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SIPPET trial: The answers

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The lives of persons with haemophilia were revolutionised once home treatment with clotting factor concentrates was introduced in the 1970s(1). The use of dual viral inactivation has practically eliminated the infection risks seen in the 1980s, yet theoretical risks especially of prion transmission remain. Nowadays the development of an alloantibody (inhibitor) in persons with haemophilia is the most serious complication of treatment(2)(3).

When recombinant products were first introduced, there was concern that they were associated with a higher rate of inhibitor development than the previously used plasma derived concentrates. Later a large systematic review by Wight and Paisley from Sheffield reported a higher rate of inhibitors with recombinant compared to plasma derived factor VIII (FVIII) concentrates(4). In a subsequent systematic analysis of 24 studies involving 1167 PUPs treated with plasma derived FVIII and 927 treated with recombinant FVIII, Iorio and colleagues reported that the initial higher risk observed with the recombinant products was largely eliminated once the effects of study design, study period, testing frequency and length of follow-up were accounted for (5). The debate has, however, continued with discrepant results between studies(6).

Mannucci and colleagues in Milan felt that there was sufficient equipoise to warrant a randomised trial between plasma derived concentrates rich in von Willebrand factor and recombinant FVIII products in previously untreated patients with severe haemophilia A(7). In the SIPPET trial 264 haemophilia A PUPs were randomly assigned to one of four plasma derived or one of four recombinant FVIII concentrates. The intention of the study was to investigate the class effect (i.e. plasma vs recombinant concentrates) rather than the rate of inhibitors with specific products. The SIPPET trial was terminated earlier than anticipated following the publication of the RODIN study, which reported a higher rate of inhibitors with one recombinant concentrate(8). Since this concentrate accounted for 48.4% of the recombinant products used in the SIPPET trial it made ongoing randomization difficult. The SIPPET study found a higher inhibitor rate for recombinant compared to plasma derived products (87% higher rate for all inhibitors and 69% for high titre inhibitors)(7). Ironically, the RODIN study that led to the early termination of the SIPPET trial did not find a difference in the rate of inhibitor development in haemophilia A PUPs between plasma derived and recombinant products(8).

The results of the SIPPET trial clearly have major implications in the treatment of every PUP with severe haemophilia A. Since the publication of the SIPPET study, we have observed that the results were discussed at every large haemostasis or haemophilia meeting and multiple additional meetings were convened to specifically consider their implication. We noted that many of the questions asked were frequently the same. Normally some of these points would have been answered in the correspondence columns of the original journal but the New England Journal of Medicine did not accept any letters on the SIPPET trial.

As editors, we felt it would be valuable to ask the authors of the SIPPET trial to respond to these questions formally in print. We received three letters to the
editor (9, 10, 11) and together with a number of questions we had ourselves, we reached agreement with the authors to produce a manuscript to address these questions and their manuscript (12) is published in this issue of the Haemophilia journal. We hope that our readers will be able to make a more informed decision on how to manage their severe haemophilia A PUPs after reading these contributions.

Disclosures:
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