
Article:
Makris, M. and Kessler, C.M. (2017) SIPPET trial: the answers. Haemophilia, 23 (3). pp. 344-345. ISSN 1351-8216

https://doi.org/10.1111/hae.13239

SIPPET trial: The answers

Makris M (1, 2)
Kessler CM (3)

Addresses:

1. Sheffield Haemophilia and Thrombosis Centre, Royal Hallamshire Hospital, Sheffield, UK
2. Department of Infection, Immunity and Cardiovascular disease, University of Sheffield, UK
3. Georgetown University Medical Center, Washington DC, USA

Correspondence to: Professor Mike Makris.
Telephone: +44 114 271 2760
Fax: +44 114 2756126

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:
MM has acted as consultant to CSL Behring, Grifols and NovoNordisk. He is the project leader of EUHASS which receives funding from Bayer, Biotest, BPL, CSL Behring, Grifols, Kedrion, LFB, NovoNordisk, Octapharma, Pfizer, Shire (Baxalta) and SOBI.
CAK has received consulting income from Alnylam, Bayer, Baxter, Grifols, NovoNordisk, Octapharma, Pfizer and Roche; research funding from Bayer Grifols, Octapharma and NovoNordisk; non-monetary research support from Bayer, Baxter, Grifols, NovoNordisk, Octapharma and Pfizer.

References

1. Ingram GI., Dykes SR, Creese AL, et al. Home treatment in haemophilia: Clinical, social and economic advantages. Clin Lab Haematol. 1979;1:13–27.
2. Lassila R, Makris M. Safety surveillance in haemophilia and allied disorders. J Intern Med. 2016;279(6):515–23.
3. Fischer K, Lassila R, Peyvandi F, Calizzani G, Gatt A, Lambert T, et al. Inhibitor development in haemophilia according to concentrate: Four-year results from the European haemophilia safety surveillance (EUHASS) project. Thromb Haemost. 2015;113(5):968–75.
4. Wight J, Paisley S. The epidemiology of inhibitors in haemophilia A: a systematic review. Haemophilia. 2003;9(4):418–35.
5. Iorio a, Halimeh S, Holzhauer S, Goldenberg N, Marchesini E, Marcucci M, et al. Rate of inhibitor development in previously untreated hemophilia A patients treated with plasma-derived or recombinant factor VIII concentrates: a systematic review. J Thromb Haemost. 2010;8(6):1256–65.
6. Peyvandi F, Ettingshausen CE, Goudemand J, Jiménez-Yuste V, Santagostino E, Makris M. New findings on inhibitor development: from registries to clinical studies. Haemophilia. 2017;23:4–13.
7. Peyvandi F, Mannucci PM, Garagiola I, El-Beshlawy A, Elalfy M, Ramanan V, et al. A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A. N Engl J Med. 2016;374(21):2054–64.
8. Gouw SC, van der Bom JG, Ljung R, Escuriola C, Cid AR, Claeyssens-Donadel S, et al. Factor VIII Products and Inhibitor Development in Severe Hemophilia A. N Engl J Med. 2013;368(3):231–9.
9. van den Berg HM, Pipe S, Ljung R. Plasma products do not solve the inhibitor problem. Haemophilia 2017; (in press)
10. Fischer K, Blatny J. Do the SIPPET study results applyto the patients I

treat? Haemophilia 2017; (in press)
11. Iorio A. Research and policy implications of a recently published controlled study in previously untreated haemophilia patients at high risk of inhibitor development. Haemophilia 2017; (in press)
12. Peyvandi F, Mannucci PM, Palla R, Rosendaal F. SIPPET: methodology, analysis and generalisability. Haemophilia 2017; (in press)