULAR) criteria for RA, are able to distinguish the disease from other established rheumatic disorders (14-15). They are both internationally recognised classification criteria which define homogenous groups of patients for inclusion in clinical trials and registries. Their use facilitates the enrolment of homogeneous subsets of well-classified patients with RA.

The objective of our study was to develop an observational register for patients with RA, in particular to monitor the clinical efficacy, including the prevention of joint damage and the safety of biological agents, and compare the data on the efficacy and safety of biological agents in the patients resident in Emilia-Romagna with those drawn from other patient populations (English and Swedish) for whom biological registries already exist.

Patients and methods

Emilia-Romagna Region Rheumatoid Arthritis (ERRRA) registry

The Emilia-Romagna Region Rheumatoid Arthritis (ERRRA) Registry collects detailed data on patients with RA resident in this region. All patients diagnosed according to the revised 1987 ACR criteria for RA or the 2010 ACR/EULAR Classification Criteria for RA were enrolled between April 2012 and March 2015. Inclusion criteria were newly diagnosed RA patients, previously diagnosed RA patients starting therapy with bDMARDs, and previously diagnosed RA patients with High Disease Activity (HDA) (DAS28≥4.2) continuing their treatment with conventional DMARDs (cDMARDs). The third group of patients has been included as a control group for bDMARDs patients, with comparable age, disease activity and disease duration. Patients were recruited as consecutive out-patients and in-patients referred to the 12 rheumatology centres in Emilia Romagna involved in the study.

In ERRA, the baseline data collected include demographics [gender, age, Body Mass Index (BMI), smoking habit), clinical features [RA date of onset, RA date of diagnosis, tender and swollen joint count, patient and physician global assessment on a visual analogue scale (VAS), Health Assessment Questionnaire (HAQ), Disease Activity Score-28 (DAS28) as composite disease activity measure], extra-articular involvement such as fatigue, sicca symptoms, rheumatoid nodules, lung fibrosis and concomitant illnesses [arterial hypertension, dyslipidaemia, diabetes mellitus, kidney disease, hepatitis, chronic obstructive pulmonary disease (COPD)], laboratory features such as inflammatory markers [erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)], immunological markers [rheumatoid factors (RF) and anti-citrullinated protein antibodies (ACPA)], serology for chronic infections such as hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), latent tuberculosis (TB) using the Quatiferon-TB test, imaging evaluations [conventional x-ray (CR), ultrasonography (US) or magnetic resonance imaging (MRI)] and prescribed drugs [NSAIDS, corticosteroids (CCS), cDMARDs and bDMARDs)]. All these parameters, except the immunological markers, which were performed yearly, and imaging, which was performed every six months, were repeated at each follow-up (after 3 months, 6 months, 12 months and every 12 months thereafter) as well as AE reporting. Based on the European League against Rheumatism (EULAR) Improvement Criteria [16; Fig. 1)], patients were classified into three groups: no response, moderate response and good response, based on their follow-up visit DAS28 and absolute change in DAS28 from baseline.

DAS-44 at baseline	DAS-44 or DAS – 28 reduction from baseline values			DAS-28 at baseline
	> 1,2	> 0,6 and ≤ 1,2	≤ 0,6	
≤ 2,4	Good response	Moderate response	No response	≤ 3,2
> 2,4 and ≤ 3,7	Moderate response	Moderate response	No response	> 3,2 and ≤ 5,1
> 3,7	Moderate response	No response	No response	> 5,1

Fig. 1. ACR/EULAR criteria.

Experts developed the database model. This multidisciplinary approach and the comparison with track records of existing databases allowed us to define a core-set of the variables of interest relative to the appropriate management and follow-up of patients and in line with international practices. The ERRRA registry was created and structured in order to allow for the standardised processing of data from all the participating rheumatology centres. Data were collected in electronic format using a predefined form accessible on the web. Forms were protected by centre-specific usernames and passwords. The form was divided into distinct, easily accessible specific data sections: social and demographic patient data with additional information on work activity and smoking habits at the time of entry, medical history (diagnosis, swollen and tender joint count, patient and physician global assessment of disease activity), any comorbidities present at the time of entry, past (over the last 12 months) and current drug history as well as new prescriptions, clinical and pharmacological data at follow-up including assessment of disease activity and function as well as prescriptions made after the first visit, any drug-related AEs detailing date of onset, type and severity.

