THE IMPACT OF FACTOR VIII CONCENTATE ON THE DEVELOPMENT OF INHIBITORS IN CHILDREN WITH SEVERE HEMOPHILIA A: TURKISH PUP REGISTRY STUDY

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- **Introduction:** The development of inhibitors against factor VIII (FVIII) is considered to be the most severe complication. Inhibitors mainly occur in previously untreated patients (PUPs) with severe hemophilia A during the first 50 exposure days (EDs), and incidence ranges between 10-30%. Data on impact of type of FVIII product on inhibitor incidence for PUPs is conflicting. In this study, our aim was to evaluate the impact of the type of FVIII concentrate during first 50 EDs on inhibitor development after the availability of the first and second generation recombinant products in Turkey since 2007.

- **Material and Methods:** The members of Turkish Pediatric Hematology Society from 30 hemophilia treatment centers, conducted a retrospective, multicentre study to assess the inhibitor development in 143 PUPs with only severe haemophilia A who were born after 2007. These centers are as following:

1. Ege University School of Medicine, Division of Pediatric Hematology (Kaan Kavakli), Izmir
2. Istanbul University, Istanbul School of Medicine, Division of Pediatric Hematology&Oncology (Aysegul Unuvar), Istanbul
3. Kanuni Sultan Suleyman Education and Research Hospital, Pediatric Hematology&Oncology Unit (Zafer Salcioglu), Istanbul
4. Cukurova University School of Medicine, Division of Pediatric Hematology&Oncology (Yurdanur Kilinc), Adana
5. Van Yuzuncu Yil University School of Medicine, Division of Pediatric Hematology (Ahmet Faik Oner), Van
6. Behcet Uz Children's Hospital, Education and Research Hospital, Pediatric Hematology&Oncology Unit (Yilmaz Ay), Izmir
7. Istanbul University, Cerrahpasa School of Medicine, Division of Pediatric Hematology&Oncology (Tiraje Celkan), Istanbul
8. Samsun University School of Medicine, Division of Pediatric Hematology&Oncology (Canan Albayrak), Samsun
9. Goztepe Education and Research Hospital, Pediatric Hematology Unit (Cetin Timur),Istanbul
10. Hacettepe University School of Medicine, Division of Pediatric Hematology (Selin Aytac Eyupoglu, Mualla Cetin), Ankara
11. Akdeniz University School of Medicine, Division of Pediatric Hematology&Oncology (Alphan Kupesiz), Antalya
12. Istanbul University, Oncology Institute, Division of Pediatric Hematology&Oncology (Bulent Zulfikar, Basak Koc), Istanbul
13. Eskisehir University School of Medicine, Division of Pediatric Hematology (Ozcan Bor), Eskisehir
14. Uludag University School of Medicine, Division of Pediatric Hematology (Adalet Meral), Bursa
15. Kocaeli University School of Medicine, Division of Pediatric Hematology (Nazan Sarper), Kocaeli
16. Gaziantep University School of Medicine, Division of Pediatric Hematology (Ali Bay), Gaziantep
17. Gazi University School of Medicine, Division of Pediatric Hematology (Turkiz Gursel, Zuhre Kaya), Ankara
18. Kayseri University School of Medicine, Division of Pediatric Hematology (Turkan Patiroglu), Kayseri
19. Pamukkale University School of Medicine, Division of Pediatric Hematology (Yasemin Isik Balci), Denizli
20. Dortcelik State Hospital, Pediatric Hematology Unit, (Elif Kazanci), Bursa
21. Yildirim Beyazit University School of Medicine, Division of Pediatric Hematology&Oncology, (Bahattin Tunc), Ankara
22. Adnan Menderes University School of Medicine, Division of Pediatric Hematology (Yusuf Ziya Aral), Aydin
23. Dicle University School of Medicine, Division of Pediatric Hematology, (Murat Soker), Diyarbakir
24. Dokuz Eylul University School of Medicine, Division of Pediatric Hematology (Hale Oren), Izmir
25. Konya Necmettin Erbakan University School of Medicine, Division of Pediatric Hematology (Umran Caliskan), Konya
26. Denizli State Hospital, Pediatric Hematology Unit, (Mehmet Akin)
27. Celal Bayar University School of Medicine, Division of Pediatric Hematology (Huseyin Gulen), Manisa
28. Tepecik Education and Research Hospital, Pediatric Hematology Unit ((Berna Atabay), Izmir
29. Medical Park Hospital, Pediatric Hematology Unit, (Tunc Fisgin), Samsun
30. Karadeniz Technical University School of Medicine, Division of Pediatric Hematology (Erol Erduran), Trabzon

