



Original article

A comparison of leflunomide and subcutaneous methotrexate in the treatment of rheumatoid arthritis: an approximation based on the number needed to treat

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ABSTRACT

Objective: To compare, in the Spanish setting, 2 drugs for adults with rheumatoid arthritis (RA): leflunomide and subcutaneous methotrexate (SC). The high price of methotrexate SC compared with traditional presentations of methotrexate justifies conducting an economic evaluation comparing it with leflunomide.

Methods: The analysis considered the annual costs of the drugs and their effectiveness, measured with a number needed to treat (NNT) approach, considering both the ACR20 and ACR50 criteria for effectiveness. Data about efficacy and dosage were derived from the clinical trial US310, a randomized, double-blinded controlled trial, which compared efficacy and safety of leflunomide (20 mg/daily) versus placebo versus methotrexate (7.5-15 mg/weekly) in 482 patients with active RA. Data about use of medical resources for drug monitoring (visits to rheumatologists and diagnostic procedures) were derived from the manufacturers' summary of product characteristics. Direct costs (drugs and monitoring) were obtained from 2 Spanish databases. The analysis has been performed under the Spanish National Health System perspective.

Results: Using the ACR20 criteria, the NNT with leflunomide and methotrexate are 4 (95% CI, 2.56-7.71) and 5 (95% CI, 3.03-14.3) respectively. Using the ACR50 criteria, NNT are 4 (95% CI, 2.72-6.54) and 7 (95% CI, 4.03-19.3). In the case of leflunomide, annual treatment costs per patient-year equals €1793.30; in the case of methotrexate total treatment costs amounts to €2149.20.

Conclusions: Combining these results the cost of a controlled patient according to ACR20 would amount €7173 for leflunomide and €10 746 for methotrexate SC. Results considering ACR50 are €7173 and €15 044 for leflunomide and methotrexate respectively.

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Comparación de leflunomida y metotrexato subcutáneo en el tratamiento de la artritis reumatoide: una aproximación basada en el número de pacientes que es necesario tratar

RESUMEN

Objetivo: Comparar 2 fármacos para la artritis reumatoide (AR): leflunomida y metotrexato subcutáneo (s.c.) (jeringas precargadas), considerando tanto costes anuales de tratamiento como la efectividad medida a través del número de pacientes que es necesario tratar (NNT).

Métodos: Los datos de eficacia y dosis fueron extraídos del ensayo clínico US310, ensayo aleatorizado y doble ciego, que tuvo por objetivo comparar la eficacia y la seguridad del tratamiento a 12 meses con leflunomida (20 mg/día) frente a placebo y metotrexato (7,5-15 mg/semana) en 482 pacientes con AR activa. La información sobre los actos médicos para los seguimientos de control se obtuvo de la ficha técnica del producto. El estudio de costes se ha realizado con la perspectiva del Sistema Nacional de Salud español.

Resultados: Considerando el criterio de ACR20, el NNT de leflunomida es 4 (intervalo de confianza [IC] del 95%, 2,56-7,71) y el de metotrexato s.c., 5 (IC del 95%, 3,03-14,3); para el criterio de ACR50, el NNT de

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leflunomida es 4 (IC del 95%, 2,72-6,54) y el de metotrexato s.c., 7 (IC del 95%, 4,03-19,3). El coste anual del fármaco fue 1.112,52 euros para la leflunomida y 1.438,91 euros para el metotrexato s.c. Los costes anuales de monitorización fueron 680,76 euros para la leflunomida y 710,26 euros para el metotrexato s.c.

Conclusiones: Combinando la información, el coste de un paciente respondedor según ACR20 sería de 7.173 euros con leflunomida y 10.746 euros con metotrexato s.c.; los resultados considerando ACR50 oscilarían entre los 7.173 euros para la leflunomida y 15.044 euros para el metotrexato s.c.

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Introduction

Rheumatoid arthritis (RA) is a chronic rheumatic disease with prevalence in adults from our country found between 0.3 and 1.6%, with a mean of 0.5%,^{1,2} which supposes the current existence of around 200 000 patients.³ Both leflunomide as methotrexate are indicated for treatment of active RA adult patients as disease modifying drugs (DMARD). The effectiveness of both treatments has been studied in one of the leflunomide registry studies (reference US301), a randomized, double blind clinical trial that established the objective of comparing efficacy and treatment safety of a 12 month treatment with leflunomide (20 mg/d) versus placebo and methotrexate (7,5–15 mg/w) in 482 patients with active RA.⁴

