Is There a Difference in Inhibitor Incidence With Recombinant Products? A Meta-analysis of 2000 Previously Untreated Patients

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INTRODUCTION

- Development of inhibitory antibodies to coagulation factor VIII (FVIII) are the most challenging complication in the treatment of patients with hemophilia A. Inhibitors occur in about 35% of previously untreated patients (PUPs) and neutralize FVIII, making treatment with FVIII ineffective.[1]
- Large cohort studies investigated the association of inhibitor development with different patient-related (ethnicity, FVIII gene defect, polymorphism in immune response genes) and environment-related risk factors (age at first exposure, intensity of treatment, surgery, treatment regimens prophylaxis/on demand, immunological challenges, infections, vaccinations, abnormal FVIII molecules and FVIII product type).[2]
- Recent cohort studies showed differences in inhibitor incidence in previously untreated patients (PUPs) with hemophilia A treated with recombinant factor VIII concentrates (rFVIII).[3-5]

OBJECTIVE

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

METHODS

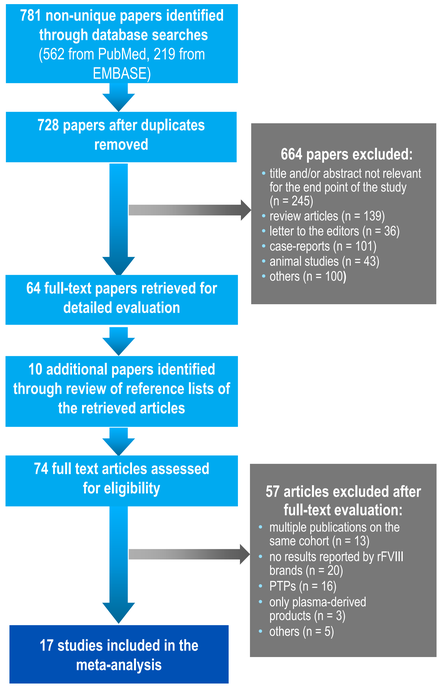
- Prospective and retrospective clinical studies, published from 1 January 1988 to 31 August 2015, with PUPs and MTPs with severe and moderate hemophilia A were identified in a systematic literature search in electronic databases (MEDLINE and EMBASE).
- Studies were included in the meta-analysis if they 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 rFVIII;
  - ii. Published original full-text articles were included. Letters, reviews and meta-analyses were excluded, while conference abstracts 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-analytic estimates according to the rFVIII product used by applying the inverse-variance method, assuming a fixed, or a random-effects model if significant between-studies heterogeneity was present.

RESULTS

Literature Review

- We identified 728 unique papers, of which 664 papers were excluded (duplicates; not relevant for the endpoint; review articles; letter to the editor; case-reports; animal studies; and others).
- Sixty-four full-text papers were evaluated, plus ten additional papers identified through review of references of the retrieved articles.
- Of these, 57 articles were excluded after full-text review (incompleteness of data, overlapping cohort); 17 studies were included in the final meta-analysis (Figure 1).

Figure 1: Selection of Studies for Inclusion in the Meta-analysis



Meta-analysis

- 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 ≤ 1%), the pooled estimate of all inhibitors was 0.27 (0.22–0.32 (Figure 3).
- Similar patterns were observed in subpopulations of patients with high (Figure 4) or low titer inhibitors.
- Significant heterogeneity due to different incidences among studies was found for Recombinate® and Kogenate®. Pooled inhibitor incidence estimates among products ranged from 0.20 to 0.42 without heterogeneity between products.

Multivariable Adjusted Analysis

- A few studies reported inhibitor hazard ratios with the different products used, taking into 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 0.63 (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 rFVIII were not significantly different.

Figure 2: Inhibitor Rate in PUPs or MTPs

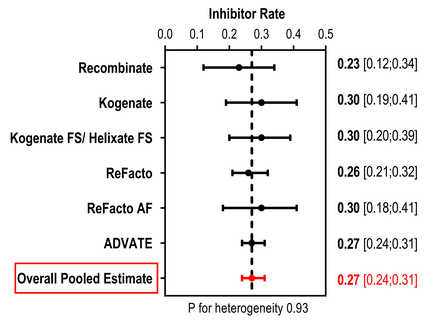


Figure 3: Inhibitor Rate in Severe PUPs

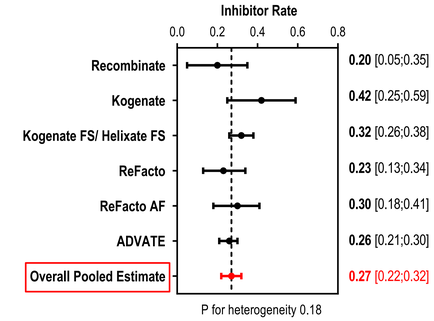


Figure 4: High Titer Inhibitor Rate in Severe PUPs

Figure 5: Multivariable Adjusted Analysis

CONCLUSION

- No significant differences in crude inhibitor incidence among rFVIII 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 SIPPET study (44.5% for recombinant class)
- However, the SIPPET study compares classes of products, where the different products are represented differently: e.g 120 patients treated with a second generation rFVIII product (Kogenate®), while only 20 with third generation products (13 with Advate® and 7 with Refacto®), making any conclusion on single products difficult if not impossible.[7]
- 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.

Figure 5: Forest plot of study-specific and pooled all inhibitors maximally adjusted hazard ratios (HRs) among PUPs or MTPs according to the type of rFVIII product. Only studies investigating more than one type of rFVIII product were considered. Maximally adjusted HRs estimates of all inhibitors incidence were computed using Product C as a reference rFVIII product

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DISCLOSURES

*Author is an employee of Baxalta ([3]Baxalta Innovations GmbH), now part of Shire.
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