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Cost-effectiveness of clinical remission by treat to target strategy in established rheumatoid arthritis: results of the CREATE registry

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Abstract To analyse the cost-effectiveness, in daily clinical practice, of the strategy of treating to the target of clinical remission (CR) in patients with established rheumatoid arthritis (RA), after 2 years of treatment with biological therapy. Adult patients with established RA were treated with biological therapy and followed up for 2 years by a multidisciplinary team responsible for their clinical management. Treatment effectiveness was evaluated by the DAS28 score. The direct costs incurred during this period were quantified from the perspective of the healthcare system. We calculated the cost-effectiveness of obtaining a DAS28 < 2.6, considered as CR. The study included 144 RA patients treated with biological therapies. After 2 years of treatment, 32.6% of patients achieved CR. The mean cost of achieving CR at 2 years was 79,681 ± 38,880 euros. The strategy of treatment to the target of CR is considered the most effective, but in actual clinical practice in patients with established RA, it has a high cost.

Keywords Rheumatoid arthritis · Treat to target · Clinical remission · Cost-effectiveness · Biological drugs · Real clinical practice

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Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterised by pain, chronic inflammation, and joint destruction. In most cases, the progressive course of the disease leads to irreversible joint damage, functional impairment, reduced quality of life, and premature mortality. RA is estimated to affect 1% of the adult population [1, 2].

The general objective of RA treatment consists of controlling pain and inflammation, minimising joint damage and disability, controlling extra-articular manifestations, improving patients' quality of life, and achieving disease remission, or at least sustained low clinical activity [3].

Nowadays a strong current of opinion advocates addressing RA management by a treatment strategy based on "treat to target" (T2T), whose key points are establishment of concrete objectives, close patient follow-up, monitoring of disease activity, and adjustment of treatment in accordance with established protocols [4, 5].

Clinical trials and observational studies have shown that this strategy is more efficacious and effective than standard treatment to reduce disease activity and to achieve the target of clinical remission (CR) [5–7]. This strategy requires an additional investment of resources, but has been shown to be cost-effective beginning in the third year, as compared to maintaining a strategy of standard treatment and monitoring, when applied to patients with early RA [8]).

In patients with persistent established RA after treatment with at least two of the classic disease-modifying antirheumatic drugs (DMARDs) and a DAS28 value >5.1, the use of biological therapy is recommended [9]. However, due to the lack of sufficient clinical evidence, no agreements have been reached on essential points involved in T2T, such as intensive treatment with biological therapy or whether the objective should be to reach CR [10].

Given the current economic crisis and the need to adjust healthcare budgets, it is desirable to know the cost-effectiveness of the strategy developed in real clinical practice and from the hospital perspective, in order to select the one that can best fit the available budget achieving the best possible health outcomes. So, the objective of this study is to analyse the clinical effectiveness and cost-effectiveness of the T2T strategy in achieving CR in actual clinical practice in patients with established RA after 2 years of treatment with biological therapy, a further analysis of the CREATE registry [11].

Methods

Patients

The data for this study were taken from the cohort of patients included in the Córdoba Rheumatoid Arthritis Team (CREATE) registry [11], made up of patients diagnosed with established RA who began treatment with biologicals in the Reina Sofía University Hospital between 1 January 2007 and 31 December 2012, who had at least 2-year follow-up of their progress and no missing data.

The CREATE registry is a prospective database that systematically includes each patient with inflammatory rheumatoid disease who begins treatment with biological therapy. For each patient diagnosed with RA, information is collected on demographics, disease characteristics, previous treatments used, their duration and reason for suspension, current treatment and its duration, disease activity [number of tender joints (NTJ), number of swollen joints (NSJ), erythrocyte sedimentation rate (ESR), C-reactive protein (PCR), and the Disease Activity Score (DAS28)], patient data that could influence treatment, biological drug chosen, and concomitant treatment. Each patient is followed up prospectively to monitor the clinical variables collected and any adverse effects that may occur.

