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Original Article

Cost Analysis of Biologic Drugs in Rheumatoid Arthritis First Line Treatment After Methotrexate Failure According to Patients' Body Weight☆

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ABSTRACT

Objective: The objective was to assess the influence of patients' weight in the cost of rheumatoid arthritis treatment with biologic drugs used in first line after non-adequate response to methotrexate.
Patients and method: Pharmaceutical and administration costs were calculated in two scenarios: non-optimization and optimization of intravenous (IV) vials. The retrospective analysis of 66 patients from a Spanish 1000 beds-hospital Rheumatology Clinic Service was used to obtain posology and weight data. The study time horizon was two years. Costs were expressed in 2013 euros.
Results: For an average 69 kg-weighted patient the lowest cost corresponded to abatacept subcutaneous (SC ABA) (€21,028.09) in the scenario without IV vials optimization and infliximab (IFX) (€20,779.29) with optimization. Considering patients' weight in the scenario without IV vials optimization infliximab (IFX) was the least expensive drug in patients ranged 45–49 kg, IV ABA in 50–59 kg and SC ABA in patients over 60 kg. With IV vials optimization IFX was the least expensive drug in patients under 69 kg and SC ABA over 70 kg.
Conclusions: Assuming comparable effectiveness of biological drugs, patient's weight is a variable to consider, potentials savings could reach €20,000 in two years.

Análisis de costes de la utilización de fármacos biológicos para la artritis reumatoide en primera línea de tratamiento tras respuesta inadecuada a metotrexato en función del peso de los pacientes

Palabras clave:
Artritis reumatoide
Costes
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RESUMEN

Objetivo: Evaluar la influencia del peso de los pacientes en el coste de tratamiento de la artritis reumatoide con fármacos biológicos indicados en primera línea tras respuesta inadecuada a metotrexato.
Pacientes y método: Se incluyeron costes farmacológicos y de administración considerando no optimización y optimización de viales de los fármacos intravenosos. Los datos de posologías y peso de pacientes se obtuvieron de forma retrospectiva de 66 pacientes atendidos en un servicio de Reumatología Clínica de un hospital terciario en España. El horizonte temporal del estudio fue de 2 años. Los costes se expresaron en euros de 2013.

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Resultados: En un paciente promedio de 69 kg de peso, abatacept subcutáneo (ABA SC) fue el fármaco de menor coste (21.028,09 €) sin optimización de viales, e infliximab (IFX) (20.779,29 €) con optimización de viales. Considerando el peso de los pacientes, sin optimización de viales, IFX fue menos costoso en pacientes de 45-49 kg, ABA intravenoso en pacientes de 50-60 kg y ABA SC en pacientes ≥ 60 kg. Con optimización de viales IFX sería menos costoso en pacientes < 70 kg y ABA SC pacientes ≥ 70 kg.
Conclusiones: Suponiendo efectividad comparable de fármacos biológicos, el peso de los pacientes es una variable relevante, pudiendo alcanzarse ahorros potenciales superiores a 20.000 € en pacientes de más de 100 kg de peso en 2 años de tratamiento.

Introduction

Rheumatoid arthritis (RA) has a great impact on patient quality of life, and the social and economic costs are elevated.[1] It has a negative effect on the morbidity and disability of the patients,[2] who see their life expectancy reduced by 5–10 years,[3] and severely affects their activities of daily living.[4,5]

There have been important advances in its treatment, due in part to disease-modifying antirheumatic drugs (DMARDs), which are the treatment of choice in RA.[6] After a first-line treatment with conventional DMARDs like methotrexate (MTX), the next therapeutic option is comprised of the so-called biologic DMARDs, produced in cell culture using genetic engineering.[7]

