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Optimization of biological therapy in rheumatoid arthritis patients: outcomes from the CREATE registry after 2 years of follow-up

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Abstract The current strategy for managing rheumatoid arthritis (RA) focuses on achieving clinical remission. Once remission is achieved and sustained over time, the most efficient strategy is dose optimization. This work describes the results of dose optimization after 2 years of follow-up in patients with RA treated with biological therapy and identifies predictive variables of response. Cohort: patients from the CREATE registry who, as of 1 November 2013, had been in clinical remission (DAS28 $\leq$2.6) for at least 6 months. Intervention: Dose optimization was 20–50% of the standard dose. Outcome measurement were effectiveness (percentage of patients who continued to meet criteria for clinical remission) and efficiency (dose reduction and mean savings). Sixty-eight patients with RA were optimized, with initial mean DAS28 of 2.2 $\pm$ 0.7. After 2 years of follow-up, the mean DAS28 was 2.4 $\pm$ 0.7, a non-statistically significant difference. Twenty-eight patients (41.2%) continued in clinical remission with dose optimization after 2 years. Mean survival time was 14.2 months (95% CI 12.0–16.5). Of the 40 patients who needed to return to a standard dose, 57.5% managed to achieve remission again at 2 years. Mean dose reduction at 2 years was 21.17%, reaching a mean saving of €5576 $\pm$ 5099 per patient. In actual clinical practice, over 40% of patients with established RA who had been in sustained clinical remission managed to continue in remission 2 years after receiving optimized doses. The savings achieved was about 21% of the actual direct health costs for patients in the CREATE registry.

Keywords Rheumatoid arthritis · Clinical remission · Biological therapy · Optimization · Cost-effectiveness · Real clinical practice

Introduction

Biological therapy (BT) is the most important recent advance in the treatment of rheumatoid arthritis (RA) and is helping to modify its prognosis. RA treatment aims to control pain and inflammation, reduce joint damage and disability to the extent possible, control extra-articular manifestations, improve patients' quality of life, and achieve disease remission, or at least sustained low disease activity [1, 2]. The data available from registries of treatment with biological drugs in RA show that clinical remission is achieved in 19–39% of patients [3, 4].

Despite evidence of its efficacy and effectiveness, BT is costly and is not without risks and potential adverse effects. These facts have led to questions about how to manage this type of treatment once the patient has achieved sustained remission over time [5].

Data available from clinical trials and other studies have shown that discontinuing treatment in patients with early RA results in relapse rates of 40–75% [6–12]. Alternatively, for patients with established RA, dose reduction has been suggested as a potentially efficient management strategy [6, 13, 14].

In this regard, the Spanish Societies of Clinical Rheumatology and Hospital Pharmacy have developed a consensus document with recommendations for the management

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of patients in clinical remission [15]. This document suggests that a 20–50% dose reduction is possible in patients with RA who reach and maintain their therapeutic goal for more than 6 months. It also proposes strategies for managing relapses, all with the objective of reducing variability in clinical practice.

The objective of this study was to evaluate the effectiveness and efficiency in routine clinical practice of dose reduction in RA patients in sustained clinical remission. The secondary objectives were to identify predictive variables of response to optimization.

Methods

Patients

The data for this study were taken from the registry of the Multidisciplinary Team for RA in Cordoba (CREATE registry) [16] and included patients diagnosed with RA according to 1987/2010 criteria of the American College of Rheumatology. All patients were evaluated by conducting a clinical history, physical examination, complementary laboratory tests (hemogram, biochemistry, presence of antibodies), and radiographs of the chest, hands and feet. Disease activity was assessed by the clinician using the Disease Activity Index on 28 joints (DAS28). The CREATE Registry is a database which systematically and prospectively includes all patients with inflammatory rheumatic disease who begin treatment with BT. All patients must follow the Andalusian Health Service treatment protocol for BT, based on the recommendations of the Spanish Society of Rheumatology [1] and the European League Against Rheumatism [2]. Patients beginning BT had to have active RA despite treatment for at least 3 months with at least two of the following drugs at the maximum authorized doses: methotrexate, leflunomide, or sulfasalazine. The initial BT is selected based on the characteristics of each patient and drug, as well as the cost of each drug to the hospital. In the absence of any limiting constraints (inability to attend the day hospital or to self-administer treatment, or presence of intestinal inflammatory disease for which biological treatment with infliximab, adalimumab or golimumab are indicated), the lowest cost drug was used.