RA is diagnosed in accordance with the 1987/2010 ACR criteria, based on the medical history, physical examination, complementary tests, chest and joint radiography, and clinical assessment of disease activity using the DAS28.

All the patients had to fulfil the requirements of the treatment protocol developed jointly by the Departments of Clinical Rheumatology and Hospital Pharmacy and approved by Hospital Management. This protocol is based on the recommendations of the Spanish Society of Rheumatology (SER) [12] and the European League against Rheumatism (EULAR) [3] and approves beginning treatment with biological therapy for patients with active RA (DAS28 > 5.1) despite at least 3-month treatment with at least two of the following drugs at the maximum authorised doses: methotrexate, leflunomide or sulfasalazine.

Treatment decisions

The treatment decisions for these patients followed a model of clinical management based on efficiency, in which a multidisciplinary team of rheumatologists and clinical pharmacists shares responsibilities related to the objectives of health costs and outcomes.

The multidisciplinary team meets monthly to review patients with established RA who are eligible to begin treatment with biologicals, and to monitor those in active treatment. The choice of biological treatment is based on patient characteristics and the evidence on the efficiency of each drug.

The T2T strategy of remission (DAS28 < 2.6) was applied to all patients. This involves application of standardised treatment protocols to achieve this objective, and review and follow-up of all patients at least every 2 months.

Outcome variable

The outcomes of the T2T strategy were evaluated based on the DAS28 score [13]. In accordance with this scale, treatment was considered to be effective if the patient achieved a DAS28 value of less than 2.6 and maintained it by the end of 2 years.

Variables of resources used and costs

For the cost analysis, we considered the health system perspective, taking into account the use of the following direct healthcare resources: cost of purchasing the drugs [ex-factory price (EFP)], specialist consultations in Rheumatology and other clinical Services, emergency care, complementary tests performed, need for hospitalisation, and use of the day hospital for intravenous drug administration.

Drug use was obtained from the databases of the Pharmacy Department. For drugs dosed based on weight (infliximab, abatacept, and tocilizumab), the cost was adjusted to the milligrams actually used since individual doses were prepared in the Pharmacy Department, making it possible to avoid drug wastage. The remaining resources consumed were obtained from the database of the reports manager of the Reina Sofía University Hospital.

The cost of each drug was obtained using the official EFP, and the cost of the rest of the resources used was obtained from the price catalogue of the Economics Directorate of the Reina Sofía University Hospital (2014, in euros).

A sensitivity analysis to estimate cost-effectiveness from a social perspective was made considering indirect and nonmedical costs published in similar hospitals, regions, and patients characteristics [14, 15].

Table 1 Baseline characteristics of patients in the total sample and by DAS28 outcomes

Baseline characteristics	Total	DAS28 achieved and maintained at 2 years		*p*
		DAS28 ≤ 2.6	DAS28 > 2.6	
n (%)	144 (100%)	47 (32.6%)	97 (67.4%)	–
Sex (female)	80.6%	70.2%	85.6%	0.085
RF + (%, *n*/*N*)	72.2% (104/144)	70.2% (33/47)	73.2% (71/97)	0.708
AntiCCP + (%, *n*/*N*)	74.2% (72/97)	78.1% (25/32)	72.3% (47/65)	0.538
Age (years)[a]	53.43 ± 13.32	50.43 ± 13.77	54.88 ± 12.93	0.186
Weight (kg)[a]	75.85 ± 15.96	76.76 ± 15.96	75.39 ± 16.14	0.751
Age at diagnosis (years)[a]	44.21 ± 13.35	40.79 ± 13.03	45.87 ± 13.25	0.085
Time since diagnosis (years)[a]	9.21 ± 7.50	9.15 ± 7.60	9.24 ± 7.49	0.948
Initial DAS28[a]	5.69 ± 1.00	5.50 ± 1.03	5.79 ± 0.98	0.107
Initial NTJ28[a]	10.32 ± 6.35	10.23 ± 6.25	10.36 ± 6.42	0.911
Initial NSJ28[a]	7.08 ± 4.92	7.32 ± 4.93	6.96 ± 4.93	0.682
Initial ESR[a]	33.01 ± 17.78	26.87 ± 17.20	36.07 ± 17.35	0.085
Initial CRP[a]	19.42 ± 17.94	18.03 ± 19.30	20.12 ± 17.28	0.517
Initial PGA[a]	69.91 ± 16.73	68.85 ± 14.78	70.43 ± 17.68	0.598