In this study, the main outcome measures employed were: a) the rate of success as defined by the American College of Rheumatology criteria,⁵ that require an improvement of $\geq 20\%$ (defined as ACR20) both in the number of swollen and painful joints, as well as in the following three measures: functional capacity patient self-evaluation (through the modified Health Assessment Questionnaire [MHAQ]), general assessment by the patient and general assessment by the physician, general assessment by the patient regarding pain, acute phase reactants evaluated using the erythrocyte sedimentation rate (ESR, Westergren) or C reactive protein (CRP); b) progression of the disease evaluated from conventional x-rays; and c) improvement in functional capacity and quality of life of patients. Results indicated that leflunomide is as effective as methotrexate (administered concomitantly with folate supplements) in the treatment of adult patients affected by active RA. Response to treatment, according to the ACR20 and ACR50 criteria, of the patients receiving leflunomide and methotrexate was significantly higher than that of the patients receiving placebo, and there were no significant differences between both active treatments⁴: 52% and 41% for leflunomide versus 46% and 35% for methotrexate, versus 19% for placebo ($P < .001$). These similar results for both drugs regarding their efficacy where then confirmed by another registry clinical trial (reference MN302) which also compared leflunomide (20 mg/day) with methotrexate (10–15 mg/week),⁶ and were recognized by the Pharmaceutical Specialties Committee in its Leflunomide Public Evaluation European Report.⁷

The cost of leflunomide has been manifested in an economical analysis that estimated the 3-year results of incremental cost-effectiveness and cost-utility of the introduction of leflunomide in the sequential DMARD treatment of patients with RA.⁸ This study concludes that the use of leflunomide can save costs when it takes into account total costs, both direct and indirect.

In Spain, subcutaneous (SC) methotrexate has recently been introduced into the market in prefiled syringes. This pharmaceutical form attempts to simplify the administration and dosage of the product both to patients and health personnel, but the cost of treatment with this new formulation increases significantly with respect to existing forms on the market (oral and parenteral). Although some data has been published regarding the possibility

of greater efficacy with methotrexate SC to other formulations, there is no controlled clinical trial evidence that allows to confirm this; only 1 observational study with 143 patients⁹ concludes that the intramuscular route is more effective than the oral route, having less side effects. In addition, 2 Letters to the Editor have been published^{10,11} in which the authors state that its greater efficacy is likely, although one of them¹⁰ recognizes that the cost of administration when compared to the oral formulation rises seven-fold.

This article presents the results of an economic evaluation (EE) that has calculated the annual costs of treatment with leflunomide versus methotrexate SC in Span. These results have been combined with a calculation of the number of patients who need to be treated (NNT) associated with each drug, according to the ACR 20 and ACR50 criteria.

Methods

NNT expresses the number of patients who need to receive treatment in order for one of them to obtain the expected benefit of the drug. For the calculation of this efficacy parameter, the number of events that occurred during treatment (incidence in the experimental or treatment group) are compared to the numbers in the control group (incidence in the control group). In this manner, NNT would be the inverse of the absolute risk reduction. In this last instance, NNT represents the number of patients that should receive the experimental treatment instead of the control treatment in order for an additional patient to obtain the expected treatment benefit. Therefore, it is considered one of the best effectiveness measures in the confrontation of therapeutic options in terms that allow for easy comparisons of the advantages and inconveniences of medication.¹² Another way of understanding it is that NNT measures the therapeutic "effort" that must be carried out in order to obtain a benefit in one patient; it is easy and intuitive to use in pharmacoeconomics, because the objective is only to translate said "effort" to its economic quantification within an EE study.

The cost studies that have been carried out from the National Health System perspective, and the clinical horizon under consideration is of 1 year. Total cost of treatment with leflunomide and methotrexate SC has been grouped in two large categories: a) compared drugs, and b) examinations of clinical follow-up and review of the patients.

The information relative to the medical acts related to control follow-up in Spain was obtained following the guidelines set by the review of product characteristic, after consulting the technical insert of the product obtained from the Agencia Española del Medicamento.¹³ Unit costs for the drugs have been obtained from the *Vademecum Internacional*, published online¹⁴ by CMP Medicom Editorial S.A. Unit costs of the medical acts for follow-up were obtained from the *Base de Información Económica del Sector Sanitario (eSalud)*, also published online¹⁵ by Oblisque Consulting, S.L.

