Dose down-titration of biological DMARDs in patients with rheumatoid arthritis over time and in daily clinical practice

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Abstract

Objective

To describe and compare dosing optimisation in biological DMARDs (bDMARDs) and relapses after that, in a cohort of rheumatoid arthritis (RA) during clinical practice.

Methods

Observational retrospective longitudinal study of RA patients taking bDMARDs from December 1999 to November 2013. Optimisation was defined as a 15% decrease in dose either reducing single dose or separating dose interval administration, for at least 4 times the recommended period between dosages. Relapse was defined as suspension or starting again with the recommended dose after optimisation. Incidence rates (IR) per 100 patient-years were estimated using survival techniques. Cox multivariate models were conducted to compare bDMARDs expressed in hazard ratios (HR) and confidence intervals [95%CI].

Results

443 patients and 752 different courses of bDMARD treatments were included. We observed 146 optimisations with an IR of 8.1. The HR of optimisation in: a) adalimumab, etanercept and rituximab compared to infliximab was 1.56 [1.01–2.4], 1.5 [0.9–2.4] and 0.6 [0.3–1.4], respectively; b) adalimumab, etanercept compared to rituximab were 2.3 [1.2–4.5] and 2.2 [1.2–4.3]. There were no statistically significant differences between adalimumab and etanercept. Following optimisation, 36% relapsed (78% due to disease activity). The IR related to disease activity was 6.3, and was lower for adalimumab and etanercept compared to infliximab (HR: 0.42; [0.19–0.94]; HR: 0.34; [0.13–0.89], respectively). There were no statistically significant differences between etanercept and adalimumab. No patients on rituximab relapsed.

Conclusion

Optimisation was similar between adalimumab and etanercept, and was lower for infliximab and rituximab. After optimisation, rituximab did not relapse, but infliximab did with the highest hazard.

Key words

rheumatoid arthritis, optimisation, observational study, biological DMARDs

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Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder, affecting 1% of the population world-wide (1), and 0.5% in Spain (2). RA is associated with severe morbidity, impaired functional capacity leading to decreased quality of life and increased mortality (3-5).

During the past two decades, RA treatment has been substantially improved mainly due to an early and/or aggressive treatment and the emergence of new biological drugs (6, 7). Currently the main goal of RA treatment is to prevent joint damage and disability, targeting remission or at least low disease activity. A better prognosis of RA in recent decades might be a reflection of early diagnosis and appropriate treatment rather than a change in the disease characteristics (8).

The use of biologic DMARDs (bDMARDs) is recommended in patients with new RA, high disease activity and poor prognostic features, and in those with established RA and moderate or high disease activity, after no response to non-biologic DMARD treatment (9, 10). Several bDMARDs are available, with different mechanisms of action, route, and frequency of administration. These differentiating characteristics, as well as patient preferences and clinical considerations, are likely to affect the suitability of any of these medications for individual patient use and thus their therapeutic application in real-world settings.

Moreover, the use of these drugs is not exempt from risk and represents an increase of costs, raising the question of what to do with those patients with low disease activity and sustained remission. Discontinuation of bDMARDs has been attempted to overcome these drawbacks (11-13), however, the results did not provide enough evidence to recommend it. Another alternative would be the optimisation of bDMARDs by dose down-titration or dose interval expansion. Although this practice is being done in routine daily clinical assistance by rheumatologists, few studies are published about patterns of optimisation and relapses after treatment (13-19). The results seem to be positive, but the designs, length of follow-up, sample size and specific bDMARDs used do not allow us to establish definitive conclusions.

The purpose of this study was to provide new insights into the long-term use of bDMARDs. Thus, we wanted to evaluate and to compare the incidence rate of optimisation and to evaluate the sustained effect after lowering dose measuring their relapses in bDMARDs in a large cohort of non-selected RA patients in clinical practice.

Methods

Setting

This study was carried out in one of the tertiary public health hospitals of the Community of Madrid (Hospital Clínico San Carlos), which covers a catchment area of approximately 400,000 people.