Quantitative variables: comparison of means by independent "*t*" Student test and Finner's test adjusted *p*

Qualitative variables: Contingency table with significance according to Pearson's Chi-square and Finner's test adjusted *p*

RF+ positive rheumatoid factor, *AntiCCP*+ positive anti-cyclic citrullinated peptide antibody, *DAS28* disease activity score on 28 joints, *NTJ28* number of tender joints on 28 joints, *NSJ28* number of swollen joints on 28 joints, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *PGA* Patient Global Assessment

[a] Data expressed as mean ± standard deviation

Cost-effectiveness analysis

To calculate cost-effectiveness, the mean total cost for each patient was divided by the percentage of patients who achieved the outcome variable. The mean and standard deviation (SD) of this value were calculated to show the mean cost per patient to achieve CR.

A descriptive analysis was performed by calculating the absolute and relative frequencies for the qualitative variables, and the arithmetic mean and standard deviation for the quantitative variables.

Ethics

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-authorisation 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.

Results

During the study period, 144 patients met the inclusion criteria. Of these, 55 were treated with infliximab, 44 with etanercept, 31 with adalimumab, 4 with tocilizumab, 4 with golimumab, 3 with abatacept, 2 with certolizumab, and 1 with rituximab. The baseline characteristics of the patients for the overall sample are shown in Table 1.

Effectiveness

After completing 2 years of treatment, 47 patients (32.6%) achieved and maintained CR. No differences in baseline characteristics were found between patients who did and did not achieve CR at 2 years. Mean ± SD DAS28 at 2 years in patients achieving CR was 2.10 ± 0.43 (95% CI 0.40–2.60) and was similar for each biological therapy used.

Use of resources and costs

Table 2 presents the data on resources consumed and costs. The second column contains the mean and standard deviation of the units of resources consumed per patient at the

Table 2 Resources and costs at 2 years of biological therapy

	Units of resources consumed (mean ± SD)	Cost of resources (euros) (mean ± SD)	% of cost (cumulative)
Drug cost, EFP	–	21,682.65 ± 7125.65	83.47%
Consultations			
Rheumatology	13.31 ± 3.56	786.18 ± 194.03	
Emergency	0.33 ± 0.65	41.36 ± 81.84	
Total	13.64 ± 3.79	827.54 ± 231.44	3.19% (86.66%)
Complementary tests	23.24 ± 10.39	962.01 ± 382.75	3.70% (90.36%)
Laboratory	13.78 ± 4.91	861.52 ± 307.16	
CT	0.28 ± 0.86	17.11 ± 61.17	
NMRI	0.19 ± 0.49	15.66 ± 40.69	
Simple X-ray	8.76 ± 6.49	60.95 ± 45.20	
USG	0.24 ± 0.51	6.77 ± 14.06	
Days of hospitalisation	2.73 ± 18.39	1720.85 ± 11,596.47	6.62% (96.98%)
Day hospital for drug administration	6.90 ± 7.88	783.00 ± 866.62	3.02% (100%)
Total	–	25,976.05 ± 12,675.02	100%

SD standard deviation, *EFP* ex-factory price, *CT* computed tomography scan, *NMRI* nuclear magnetic resonance imaging, *USG* ultrasonography

end of the 2 years of follow-up (mean number of consultations attended, mean number of laboratory tests performed, etc.). The third column shows the mean cost of each resource, considering the official EFP for the drugs and the hospital price catalogue for the other resources. Finally, the last column reflects the percentage of the total cost represented by each resource.

The mean cost of the direct healthcare resources at 2 years was € 25,976 (95% CI 23,888–28,063). The main cost component was the drug, at 83.47% of the total.