Table 1
Annual cost of follow-up and control examinations in patients treated with leflunomide and methotrexate subcutaneous

Complementary tests	Cost per unit ¹⁵ , €	Leflunomide		Methotrexate SC	
		Units/year ¹³	Total/Year	Units/year ¹³	Total/year, €
Chest x-ray	18	–	–	3	54.01
Renal function	2.14	–	–	9	19.26
Liver function	4.21	18	75.78	9	37.89
Lung function	43.61	–	–	3	130.83
Complete hemogram	15.19	18	273.42	9	136.71
Rheumatology consult	55.26	6	331.56	6	331.56
Total per patient and per year of treatment			680.76		710.26

Results

Calculation of the NNT was obtained in a differentiated form according to the ARC20 and ACR50 criteria from the data of effectiveness of the US301 trial.⁴ According to the ACR20 criteria, the NNT associated to leflunomide would be 4 (95% confidence interval [CI], 2.56–7.71) and the one associated to methotrexate SC, 5 (95% CI, 3.03–14.3). When considering ACR50, a stricter effectiveness criterion, the NNT associated to leflunomide was still 4 (95% CI, 2.72–6.54) and that for methotrexate SC, 7 (95% CI, 4.03–19.3).

Costs of drug treatment

According to the technical insert, treatment with leflunomide starts with an attack dose of 100 mg once a day for 3 days, followed by a recommended maintenance dose of 10 to 20 mg once a day, depending on disease severity. In this EE, for the calculation of costs, a daily dose of 20 mg has been considered, making it the same as the one chosen for the US301 clinical trial.⁴

In Spain, the presentation with 3 pills of 100 mg each costs (PVP+VAT) €33.72, while the 30 pill presentation of 20 mg each costs €89.90. According to this data, the annual cost of this treatment requires 12 packages of 20 mg pills and a single package of 100 mg pills, supposing a total of €1112.52 per patient and year of treatment.

Regarding the cost of treatment with methotrexate SC according to the products technical insert, the initial recommended dose in patients with RA is 7.5 mg once a week. Depending on the individual activity of the disease and the tolerance of the patient, the initial dose can be increased to a maximum of 25 mg a week. In the US301 clinical trial⁴ an initial dose of 7.5 mg/week was administered and increased from weeks 7 to 9 (8 for the present analysis effects) to 15 mg/week in 61% of patients.

A 1 mL/10 mg syringe of methotrexate SC costs (PVP+VAT) €25.87, and a 1.5 mL/15 mg syringe, €29.36. Treatment with 7.5 mg supposes the use of a 1 mL/10 mg syringe, although part of the product is wasted. In 61% of the cases, 8 weeks of treatment with this dose suppose €206.96 euros, to which one must add the remaining 44 weeks of treatment with 15 mg (€1291.84), meaning a total €1498.80 euros/year. For patients (39%) who remain on 7.5 mg, treatment, the total cost is 1345.24 €/year. The weighed combination for 100% of the patients assumes a total of €1438.91 per patient and year of treatment.

All of the patients in the clinical trial,⁴ including those treated with leflunomide as well as those treated with methotrexate, received folic acid supplementation (1 mg, once or twice a day) during treatment. Because the cost is undifferentiated for both treatments, it was not taken into account for this analysis, in coherence with the methodology of EE studies.

Cost of clinical follow-up examination of patients treated with leflunomide and methotrexate

According to the technical insert of the product, with leflunomide it is important to determine the concentrations of alanine-aminotransferase (ALT) and glutamic-pyruvic dehydrogenase (SGPT) and a complete blood count, including a differential count of leukocytes and platelets; they must be determined simultaneously and with the same frequency: before starting treatment and every 2 weeks for the first 6 months of treatment and then every 8 weeks.

With methotrexate, also according to the technical insert, before starting treatment it is necessary to perform a complete blood count with leukocyte and platelet counts, liver enzymes, bilirubin, serum albumin, chest x-ray, and renal function tests. During treatment it is necessary to perform determinations every month for the first 6 months and then every 3 months; patient must be examined for alterations of oral and throat mucosa, a complete blood count and with leukocyte and platelet counts and liver, renal, and lung studies. The number of the rheumatology consultations has been estimated as equivalent for both treatments.

The use of resources associated to follow-up of each drug and unit costs are shown on Table 1. Combining information on the use of sanitary resources and their respective unitary costs, it has been concluded that the medical cost of follow-up of 1 year of treatment with leflunomide is €680.76, versus €710.26 for methotrexate SC. Combining the information on costs of pharmacologic treatment and the follow-up examinations, it can be concluded that the annual cost per patient treated with leflunomide is €1793.28 and with methotrexate SC, €2149.17. Table 2 presents the results of cost per patient and per event avoided (responding patient) with each treatment, according to the ACR20 and ACR50 criteria. In the first case, the use of leflunomide could be associated to a savings with respect to methotrexate SC of over €3500 per responding patient, a number that could exceed €7800 when considering the NNT that corresponds to ACR50.