Design

An observational retrospective longitudinal study was conducted, with a maximum follow-up of 14 years.

Subjects

The reference population consisted of all individuals from Hospital Clínico San Carlos catchment area. Subjects included all patients attending the rheumatology outpatient clinic of our centre, with diagnosis (according to ICD-10) of RA given by their rheumatologists, aged ≥18 years and who started treatment with dDMARDs between December 31st 1999, and November 15st 2012.

Data sources

Patient data were obtained during routine clinical practice with the informed consent of patients to be treated in a service that has clinical assistance and research work. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices, and was approved by the HCSC Ethics Committee.

The investigators retrospectively reviewed all medical records to collect the variables. Medical records were realised on paper for all patients seen and followed from 1999 to December 2006. After that period, at each outpa-

tient routine visit, rheumatology patients' clinical data were registered in the information system of the electronic health record (MEDI <log>).

Variables

One main outcome was the optimisation of the different bDMARDs used. Optimisation or dose reduction was defined as at least a 15% decrease in the recommended dosage either reducing the single dose if possible or separating the dose interval administration, during at least 4 times the recommended period between dosages. The optimisation did not follow any pre-established protocol, and was performed on the consideration of each rheumatologist. The other main outcome was relapses after optimisation, defined as suspension of the bDMARDs or starting again with its recommended dose.

The following predictive and confounding factors were considered: (1) sociodemographic baseline variables including sex, age, marital status, education level (any study degree *vs*. no studies), job status (active, retired, housewife, student, unemployment), and permanent work disability. (2) Disease related variables, including the date of RA onset and diagnosis, erythrocyte sedimentation rate (ESR) (or mean value during the first year before first bDMARDs therapy), positive rheumatoid factor (RF), comorbid baseline medical conditions (defined by the rheumatologist medical judgment), DAS-28, HAQ (both defined as mean value during the first year before first bDMARDs therapy). (3) Pharmacological variables including type of bDMARDs (Anti-TNF: etanercept (Etn), golimumab (Goli), certolizumab (Ctz), infliximab (Ifx) and adalimumab (Ada); other biologics: Rituximab (Rtx), abatacept (Aba), tocilizumab (Tzl)). Moreover, we collected drugs also prescribed as follows: a) concomitant corticoids (yes or no during the first three months from the beginning of the bDMARDs); b) concomitant NSAIDs (yes= at least for three months since the start of the bDMARDs); and c) number of previous disease-modifying antirheumatic drugs (DMARDs) and also concomitant DMARDs (number during the follow-up of the study), d) Previous bDMARDs taken. (4) Calendar time: we divided the start time of each bDMARDs in 5-year intervals (from 1st Jan 1999 until 31th Dec 2003; 1st Jan 2004 to 31th Dec 2008; and 1st Jan 2009 to 15th Nov 2012).

Data analysis

A description of the sociodemographic and clinical characteristics of the patients were explored with frequency distribution and the mean and standard deviation or median and percentiles.

To evaluate dose reduction for any cause, we included all the patients with RA and to evaluate relapses only RA patients that achieved optimisation were included in the analysis. Longitudinal analysis started at the baseline visit (starting date of bDMARDs therapy) for dose reduction evaluation; and at the optimisation visit (first date when the reduced doses started) for relapses assessment. Time of exposure was conducted until the occurrence of any of the following cut off points: loss of follow-up, main outcome, or the end of the study (December 2013). Kaplan-Meier curves were set to account for optimisation and relapses over time. Incidence rates (IR) of optimisation or relapses were estimated using survival techniques (allowing for multiple-failure per patient), and results were expressed per 100 patient-years with their respective confidence interval (95%CI).

Cox bivariate analyses were done to asses differences between sociodemographic, clinical covariables and the main outcomes. Cox multivariate regression analyses were run to compare the different bDMARDs in the development of optimisation and relapses. In multivariate analysis we included age, sex, calendar time, and all variables with a $p<0.1$ in the bivariate analysis, to adjust for confounders. Results were expressed by hazard ratio (HR) and 95% CI. Proportional hazard assumption was tested using Schoenfeld residuals and the scaled Schoenfeld residuals. All analyses were performed in Stata v. 12 statistical software (Stata Corp., College Station, TX, USA). A two-tailed p-value <0.01 was considered to indicate statistical significance.