In Spain, after an inadequate response to MTX, first-line treatment includes subcutaneous abatacept (SC ABA), intravenous abatacept (IV ABA), adalimumab (ADA), certolizumab (CZP), etanercept (ETN), golimumab (GLM), infliximab (IFX), tocilizumab (TCZ) and anakinra. Although there are a few studies that directly compare any of these agents, such as the AMPLE[8] and ADACTA[9] trials, much of the available information comes from indirect comparisons, which show slight differences in terms of safety or efficacy.[10]

The doses of those biologic agents that are administered IV (IFX, ABA and TCZ) are adjusted according to patient weight. The remainder, including SC ABA, are administered subcutaneously at fixed doses, independent of body weight. The main objective of this study was to evaluate the influence of patient weight on the cost of RA treatment with biologic agents indicated as first-line therapy after an inadequate response to MTX.

Patients and Methods

Design

A model for calculating the acquisition and administration costs was designed using Microsoft® Excel®. The DMARDs included were SC ABA, IV ABA, ADA, CZP, ETN, GLM, IFX and TCZ. Anakinra was excluded because of its limited use in clinical practice. We established a 2-year time horizon for which the induction doses and possible dose escalation were always considered in the first year.

To determine the demographic characteristics of patients with RA in Spain, retrospective data on gender, age and body weight were collected on a consecutive series of 66 patients treated in a 1000-bed tertiary care hospital in the Valencian Community in eastern Spain.

Calculation of Costs

We estimated the overall cost of DMARD therapy for an average patient whose weight coincided with the mean weight for the selected sample, as well as the difference in cost over the least costly agent, considering scenarios without and with vial optimization, that is, discarding or using what remains in partially used vials, respectively.

The costs for weight ranges of 5 kg were estimated, including the minimum and maximum weights of the patients in the sample. We also calculated the cost per biologic DMARD in a hypothetical 100-patient cohort that would reflect the distribution of weights observed in the sample, assuming a normal distribution, with sample mean ± standard deviation.

Resources and Costs

We took the hospital perspective, considering direct costs of acquisition of each drug and those associated with its administration. No other costs were included as we assumed that they were similar for all the alternatives. The costs of acquisition were calculated according to the doses being administered in the hospital, based on information provided by rheumatologists (Table 1), taking the cost of acquisition from the pharmaceutical company,[11] applying the deduction stipulated in Spanish Royal Decree-Law8/2010[12] (7.5%) and adding the value added tax (4%).

The cost of IV DMARD administration was calculated on the basis of the technical specifications (IV ABA, 30 min; TCZ, 60 min; IFX, 60–120 min).[13–15] The unit costs associated with administration were obtained from a Spanish health costs database.[16] The costs were expressed in 2013 euros, without taking into consideration an annual discount rate (Table 2).

Two sensitivity analyses were performed: (1) utilization of doses of 3 mg/kg in the 2nd year in patients treated with IFX, instead of the 4 mg/kg of the base case; and (2) utilization of doses of 6 mg/kg in the 2nd year in patients treated with TCZ, rather than the 8 mg/kg of the base case.

Results

We analyzed the data of a consecutive series of 66 patients (24% men), with a mean age of 56.8 ± 11.7 years and mean weight of 69.0 ± 13.1 kg (range 44–103 kg); 30% of the patients weighed between 65 and 74 kg and 77% weighed between 55 and 84 kg.

Cost Analysis Corresponding to the Average Patient

In the case of an average patient, in the scenario without vial optimization, SC ABA was the least costly agent (€21,028.09) over 2 years (Table 3). With vial optimization, the least costly drug was IFX (€20,779.29). Subcutaneous ABA was the least costly during the 2nd year (€10,514.04) (Table 4).

Cost Analysis According to Weight

We calculated the total 2-year cost per patient for each of the alternatives according to weight. Without optimization, IFX was the least costly in patients weighing 44–49 kg, IV ABA in patients weighing 50–59 kg and SC ABA from 60 kg on. With optimization,

Table 1
Treatment Regimens Included in the Study.