When the cost of these drugs was considered, taking into account that patient contribution is reduced, the annual cost for the patient taking leflunomide, charged by the Social Security System, was only €1078.20, and for methotrexate SC, €1302.98, leading to the conclusion that treatment with leflunomide, under these circumstances, represents a savings of €224.77/patients/year to the Social Security System. When recalculating the annual costs and applying the ACR20 criteria. The cost per responding patient with leflunomide would be €7036 (4053–13562) versus 10 066 (6100–28 789) euros that would cost to have a responding patient treated with methotrexate SC. Costs related to the ACR50 criteria would be €7036 (4784–11 504) for leflunomide and €14 093 (8113–38 855) for methotrexate SC, respectively.

Table 2
Annual cost per responding patient

	Annual cost*, €	NNT (95% CI)	Annual cost (euros) per NNT, (95% CI)
ACR20			
Leflunomide	1793.30	4 (2.56–7.71)	7173 (5380–14 346)
Methotrexate SC	2149.20	5 (3.03–14.3)	10 746 (8596–32 238)
ACR50			
Leflunomide	1793.30	4 (2.72–6.54)	7173 (5380–12 553)
Methotrexate SC	2149.20	7 (4.03–19.3)	15 044 (10 746–42 984)

Abbreviations: CI, confidence interval; NNT, number needed to treat; SC, subcutaneous.

* Includes annual medication, follow-up examinations, and periodic reviews according to the products technical insert.¹³

Discussion

Several currently available^{4,6} have pointed out a similar efficacy between leflunomide and methotrexate in the management of patients with RA. As for their comparison in pharmacoeconomic terms, the relationship between cost and effect for leflunomide has been compared with that of methotrexate and sulphasalazine in a study performed in the United Kingdom¹⁶ using a Markov model based on a cohort of patients with RA followed for more than 15 years in 9 rheumatology units in that country. The mean effectiveness of leflunomide was calculated using the data from 2 European trials, one versus methotrexate⁶ and the other one versus sulphasalazine,¹⁷ and a third one, an American trial, versus methotrexate.¹⁸ The results versus sulphasalazine were favorable to leflunomide, but versus methotrexate the results were contradicting: when employing the data from the American trial, the results showed the superiority of leflunomide versus methotrexate, but when using the data from the European study, the contrary is true. On the other hand, in an RA treatment cost-minimization study with leflunomide versus a combination of oral methotrexate and infliximab, performed in Spain in 1999, the results showed a lower annual cost of treatment in the case of leflunomide.¹⁹

The appearance of a new formulation of methotrexate with higher costs when compared to traditional presentations justifies the performance of an analysis that evaluates the pharmacoeconomic implications of the use of these drugs. According to the results obtained by this EE and considering the costs accumulated for 1 year, both the pharmacologic treatment with leflunomide as well as the cost of the complementary examinations associated directly to treatment are cheaper than treatment with methotrexate SC.

This study has some limitations; among them stands out the methodologic assumption that the recommendations for the performance of periodic follow-ups in patients treated with each of the drugs considered in this study adjust to the reality of the Spanish clinical practice. The impact of this assumption in the final results, however, is minimized after employing the same information source in order to obtain such data for both drugs. It might be possible that among the variability of the common clinical practice, the number and frequency of examinations and diagnostic procedures do not always correspond to the ones employed in the current analysis, but there is no reason to believe that this variability of clinical practice would affect differently leflunomide and methotrexate.

Another important limitation is that, although the value of the specific estimate of NNT associated to leflunomide has been in all cases inferior to the one associated to methotrexate, indicating a greater efficacy of leflunomide, a 95% CI test indicated that the differences are not statistically significant, because the CI is severed. In spite of the fact that the US301 trial has not been able to show statistical superiority of leflunomide versus methotrexate, it must be indicated that the CI of the NNT are narrower in the case of leflunomide, which indicates a greater certainty on the

value of specific estimate. If future comparative trials between leflunomide and subcutaneous methotrexate are performed, the estimates will have to be performed again and maybe with firmer evidence, because in this analysis we have parted from the fact of considering that methotrexate sc has the same efficacy as oral methotrexate. A study published recently comparing the efficacy and safety of subcutaneously administered methotrexate with the oral formulation, showed favorable results in effectiveness for the subcutaneous route and equal tolerability.²⁰

The EE here presented has shown that, if the injected form of methotrexate is being considered, leflunomide is a cheaper option, regarding both the drug as well as the follow-up examinations. In the future, when comparative studies between leflunomide and methotrexate SC are available, it would be convenient to perform a complete economic evaluation, in order to obtain the cost by AVAC.

Finally, another element to take into account when choosing a treatment and which has not been included in this analysis is the presumed preference of the patient for an oral treatment versus injections, due to the fear that some patients, 30% according to some authors,²¹ have of the latter.

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