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Reply

Deferiprone versus deferoxamine in patients with thalassemia major: a randomized clinical trial

We appreciate the interest of Dr. A.D. Tsakok in our article [1] reporting on a randomized controlled trial of deferiprone versus deferoxamine for thalassemia major and suggesting equivalence between the two treatments. However, he seems to have missed the objective and therefore the methods of the study as well as the results. In fact, with reference to Table 3, he commented on the method we used for several comparisons, which in fact we did not do, in accordance with the study aims and methods. The same applies to the comments for Table 4.

In the Methods section of our article, under the "Objectives" subheading, we reported "*the study objective was to compare the two treatments in the reduction of iron overload or to prevent its increase*". Accordingly, the main measure outcome to assess the treatment efficacy was "*the difference between the serum ferritin concentration before and after one year of treatment*" in each trial arm, as clearly reported under the "Outcomes" subheading. For these reasons, it would be misleading to compare the end-treatment values of those parameters to which Dr. Tsakok refers in his comments.

To compare the differences between *before* and *after* treatment values in the two study arms, we planned, in the protocol phase, to use a *t* test with equal variances. In fact, because of randomization and because of the underlying equivalence hypothesis of the study, we had no reason to predict different variances between the study groups. Therefore, although we are aware that several of the standard deviations of the assessed means (see the column "*Difference*" in Tables 3 and 4) may be unequal between the study groups, we conducted the analysis according to the predefined study protocol, as suggested elsewhere [2]. It must be noted however, that the absence of any statistically significant difference in treatment outcome between the study groups is confirmed also by the *t* test for unequal variances. As it may be seen by the data reported in Table 3 in our article, the difference in serum ferritin levels from before to after treatment was not significantly different in the two study groups either by using a *t* test for equal variances ($P = 0.9323$) or for unequal variances ($P = 0.9325$). The same is true for Table 4.

Regarding the Tsakok method, it is not included in the most frequently used statistical packages, worldwide (SAS, SPSS, BE, Epi Info, SUDAAN, S-PLUS, StatXact, StatView BMDP, JMP, Statistics, Epicure, Review Manager, True Epistat, Egret, Prism, Excel, SigmaStat, MlwiN, WesVar, NCSS 2000, CART, InStat, EXACT Software, Minitab, Systat) [3]. We used a well-known and widely used statistical package, STATA 6 (1999 Stata Corporation, College Station, TX). This program supplies the "Welch" or "Satterthwaite" method for dealing with non-homogeneity of variances. Moreover, a MEDLINE search disclosed that the Tsakok method is only quoted in few letters, written by Dr. Tsakok himself, confirming that the scientific statistical community has not yet recognized this as a valid statistical method. Clearly, should this method provide a basis for a diverse interpretation of the many thousands of randomized controlled trials published each year and comparing means as a measure of the treatment outcome, then it would be a responsibility of the scientific community to adopt such a method. This may only be achieved after a valid full publication of the method in a primary statistical scientific journal.

Finally, the statistically significant differences Dr. Tsakok claims to be identified only by its method in Tables 3 and 4 in our article, although not pertinent to the study aims, methods and results, are significant also by the commonly used methods for equal or for unequal variances, as any reader may easily verify from the data provided.

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