Intramuscular IFNβ-1a in multiple sclerosis: 'no proof of effectiveness' or 'proof of no effectiveness'? A. Messori, V. Fadda, D. Maratea and S. Trippoli HTA Unit, ESTAV Toscana Centro, Regional Health Service, Florence, Italy

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The debate on the effectiveness of interferons in multiple sclerosis (MS) has recently been fuelled by a meta-analysis of the Cochrane Collaboration [1]. One controversy regards intramuscular IFNβ₁α (iIFNβ₁α); given the lack of convincing efficacy data, this agent demonstrated an unfavourable benefit-risk profile in relapsing-remitting MS and, furthermore, showed no evidence of efficacy in decreasing disability progression in progressive disease.

Two separate questions were addressed by Filippini et al.: superiority of iIFNβ₁α versus placebo; and inferiority of iIFNβ₁α versus other active agents. While the second question was settled by demonstrating inferiority, the first remained open as the conclusion of Filippini and co-workers was mid-way between 'no proof of effectiveness' and 'proof of no effectiveness'[2,3].

Trial-sequential analysis (TSA) is a statistical technique that improves the interpretation of meta-analyses, and particularly those generating negative results [3]. One merit of TSA is that this technique classifies each non-significant meta-analysis into one of two mutually exclusive categories: inconclusive result; or proof of no effectiveness (i.e. 'futility').

We applied TSA to re-examine the three randomized trials comparing iIFNβ₁α versus placebo studied by Filippini et al. Our analysis was focused on MS of all types, and considered the end-point of relapse over 24 months. Assumptions included two-sided testing, risk of type-1 error 5%, power 80%. The event frequency with placebo was assumed to be 48% (i.e. the overall arithmetic rate of the three control groups).

The expected benefit with iIFNβ₁α was set at a relative improvement of at least 15%. As usual, the main result of TSA was expressed through cumulative z-curve. Further methodological details have been described previously [3]. Our results (Fig. 1) indicated the futility of iIFNβ₁α, i.e. proof of no effectiveness: clearly, this result is more informative than the simple conclusion of no proof of effectiveness. Furthermore, our TSA estimated that the optimal information size would be 1496 patients, but at the cumulative number of 787 patients the results were already sufficient to reach the conclusion of futility.

The main limitation is that separate conclusions for relapsing-remitting and progressive disease could not be made due to the insufficiency of the clinical material.

**Disclosure of conflict of interest**
The authors declare no financial or other conflicts of interests.

**References**