Forms filled out by the participating centres were transmitted to the central system Administrator (Regione Emilia-Romagna), who anonymised the patient data. Each patient was solely and uniquely identified by a serial number that was linked to other regional databases (mortality registry, hospital discharge records, pharmacies, outpatient clinic-based specialists). Centres could only access the data of their respective patients.

Data quality

Queries regarding missing data and patients with incomplete follow-up were sent to the rheumatology centres. Furthermore, all the centres participating in the ERRRA registry were regularly audited in order to optimise data quality.

Statistical analysis

All analyses were performed using the SAS 9.1 system (SAS Institute, Cary, NC, USA) and the STATA 13.1 (STATACorp LP, College Station, TX, USA). Baseline characteristics (gender, age, BMI, smoking habit), clinical features (RA age at disease onset, RA age

at diagnosis, tender and swollen joint count, patient and physician global assessment, HAQ), extra-articular involvement, laboratory features such as inflammatory markers and immunological markers, RF and ACPA, were compared among the three groups. Continuous variables were expressed as median, minimum and maximum and compared using ANOVA. Categorical variables were expressed as percentages and the Chi-square test was used for comparison. The outcomes were categorised in two or three levels and analysed, respectively, with a logistic or multinomial model. Multinomial logistic regression models were used to identify factors associated with EULAR response (moderate and good) and remission/low disease activity (LDA). For each model, the variables included in the analysis were selected using a stepwise approach. We reported the relative risk ratios (RRR), with 95% confidence intervals (CIs), to explain the results deriving from the multinomial logit model. Similarly, odds ratios (ORs) and CIs from the logistic model were reported.

Patients underwent one year of follow-up after the date of inclusion in the register and outcome assessment was performed on data collected at the last follow-up visit.

All statistical tests were two-sided: $p<0.05$ was considered to be significant.

Results

Between April 2012 and March 2015, 1256 patients affected by RA were included in the ERRRA registry. Complete evaluations were present for 1087 subjects: 414 (38.1%) with newly diagnosed RA, 477 (43.9%) with previously diagnosed RA with HDA who started therapy with new bDMARDs and 196 (18.0%) patients with previously diagnosed HDA who continued on cDMARDs. Among the 1087 patients evaluated, 865 (80%) were females. Table I shows the baseline demographic and clinical findings in the 3 groups of patients. Among the 3 groups of patients, there were statistically significant differences regarding median age at enrolment ($p=0.0002$), sex ($p=0.003$), ACPA ($p=0.004$) and RF positivity ($p=0.004$). Among the 1087 patients, 269 (24.7%) were smokers and no statistically significant differences were observed in the 3 groups. 487 (44.8%) subjects had a BMI ≥25 and 153 (14.1%) had a BMI ≥30, 774/1008 (76.8%) patients were ACPA positive, while 790/1031 (76.6%) showed RF positivity. A baseline HAQ ≥1 was observed in 597/932 patients (64.1%). Among the 3 groups of patients, there was a statistically significant difference in the frequency of patients with HAQ ≥1 at diagnosis ($p<0.001$). 719 patients out of 789 (91.1%) showed active US or MRI-confirmed synovitis, and 466/879 (53.0%) already had bone ero-

Table IA. Baseline demographic and clinical features.

	Group 1 Newly diagnosed RA 414 (38.1%)	Group 2 Previously diagnosed RA, bDMARDs 477 (43.9%)	Group 3 Previously diagnosed RA, cDMARDs 196 (18.0%)	*p*-value
Age at enrolment, (median, min-max)	59.0 (17.0 – 88.0)	57.0 (18.0 – 87.0)	64.0 (22.0 – 84.0)	0.0002*
Female, n° (%)	313/414 (75.6)	402/477 (84.3)	150/196 (76.6)	0.003^
BMI≥25, n° (%)	180/395 (45.6)	217/461 (47.1)	90/160 (56.3)	0.065^
BMI≥30, n° (%)	63/395 (15.9)	65/461 (14.1)	25/160 (15.6)	0.734^
Smokers, n° (%)	112/414 (27.1)	117/477 (24.5)	40/196 (20.4)	0.204^
ACPA +, n° (%)	288/400 (72.0)	337/431 (78.2)	149/177 (84.2)	0.004^
RF +, n° (%)	291/407 (71.5)	349/443 (78.8)	150/181 (82.9)	0.004^
HAQ ≥1, n° (%)	186/366 (50.8)	330/446 (74.0)	81/120 (67.5)	<0.001^
DAS28 (median, min-max)	4.9 (0.9 – 8.7)	5.3 (0.6 – 57.0)	5.1 (1.7 – 435.0)	0.094

*ANOVA. ^Chi-Square.