Results

443 patients with RA were included in the study, with 752 different courses of bDMARDs therapies, and a total follow up of 1,808.5 patient-years. 81% were women with a mean age at diagnosis of 52 years and a median elapsed time to the first anti-TNF of 3.8 [p25–75: 1.4–7.2] years. About a half of the patients had low educational level, 37% were still working and 5.5% had developed permanent work disability prior the starting of bDMARDs. 80% of the patients had at least one comorbid condition being hypercholesterolemia, depression, hypertension and diabetes mellitus the most prevalent ones. Most of the patients had at least moderate disease activity at the beginning of the study (mean DAS of 4.7±1.3), with a moderate level of disability (mean HAQ of 1.1±0.96). Two thirds of the patients had positive rheumatoid factor. Anti-CCP determination was available in 288 patients, of which 60% were positive.

Almost all patients (98%) were taking bMARDs at the beginning of the bDMARDs therapy, being MTX the most frequent. The mean number of previous DMARDs was 3±1, with a maximum of 7. After the starting of bDMARDs, the median number of concomitant DMARDs was 1 [p25–75: 1-2]. In relation to corticoids, 80.5% of the patients were taking this drug at the time of bDMARDs therapy, with a median dose of 5 [p25–75: 4.5–7.5]mg. 88% of the patients were taking NSAIDs at baseline. 58% of the courses did not have previous bDMARDs therapy. The bDMARDs most frequently used was Ada, followed by Etn, Ifx, and Rtx (Table I).

We observed 146 optimisations (19.5%), and most of them (90%) were related to dose interval expansion. 90-95% of the optimisations reduced by at least 20%, and half of them by 50%. IR of optimisation was estimated in 8.1 [6.8–9.5] per 100 patient-years, due to disease improvement (97%) or infections (3%). The mean elapsed time to optimisation decreased over time of bDMARDs starting (pre Dec 2003: 4.2±3.8, Jan 2004–Dec 2008: 2.9±1.6 and post Jan 2009: 1.1±0.7 years; $p<0.001$) and the IR increased over time (pre Dec 2003:

Table I. Sociodemographic and clinical characteristics at baseline.

Number of patients	443	
Female, n (%)	356	(81.1)
Age at diagnosis (years), mean ± SD	52.38 ± 13.67	
Married, n (%)	246	(62.1)
No studies or primary school, n (%)	221	(55.8)
Actives, n (%)	147	(37.5)
Permanent work disability, n (%)	22	(5.5)
Courses of BDMARDS treatment	755	
Lag time to the first bDMARDs (years) median [p25-p75]	3.76	[1.4-7.2]
ESR (mm/h), median [p25-p75]	26	[17-43]
Positive RF, n (%)	308	(72)
CCP antigen positive (n=288), n (%)	151	(60)
DAS, median [p25-p75]	4.7	[3.8-5.7]
HAQ, median [p25-p75]	1	[0.5-1.75]
Comorbid conditions (n=415),%		
Hypertension	25	
Hypercholesterolemia	50.1	
Cardiovascular disease	11.3	
Diabetes mellitus	13.9	
Depression	30	
Renal failure	5	
Chronic obstructive pulmonary disease	5	
Corticoids, %	80.5	
DMARDs, %	97.8	
Number of DMARDs before bDMARDs, median [p25-p75]	3	[2-4]
Biologic agents: (n=752), %		
Adalimumab	32.6	
Etanercept	24.7	
Infliximab	19.1	
Rituximab	14	
Abatacept	3.3	
Certolizumab	3	
Tocilizumab	2.1	
Golimumab	1.2	

Table II. Dose down-titration and relapses: incidence rates per 100 patient-years, by gender, calendar time and bDMARDs in rheumatoid arthritis patients.

