Response of the author to the letter "Cost-effectiveness study of leflunomide versus methotrexate"

Respuesta del autor a la carta «Estudio coste-efectividad de leflunomida frente a metrotexato»

To the Editor:

In reference to the letter sent to the editor on our article "Comparison of leflunomide and subcutaneous methotrexate in the treatment of rheumatoid arthritis: an approximation based on the number of patients needed to treat",[1] the authors wish to clear some aspects that have been criticized in our study.

In first place, it is not an economic evaluation of drug usage, such as those collected in several publications; rather it is the type of economic evaluation that is currently being employed in many Spanish hospitals when there is need to introduce a new drug into the hospital therapeutic arsenal and is based on the Guidelines for the incorporation of new drugs[2] proposed by the Hospital Virgen del Rocío (Sevilla) and the *Agencia Andaluza de Evaluación de Tecnologías Sanitarias* (AETSA).

In the analyzed clinical trials there were no statistically significant differences between leflunomide (LEF) and methotrexate (MTX), but there were between both and placebo. In none of the tables presented in our article did we present cost-effectiveness ratios, but the cost of a patient reaching the proposed therapeutic objectives (American College of Rheumatology 20 [ACR20]), in other words, what is the cost of "curing" the patient? In spite of detractors with respect to the use of numbers needed to treat (NNT) in pharmacoeconomic evaluations,[3] we did not find enough evidence to not use them, always specifying bias and being perfectly aware of the limitations of this tool,[4] something that was performed in our articles discussion.

It is true that the article by Braun et al[5] was not taken into account in the results of our study, although it was cited in the discussion of our work because of the new information it provides. If we calculated all of the NNT data from the article by Braun J, 2008, then we would only be able to obtain this parameter for a comparison between the oral and subcutaneous form (see the final part), not with respect to placebo, which is how the NNT should be employed when comparing 2 drugs and when there is no real previous comparison between these same medications (LEF vs MTX by themselves). If we had performed this calculation, the NNT would only inform us of how many more patients would need to be treated with one therapy over the other and this was not the objective of the study, such as it is explained in pages 2 and 6 of our contribution. In any case, the article by Braun reflects an economic evaluation performed in another country and, therefore, with different data of resource use and unit costs than is Spain, making it impossible to extrapolate the results from one country to another and justifies the practice of adapting locally the economic evaluations performed in different countries.

In order to correctly calculate the efficacy of a drug using NNT, this drug has to be compared to placebo, because the NNT formula is derived from the difference of effects between two study groups and its reading is incomplete if the risk for the base of the control group, ie, the placebo group, is not mentioned.[4]

In addition, in the article by Braun J, 2008,[5] the data presented as totals correspond to the arms, including rescue therapy (when the ACR20 was not met), in other words, increasing the dose in one arm and adding subcutaneous methotrexate (MTX SC) in the oral methotrexate arm, making us therefore unable to infer the "real" efficacy of MTX SC versus the oral form, only the efficacy of one regime versus the other. The arms of the study were MTX 15 mg oral+MTX 15 mg SC as rescue therapy (in 30 patients) versus MTX SC 15 mg+MTX SC 20 mg as rescue therapy (in 22 patients). This increase in the dose of the second arm with respect to the first can be the cause of a larger efficacy seen for the SC form compared to oral.

We are unable to understand the concept mix the author of the letter to the editor refers to when expressing that "common clinical practice in our country has evolved in such a way that the doses used in the article by García et al[1] are low in comparison to those recommended by the Spanish Society of Rheumatology (7.5 to 10 mg/week during the first 4 weeks, increasing to 20 mg/week starting on week 8)." We believe that it is bold to make such an affirmation based on only one recommendation (Spanish Society of Rheumatology) and there are no published studies supporting such a statement, because one thing is a recommendation and another, very different, is "my patient." On the other hand it would be untruthful of us to change the dosages analyzed in the study that originated this publication. In any case, the use of data of the drug insert is mentioned as a limitation of our work.

