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5 Source of Factor VIII Replacement (PLASMATIC OR RECOMBINANT) and Incidence of Inhibitory Alloantibodies in Previously Untreated Patients with Severe Hemophilia a: The Multicenter Randomized Sippet Study📄

Plenary

Program: General Sessions

Session: Plenary Scientific Session

Sunday, December 6, 2015, 2:00 PM-4:00 PM

Hall D, Level 2 (Orange County Convention Center)

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Background

We conducted an investigator-driven, multicenter, open label, randomized study to establish whether the source of factor VIII (FVIII) replacement (plasma-derived, pd; or recombinant, r) affects the rate of inhibitory alloantibodies in previously untreated patients (PUPs) with severe hemophilia A.

Methods

Between 2010 and 2014, 303 PUPs who provided consent through their tutors were screened at 42 participating sites in 14 countries from Africa, the Americas, Asia and Europe. The original aim was to screen 300 patients, randomize 270 (10% screening failure) and follow them for 50 exposure days (ED) or 3 years. Once the intended numbers were included, follow-up was terminated due to logistic and budgetary reasons. Screening criteria were age <6 yrs, plasma FVIII activity <1%, no previous treatment with FVIII concentrates, minimal exposure (less than 5 times) to blood components. Eligible patients were 1:1 block-randomized to a FVIII source class and exclusively treated with a single pd- or rFVIII product, that within each class was allocated on the basis of site licensing and availability. Patients were monitored for inhibitor onset at pre-established and frequent time intervals. Primary outcome was any FVIII inhibitor at titres ≥ 0.4 BU/ml as assayed centrally. High-titred inhibitors (peak levels >5 BU/ml) were a secondary outcome. Patients were censored at the end of the follow-up (50 EDs, 3 years or study end), at inhibitor development or drop-out. Kaplan-Meier and Cox regression survival analyses took into account as putative confounders FVIII gene mutations, ethnicity, hemophilia and inhibitor family history, previous blood component exposure, therapeutic regimen, age at first treatment and country site.

Results

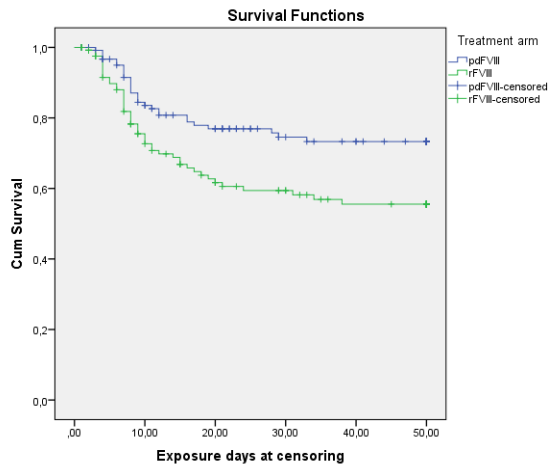
Of 303 screened patients, 39 were screening failures, and 13 were excluded because 3 patients had received >5 treatments with blood components and 10 were not infused after randomization. The remaining 251 patients were analysed and 35 had truncated follow-up (25 dropout, 10 study termination). Patients were aged 0-81 months at randomization (median 14 months) and received between 1 and 50 infusions of FVIII concentrates (median 22). Of those who did not develop an inhibitor, over 70% had >20 ED. 76 patients developed an inhibitor, of which 50 were high-titred. The cumulative inhibitor incidence was 35.4% (95% confidence interval (CI95) 28.9-41.9%). 90% of inhibitors developed within 20 EDs, both for all and high-titre inhibitors. After randomization 125 patients received pdFVIII and 126 rFVIII. The putative confounders were equally divided between the two product class arms. There were 29 inhibitors (20 high-titred) in the group treated with the class of pdFVIII and 47 (30 high-titred) in those treated with rFVIII. The cumulative inhibitor incidence was 26.7% (CI95 18.3-35.1%) for pdFVIII and 44.5% (CI95 34.7-54.3%) for rFVIII (Figure). For high-titre inhibitors the cumulative incidence was 18.5% (CI95 12.1-26.9%) for pdFVIII and 28.4% (CI95 19.6-37.2%) for rFVIII.