	Patient-years	Events (n)	IR	95% CI	Patient-years	Events (n)	IR	95% CI
Global	1808.5	146	8.1	6.8-9.5	632.1	52	8.2	6.2-10.7
Gender:								
Men	298.2	24	8.2	6.8-9.8	106.7	9	8.4	4.3-16.2
Women	1484.8	122	8.05	5.4-12.0	525.4	43	8.2	6.0-11.0
Calendar time:								
Jan 99-Dec 03	489.6	19	3.8	2.5-6.1	171.6	9	5.2	2.7-10.1
Jan 04-Dec 08	786.0	62	7.8	6.2-10.1	286.5	28	9.7	6.7-14.1
Jan 09-Nov 12	532.8	65	12.2	9.6-15.5	174.6	15	8.6	5.2-14.2
Biologic agents:								
Adalimumab	690.6	72	10.4	8.3-13.1	297.2	24	8.1	5.4-12.0
Etanercept	408.1	39	9.6	6.9-13.1	156.3	14	8.9	5.3-15.1
Infliximab	441.5	19	4.3	2.7-6.7	128.2	13	10.1	5.8-17.4
Rituximab	176.8	8	4.5	2.3-9.0	-	-	-	-
Other TNF-α: Golimumab Certolizumab	31.3	4	12.7	4.8-34.0	5.1	1	19.5	2.7-138
Other bDMARDs: Tocilizumab Abatacept	60.1	4	6.6	2.5-17.8	-	-	-	-

3.8, Jan 2004–Dec 2008: 7.8 and post Jan 2009: 12.2; $p<0.008$). In relation to bDMARDs, 29%, 20%, 13%, 7.7%, 12.9% and 9.7% of Ada, Etn, Ifx, Rtx, Other TNF and Other bDMARDs optimised dosages during the follow-up, with an IR of 10.4 [8.2–13.1], 9.5 [6.9–13.1], 4.3 [2.7–6.7], 4.5 [2.3–9.0], 12.7 [4.8–34.1] and 6.6 [2.5–17.7], respectively (Table II; Fig. 1).

Table III displays the bivariate analysis. In relation to sociodemographic characteristics of the patient, only the job status achieved statistical significance. In disease related baseline variables patients with HAQ higher than 1.5 had 85% less probability to develop dose reduction than those with lower levels of disability. Calendar time clearly influenced in optimisation, as well as previous bDMARDs used, and the different types of bDMARDs analysed. Other factors such as comorbidity, positive rheumatoid factor, concomitant corticoids or DMARDs only achieved a trend, and they were also included in the multivariate analysis.

The multivariate analysis is shown in Table IV. Finally, it was adjusted by age, sex, calendar time, and previous bDMARDs used. The rest of variables did not fit in the final model ($p>0.1$). The HR of optimisation in Ada, Etn and Rtx compared to Ifx was 1.56 ($p=0.04$), 1.5 ($p=0.09$) and 0.6 ($p=0.3$), respectively. The HR of optimisation in Ada, Etn and Ifx compared to Rtx were 2.3 ([1.2-4.5], $p=0.014$), 2.2 ([1.2-4.3], $p=0.015$) and 1.5 ([0.7-3.2], $p=0.3$). There were no statistically significant differences between Ada compared to Etn (HR: 1.03; [0.74-1.4], $p=0.8$).

In those bDMARDs after optimisation, drug was suspended or was returned to the recommended dose in 35.6% of the cases (78% relapse due to disease activity, 14% related to adverse events mainly infections, 4% due to remission and 4% as a result of diagnosis of Cancer) in Ada (33%), Etn (36%), Ifx (68%) and Other TNFs (25%). The IR of relapses was 8.2 [6.3–10.8], and the IR seemed to be lower in the first period of time. No patients in Rtx or Tzl or Aba with optimised doses relapsed (Table II). The IR of relapse due to disease activity was 6.3 [4.6–8.6], and the median lag time was 0.8 [p25–75: 0.4–1.9] years, being for Etn 0.7 [p25–75: 0.4–2.4], for Ada 0.7 [p25–75: 0.3–1.4] years, and for Ifx 2.2 [p25–75: 0.8–4.3] years. In the survival analysis, the rate of relapse due to disease activity was 1% at 6 months, 3% at 12 months, 19% at 30 months, 30% at 5 years. 75% of the patients that relapsed due to disease activity, responded after restore treat-