Alternative	1st year	2nd year
IV ABA	Induction phase in weeks 0, 2 and 4 of the 1st year 2 vials in patients weighing <60 kg; 3 vials in those weighing ≥60 kg and ≤100 kg; 4 vials in those weighing >100 kg 10 mg/kg in a scenario of vial optimization Administration of a maintenance dose every 4 weeks A total of 14 injections	10 mg/kg in a scenario of vial optimization 2 vials in patients weighing <60 kg; 3 vials in patients weighing ≥60 kg and ≤100 kg; 4 vials in those weighing >100 kg Administration of a maintenance dose every 4 weeks A total of 13 injections
SC ABA	Administered in 52 weekly doses of 125 mg No intravenous loading dose	Administered in 52 weekly doses of 125 mg
ADA	26 doses of 40 mg administered at 2-week intervals	26 doses of 40 mg administered at 2-week intervals
CZP	Initial doses of 400 mg in weeks 0, 2 and 4 Thereafter, 200 mg are administered every 2 weeks Administration of 3 doses of 400 mg and 23 of 200 mg	Administered in 26 doses of 200 mg
ETN	Administration of 52 doses of 50 mg	Administration of 52 doses of 50 mg
GLM	Administration of 12 monthly doses of 50 mg	Administration of 12 monthly doses of 50 mg
IFX	3 induction doses of 3 mg/kg during the first 6 weeks After week 6, doses of 3 mg/kg every 8 weeks, administration of 5 doses	Administration of 7 doses of 4 mg/kg
TCZ	Administration of doses of 8 mg/kg every 4 weeks, for a total of 13 doses	Administration of doses of 8 mg/kg every 4 weeks, for a total of 13 doses

IV ABA: intravenous abatacept; SC ABA: subcutaneous abatacept; ADA: adalimumab; CZP: certolizumab pegol; ETN: etanercept; GLM: golimumab; IFX: infliximab; TCZ: tocilizumab.

Table 2
Unit Costs Employed in the Cost Estimation.

	Unit pharmacy costs			
	Pharmaceutical company	Administration route	Presentation	AAC per package, €
Active ingredient Brand name				
Abatacept Orencia®	[1,0]BMS	IV	250 mg/vial; 1 vial per package	334.82
		SC	125 mg/vial; 1 vial per package	840.72
Certolizumab pegol Cimzia®	UCB Pharma	SC	200 mg/syringe; 2 syringes per package	948.00
Golimumab Simponi®	MSD	SC	50 mg/pen; 1 pen per package	1117.00
Etanercept Enbrel®	Pfizer	SC	50 mg/vial; 4 vials per package	947.22
Infliximab Remicade®	MSD	IV	100 mg/vial; 1 vial per package	536.28
Tocilizumab RoActemra®	Roche	IV	80 mg/vial; 1 vial per package	139.60
			200 mg/vial; 1 vial per package	349.00

Costs of administration of intravenous drugs		
Active ingredient	Personnel costs	Unit cost, €
Abatacept	Drug infusion less than 1/2 h	123.76
Infliximab	Drug infusion between 1/2 h and 2 h	151.25
Tocilizumab	Drug infusion between 1/2 h and 2 h	

AAC, average acquisition cost; BMS, Bristol-Myers Squibb; IV, intravenous; MSD, Merck Sharp & Dohme; SC, subcutaneous.

Table 3
Costs per Patient Weighing 69 kg Without Vial Optimization, €.