For each patient included, data are collected on demographics, disease characteristics, previous treatments used, duration and reason for withdrawal, current treatment and its duration, disease activity [number of tender joints (NTJ), number of swollen joints (NSJ), erythrocyte sedimentation rate (ESR) (mm/1 h) and C-reactive protein (CRP) (mg/L)], DAS28, patient-related information that could condition treatment, biological drug chosen and concomitant treatment. Each patient included is followed prospectively, with information on the evolution of the clinical variables registered at 6 months and then annually thereafter.

From this CREATE registry, we selected for the study the subpopulation of patients treated with any TNF antagonist, tocilizumab and abatacept, who on 1 November 2013 had been in sustained clinical remission (DAS28 $\leq$2.6) for at least 6 months. Exceptionally, patients with DAS28 >2.6 were included if they were assessed by the physician as being in clinical remission and agreed to participate (this occurred in some cases with DAS28 >2.6 resulting from an elevated score on the visual analogue scale, ESR or CRP due to diseases other than RA, but after sustained reduction of the number of painful and swollen joints to zero). All patients were followed prospectively for 2 years.

Decisions on treatment and dose reduction of BT were made by a multidisciplinary team comprised of rheumatologists and clinical pharmacists in a tertiary level hospital. This involved the application of protocols and patient follow-up at least every 2 months. In accordance with the consensus of the Spanish Societies of Rheumatology and Hospital Pharmacy, dose optimization refers to reduction of 20–50% of the dosage by lengthening the interval between doses of BT. This criterion was applied in accordance with the BT used and the response achieved (Table 1). Concomitant treatment was maintained.

Table 1 Dose optimization by drug

Drug	Standard dose	Optimization 1	Optimization 2
Infliximab	3 mg/kg/8 weeks	3 mg/kg/9 weeks	3 mg/kg/10 weeks
Etanercept	50 mg/7 days	50 mg/10 days	50 mg/14 days
Adalimumab	40 mg/2 weeks	40 mg/3 weeks	40 mg/4 weeks
Golimumab	50 mg/month	50 mg/5 weeks	50 mg/6 weeks
Tocilizumab	8 mg/kg/4 weeks	4 mg/kg/5 weeks	4 mg/kg/6 weeks
Abatacept	(Dosage by weight: 500 mg/750 mg/1 g)/4 weeks	(Dosage by weight: 500 mg/750 mg/1 g)/5 weeks	(Dosage by weight: 500 mg/750 mg/1 g)/6 weeks
Certolizumab Pegol	200 mg/2 weeks	200 mg/3 weeks	200 mg/4 weeks

If the DAS28 exceeded 2.6 during follow-up, and with the patients' consent, they returned to the treatment regimen that immediately preceded this change.

Effectiveness

The effectiveness of treatment in actual clinical practice was evaluated by the DAS28 [17]. A value lower than 2.6 was considered clinical remission. We evaluated the outcome after 2 years of dose optimization, taking into account the DAS28 after the first year and the percentage of patients who remained in clinical remission. We also evaluated the time to relapse (failure of dose optimization).

Costs

The cost analysis was made from the perspective of the healthcare system, considering the cost of purchasing the drug, using the official ex-factory price (EFP).

Drug use was obtained from the databases of the Pharmacy Service. In the cases of infliximab, tocilizumab and abatacept, which are dosed by weight, the cost was adjusted to the milligrammes actually used since the fact that they are prepared in the Pharmacy Service makes it possible to avoid drug wastage.

