LETTER TO THE EDITOR

Parenteral vs oral iron in patients with inflammatory bowel disease: Quantifying information size by trial sequential analysis

Dear Sir,

In patients with inflammatory bowel disease (IBD), iron replacement therapy is beneficial because of its ability to improve hemoglobin. Parenteral formulations are thought to be more effective than oral iron, but despite the availability of several randomized trials no study has thus far quantified the information size needed to adequately compare these two routes of administration. Information size is a new parameter proposed in the framework of trial-sequential analysis (TSA) with the aim to establish whether or not further trials are needed on a given therapeutic issue.

Quite recently, one meta-analysis carried out by Lee et al. has addressed the issue of iron in IBD and has found that parenteral iron yields significantly greater improvement in hemoglobin levels than oral iron; three randomized trials were included in Lee's analysis.

Application of TSA to controversial therapeutic issues can be of value because this statistical technique not only studies information size, but classifies each meta-analysis into one of four mutually exclusive categories (superiority, inferiority, futility, or inconclusive result). In addition, it should be recalled that TSA adopts more conservative thresholds than standard meta-analysis for demonstrating superiority or inferiority.

We applied TSA to re-examine the three randomized studies evaluated by Lee et al. Our analysis considered the end-point of hemoglobin improvement. Our main assumptions included two-sided testing, risk of type I error = 5%, and power = 80%. The intervention effect was set at an anticipated absolute

Figure 1 Trial sequential analysis based on the three available randomized trials. In the z-curve (represented in blue), individual trials correspond to individual segments; trials are plotted in chronological order (from left to right) with the x-axis indicating the cumulative number of patients; the starting point of the z-curve is at x = 0, i.e. inclusion of no trials; at the cumulative number of 333 included patients, the curve has already crossed the red boundaries thus reaching the superiority area; on the other hand, the third trial leads the final position of the z-curve at limits between superiority and inconclusive result. Abbreviations and symbols: red lines are the boundaries for superiority or inferiority while green lines are the boundaries for futility. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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improvement in hemoglobin of at least 10 g/L. As usual, the main result of TSA was expressed through the graph of cumulative z-curve. With reference to this graph, the boundaries for concluding superiority or inferiority or futility were calculated according to the O'Brien-Fleming alpha-spending function. Our analysis employed a specific statistical software (user manual for TSA, Copenhagen Trial Unit 2011, see www.ctu.dk/tsa).

Fig. 1 shows our results. Application of TSA to these three randomized trials generated a result very close to the conclusive demonstration of superiority of parenteral iron. In particular, our analysis estimated that the optimal information size would be 478 patients; however, the cumulative number of 333 patients (included in the three trials published thus far) was very close to conclusively demonstrate the superiority of parenteral iron. Further details on our TSA are given in the Supplementary material posted on the web (Appendix A).

In summary, the results of our analysis can be seen as a (nearly) conclusive proof that parenteral iron improves hemoglobin in these patients more than oral iron does. Our evaluation is also a practical example of the role that TSA can play to integrate the results of “traditional” meta-analyses.

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Statement of authorship: the three authors contributed to a similar extent to the present study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.crohns.2013.04.014.

References


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Appendix A: supplementary information posted on the web.

1) Repetition of the meta-analysis carried out by Lee et al.: this repetition had the propose to verify the agreement of all trial-specific data between Lee and coworkers’ meta-analysis and our re-analysis. Graph and statistical calculations according to the OMA software.
2) Detailed information about the assumptions adopted for running our TSA: Calculations according to the TSA software.