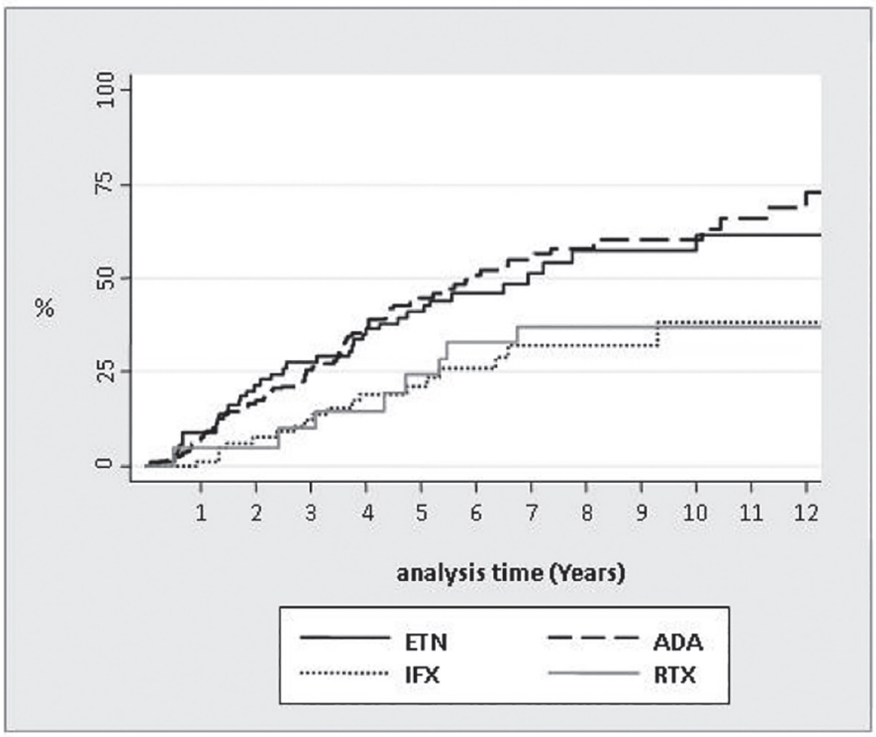

Fig. 1. Dose down-titration: Kaplan-Meier failure estimates by bDMARDs.

ment of the full dose of bDMARDs, the rest of them had to switch to other bDMARDs. The median dose of Etn, Ada and Ifx when they relapse due to disease activity was 50 mg every 1.5 [p25–75: 1.5–2] weeks, 40 mg every 3 [p25–75: 2.5–3] weeks and 3 mg/kg every 10 [p25–75: 10–10] weeks respectively.

In the bivariate analysis for relapses due to disease activity after optimisation (Table III), baseline concomitant corticoids and the presence of depression at baseline was associated with less hazards of relapses. Other variables achieved a trend of less probability such as disability, severe disease activity or taking NSAIDs at baseline. In the multivariate analysis (Table V), the final model to compare different types of bDMARDs included age, sex, calendar time, baseline concomitant corticoids and also depression. The hazard of relapses due to disease activity after optimisation increases over time, and in relation to the bDMARDs, being much lower for Ada and for Etn compared to Ifx. There were no statistically significant differences between Etn compared to Ada (HR: 1.20; [0.55–2.64], p=0.6). Proportionality of both regression models was tested using the Schoenfeld and the scaled Schoenfeld residuals. In all models, p-values were ≥0.6.

Discussion

We show the incidence of optimisation in bDMARDs and their relapses after dose down-titration or time expansion in RA patients, over time and in clinical practice. Moreover, we have also been able to compare this optimisation and their relapses due to disease activity in the different bDMARDs.

