We review articles (n = 139) were not significantly different. Development of inhibitory antibodies to coagulation factor VIII (FVIII) are the 100; [The Review].

OBJECTIVE

This study aimed to evaluate the risk of inhibitor development and to clarify the relationship between FVIII product used and inhibitor development in PUPs and minimally treated patients (MTPs).

METHODS

• Prospective and retrospective clinical studies, published from 1 January 1988 to 31 August 2016, with PUPs and MTPs with severe and moderate hemophilia A were identified in a systematic literature search in electronic databases (MEDLINE and EMBASE).

• Studies were included in the meta-analysis if they met the following inclusion criteria:
  i. Prospective or retrospective studies reporting incidence, or multivariable adjusted Hazard Ratios (HRs) with their corresponding 95% confidence intervals (CIs), of inhibitor development in severe or moderately severe hemophilia A PUPs or MTPs treated with any specific FVIII.
  ii. Published original full-text articles were included, Letters, reviews and meta-analyses were excluded, where confidence intervals were considered for inclusion when they reported enough data for the purpose of the meta-analysis.

• The primary outcome measure was development of clinically relevant inhibitors.

• The secondary outcome measure was development of a high-titer inhibitor, defined as peak titer of at least 5 BU/mL up to the 75th exposure day.

• We computed pooled meta-analysis estimates according to the FVIII product used by applying the inverse-variance method, assuming a fixed, or a random-effects model if significant heterogeneity was present.

RESULTS

• In the overall population considered, 548 out of 1,852 PUPs/MTPs developed an inhibitor.

• The pooled estimate was 0.27 (95% CI 0.24–0.31) (Figure 2).

• Also, in only PUPs with severe hemophilia (FVIII activity ≤ 5%), the pooled estimate of all inhibitors was 0.27 (0.22–0.32) (Figure 3).

• Similar patterns were observed in subpopulations with high FVIII (Figure 4) or low inhibitors.

• Significant heterogeneity due to different incidences among studies was found for Recombinate® and Kogenate®. Pooled inhibitor incidence estimates among products ranged from 0.2 to 0.4 without heterogeneity between products.

Multivariable Adjusted Analysis

• A new studies reported inhibitor hazard ratios with the different products used, taking account potential risk factors.

• A meta-analysis of these studies, adjusted to different risk factors, showed PUPs/MTPs treated with ADVATE® had a pooled inhibitor hazard ratio estimate of 0.83 (95% CI: 0.48–0.83) as compared to patients treated with Kogenate® FS® or Helixate FS®. No heterogeneity in pooled HRs across different products was found (p = 0.74).

• The pooled estimates of other FVIII products were not significantly different.

CONCLUSION

• No significant differences in crude inhibitor incidence among FVIII products were found.

• The overall incidence of inhibitors with rFVIII products in PUPs/MTPs included in this meta-analysis was 27%, which is much lower than what was found in the SHIPPE study (44.3% for recombinant class).

• The SHIPPE study comprises classes of products, whereas the different products are represented differently, e.g. 120 patients treated with a second generation FVIII product (Kogenate®), while only 20 with first generation products (13 with Advate® and 7 with Recombinate®, making any conclusion on single products difficult it is impossible.

• In our meta-analysis, differences between rFVIII products were only found considering hazard ratios in which potential confounders were taken into account.

• In conclusion, to our knowledge, this study is the most complete meta-analysis in this patient population, and updates previously carried out meta-analyses.

REFERENCES


DISCLOSURES

*Author is an employee of Boehringer Ingelheim Canada Ltd., now part of Shire. The study was sponsored by Boehringer, now part of Shire.