Table IB. Follow-up clinical features.

Follow-up clinical features (n,%)	Group 1 Newly diagnosed RA	Group 2 Previously diagnosed RA, bDMARDs	Group 3 Previously diagnosed RA, cDMARDs	*p*-value
Active synovitis	6/153 (3.9)	3/37 (8.1)	2/44 (4.5)	<0.001**
New bone erosions	13/100 (13)	19/85 (22.4)	14/43 (32.6)	0.004**
No EULAR response	69/343 (20.1)	103/409 (25.2)	61/156 (39.1)	0.0004
Moderate EULAR response	48/343 (14.0)	53/409 (13.0)	15/156 (9.6)	0.0004
Good EULAR response	246/343 (71.7)	253/409 (61.9)	80/156 (51.3)	0.0004
Remission/LDA	226/343 (65.9)	249/409 (60.9)	79/156 (50.6)	<0.001

Table S1. Concurrent illnesses.

New comorbidities at follow-up (n,%)	Group 1 Newly diagnosed RA	Group 2 Previously diagnosed RA, bDMARDs	Group 3 Previously diagnosed RA, cDMARDs	*p*-value
Hypertension	138/342 (40.3)	153/404 (37.9)	69/155 (44.5)	0.350
Heart disease	29/342 (8.5)	22/407 (5.4)	13/154 (8.4)	0.203
Dyslipidaemia	74/309 (23.9)	98/381 (25.7)	34/144 (23.6)	0.818
COPD	22/307 (7.2)	27/405 (6.7)	20/150 (13.3)	0.029
Kidney disease (renal failure)	10/342 (2.9)	13/408 (3.2)	7/156 (4.5)	0.652
Liver disease	26/322 (8.1)	57/406 (14.0)	15/152 (9.9)	0.034
Interstitial lung disease	4/314 (1.3)	17/405 (4.2)	8/149 (5.4)	0.030
Diabetes	36/343 (10.5)	32/409 (7.8)	19/155 (12.3)	0.215
Cerebrovascular disease	9/343 (2.6)	10/409 (2.4)	7/156 (4.5)	0.405
Demyelinating disease	6/342 (1.7)	6/408 (1.5)	2/156 (1.3)	0.912
Tuberculosis	8/103 (7.8)	47/395 (11.9)	17/70 (24.3)	0.004

Table IIA.

Moderate response		
	Relative risk ratio (RRR)	*p*-value
Group 2 – Previously diagnosed RA, Bdmards	1.65	0.16
Group 1 – Newly diagnosed RA	2.49	0.01
RF positive patients	0.70	0.40
ACPA positive patients	1.62	0.26
Disease duration <180 DAYS	0.86	0.70
Disease duration 180 days > and ≤360 days	0.49	0.09
Disease duration >360 days	1.25	0.50
Good response		
	Relative risk ratio (RRR)	*p*-value
Group 2 – Previously diagnosed RA, bDMARDS	2.00	<0.0005
Group 1 – Newly diagnosed RA	2.20	<0.0005
RF positive patients	0.66	0.15
ACPA positive patients	1.03	0.91
Disease duration <180 days	0.88	0.61
Disease duration 180 days> and ≤360 days	0.67	0.12
Disease duration >360 days	0.68	0.11
Remission/LDA		
	Relative risk ratio (RRR)	*p*-value
Group 2 – Previously diagnosed RA, bDMARDS	1.42	0.08
Group 1 – Newly diagnosed RA	2.36	<0.0005
Area under the ROC curve 0.63		

Table IIB.

