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Letter to the Editor

Cost-effectiveness study of leflunomide versus methotrexate

Estudio coste-efectividad de leflunomida frente a metotrexato

To the Editor:

In reference to the article "Comparison of leflunomide and subcutaneous methotrexate for the treatment of rheumatoid arthritis: an approximation based on the number of patients needed to treat",[1] we believe that it is necessary to make some comments after its careful reading.

The economic evaluation of rheumatoid arthritis (RA) of the above mentioned article is based on a randomized clinical trial (RCT) lasting 12 months, comparing leflunomide, oral methotreate and placebo.[2] The resulting economic analysis would be reasonable if the same options were compared in the RCT, but the authors have extrapolated the efficacy of oral methotrexate to subcutaneous methotrexate, when it is known—the authors themselves point this out in the discussion—, that subcutaneous methotrexate has a greater efficacy, demonstrated in a multicenter RCT lasting 24 weeks[3] (Table). This circumstance, we believe, invalidates the main premise of the study by García et al.[1] In addition, the 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).[4] Therefore, the low dose of methotrexate administered could be underestimating its efficacy in this study.

On the other hand, and although the methodology employed in the study is initially correct (not the main premise that oral methotrexate is the same as subcutaneous), we believe that is not the case with the interpretation of the results. Therefore, the lack of a statistically significant difference in terms of efficacy, recognized by the authors themselves, is also reflected in the yearly cost analysis per number necessary to treat (NNT), with overlapping confidence intervals in both cases, making it difficult to interpret the results and leading to arguable affirmations such as "the use of leflunomide with respect to methotrexate sc could represent savings of more than 3500 euros per responding patient."

In this sense, it must be mentioned that a previous study[5] evaluated the economic consequences of leflunomide treatment in comparison to oral methotrexate based on the same RCT by Strand et al,[2] with different results than those of García et al,[1] showing that the costs associated to leflunomide are significantly higher than with oral methotrexate when the expense of buying the drug and follow-up studies are factored in ($P<.0001$), and only if this is excluded, do they result similar.[5]

On the other hand, Crespo et al[6] carried out a complete economic evaluation based on the study by Braun et al[3] concluding that subcutaneous methotrexate versus oral methotrexate increases patient survival between 0.308 and 0.396 years of life, adjusted for quality, with reasonable costs making this option an efficient intervention for the Spanish health system.[7]

There are other minor points which could be discussed, such as not considering the costs of adverse events, some of which were more frequent with leflunomide (diarrhea, allergic reactions, etc) or the assumption that the use of a preloaded syringe of subcutaneous methotrexate derives in the waste of the remaining methotrexate when treating patients with a prescribed dose of 7.5 mg using preloaded 10 mg syringes. It must be pointed out that the Spanish marketplace has had 7.5 mg subcutaneous methotrexate preloaded syringes available since 2007,[8] the use of which would result in a total methotrexate cost reduction of 150.21€.

In summary, we believe that the study by García has questionable aspects that could be overestimating the advantages—both clinical and economic—of leflunomide versus methotrexate.

Tabla
Efficacy of the randomized clinical trial of Braun et al[3]

	Oral methotrexate, n=187	*Subcutaneous methotrexate, n=188*
ACR20	70%	78%[a]
ACR50	59%	62%
ACR70	33%	41%[a]

[a] *P*-valor<.05.

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