Letter to the Editor

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Pegylated interferon-α2a versus pegylated interferon-α2b in hepatitis C: reappraisal of effectiveness on the basis of trial sequential analysis

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Two pegylated interferons [interferon-α2a (pIFN-α2a) and interferon-α2b (pIFN-α2b)] are available for the treatment of hepatitis C, but their respective therapeutic profile remains controversial. Randomized-controlled trials (RCTs) have yielded conflicting results [1–3]. With respect to the end-point of sustained virologic response (SVR), a Cochrane review [4] has concluded that pIFN-α2a is significantly more effective than pIFN-α2b (relative risk = 1.11 in favour of pIFN-α2a; 95% confidence interval: 1.04–1.19; eight trials; 4335 patients). However, another meta-analysis examining genotype 1 patients [5] has suggested that there are no differences (relative risk = 1.08 in favour of pIFN-α2a; 95% confidence interval: 0.99–1.18; seven trials). This question therefore remains open [5,6].

Trial sequential analysis (TSA) is increasingly being recognized to facilitate the interpretation of controversial meta-analyses [7–10]. Its advantage is that this technique can differentiate between superiority (proof of effectiveness), inconclusiveness (no proof of effectiveness) and futility (proof of no effectiveness).

We applied TSA to the same eight RCTs examined by the Cochrane review [4]. The end-point was SVR expressed as failure rates. Our assumptions included two-sided testing, type 1 error of 5%, power of 80%. The expected improvement with pIFN-α2a was set at a relative risk reduction (RRR) of 20% or 12% or 8%. The event rate for the pIFN-α2b group was assumed to be 58% (i.e. the cumulative arithmetic rate in the eight RCTs). The graph of a cumulative z-curve was generated; the boundaries for concluding superiority/inferiority/futility were determined according to the O’Brien–Fleming α-spending function.

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Fig. 1

Fig. 1: Trial sequential analysis of eight randomized-controlled trials comparing two pegylated interferons according to sustained virologic response rates in patients with hepatitis C. The expected relative risk reduction (ERRR) was assumed to be 20% (a) or 12% (b) or 8% (c). In the z-curve (represented in blue), individual trials correspond to individual segments; trials are plotted in chronological order (from left to right). The x-axis indicates the cumulative number of patients; the starting point of the z-curve is always at x=0, that is, inclusion of no trials. The results shown in (a–c) indicate futility, inconclusiveness and inclusiveness, respectively; in (b), the boundary for superiority was closely approached but the z-curve did not cross the red line. The vertical red line indicates the optimal information size to demonstrate the incremental benefit, whereas the total of 4335 patients refers to the eight trials. C, control arm (pIFN-α2b, no pump); T, treatment arm (pIFN-α2a). Red lines are the boundaries for superiority or inferiority and green lines are for futility (or proof of no difference).

Our TSA is summarized in Fig. 1 (for details, see the supplementary material, Supplemental digital content 1, http://www.observatoriumnocazione.net/supplements/en2013-supplementary-material.pdf). In Fig. 1a, where the criterion of no difference was extensive (no difference if ERR ≤ 20%), our results provided the proof of no difference; in contrast, the more challenging criterion of no difference if ERR is 8% or less yielded a clearly inconclusive result (Fig. 1c). The result shown in Fig. 1b (assumption: no difference if ERR ≤ 12%) was the more intriguing one. On the one hand, the TSA threshold between superiority and futility (ERR = 12%) approximately coincided with the pooled result found in Awad’s meta-analysis; on the other hand, the last point of the z-curve closely approached the superiority boundary, but did not cross it. Interestingly, the optimal information size was estimated at 5569 patients. Hence, the result of Fig. 1b is inconclusive.

Overall, the three analyses described here (showing inconclusiveness in two cases or futility) do not confirm the conclusion made in previous studies that pIFN-α2a is more effective than pIFN-α2b according to SVR rates. A trend favouring pIFN-α2a was actually observed under some analytical circumstances, but this trend seemed to have little clinical relevance if one considers its (hypothetical) magnitude and the lack of a statistical proof. Consequently, the most appropriate conclusion for the comparison between the two pegylated interferons according to the end-point of SVR cannot be the superiority of pIFN-α2a.

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Conflicts of interests

There are no conflicts of interest.

References

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