On the other hand, we are criticized for interpreting the results with respect to the difference of costs between one option and the other; we want to clear up the fact that the lack of significant differences in efficacy means just that, that they are not significant ($P<.05$), not that they are not relevant to cost, such as can be observed in Table 2 of our publication, because from a purely economic standpoint several conclusions can be extracted. Even by reducing the cost of acquiring MTX SC at 150.21€/year by adjustments in the size of the syringes, just as the author of the letter to the editor refers, the difference between both would still be important and nearing 3000€/year per patient reaching ACR20 (these differences would have a mean, 2821€; 95% CI, 1465–14 757€).

In the introduction of our work we cited 2 letters to the editor in which the authors state that the MTX SC is probably more effective than oral,[6,7] one of which[6] also recognizes that the cost of administration with respect to the oral form increases more than sevenfold. In the economic evaluation by Maetzel et al,[8] the existing differences between the costs of LEF and MTX with respect to our study are mainly due to the fact that costs were adjusted to Canadian currency in 1888 and that drug prices in the US and Canada are much higher than ours; the cost of acquiring LEF as reflected in that study[8] was $Can 3853 versus 1112.5€ per patient and year of LEF treatment in our country in 2008, including the loading dose. These differences are vast enough to justify a study in our country and not to draw economic conclusions based on the abovementioned article.

By not having publications with the real data on how the treatment of rheumatoid arthritis is carried out (dose, duration, regimen, etc) and the real efficacy (effectiveness) of the mediation employed, we have to base our study on the drug inserts approved by the Ministry of Health and Consumption for these medications as part of the documents presented by the manufacturing laboratories themselves, in other words, their clinical trials.

With respect to the pharmacoeconomics study performed by Crespo et al and presented at the Spanish Society of Rheumatology congress of 2008, we lack enough data to perform a critical analysis, because it is not published, except for the abstract book.

In summary, our study provides enough information for the decision-maker regarding costs necessary to reach ACR20 in a patient with the baseline characteristics of the studies under analysis. At no time have we overestimated the advantages of LEF over MTX, and the supposed economic advantages derive from a recognized and reasonable methodology. There are, undoubtedly, limitations in this evaluation, something inherent to all economic evaluations, but we, the authors, have manifested so in the discussion; therefore, all of the information has been put in the hands of the readers in order to enable them to reach pertinent conclusions impacting their clinical practice.

References

1. García Ruiz JA, Montesinos Gálvez AC, Pérez Costillas L, Rebollo P. . 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. Reumatol Clin. 2009;5:66-70.
2. Agencia de Evaluación de Tecnologías Sanitarias de Andalucía. Guía para la Incorporación de Nuevos Fármacos. Apoyo a la toma de decisiones en los hospitales del Sistema Sanitario Público de Andalucía [Internet]. Versión 2.0. Sevilla: AETSA; 2004 [consulted 6/2/2009]. Available from: URL: http://www.juntadeandalucia.es/salud/orgdep/aetsa/pdf/Guía GINF v2.pdf.
3. Kristiansen IS, Gyrd-Hansen D. Cost-efectiveness analysis based on the number-needed-to-treat: Common sense or non-sense? Health Econ. 2004;13:9-19.
4. Figueredo E, Canosa L. Limitaciones y falacias de la fórmula del "número de pacientes que será necesario tratar". Med Clin (Barc). 1999;112:36.
5. Braun J, Kästner P, Flaxenberg P, Währisch J, Hanke P, Demary W, et-al. Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis: Results of a six-month, multicenter, randomized, double-blind, controlled, phase IV trial. Arthritis Rheum. 2008;58:73-81.
6. Moitra RK, Ledingham JM, Hull RG, McCrae FC, Thomas AL, Shaban R, et-al. Caveats to the use of parenteral methotrexate in the treatment of rheumatic disease. Rheumatology. 2005;44:256-7.
7. Bingham SJ, Buch MH, Lindsay S, Pollard A, White J, Emery P. Parenteral methotrexate should be given before biological therapy. Rheumatology. 2003;42:1009-10.
8. Maetzel A, Strand V, Tugwell P, Wells G, Bombardier C. Economic comparison of leflunomide and methotrexate in patients with rheumatoid arthritis: An evaluation based on a 1–year randomised controlled trial. Pharmacoeconomics. 2002;20:61-70.

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