Efficiency

To estimate the savings in doses, we quantified the total dose actually received per year and divided it by the annual overall dose that would have been used according to the standard guidelines in the product specifications.

Efficiency was estimated by considering the effectiveness (percentage of patients who remained in clinical remission after the first year) and the cost savings based on the dose reduction achieved.

Statistical analysis

A descriptive study was conducted, calculating the mean and standard deviation for quantitative variables, and absolute and relative frequencies for qualitative variables. An intention-to-treat analysis was made for each treatment branch.

The bivariate analysis of quantitative variables was made using the one-way ANOVA test and mixed ANOVA. Post hoc comparisons were conducted using the Hochberg or Games–Howell tests. We used the log-rank test to compare the survival curves for the different drugs optimized.

Different univariate logistic regression analyses were made considering as the main variable relapse after one year of optimization (no/yes), and as potentially predictive variables: initial DAS28, anti tumour necrosis factor (TNF) (no, yes), use of disease-modifying antirheumatic drugs (DMARDs) (no, yes), previous BT (no, yes) and previous time in remission (<12 months, ≥12 months). The degree of association was estimated by the odds ratio (OR) and Cornfield's 95% confidence interval.

We also conducted univariate Cox regression analyses taking as the main variable the time to relapse (months). The degree of association was estimated by the hazard ratio (HR) and Cornfield's 95% confidence interval.

All comparisons were two-sided and were considered significant for values of $p < 0.05$. The data were processed, tabulated and analysed using SPSS v17 software.

The study meets the requirements of the WHO Guidelines for Good Clinical Practice, the principles of the Declaration of Helsinki, and SAS Order 347/2009 of 16 December, which develops guidelines for observational post-authorization studies for medicinal products for human use in Spain.

Patient data were coded to maintain their anonymity in the study and to protect their identity from third parties. The study was approved by the Ethics Committee of the Reina Sofiá University Hospital of Córdoba.

Results

This observational prospective study included a total of 68 patients with RA who, on 1 November 2013, had been in clinical remission for at least 6 months. The baseline characteristics of these patients are shown in Table 2. Mean DAS28 of these patients at the beginning of optimization was 2.2 ± 0.7. Prednisone daily mean dose received was 5.56 ± 1.44 mg.

Effectiveness

Considering all the patients included, two years after beginning dose optimization, no significant difference was found between initial mean DAS28 (2.23 ± 0.72) and mean DAS28 at 2 years (2.43 ± 0.72). However, the mean DAS28 after the first year was significantly higher than the baseline value (Table 3).

These results were similar for the subgroup of patients who relapsed and returned to standard dose. In this subgroup of patients, the mean DAS28 after the first year was also significantly higher than the baseline value, even >2.6 (2.80 ± 0.13), though returned to 2.6 at the second year.

Nevertheless no significant differences between DAS28 at baseline and the score at the first or second year were seen in the subgroup of patients who did not relapse.

Two year after beginning dose optimization, 28 patients (41.2%) continued with optimized doses.

Table 2 Baseline patient characteristics ($n = 68$)

Characteristics	*N* (%) or mean ± SD
Sex (female)	56 (82.4)
RF +	43/62 (69.4)
Age at optimization (years)	57.04 ± 13.92
Weight (kg)	82.14 ± 19.68
Age at diagnosis (years)	43.54 ± 12.26
Time since diagnosis (years)	13.76 ± 8.20
Initial DAS28	2.23 ± 0.72
Initial NTJ 28	0.94 ± 1.40
Initial NSJ28	0.32 ± 0.85
Initial ESR (mm/1ªh)	14.91 ± 12.68
Initial CRP (mg/L)	4.00 ± 6.46
Initial PGA (cm)	35.91 ± 18.21
Mean time of BT treatment (years)	3.73 ± 2.75
Mean time of remission at baseline (months)	18.39 ± 18.75
Type of biological drug *n* (%)	
TNF antagonists	
Infliximab	10 (14.7)
Etanercept	25 (36.8)
Adalimumab	10 (14.7)
Golimumab	3 (4.4)
Certolizumab	1 (1.5)
Abatacept	7 (10.3)
Tocilizumab	12 (17.6)
Concomitant treatment	
Methotrexate	26 (38.2)
Leflunomide	25 (36.8)
Corticosteroids	53 (77.9)
Sulfasalazine	4 (5.9)
Number of previous biological treatments	
None	48 (70.6)
One	12 (17.6)
Two	4 (5.9)
More than two	4 (5.9)