	IV ABA[b]	SC ABA	ADA	CZP	GLM	ETN	IFX[b]	TCZ[b]
Costs of 1st and 2nd years of treatment								
Total	29,431.36	21,028.09	25,719.59	25,535.33	25,789.30	23,691.87	25,484.31	28,374.23
Difference with respect to SC ABA[a]	8403.28		4691.50	4507.24	4761.21	2663.78	4456.22	7346.14
Difference with respect to SC ABA, %[a]	40.0%		22.3%	21.4%	22.6%	12.7%	21.2%	34.9%
Second year (maintenance)								
Total	14,170.66	10,514.04	12,859.79	11,855.69	12,894.65	11,845.93	11,892.68	14,187.11
Difference with respect to SC ABA[a]	4746.66		2345.75	3165.60	2380.60	1331.89	3077.59	3673.07
Difference with respect to SC ABA, %[a]	45.1%		22.3%	30.1%	22.6%	12.7%	29.3%	34.9%

ADA, adalimumab; CZP, certolizumab pegol; ETN, etanercept; GLM: golimumab; IFX: infliximab; IV ABA, intravenous abatacept; SC ABA, subcutaneous abatacept; TCZ: tocilizumab.

[a] Positive values indicate a lower cost with SC ABA.

[b] Includes costs of intravenous administration.

Table 4
Costs per Patient Weighing 69 kg With Vial Optimization, €.

	IV ABA[b]	SC ABA	ADA	CZP	GLM	ETN	IFX[b]	TCZ[b]
Costs of 1st and 2nd years of treatment								
Total	27,344.18	21,028.09	25,719.59	25,535.33	25,789.30	23,691.87	20,779.29	28,025.06
Difference with respect to IFX[a]	6564.89	248.80	4940.30	4756.04	5010.01	2912.58		7245.77
Difference with respect to IFX, %[a]	31.6%	1.2%	23.8%	22.9%	24.1%	14.0%		34.9%
Second year (maintenance)								
Total	13,165.71	10,514.04	12,859.79	11,855.69	12,894.65	11,845.93	11,025.96	14,012.53
Difference with respect to SC ABA[a]	2651.67		2345.75	1341.64	2380.60	1331.89	511.92	3498.49
Difference with respect to SC ABA, %[a]	25.2%		22.3%	12.8%	22.6%	12.7%	4.9%	33.3%

ADA, adalimumab; CZP, certolizumab pegol; ETN, etanercept; GLM: golimumab; IFX: infliximab; IV ABA, intravenous abatacept; SC ABA, subcutaneous abatacept; TCZ: tocilizumab.

[a] Positive values indicate a lower cost with IFX or SC ABA.

[b] Includes costs of intravenous administration.

IFX was the least costly in patients weighing 69 kg or less and SC ABA in those weighing ≥70 kg.

These results were slightly sensitive to the maintenance of the IFX dose of 3 mg/kg throughout the 2nd year. Without optimization, IFX was the least costly drug in patients weighing less than 64 kg, whereas, with optimization, IFX was the least costly at weights under 84 kg. The reduction of the TCZ dose to 6 mg/kg did not change the results.

Estimate of the Savings Resulting From Treating According to Patient Weight

Assuming a normal distribution of body weight, in a hypothetical sample of 100 patients, we estimated that the majority would weigh 60 kg or more. Fig. 1 shows the cost of treatment of that cohort according to weight distribution both without (1A) and with (1B) vial optimization.

