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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ARTICLE INFO

Artículo: Comparar 2 fármacos para la artritis reumatoide (AR): leflunomida y metotrexato subcutáneo (s.c.) (jeringas precargadas), considerando tanto costos 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
leflunomide is 4 (IC del 95%, 2.72-6.54) and the 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 respondido 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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Table 1
Annual cost of follow-up and control examinations in patients treated with leflunomide and methotrexate subcutaneous

<table>
<thead>
<tr>
<th>Complementary tests</th>
<th>Leflunomide</th>
<th>Methotrexate SC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost per unit 15 €</td>
<td>Units/year</td>
<td>Total/Year</td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>18</td>
<td>–</td>
</tr>
<tr>
<td>Renal function</td>
<td>2.14</td>
<td>–</td>
</tr>
<tr>
<td>Liver function</td>
<td>4.21</td>
<td>18</td>
</tr>
<tr>
<td>Lung function</td>
<td>43.61</td>
<td>–</td>
</tr>
<tr>
<td>Complete hemogram</td>
<td>15.19</td>
<td>18</td>
</tr>
<tr>
<td>Rheumatology consult</td>
<td>55.26</td>
<td>6</td>
</tr>
<tr>
<td>Total per patient and per year of treatment</td>
<td>680.76</td>
<td>710.26</td>
</tr>
</tbody>
</table>

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-piruvic 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 €224.7/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 methotrexte SC, respectively.
### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Annual cost*, €</th>
<th>NNT (95% CI)</th>
<th>Annual cost (euros) per NNT, (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACR20</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leflunomide</td>
<td>1793.30</td>
<td>4 (2.56–7.71)</td>
<td>7173 (5380–14 346)</td>
</tr>
<tr>
<td>Methotrexate SC</td>
<td>2149.20</td>
<td>5 (3.03–14.3)</td>
<td>10 746 (8596–32 238)</td>
</tr>
<tr>
<td><strong>ACR50</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leflunomide</td>
<td>1793.30</td>
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<tr>
<td>Methotrexate SC</td>
<td>2149.20</td>
<td>7 (4.03–18.3)</td>
<td>15 044 (10 746–42 984)</td>
</tr>
</tbody>
</table>

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.

### Discussion

Several currently available 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 Kingdom using a Markov model 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 methotrexate and the other one versus sulphasalazine, and a third one, an American trial, versus methotrexate. The results versus sulphasalazine were favorable to leflunomide, but versus methotrexate the results where 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 a 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.

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-up 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.

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, have of the latter.

### References