Cost-effectiveness

After 2 years of treatment, the mean cost-effectiveness of each CR achieved and maintained in our study was € 79,681 ± 38,880.

Sensitivity analysis

To estimate the cost-effectiveness from a social perspective which includes indirect and nonmedical cost, we have chosen data published by Ruiz-Montesinos et al. [14, 15]. The estimations were: of total costs, 74% were direct costs and 26% were indirect cost. Medical cost represented 81% of direct cost.

According to those data and considering our results, after 2 years of treatment, mean cost-effectiveness of each CR achieved and maintained would be more than €132,000 from the social perspective.

Discussion

The current tendency in RA management to treat patients by objectives (T2T) and to expend all possible efforts to achieve CR [4, 10] may have a high cost, especially in patients with established AR when biologics are needed to achieve it, though Radner et al. [16] found that patients with CR showed better function and that, from a cost perspective, CR was also superior to achievement of low disease activity.

The results of the CREATE registry suggest that, in actual clinical practice, the strategy of treating to the target of CR is achieved in approximately one-third of patients with established RA after 2 years of biological therapy, albeit at a high cost.

Our study has limitations and advantages. One of its strengths lies in the registry database, which systematically includes all patients treated with biological therapy (CREATE registry), with prospective follow-up of all these patients by a multidisciplinary team for decision-making and following standardised work protocols, in routine clinical practice conditions. These strengths support the rigour and exhaustiveness of the results. The cost data for the different health resources used were provided by the Pharmacy Department, and the statistical analysis was performed by an independent investigator, which ensures high-quality data collection and processing.

The observational design is recommended to advance our knowledge of actual cost-effectiveness [17], in contrast to other studies in health economics which use models

with numerous assumptions or data from clinical trials with highly selected patients. However, it has the limitation of being open and non-random, although all patients received the best possible treatment according to the characteristics of each patient and drug. In the absence of any limiting constraints (inability to attend the day hospital or to self-administer treatment, compliance problems, presence of intestinal inflammatory disease, etc.), the drug with lowest cost to the hospital as advised by the pharmacist is used.

The cost analysis was made from the perspective of the health system, which includes the costs of all the health resources involved in this pathology, rather than from the societal perspective. This perspective was chosen to reflect real data and to avoid having to make estimates based on assumptions, given that indirect and intangible costs are difficult to quantify [17].

Our results are in line with other studies: Schoels et al. [18] found that most studies assessing early biologics reported cost-effectiveness ratios of over $50,000. Van der Velde et al. [19] published a systematic study which found that, in patients who had no response to treatment with methotrexate in combination with leflunomide or sulfasalazine, the use of biologics was cost-effective in 14 out of 35 comparisons at a willingness-to-pay threshold of Can $100,000 per quality-adjusted life year.

Considering the social perspective, cost-effectiveness estimation made with available data from other studies of the same country and characteristics [14, 15] is lower than studies made in other countries like works made in Germany [20] or Italy [21]. In those cases, indirect costs were estimated to be 50–70% of total costs, due mainly to a long-term estimation of permanent work disability.

In any event, considering the real direct costs to the healthcare system, achieving CR involves a high cost in established AR. Some options to optimise resources could be:

- Determination of the most efficient drug to achieve CR. Large observational studies or meta-analyses of published studies of cost-effectiveness in actual clinical practice are needed.
- Once CR has been maintained over time, other options could be considered for these patients, such as reducing the dosage or therapeutic vacations [22]. This strategy has been shown to be efficient in the PRESERVE study [23] and is the basis for the current recommendations to optimise biological therapy in RA patients [24].
- Participation of clinical pharmacists in the treatment decisions can help to improve the efficiency of therapy.

Conclusions

The T2T strategy of CR is considered to be the most effective, but in daily clinical practice in patients with established RA it has a high cost. The development of clinical management based on efficiency may make it possible to optimise the most effective strategies so that they will also be the most efficient.

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Compliance with ethical standards

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

Ethical standard 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-authorisation 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.

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