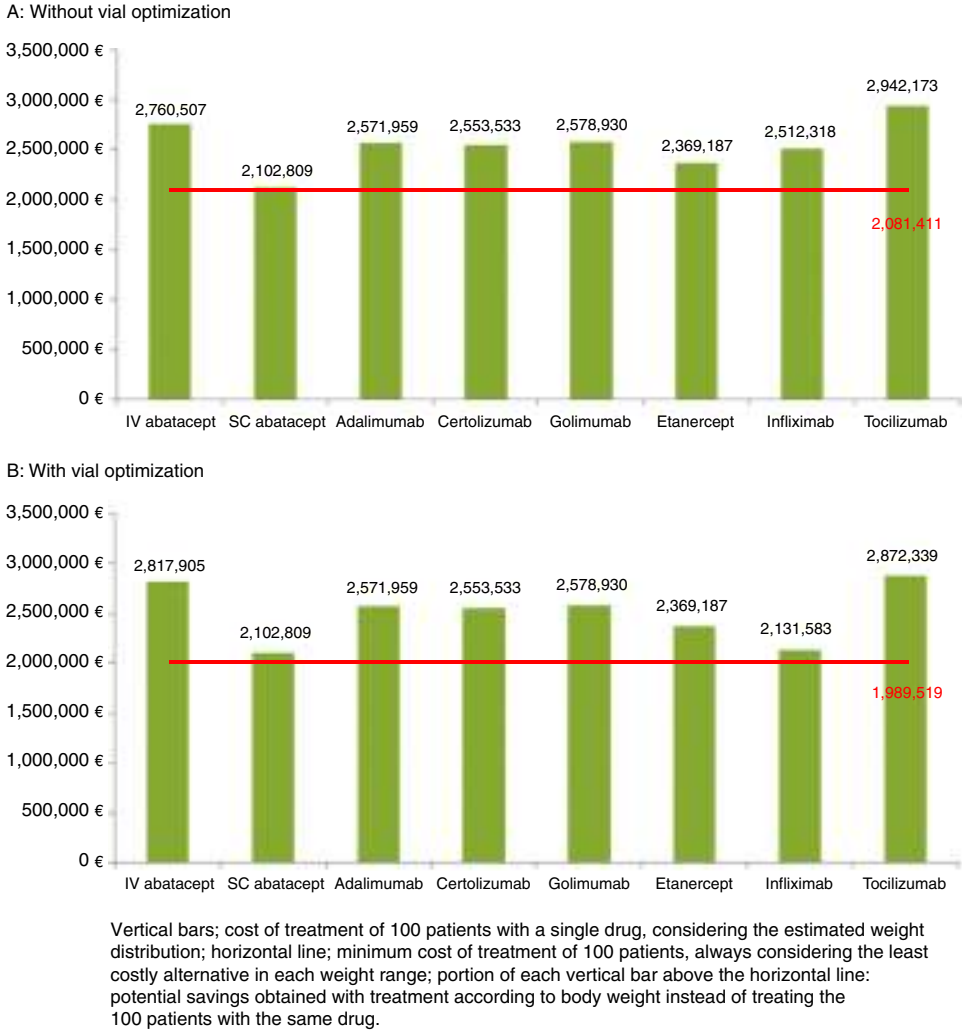

Fig. 1. Cost of treating a hypothetical cohort of 100 patients with each of the alternatives, according to the estimated distribution of patient body weights.

Table 5
Estimated Savings per Patient Over 2 Years of Treatment With the Least Costly Alternative Based on the Cost per Patient Without Vial Optimization, €.

Weight (kg)	IV ABA	SC ABA	ADA	CZP	GLM	ETAN	IFX	TCZ
45–49	2988.96	3282.30	7973.80	7789.54	8043.51	5946.08	NA	3645.09
50–54	NA	293.34	4984.84	4800.58	5054.55	2957.12	622.35	4147.80
55–59	NA	293.34	4984.84	4800.58	5054.55	2957.12	622.35	4147.80
60–64	8403.28	NA	4691.50	4507.24	4761.21	2663.78	329.01	7346.14
65–69	8403.28	NA	4691.50	4507.24	4761.21	2663.78	4456.22	7346.14
70–74	8403.28	NA	4691.50	4507.24	4761.21	2663.78	4456.22	9091.98
75–79	8403.28	NA	4691.50	4507.24	4761.21	2663.78	8067.53	10,837.81
80–84	8403.28	NA	4691.50	4507.24	4761.21	2663.78	8067.53	10,837.81
85–89	8403.28	NA	4691.50	4507.24	4761.21	2663.78	8067.53	14,329.49
90–94	8403.28	NA	4691.50	4507.24	4761.21	2663.78	8067.53	16,075.33
95–99	8403.28	NA	4691.50	4507.24	4761.21	2663.78	8067.53	17,821.16
100–104	17,099.89	NA	4691.50	4507.24	4761.21	2663.78	15,806.05	21,312.84

ADA, adalimumab; CZP, certolizumab pegol; ETN, etanercept; GLM: golimumab; IFX: infliximab; IV ABA, intravenous abatacept; NA, not applicable; SC ABA, subcutaneous abatacept; TCZ: tocilizumab.