BT biological therapy, *CRP* C-reactive protein, *DAS* disease activity index, *ESR* erythrocyte sedimentation rate, *NST* number of swollen joints, *NTJ* number of tender joints, *PGA* patient global assessment, *RF* rheumatoid factor, *TNF* tumour necrosis factor

The mean survival time was 14.2 months (95% CI 12.0–16.5) and median survival time was 14.3 months (95% CI 4.5–24.0).

As seen in Fig. 1, no significant differences were seen among the survival curves for each drug [(Log-Rank test (Mantel-Cox), $p = 0.20$].

Of the 40 patients who needed to return to a standard dose before the second year, 23 of them (57.5%) again reached remission, and 13 more achieved at least low disease activity. Thus, 36/40 of the patients (90%) achieved either remission or at least low disease activity after returning to a standard dose (Fig. 2).

Efficiency

Table 4 presents the variables for overall effectiveness and efficiency by optimized drug. Taking into account that patients who failed BT returned to a standard dose, the overall mean dose reduction of BT at 2 years and so, the mean savings obtained was 21.17%. Mean savings per patient at 2 years was €5,576 ± 5,099.

In comparing the results shown in Table 4, it can be observed that in the first year, the mean difference in savings is statistically significant for adalimumab over infliximab (€3577 ± 1195; $p = 0.038$). In the second year, no differences were found among drugs. Overall at 2 years, significant differences were found again in mean savings in favour of adalimumab over infliximab (€7143 ± 2134; $p = 0.014$), with no differences seen in the baseline clinical or demographic characteristics in these groups of drugs.

Patients were analysed in two groups based on the type of optimized drug: antiTNF drug (infliximab, etanercept, adalimumab, golimumab and certolizumab pegol) and non-antiTNF drug (tocilizumab, abatacept). No statistically significant differences were found in the comparison of either the baseline clinical-demographic characteristics or in the variables of effectiveness or efficiency described.

Lastly, results of the logistic regression show that DAS28 was the only predictive factor of relapse at 2 years (OR = 2.96; 95% CI = 1.34–6.52), $p = 0.007$. Similar results were obtained from the univariate Cox regression analyses, which also shows that DAS28 as the only predictive factor of time to relapse at 2 years (HR 2.03; 95% CI 1.254–3.31), $p = 0.004$. It was not possible to adjust a significant univariate model in either of the two types of analysis.

Discussion

In this study of patients with established RA, we evaluated the effectiveness and efficiency of a strategy of dose optimization, lengthening the interval between doses of BT in patients in clinical remission for at least 6 months. Different strategies have been considered for the management of these patients. In the case of patients with established RA, data from published studies indicate that suspension of the biologic leads to relapses in 50–90% within a year, and therefore, the option of reducing the dose or lengthening the interval between doses may be more effective and efficient [18, 19].

Our results suggest that remission can be maintained at 2 years with an optimized dose in 40% of patients. Some 32.5% of those who go back to a standard dose achieve remission in 1 year. Another 50% of patients do not achieve remission but do achieve at least low disease activity.