The cohort included in this study can be considered representative of the RA population in Spain (20, 21) most of them middle aged women, with mean disease duration of 10 years.

The bDMARDs are effective in treating patients with RA, but they are associated with dose-dependent adverse effects and high costs. Thus, several trials have assessed the effectiveness of optimisation or discontinuation in remission or in low disease activity patients. Discontinuation has been attempted in several studies but is seems inferior to continuation of treatment (13). Whether optimisation by dose down-titration or dose interval expansion has been studied, it is not fully established yet. Previous, mostly uncontrolled studies suggested that dose reduction of Anti-TNF could be achieved in a relevant proportion of patients with RA without loss of disease control (22-24). With regard to controlled trials, several studies have shown that in patients with remission, dose reduction of Etn was effective (14, 16, 23). Recently, a meta-analysis has been conducted, concluding that dose reduction of Etn 50 mg to 25 mg weekly, after at least three to 12 months of low disease activity, seems to be as effective as continuation of the standard dose, in terms of disease activity and functional outcomes. Nevertheless the heterogeneity between studies, the restriction to specific bDMARDs, the short follow-up and the suboptimal design choices preclude definitive conclusions (13).

Other studies have also shown that, after a clinical response to an initial course of Rtx at a dose of 1000 mg x 2, retreatment with Rtx at 1000 mg x 1 resulted in similar efficacy outcomes compared with standard doses (25). studies in ankylosing spondylitis or psoriatic arthritis reducing doses of Etn and Ada, have been show promising results (26, 27).

An observational study carried out in low disease activity RA patients treated with Ifx during one year concluded that down-titration of Ifx did not influence in quality of life (24). Moreover another concluded that it was possible to reduce doses and costs of anti-TNF agents while controlling disease activity in RA patients over a 4-year period (28). In a transversal study, patients with chronic arthritis and remission or low activity receiving low dose of bDMARDs, preserved a good control of the disease (29). Recently, González-Alvaro has published a consensus on recommendations for biologics optimisation in patients with RA, Ankylosing Spondylitis and Psoriatic Arthritis, that might help rheumatologist to improve treatment efficiency (17). However, long term safety, cost effectiveness and feasibility in clinical practice still remain uncertain.

In our study, almost 20% of the patients achieved optimisation, and most of them after one year with sustained

Table III. Dose down-titration and relapses due to disease activity: bivariate analysis.

	Dose down-titration			Relapses		
	HR	95%CI	*p*	HR	95%CI	*p*
Age, years	0.99	0.98-1.003	0.2	1.01	0.98-1.03	0.4
Gender, women	0.95	0.6-1.4	0.8	0.83	0.37-1.8	0.6
Disease duration, years	0.98	0.95-1.01	0.3	1.0	0.93-1.07	0.8
Married	1.12	0.82-1.53	0.46	0.77	0.41-1.47	0.4
No studies or primary school	1.17	0.78-1.61	0.26	1.09	0.55-2.17	0.8
Actives	1.49	1.11-1.99	0.007	1.19	0.63-2.26	0.5
Calendar time:						
Jan 09-Nov 12	1	-	-	1	-	-
Jan 04-Dec 08	0.62	0.46-0.83	0.001	0.78	0.36-1.69	0.5
Jan 99-Dec 03	0.32	0.22-0.48	0.000	0.27	0.08-0.94	0.04
Positive RF	1.27	0.9-1.7	0.15	0.88	0.4-1.7	0.7
Baseline disease activity: DAS						
Remission or Low: <3.2	1	-	-	1	-	-
Moderate: 3.2-5.1	0.9	0.47-1.7	0.7	0.16	0.01-1.67	0.12
High: 5.1	0.7	0.35-1.39	0.3	0.14	0.01-1.4	0.09
Baseline HAQ, >1.5	0.54	0.3-0.89	0.02	0.39	0.13-1.19	0.1
Comorbid conditions						
Hypertension	0.79	0.59-1.05	0.11	1.27	0.67-2.3	0.4
Hypercholesterolemia	0.97	0.72-1.3	0.8	1.07	0.57-2.01	0.8
Cardiovascular disease	0.68	0.38-1.2	0.18	0.52	0.14-1.9	0.3
Diabetes mellitus	0.91	0.59-1.3	0.6	0.95	0.3-2.3	0.9
Depression	0.83	0.59-1.16	0.28	2.2	1.13-4.27	0.019
Renal failure	1.1	0.6-1.8	0.7	1.46	0.46-4.6	0.5
Chronic obstructive pulmonary disease	1.11	0.6-2.0	0.7	1.57	0.5-4.8	0.4
Concomitant NSAIDs	0.9	0.6-1.4	0.7	4.6	0.65-33.3	0.12
Concomitant Corticoids	0.88	0.6-1.18	0.4	3.2	1.4-7.35	0.006
Concomitant DMARDs	1.15	0.99-1.33	0.06	1.15	0.8-1.6	0.4
Previous bDMARDs	0.69	0.5-0.96	0.028	1.06	0.6-1.7	0.7
bDMARDs:						
Infliximab	1	-	-	1	-	-
Adalimumab	2.37	1.5-3.7	0.000	0.96	0.45-2.02	0.9
Etanercept	2.17	1.38-3.4	0.001	1.09	0.47-2.5	0.8
Rituximab	1.1	0.5-2.2	0.7	-	-	-
Other TNF-α: Golimumab Certolizumab	3.2	1.3-7.8	0.009	2.6	0.23-30.3	0.4
Other bDMARDs: Tocilizumab Abatacept	1.4	0.5-3.8	0.4		-	-