Both without optimization (€21,398 [€2,102,809 – €2,081,411] in 100 patients) and with optimization (€113,290 [€2,102,809 – €1,989,519] in 100 patients) the smallest savings corresponded to SC ABA, which was the alternative with the lowest cost and that which came nearest to the minimum cost. Without optimization, the maximum possible savings were over €21,000 per patient weighing 100–104 kg treated with SC ABA instead of TCZ (Table 5). With optimization, the maximum savings achieved were over €19,000 per patient weighing 100–104 kg treated with SC ABA instead of TCZ (Table 6).

Discussion

The study methodology corresponds to a cost estimate of different alternatives without analyzing efficacy, assuming that the efficacies of the treatment alternatives compared in the study have been demonstrated to be high and similar.[17–22] The analysis included all the biologic DMARDs employed as first-line therapy after an inadequate response to MTX, excluding anakinra because of its limited use in routine clinical practice.

In the estimate of the overall 2-year cost per average patient, SC ABA proved to be the least costly biologic agent in the scenario without IV vial optimization (€21,028), whereas the least costly drug in the alternative scenario was IFX (€20,779). In both scenarios, SC ABA was less costly than IFX during the second year of treatment, due to the escalation of the dose of IFX from 3 mg/kg to 4 mg/kg. This escalation occurs frequently in clinical practice,[23,24] suggesting that with a time horizon longer than that considered here, SC ABA would be the least costly alternative. This finding is consistent with a recent study that analyzed the cost of therapy and showed SC ABA to be less costly than IV ABA, ADA, CZP, ETN, GLM, IFX and TCZ in RA patients initiating treatment with biologic DMARDs.[25]

The analysis by weight range indicated that patient weight is a determinant of cost, as the consideration of the least costly agent varies according to this factor and, thus, does not coincide with the initial case of 69 kg. The consideration of patient weight can result in savings in patients weighing 60–70 kg treated with SC ABA of €2600 to €9000, depending on the alternative chosen.

In the analysis, we decided to evaluate 2 scenarios according to the use made of open IV vials as optimization is becoming increasingly widespread.[26] This is only applicable in the treatment of very prevalent diseases and/or in centers that can schedule a critical number of patients to be treated simultaneously. It is an optimal situation that should be seen as a conservative premise since, in clinical practice, it does not seem to be feasible to completely avoid wastage by arranging for an exact number of patients to coincide for treatment.

Among the limitations of this study, we should point out the representativeness of the weight distribution employed in the RA patient population. In the analysis of the sample of 66 available patients, we assumed a normal distribution of the weight defined by the mean ± standard deviation of the sample. This may not be an exact reflection of the RA population in Spain. Likewise, in this sample, we did not consider variables that might be relevant to body weight, such as the loss of muscle mass experienced by patients with RA as their disease progresses. Nevertheless, we considered that, with the sample analyzed, it would be possible to achieve the objective of the study, which was to examine the influence of patient weight on the cost of treatment.

On the other hand, the analysis carried out assumed that SC drugs would not have to use health care resources for their injection, although it is probable that certain patients (those of advanced

Table 6
Estimated Savings per Patient Over 2 Years of Treatment With the Least Costly Alternative Based on the Cost per Patient With Vial Optimization, €.