By univariate Cox regression analysis rFVIII was associated with an 87% higher incidence of inhibitors than pdFVIII (hazard ratio (HR) 1.87, CI95 1.18-2.97). For high-titre inhibitors the rate was 70% increased (HR 1.70, CI95 0.96-2.99). The associations did not materially change after adjustment for putative confounders: in adjusted models the rate remained 70-90% elevated for rFVIII vs pdFVIII. When analysis was restricted to sites that had not randomized patients to a second generation full length rFVIII or pdFVIII (n=131 patients, 25 inhibitors), the risk of other rFVIII concentrates vs pdFVIII was still twofold increased (HR 1.99, CI95 1.00-3.99).

Conclusions

The rFVIII product class was associated with a 1.87-fold higher incidence of inhibitors than the pdFVIII class. This difference remained even when second generation full length rFVIII concentrate was excluded from the analyses. The results of this randomized study have implications in the choice of product for management of PUPs, as inhibitor development remains a major challenge in the management of haemophilia A.

(Funded by the Angelo Bianchi Bonomi Foundation, Italian Ministry of Health, Grifols, Kedrion and JER -



Disclosures: **Peyvandi:** Octapharma: Other: Investigator ; LFB, Kedrion, Novonordisk, Bayer, Roche, CSL Behring.: Consultancy , Honoraria , Research Funding . **Mannucci:** Novonordisk, Grifols, Kedrion, Bayer, Biotest, Baxalta: Membership on an entity's Board of Directors or advisory committees , Speakers Bureau . **Karimi:** Octapharma: Other: Investigator . **Young:** Baxter, Grifols: Consultancy , Honoraria . **Santagostino:** Roche: Speakers Bureau ; Bayer: Speakers Bureau ; Baxter/Baxalta: Speakers Bureau ; Octapharma: Speakers Bureau ; Biotest: Speakers Bureau ; Novo Nordisk: Speakers Bureau ; Kedrion: Speakers Bureau ; Biogen/Sobi: Speakers Bureau ; CSL Behring: Speakers Bureau ; Pfizer: Research Funding , Speakers Bureau . **Mancuso:** Baxter, Pfizer, CSL Behring, Baxter, Sobi/Biotest: Consultancy ; Novo Nordisk, Bayer: Speakers Bureau . **Mahlangu:** Biogen: Honoraria , Membership on an entity's Board of Directors or advisory committees , Research Funding ; Roche: Honoraria , Membership on an entity's Board of Directors or advisory committees ; Bayer: Honoraria , Membership on an entity's Board of Directors or advisory committees , Research Funding ; CSL Behring: Research Funding ; NovoNordisk: Honoraria , Membership on an entity's Board of Directors or advisory committees , Research Funding ; Biotest: Honoraria , Membership on an entity's Board of Directors or advisory committees . **Bonanad:** Baxalta: Research Funding . **Ewing:** Baxter, Novo Nordisk, Grifols, Bayer, Kedrion: Honoraria . **Owaidah:** King Abdulaziz City for Science, Novo Nordisk, Bayer: Honoraria , Research Funding . **Kobrinisky:** Octapharma: Speakers Bureau ; CSL Behring: Speakers Bureau ; Sanofi: Speakers Bureau ; Kedrion Biopharma: Membership on an entity's Board of Directors or advisory committees . **Kavakli:** Baxter: Other: advisory board member and received educational and investigational support ; Bayer: Other: advisory board member and received educational and investigational support ; Novo Nordisk: Other: advisory board member and received educational and investigational support ; Pfizer: Other: advisory board member and received educational and investigational support ; Bio Products Laboratory: Other: received educational and investigational support ; CSL Behring: Other: received educational and investigational support ; Octapharma: Other: received educational and investigational support . **Manco-Johnson:** Baxter, Bayer, Biogen, CSL Behring, NovoNordisk: Honoraria . **Neme:** Novo Nordisk and Pfizer: Other: fees for speaking . **Wicklund:** NovoNordisk, Bayer, Baxter (now Baxalta), Biogen-Idec, CSL-Behring, National Hemophilia Foundation: Honoraria , Membership on an entity's Board of Directors or advisory committees . **Zulfikar:** Eczacıbaşı-Baxter, Pfizer, Novo Nordisk: Consultancy , Honoraria , Research Funding .

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