New erosions at follow-up (number of observations 228)		
	Odds ratio (OR)	*p*-value
Group 2 – Previously diagnosed RA, bDMARDS	0.63	0.29
Group 1 – Newly diagnosed RA	0.33	0.01
RF positive patients	2.43	0.01
ACPA positive patients	N/A	N/A
Area under the ROC curve 0.69		
Persistent active synovitis (number of observations 221)		
	Odds ratio (OR)	*p*-value
Group 2 – Previously diagnosed RA, BDMARDs	4.61	0.23
Group 1 – Newly diagnosed RA	2.05	0.54
RF positive patients	2.05	0.48
ACPA positive patients	0.90	0.91
Area under the ROC curve 0.72		

sions at inclusion in the register. Baseline demographics and clinical data are reported in Table IA; follow-up clinical features are reported in Table IB. In our analyses, all patients with at least one follow-up visit were included: the median number of visits made by each group was 2, confirming that all three groups can be considered homogeneous. A significant improvement in clinical features was seen mostly in newly diagnosed RA patients, as well as in those who started bDMARDs therapy (Table IB).

Among newly diagnosed RA patients only a small number (16 patients out of 414) started a bDMARD during their follow-up.

Our analyses, performed according to EULAR response criteria, demonstrated a higher chance of obtaining a moderate response for previously diagnosed RA treated with bDMARDs as well as newly diagnosed RA, compared with the control group (HAD-RA - DAS28 ≥4.2 - who continued on cDMARDs. (Table IIA)

In our statistical model, gender, age, smoking habit, baseline HAQ value and disease duration were evaluated in order to find a potential association with response or remission/LDA: none of them showed a statistically significant association. Additionally, the presence of RF or ACPA was not associated with the response to treatment and remission/LDA at multivariate analysis. (Table IIA).

The same analysis was performed to evaluate the likelihood of a good response: our data demonstrated a relative risk ratio (RRR) of 1.58 in previously diagnosed RA with HDA who started bDMARDs (p=0.04) and 1.92 in newly diagnosed RA (p=0.01) compared with the control group.

In our statistical model, gender, age, smoking habit, baseline HAQ value, disease duration, RF and ACPA were evaluated in order to find potential predictors of treatment response: none of them showed a statistically significant association. (Table IIA) Again, when evaluating RRR for remission/LDA we found a value of 1.42 (p=0.08) in RA treated with bDMARDs and a value of 2.36 (p<0.005) in newly diagnosed RA compared with the control group (Table IIA).

Only a minority of the enrolled patients had undergone regular imaging (US or CR) at the follow-up time points. We found that RRR for structural damage progression was significantly reduced in newly diagnosed RA patients compared to the control group. A non-significant reduction was shown in previously diagnosed RA patients treated with bDMARDs. RF-positive patients had a 2-fold increased damage progression compared to RF-negative patients; no significant association with damage progression was observed in ACPA-positive patients. No significant results were found when looking at persistent active synovitis (Table IIB).

When considering comorbidities, we found a significant difference in COPD, which was increased in patients with previously diagnosed RA treated with cDMARDs. Interstitial lung disease was also significantly different, with an increased frequency seen in previously diagnosed RA treated with both bDMARDs and cDMARDs. Liver disease was significantly different in the three groups of patients, in particular it was increased in the group of patients treated with bDMARDs. No patients developed active tuberculosis. Latent tuberculosis was significantly different in the 3 groups, with the highest frequency observed in the group treated with cDMARDs. (supplementary data – Table S1)

When evaluating AEs in the 3 groups, we found a significant difference with an increase among patients who used bDMARDs ($p<0.05$). Comparing patients treated with bDMARDs and cDMARDs, no differences in the frequency of infection and neoplasia were found (Table III).

Table III.

	Adverse event category	Adverse event n° (%)
GROUP 1		**24/91 (26.4%)**
Newly diagnosed RA	Infection	3/24 (12.5)
	AE TO cDMARDs	14/24 (58.3)
	Minor AE TO bDMARDs	0
	Neoplasia	1/24 (4.2)
	Other	6/24 (25)
GROUP 2		**54/91 (59.3%)**
Previously diagnosed RA, bDMARDS	Infection	**12/54 (22.2)**
	AE to cDMARDs	3/54 (5.6)
	Minor AE to bDMARDs	16/54 (29.6)
	Neoplasia	**1/54 (1.9)**
	Other	22/54 (40.7)
GROUP 3		**13/91 (14.3%)**
Previously diagnosed RA, cDMARDS	Infection	**3/13 (23.1)**
	AE to cDMARDs	5/13 (38.5)
	Minor AE to bDMARDs	0/13 (0)
	Neoplasia	**1/13 (7.7)**
	Other	4/13 (30.8)