Table 3 Effectiveness at 2 years according to DAS28

Population	Initial DAS28 (mean ± SD)	DAS28 at 1 year (mean ± SD)	DAS28 at 2 years (mean ± SD)	Difference at 2 years (mean ± SD)	*P*
Total ($n = 68$) All optimized patients	2.23 ± 0.72	2.55 ± 0.86	2.43 ± 0.72	Initial vs. 1 year: −0.32 ± 0.82	0.006
				Initial vs. 2 years: −0.20 ± 0.82	0.146
				1 year vs. 2 years: 0.12 ± 0.82	0.592
No relapse ($n = 28$) Remission maintained	1.93 ± 0.12	2.21 ± 0.15	2.19 ± 0.13	Initial vs. 1 year: −0.28 ± 1.32	0.235
				Initial vs. 2 years: −0.26 ± 1.32	0.268
				1 year vs. 2 years: 0.014 ± 1.40	1.000
Relapsed ($n = 40$) Remission not maintained: returned to standard dose	2.44 ± 0.11	2.80 ± 0.13	2.60 ± 0.11	Initial vs. 1 year: −0.36 ± 1.07	0.027
				Initial vs. 2 years: −0.15 ± 1.07	0.568
				1 year vs. 2 years: 0.203 ± 1.15	0.411

DAS disease activity index, *SD* standard deviation

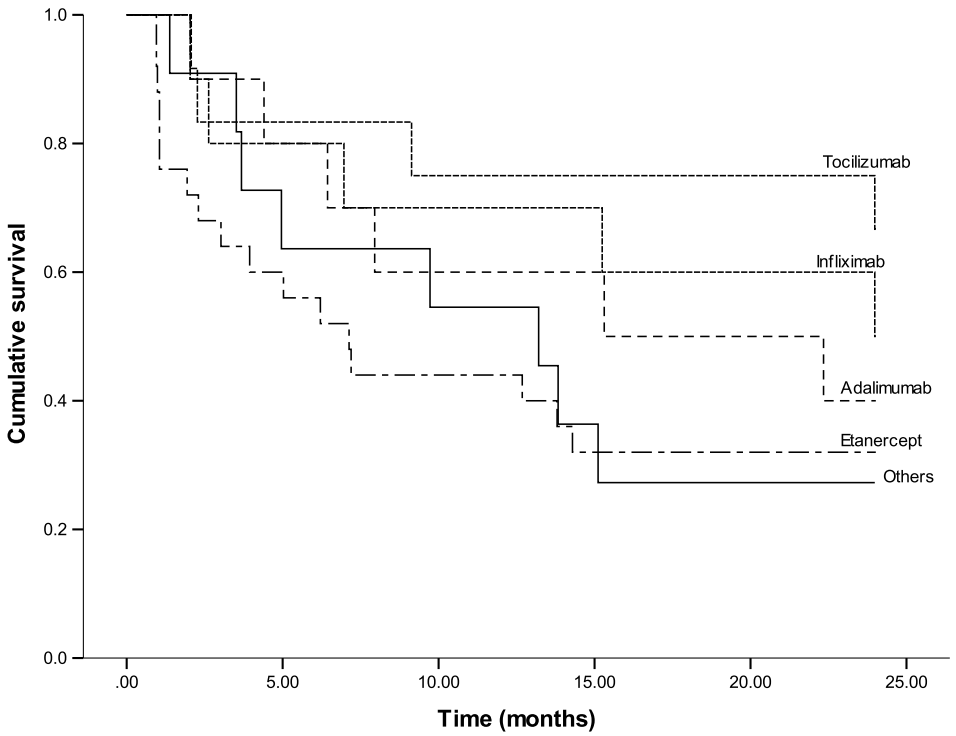

Fig. 1 Survival curves for each drug

These results are similar to those published by van Vollehoven et al. [20] in patients with established RA treated with etanercept. In that study, conducted in the framework of a clinical trial and after having achieved at least low disease activity, patients were randomized to maintain their dosage, reduce it by half (optimized dose) or receive placebo, always in association with methotrexate. At week 48, 44% of patients in the optimized dose arm had not failed optimization. In our work, the etanercept group showed a similar result at one year, although our initial guideline for optimization was etanercept at 50 mg/10 days, changing to etanercept 50 mg/2 weeks,