Weight (kg)	IV ABA	SC ABA	ADA	CZP	GLM	ETAN	IFX	TCZ
45–49	4972.97	5614.17	10,305.67	10,121.41	10,375.38	8277.95	NA	5627.79
50–54	5370.95	4272.83	8964.33	8780.07	9034.04	6936.61	NA	6032.29
55–59	5768.93	2931.48	7622.99	7438.72	7692.69	5595.26	NA	6436.78
60–64	6166.91	1590.14	6281.64	6097.38	6351.35	4253.92	NA	6841.27
65–69	6564.89	248.80	4940.30	4756.04	5010.01	2912.58	NA	7245.77
70–74	8055.41	NA	4691.50	4507.24	4761.21	2663.78	1092.55	8742.81
75–79	9794.73	NA	4691.50	4507.24	4761.21	2663.78	2433.89	10,488.65
80–84	11,534.06	NA	4691.50	4507.24	4761.21	2663.78	2702.16	10,837.81
85–89	13,273.38	NA	4691.50	4507.24	4761.21	2663.78	5116.58	13,980.32
90–94	15,012.70	NA	4691.50	4507.24	4761.21	2663.78	6457.92	15,726.16
95–99	16,752.03	NA	4691.50	4507.24	4761.21	2663.78	7799.26	17,472.00
100–104	18,491.35	NA	4691.50	4507.24	4761.21	2663.78	9140.61	19,217.83

ADA, adalimumab; CZP, certolizumab pegol; ETN, etanercept; GLM: golimumab; IFX: infliximab; IV ABA, intravenous abatacept; NA, not applicable; SC ABA, subcutaneous abatacept; TCZ: tocilizumab.

age or having fear of needles) present to a health center to request the administration of the drug. The authors consider that the percentage of patients of this type would be low and that the results would not be modified in a relevant manner.

Another limitation is the consideration that all other costs would be the same among the alternatives. The AMPLE trial[8] demonstrated that SC ABA is associated with a lower percentage of reactions at the injection site than ADA, a fact that would result in an unplanned difference in costs. On the other hand, as discounting was not applied, the costs of the second year with respect to the first may be underestimated, a circumstance that would favor agents with a higher maintenance cost.

Likewise, the costs of MTX and folic acid are not included as it is assumed that they are used with all the biologic DMARDs, as is suggested by the latest European clinical guidelines.[6] Finally, it should be pointed out that we have not included monitoring costs, which may differ from one drug to another; the reason for excluding these costs lies in the fact that differences in monitoring costs are marginal in comparison with the costs of drug acquisition or administration.

Another possible limitation is the marked variability in the use of drugs in RA. In fact, up to 45.7% of the patients may ultimately have their doses reduced,[27] and the relevance of this circumstance was pointed out in a 2014 consensus document.[28] The attempt has been made to mitigate this limitation with the sensitivity analysis, which confirmed the relevance of dosage in the cost demonstrated in studies on strategies to reduce the dose or increase the intervals between treatments.[23,29] This analysis involved only the IV drugs, as the study focuses on changes in costs related to body weight.

This report shows that patient weight may a factor to be considered in the prescription of biologic DMARDs and may enable a rational and more efficient allocation of resources. In view of the results obtained, to achieve a more rational use based on patient weight, the choice would be to administer IFX to patients weighing 45–49 kg, IV ABA to patients weighing 50–60 kg and SC ABA to patients weighing ≥60 kg without IV vial optimization. With optimization, the options would be IFX in patients <70 kg and SC ABA in patients ≥70 kg.

Ethical Disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflict of Interest/Funding

This work was funded by Bristol-Myers Squibb (BMS). Cristina Canal was employed by BMS at the time of study. Itziar Oyagüez and Manuel Gómez Barrera are employees of PORIB, a consultant specialized in the area of economic evaluation of health technology, who received funding from BMS for this article. José Andrés Román Ivorra, head of the rheumatology department, and Emilio Monte-Boquet, pharmacist, at Hospital Universitario and Politécnico La Fe de Valencia, Spain, have received fees from BMS for their advice on the development of this project. José Ivorra, rheumatologist at Hospital Universitario y Politécnico La Fe de Valencia, declares that he has no conflicts of interest. The financial support for this project has not interfered in its development.

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