low disease activity or remission. In a previous study, authors described a percentage of dose reduction greater than ours (29). These discrepancies might be attributable to differences in the study design and in the definition of optimisation. In fact, our study is by far more restrictive and had to be maintained over time. Similarly, optimisation was previously defined in several publications as a reduction of 10–50% (14-17, 24, 28, 30, 31). In our study, most of dose reductions were at least over 20–25%. This optimisation threshold was assigned according to common clinical practice, consisting in an initial dose reduction between 10–15%, and in accordance to the Spanish recommendations for bDMARD optimisation (17). The main cause of optimisation in our study was related to low disease activity or remission defined by rheumatologist clinical criteria. But, interestingly few of them (3%) also reduced doses due to recurrent infections (from the respiratory and urinary tract) in patients with partial disease control. These infections in addition to the risk involved in patient safety, required temporary withdrawal of the drug frequently, making the drug less effective. Lower doses in patients with not hospitalised inter current infections, are used in clinical practice as a management strategy to increase efficacy of these drugs as well as the security of the patient.

In our study the incidence rate of optimisation was estimated in 8% patient-years. The mean elapsed time to dose reduction dismissed by calendar time and the incidence increased over time. It makes sense since the emergence of more possibilities of therapeutic options as well as the current change in the management of RA patients (6, 7). Another interesting aspect that highlighted the multivariate analysis is that patients with previous biologic agents had lower probability of dose optimisation in the actual bDMARDs. Perhaps it has a relationship with the fact that the second line of biologic agents has less retention rates than the first one (32, 33).

In relation to sthe pecific type of bDMARDs, Ramirez-Herraiz *et al*. found that the mean doses used in clinical practice in TNF-alpha agents, were significantly lower with Etn than with Ada and Ifx (26). In our study, the mean doses seemed to be lower for Etn and Ada than for Rtx and Ifx. In fact after adjusting for the confounders, the hazard of optimisation was similar between Ada and Etn, and was significantly lower for Ifx and Rtx. Considering that the latest are given intravenously, the long length of follow-up, and that the definition of optimisation was related to a different time on each drug, it seems logical to discard the influence of their adherence neither its posology as the main component of these results. No other variables fit in the model.