Discussion

Therapy with bDMARDs (firstly TNF-α blocking agents, then anti-CD20 monoclonal antibodies, IL-6 Receptor (IL-6R) blocking agent, selective T-cell co-stimulation modulator) has revolutionised the management of RA: there is mounting evidence supporting their effectiveness in controlling clinical manifestations and in preventing disease progression in both DMARD-naive patients and in those for whom previous DMARD therapy was unsuccessful. However, a number of important questions still remain unanswered, in particular the long-term efficacy and safety of these drugs and the knowledge regarding the parameters that may predict a favourable or a worse response in individual patients, as it has recently been done by Annecchino *et al*. (17). In order to obtain more information about their safety and efficacy, efforts to establish drug registries have been made in many countries. In comparison with clinical trials, registries show data from real life with a greater numbers of patients enrolled and a reduced selection bias in terms of patient recruitment.

In order to collect reliable data on the safety and efficacy of bDMARDs, data from a parallel control group must be assessed. Therefore, we identified a comparison group, which, as seen in the British Society for Rheumatology (BSR) register, consisted of patients with active RA treated with cDMARDs: the aim of this kind of comparison was to evaluate efficacy and safety of biologics in a real life setting using as a control group a sample of patients with comparable age, disease activity and disease duration.

Our results are in line with data from studies that are already available in the literature. In particular, a higher percentage of female patients was found and a difference in achieving disease remission or low disease activity among the three groups evaluated was confirmed, with better outcomes seen in patients treated during the early phases of the disease, highlighting the need for early treatment of RA, as already demonstrated by different papers from national registries (18-20 and clinical trials (21- 22).

A recent study by Sandberg MEC (23) on a cohort of patients with RA in its early phase demonstrated that overweight at diagnosis significantly decreased the chance of achieving good disease control: in our analyses, although 44.8% of patients had a BMI higher than 25 and 14.1% higher than 30, we did not find a correlation between BMI and achieving disease remission.

In our cohort of patients with newly diagnosed RA only a small number of patients started bDMARD during follow-up (16 out of 414, 3.9%), therefore multivariate analyses were not performed in this group of patients.

Our data demonstrated a better response in RA patients with HDA on bDMARDs compared to the RA patients with HDA who continued their cDMARDs treatment. Likewise, these data were confirmed when the progression of structural damage was analysed: RA patients who started bDMARDs had a significantly slower progression of structural damage compared to RA patients who continued on cDMARDs (Table IB). It is worth noting that only a minority of patients underwent follow-up imaging evaluations, so these data need to be confirmed in a bigger sample.

Usually, data on long-term AEs in patients treated in routine practice predominantly comes from spontaneous pharmacovigilance reporting systems, however the interpretation of such data is limited and specific information from registries might be helpful.

In a paper by Galloway *et al*. published in 2011 (24), the matter of serious infections related to the TNF-alpha blockers treatment of RA patients included in the BSR register was addressed. Ac-

cording to these data, anti-TNF therapy was associated with an increased risk of severe infections when compared to cDMARDs. On the contrary, our data, in accordance with data published by Emery *et al*. (25), did not demonstrate an increased risk of severe infection among patients who used bDMARDs. On the other hand, due to its design (it is a prospective register, not a randomised trial), our study has a significant selection bias: patients who were likely to have AEs on a particular biologic probably did not start the drug and then did not have the AE. Again, when looking at neoplastic diseases, no differences were demonstrated between RA treated with bDMARDs and RA treated with continued conventional therapies (Table III). We only observed an increase in minor AEs (mainly minor reactions at injection sites) in patients treated with bDMARDs. It is well known that anti-TNF therapy may be associated with an increased risk of TB infection (26-29). As reported in the results, we did not find any cases of active TB. A significant difference among the 3 groups was observed regarding the frequency of patients who developed latent TB after one year of follow-up. Latent TB was more frequently observed in the patients with longstanding HDA treated with cDMARDs (24.3%). A less frequent, but relevant, increase was also observed in bDMARD-treated patients (11.9%) (Table S1). These data are partially in line with results published by Hatzara *et al*. in 2005 (30). This paper highlighted the fact that 20 of 70 patients (29%) treated with TNF blockers developed conversion of at least one screening test for latent TB.

The risk of neoplastic diseases associated with immunosuppressive therapy in RA has been evaluated in different studies. Data from Swedish and BSR registers (31) showed an overall increase of cancer incidence among patients with RA compared with background populations. Geborek *et al*. demonstrated an increased overall tumour risk in patients treated with conventional antirheumatic treatment, but not in those treated with TNF-blockers. These authors showed an increased risk for lymphoma associated with TNF blockers, however this observation was based on a low number of cases and needs to be confirmed.

