Practical application of statistical models aimed at assessing bioequivalence through network meta-analysis

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LETTER TO THE EDITORS

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To the editor

The two articles by Herranz et al. [1] and Ring et al. [2] have addressed the issue of how indirect comparisons of bioequivalence can be carried out by application of network meta-analysis. One merit of these articles is that a full set of statistical equations has been provided; in this way, readers can realize that these equations are essentially the same as those commonly used in the application of network meta-analysis to clinical end-points. On the other hand, one limitation of these articles is that describing the equations does not necessarily imply that people involved in bioequivalence studies can then manage the consequent computational tasks. This limitation holds true particularly when, as in these two articles, a specific software is not proposed to facilitate the application of statistical models.

Softwares designed for network meta-analysis are numerous [3]. The most simple tool in this area is represented by the ITC software (based on Bucher’s method [4]) that the Canadian Agency for Drugs and Technologies in Health has made available on its website [5]. Since bioequivalence is traditionally based on log-transformed values, ratios of area under the curve (AUC) (where unity represents bioequivalence) were preferred over percent values of bioavailability.

In the paper by Herranz et al. [1], the 90 % confidence interval (CI), expressed as AUC ratio, was 0.9306 to 1.0474 for the PharOS 5 mg formulation and 0.9924 to 1.1089 for the Sandoz 5 mg formulation (see Table 2 of reference [1]). In the indirect comparison between these two products, the relative AUC for PharOS vs Sandoz (expressed as 90 %CI) was estimated to be 0.8684 to 1.02 (according to the heteroscedastic model) or 0.8412 to 1.0530 (according to the homoscedastic model) [1].

The ITC software, as the vast majority of meta-analytic software, adopts 95 %CIs. However, converting 90 %CIs into 95 %CI and vice versa is extremely easy because equations are straightforward [6] and conversions are also available from online tools [7].

To carry out the calculations for the above example regarding tacrolimus, firstly, the 90 %CIs must be converted (e.g., through the online tool of reference [7]) into the corresponding 95 %CIs, which are calculated to be 0.9201 to 1.0593 (with point estimate at 0.9873 for PharOS) and 0.9819 to 1.1207 (with point estimate at 1.049 for Sandoz). Then, the ITC software estimates the 95 %CI for the indirect comparison of PharOS vs Sandoz. In more detail, the mean difference for this indirect comparison (calculated through the ITC software) shows a 95 %CI from −15.99 to +3.67 with a point estimate at −6.16. This 95 %CI can easily be converted—e.g., through the online tool of reference [7]—into a 90 %CI that ranges from −14.41 to 2.09. If this mean difference with its 90 %CI is reexpressed as an AUC, the AUC interval at 90 % ranges from 85.59 to 102.09, which is the final result of our reanalysis. Regardless of whether the approach of Herranz et al. was heteroscedastic or homoscedastic, our values (i.e., 85.59 to 102.09) are nearly identical to those obtained by the Spanish authors (86.84 to 102.00 or 84.12 to 105.30).

In conclusion, the information presented herein can be a useful completion of the two previous articles [1, 2] in order to facilitate the practical application of network meta-analysis in bioequivalence studies. One drawback to this approach is that network meta-analysis models and equations for handling CIs generally rely on the assumption that the data follow a normal distribution, whereas a t-distribution would be more appropriate.

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In fact, although this latter distribution converges towards a normal distribution when sample size is large, this is not generally the case with bioequivalence studies. Hence, while this approach relies on a frequently used but unproven assumption, employing the t-distribution would be the “true” solution to the problem. In this way, however, the mathematical complexity would be greatly enhanced.

Conflict of interests None declared.

References


