Letter to the Editor

Indirect meta-analytical comparison of azathioprine and of beta interferon effectiveness in all forms of multiple sclerosis pooled together

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To the Editor

In pharmacotherapy of multiple sclerosis (MS), the advantages of oral administration are increasingly being recognised [1]. Long time ago, oral azathioprine was tested in a series of small clinical studies, and two meta-analyses were published that pooled the information available at that time [2,3]. Thereafter, azathioprine has not attracted the interest of pharmaceutical industry mainly because of its low cost, and so no further randomised trials (RTs) were conducted.

Considering the recent trends favouring oral treatments for MS, we found that a re-visitation of the role of azathioprine in comparison with current treatments can be worthwhile. RTs of direct comparison of azathioprine with beta interferons (IFNs) continue to be a few [4,5]. In addition, since the information on the effectiveness of azathioprine – unfortunately – is available only with regard to all types of MS pooled altogether, also the information on the comparators must be selected according to this imperfect criterion. Despite these limitations, we thought that an analysis aimed at an indirect comparison between azathioprine and IFNs could be of interest.

1. Methods

Source of clinical data. The network meta-analysis published by Filippini et al. [6] is probably the most comprehensive work in this field. This meta-analysis systematically reviewed the therapeutic evidence for patients with MS and was specifically aimed at RTs. The effectiveness data for each treatment were presented with separate analyses focused on the different forms of MS along with an overall analysis that, for each treatment, collated all available information for patients with any type of MS. These pooled analyses published by Filippini et al. on any type of MS represent the best clinical material for an indirect comparison between azathioprine and IFNs.

Design. Our analysis was aimed at an indirect meta-analytical comparison between oral azathioprine and IFNs. The criteria for our comparison were the following: a) clinical material for azathioprine or IFNs represented by placebo-controlled RTs (direct comparisons) and b) selection of patients with any type of MS. From a preliminary examination of the previous meta-analyses [2,3,6], relapse at 24 months was the only end-point for which enough clinical material was available. The RTs included in our study were obtained from the three meta-analyses mentioned above [2,3,6], which were integrated by a further PubMed search. Search terms were (azathioprine OR “beta interferon”) AND “multiple sclerosis”; filter: “Randomised clinical trials”; period: 1966 to August 2014. All comparisons between azathioprine, IFNs, and placebo were analysed through an “all-in-one” model of the Bayesian network meta-analysis (fixed-effect model) [7]. Relapse at 24 months was the end-point. Relative risk (RR) with 95% credible intervals (CrI) was the outcome measure.

2. Results

Our PubMed search did not find any additional RT in comparison with the previous literature. Fig. 1 shows the rates of end-point achievement of the RTs versus placebo (Panel A), the estimates of RR for the three comparisons (Panel B), and the rankogram in which these results were subjected to probabilistic analysis. The indirect comparison of azathioprine vs IFNs showed a RR of 0.88 (95% CrI: 0.78 to 1.08) for the relapse rate at 24 months. In the rankogram, placebo (as expected) always ranked worst; azathioprine ranked best in nearly all simulations whilst IFNs generally ranked second. Heterogeneity remained far from statistical significance (p > 0.28).

3. Discussion

Our study confirms that oral azathioprine might still have a role in the treatment of MS particularly for patients otherwise treated with IFNs. Interestingly, the effect size found in our analysis was consistent with the preliminary results of prospective studies that compared head-to-head azathioprine with IFNs [4,5].

The main limitation of any analysis in this field is that the inclusion criteria adopted in the original trials did not differentiate between the different disease forms. Unfortunately, this limitation cannot be retrospectively overcome because old trials have never been re-published according to subgroup analyses.

To better interpret our results, a post-hoc equivalence analysis (with alpha at 2.5%) can be tried based on the CrIs reported above. According to this interpretation, azathioprine is +12% more efficacious than IFNs with margins ranging from −8% to +22%. If one accepts that margins used for power calculation represent a reference for equivalence studies [8], a recent and authoritative RT adopted a margin at ±30% for this end-point [9]. If one compares our CrIs with this margin, azathioprine and IFNs appear to be equivalent.

There was a remarkable temporal difference (around 10 years) between the RTs on the IFNs and those on the azathioprine. Since the knowledge about the disease and its course was poor at that time, the RTs on azathioprine carried out in the eighties included both relapsing...
remitting and chronic progressive patients. In this last disease form, relapses are less frequent and more difficult to prevent and therefore the sample size in the azathioprine RTs likely was inadequate to assess efficacy.

The results of our study just allow us to support the hypothesis that azathioprine efficacy on this outcome is at least equivalent to that of the IFNs. Whilst no meta-analysis can substitute RTs in the field, our hypothesis of equivalence justifies head to head comparative RTs.
Conflict of interest

None declared.

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References


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