In keeping with our results, Askling *et al*. (32) demonstrated a cancer risk in cohort of Swedish RA patients treated with anti-TNF similar to that seen in bDMARD naïve RA patients and patients starting mono or combo cDMARD therapies. Similarly, BSR register data showed that the co-administration of a TNF-α antagonist and cDMARD did not cause an increased risk of cancer in RA patients selected for anti-TNF therapy (33, 34). Our results are in line with data from other registries, confirming a good safety profile for bDMARDs, as well as their efficacy in controlling RA in terms of both early and chronic disease. On the other hand, it is important to remember that our study has some limitations: firstly, the evaluated sample, which still needs to be implemented. Secondly, being a register, as already discussed, there is a probable selection bias regarding drug safety.

Lastly, in order to confirm our preliminary results and guarantee more reliable data, a longer observation period was needed for the collection of follow-up data.

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References

1. COMBE D: Progression in early rheumatoid arthritis. *Best Pract Clin Rheumatol* 2009; 23: 59-69.
2. GERYK LL, CARPENTER DM, BLALOCK SJ, DEVELLIS RF, JORDAN JM: The impact of co-morbidity on health-related quality of life in rheumatoid arthritis and osteoarthritis patients. *Clin Exp Rheumatol* 2015; 33: 366-74.
3. HOY DG, SMITH E, CROSS M *et al*.: Reflecting on the global burden of musculoskeletal conditions: lessons learnt from the global burden of disease 2010 study and the next steps forward. *Ann Rheum Dis* 2015; 74: 4-7.
4. RUDAN I, SIDHU S, PAPANA A *et al*.: Prevalence of rheumatoid arthritis in low- and middle-income countries: A systematic review and analysis. *J Glob Health* 2015; 5: 010409.
5. BREEDVELD FC: Current and future management approaches for rheumatoid arthritis. *Arthritis Res* 2002; 4 (Suppl. 2): S16-21.
6. LARD LR, VISSER H, SPEYER I *et al*.: Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. *Am J Med* 2001; 111: 446-51.
7. COMBE D, LANDEWÉ R, LUKAS C *et al*.: EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2007; 66: 34-45.
8. PARIDA JR, MISRA DP, WAKHLU A, AGARWAL V: Is non-biological treatment of rheumatoid arthritis as good as biologics? *World J Orthop* 2015; 6: 278-83.
9. CODREANU C, DAMJANOV N: Safety of biologics in rheumatoid arthritis: data from randomized controlled trials and registries. *Biologics: targets and therapy* 2015; 9: 1-6.
10. SILMAN A, SYMMONS D, SCOTT DG, GRIFFITHS I: British Society for Rheumatology Biologics Register. *Ann Rheum Dis* 2003; 62: ii28-ii29.
11. GRIFFITHS I, SILMAN A, SYMMONS D, SCOTT DG: BSR Biologics Registry. Editorial. *Rheumatology* 2004; 43: 1463-4.
12. ASKLING J, FORED CM, GEBOREK P *et al*.: Swedish registers to examine drug safety and clinical issues in RA. *Ann Rheum Dis* 2006; 65: 707-12.
13. VAN VOLLENHOVEN RF, ASKLING J: Rheumatoid arthritis registries in Sweden. *Clin Exp Rheumatol* 2005; 23: S195-200.
14. ARNETT FC, EDWORTHY SM, BLOCH DA *et al*.: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-24.
15. ALETAHA D, NEOGI T, SILMAN AJ *et al*.: 2010 Rheumatoid Arthritis Classification Criteria. An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative. *Arthritis Rheumatism* 2010; 62: 2569-81.
16. VAN GESTEL AM, HAAGSMA CJ, VAN RIEL PL: Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. *Arthritis Rheum* 1998; 41: 1845-50.
17. ANECCHINO C, FANIZZA C, MARINO V, ROMERO M; DOSE STUDY GROUP: Drug outcome survey to evaluate anti-TNF treatment in rheumatoid arthritis: an Italian observational study (the DOSE study). *Clin Exp Rheumatol* 2015; 33: 779-87.
18. SCHIPPER LG, VERMEER M, KUPER HH *et al*.: A tight control treatment strategy aiming for remission in early rheumatoid arthritis is more effective than usual care treatment in daily clinical practice: a study of two cohorts in the Dutch Rheumatoid Arthritis Monitoring Registry. *Ann Rheum Dis* 2012; 71: 845-50.
19. SCIRÈ CA, VERSTAPPEN SM, MIRJAFARI H *et al*.: Reduction of long-term disability in inflammatory polyarthritis by early and persistent suppression of joint inflammation: results from the Norfolk arthritis register. *Arthritis Care Res* 2011; 63: 945-52.
20. KYBURZ D, GABAY C, MICHEL BA, FINCKH A; PHYSICIANS OF SCQM-RA: The long-term impact of early treatment of rheumatoid arthritis on radiographic progression: a population based cohort study. *Rheumatology* 2011; 50: 1106-10.
21. EMERY P, BURMESTER GR, BYKERK VP *et al*.: Evaluating drug-free remission with abatacept in early rheumatoid arthritis: results