In patients with optimised doses, 36% stopped or returned to the recommended dose mainly due to relapses of disease activity. In other studies the rate varies from 10% to 30% (14, 16, 26, 29, 30), but the different designs, patients, bDMARDs used, definition of relapses or length of follow-up makes it difficult to establish comparisons between them. We did not find any minimal doses of optimisation that favoured relapses, but interestingly no patients in Rtx relapsed, and Ifx did with the highest hazard compared to Ada or Etn. We also showed that the incidence rate of relapses seemed to be constant from 2004, maybe related to the emergence of the tight control approach. Finally, consistent with the majority of the studies, most of the relapsing patients

Table IV. Multivariate Cox regression analysis, comparing risk of dose down-titration between bDMARDs.

	HR	95%CI	*p*
Age, years	0.99	0.98-1.004	0.3
Gender, women	1.02	0.7-1.5	0.8
Calendar time:			
Jan 09-Nov 12	1	-	-
Jan 04-Dec 08	0.51	0.38-0.69	0.000
Jan 99-Dec 03	0.25	0.16-0.4	0.000
Previous bDMARDs (yes)	0.5	0.36-0.77	0.001
bDMARDs:			
Infliximab	1	-	-
Adalimumab	1.56	1.01-2.4	0.04
Etanercept	1.5	0.9-2.4	0.09
Rituximab	0.6	0.3-1.4	0.3
Other TNF-α: Golimumab Certolizumab	1.8	0.7-4.8	0.2
Other bDMARDs: Tocilizumab Abatacept	0.9	0.3-2.6	0.8

Table V. Multivariate Cox regression analysis, comparing risk of relapses due to disease activity after dose down-titration between bDMARDs.

	HR	95%CI	*p*
Age, years	1.01	0.98-1.04	0.3
Gender, women	1.15	0.39-3.4	0.7
Calendar time:			
Jan 09-Nov 12	1	-	-
Jan 04-Dec 08	0.47	0.17-1.26	0.11
Jan 99-Dec 03	0.1	0.03-0.38	0.001
Depression	1.89	0.79-4.53	0.1
Concomitant corticoids	2.02	0.73-5.5	0.1
bDMARDs:			
Infliximab	1	-	-
Adalimumab	0.38	0.18-0.84	0.017
Etanercept	0.32	0.12-0.81	0.017
Rituximab	-	-	-
Other TNF-α: Golimumab Certolizumab	0.63	0. 05-7.5	0.7
Other bDMARDs: Tocilizumab Abatacept	-	-	-

responded after full dose restoration of bDMARDs (13, 30). Interestingly, depression was associated with less hazards of relapses. It may be due to the worsening of patient (including subjective part of DAS28) could be associated to the depressive comorbidity and not to a failure of the bDMARDs

The study has several limitations. One important question would be the role of DMARDs in optimisation. We did not see specifically the effect of DMARDs on this, but we have adjusted in the analysis for the number of concomitants DMARDs the patients were taking. Another limitation is the follow-up length for some of the bDMARDs, mainly in those commercialised more recently. It would be more desirable to measure disease activity with and objective measure than to use the clinical judgement of the rheumatologist translated from the written medical records. We have to take into account that this is a retrospective study, from clinical practice, and specifically DAS28 is only collected at baseline and once a year independently the regimen of therapy in our RA patients.

An important strength is that this study reflects the 'real world' experience, also provides a long follow-up strength of most anti-TNF and Rtx, it is performed in non-selected patients, and takes into account many covariates on multiple potential confounders.

We have shown that the optimisation is a feasible approach and it is used in clinical practice. Rheumatologist optimised doses when improvement or remission of disease is achieved, but also as a strategy to control interrecurrent infections both to maintain efficacy and patient safety. We also conducted a direct comparison on optimisation and relapses related to the different bDMARDs, demonstrating marked differences. Relapses appeared after that in some patients, mainly due to disease activity, but most of them responded after full dose restoration of bDMARDs. Possible benefits of this management include a substantial reduction in costs and possible reduction in dose-dependent side effects.

Key messages

- bDMARD optimisation is a feasible approach and it is used in clinical practice.
- Hazard of optimisation was similar between Ada and Etn, and lower for Ifx and Rtx.
- Relapses of optimisation were higher for Ifx compared to Ada or Etn.

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