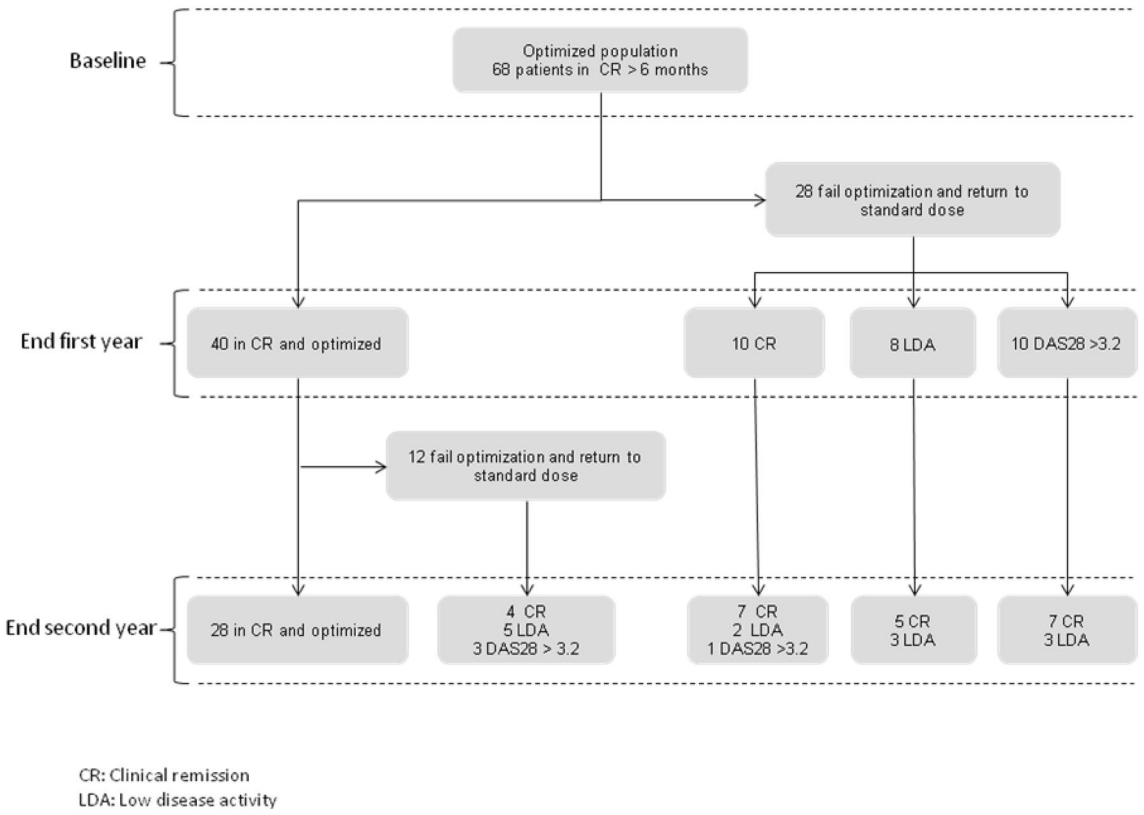

Fig. 2 Effectiveness flowchart

Table 4 Comparison of effectiveness and efficiency outcomes

	Total	Infliximab	Etanercept	Adalimumab	Tocilizumab	Others[a]
N	68	10	25	10	12	11
N (%) patients optimized at 1 year	39 (57.4)	7 (70)	11 (44)	6 (60)	9 (75)	6 (54.6)
N (%) patients optimized at 2 years	28 (41.2)	5 (50)	8 (32)	4 (40)	8 (66.7)	3 (27.3)
Mean time of optimization (months, 95% CI)	14.2 (12.0–16.5)	17.1 (11.5–22.7)	11.0 (7.2–14.8)	15.5 (10.0–90.9)	19.1 (14.3–24.0)	12.5 (7.6–17.4)
Mean savings first year (euros) (mean ± SD)	3348 ± 2790	1359 ± 980	3457 ± 2892	4937 ± 1859	3889 ± 2660	2861 ± 3631
Mean savings second year (euros) (mean ± SD)	2228 ± 2877	841 ± 989	1970 ± 3060	4407 ± 3816	3084 ± 2497	1163 ± 1782
Mean savings at 2 years (euros) (mean ± SD)	5576 ± 5099	2201 ± 1420	5427 ± 5369	9344 ± 4721	6984 ± 4916	4024 ± 5089
% savings on cost at 2 years (mean ± SD)	21.17 ± 18.28	11.45 ± 6.46	22.43 ± 22.42	33.52 ± 15.56	22.22 ± 13.23	14.75 ± 16.96