from the phase 3b, multicentre, randomized, active-controlled AVERT study of 24 months, with a 12-month, double-blind treatment period. *Ann Rheum Dis* 2015; 74: 19-26.

22. AXELSEN MB, ESHED I, HØRSLEV-PETERSEN K *et al*.: A treat-to-target strategy with methotrexate and intra-articular triamcinolone with or without adalimumab effectively reduces MRI synovitis, osteitis and tenosynovitis and halts structural damage progression in early rheumatoid arthritis: results from the OPERA randomized controlled trial. *Ann Rheum Dis* 2015; 74: 867-75.
23. SANDBERG ME, BENGTSSON C, KÄLLBERG H *et al*.: Overweight decreases the chance of achieving good response and low disease activity in early rheumatoid arthritis. *Ann Rheum Dis* 2014; 73: 2029-33.
24. GALLOWAY JB, HYRICH KL, MERCER LK *et al*.: Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. *Rheumatology* (Oxford) 2011; 50: 124-31.
25. EMERY P, GALLO G, BOYD H *et al*.: Association between disease activity and risk of serious infections in subjects with rheumatoid arthritis treated with etanercept or disease-modifying anti-rheumatic drugs. *Clin Exp Rheumatol* 2014; 32: 653-60.
26. MAINI R, ST CLAIR EW, BREEDVELD F *et al*.; AND THE ATTRACT STUDY GROUP: Infliximab (chimeric anti-tumor necrosis factor α monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomized phase III trial. *Lancet* 1999; 354: 1932-9.
27. KHANNA D, MCMAHON M, FURST DE: Safety of tumor necrosis factor-α antagonists. *Drug Saf* 2004; 27: 307-24.
28. KEANE J, GERSHON S, WISE RP *et al*.: Tuberculosis associated with infliximab, a tumor necrosis factor α-neutralizing agent. *N Engl J Med* 2001; 345: 1098-104.
29. MOHAN AK, COTE TR, BLOCK JA, MANADAN AM, SIEGEL JN, BRAUN MM: Tuberculosis following the use of etanercept, a tumor necrosis factor inhibitor. *Clin Infect Dis* 2004; 39: 295-9.
30. HATZARA, HADZIYANNIS E, KANDILI A, KOUTSIANAS C, MAKRIS A, GEORGIOPOULOS G: Frequent conversion of tuberculosis screening tests during anti-tumour necrosis factor therapy in patients with rheumatic diseases. *Ann Rheum Dis* 2015; 74: 1848-53.
31. GEBOREK P, BLADSTRÖM A, TURESSON C *et al*.: Tumor necrosis factor blockers do not increase overall tumor risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphomas. *Ann Rheum Dis* 2005; 64: 699-703.
32. ASKLING J, VAN VOLLENHOVEN RF, GRANATH F *et al*.: Cancer risk in patients with rheumatoid arthritis treated with anti-tumor necrosis factor α therapies. Does the risk change with the time since start of treatment? *Arthritis Rheum* 2009; 60: 3180-9.
33. MERCER LK, DAVIES R, GALLOWAY JB *et al*.: Risk of cancer in patients receiving non-biologic disease-modifying therapy for rheumatoid arthritis, compared with the UK general population. *Rheumatology* 2013; 52: 91-8.
34. MERCER LK, LUNT M, LOW AL *et al*.: Risk of solid cancer in patients exposed to anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. *Ann Rheum Dis* 2015; 74: 1087-93.