SD standard deviation

[a] Others: golimumab, abatacept and certolizumab

depending on the outcome obtained. However, our results differ from the optimization results in the DRESS study [21], in which both etanercept and adalimumab achieved better outcomes at 18 months with dose optimization in a population apparently similar to those in the CREATE registry.

This study has several limitations. First, since it was observational, it was an open and non-randomized study. Another limitation is that it was conducted in only one centre, thus the sample size was not large. However, the fact that it was a single centre has some advantages, such as homogeneity in the application of the protocols established

in the optimization strategy, as well as its database, the CREATE registry. Furthermore, an observational design is the type of study recommended to advance our knowledge of real-life cost-effectiveness [22].

The difference between the mean initial and final DAS28 in the total population was similar at 2 years, between 1 and 2 years, as was also the case in the patient subgroups that did and did not relapse.

Nevertheless, there was a significant difference between the mean DAS28 at baseline and at 1 year in the total population and in the subgroup of patients that relapsed, although it was not significant between baseline and 2 years, nor between 1 and 2 years. This indicates that clinical improvement is achieved by returning to the standard dose, and most patients regained clinical remission or at least achieved low disease activity in the period analysed by returning to standard dose. These data confirm this strategy would be a more suitable alternative than withdrawal of the drug to manage patients in clinical remission with established rheumatoid arthritis. A longer follow-up period would make it possible to know how many finally achieve clinical remission.

With regard to efficiency, the response to optimization was not similar in all drugs. Quantitatively, and after 2 years, tocilizumab appears to be the most efficient means of optimization in actual clinical practice. The number of patients treated with an optimized dose declined over time in all the drugs studied. The effect on savings differed due to the various possible ways to correct optimized doses.

In our case, the only significant difference for savings at 2 years was between adalimumab and infliximab. Adalimumab was also shown to be the most effective and efficient in achieving clinical remission at 2 years in another observational study of patients in the CREATE registry [23].

The only significant association in the statistical analysis was between the initial DAS28 value and relapse at 1 year. The results for the rest of the variables analysed did not reach statistical significance; for this reason, whether or not an antiTNF is used does not appear to be a decisive factor in achieving optimization. However, the small sample size limits our ability to reach conclusions on this point. Likewise, no differences were found when considering patients with 12 months previous remission, which would support current recommendations [14] that 6 months is the minimum time needed to begin dose optimization.

Conclusions

Dose optimization of BT in patients with established RA who achieve clinical remission is an efficient strategy in clinical practice, with clinical remission maintained in 40% of patients who received optimized doses after 2 years. Most patients who need to return to a standard dose again achieve clinical remission or at least low disease activity. Initial DAS28 is associated with maintenance of the optimized dose over time.

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Compliance with ethical standards

The study meets the standards of Good Clinical Practice, the principles of the Declaration of Helsinki and Order SAS 347/2009 of December 16, which develops guidelines on observational post-authorization studies for drugs used in humans in Spain. Patient data are coded to maintain anonymity in the study and to prevent their identification by third parties. The study was approved by the Ethical Committee of the Reina Sofia University Hospital of Cordoba.

Conflict of interest Cárdenas M, Font P, Castro-Villegas and Collantes-Estévez E, report grants, consulting fees, or lecture fees from MSD, Pfizer or AbbVie, none of which were related to the present work. De la Fuente S, Romero-Alonso M, Calvo-Gutiérrez J, Escudero-Contreras A and Del Prado JR have no conflict of interest.

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