Nine patients (8 in clinical trial, one only FFP) were excluded from the study. Among 134 PUPs studied; 99 patients had been treated with recombinant FVIII (rFVIII), 21 with high purity or monoclonal purified plasma-derived FVIII (pdFVIII), and 14 with switched factor products during 50 EDs.

- **Results:** Inhibitors were detected in 28 of 134 patients (21%).

The range of age at the diagnosis of (+) inhibitor was 1-6 years.

Nineteen patients were on prophylaxis; the other 9 patients were on episodic therapy.

The minimum EDs at the inhibitor development was 8 EDs.

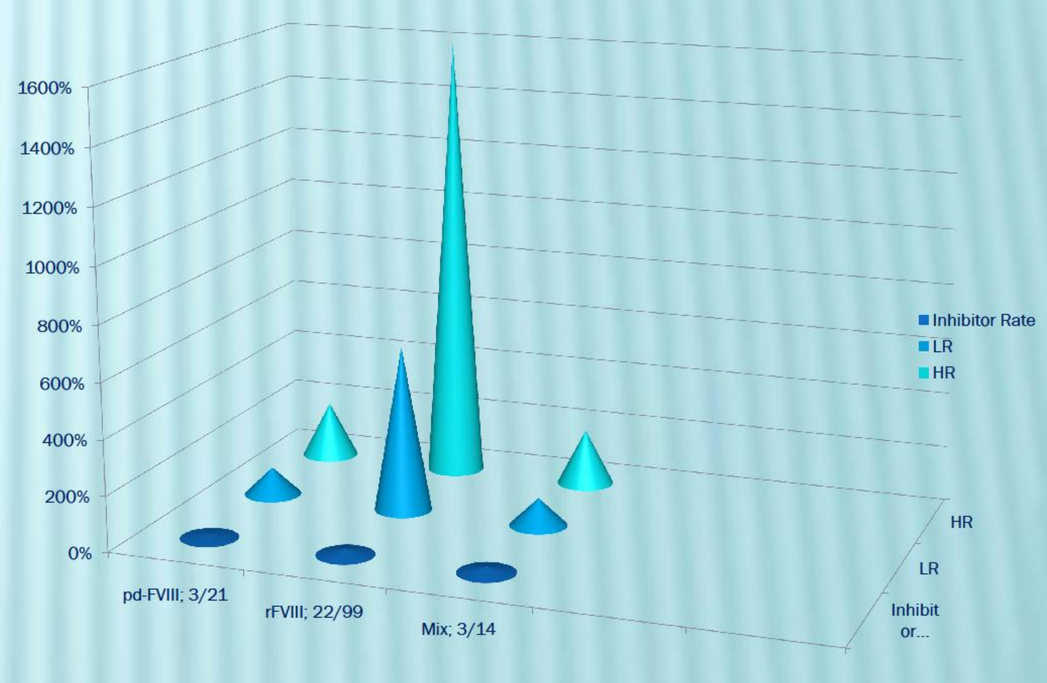
Nineteen of 28 patients had the risk factors for inhibitor development.

->5 days Factor usage: 10 patients
- Positivie family history: 7 patients
-Surgery: 5 patients
-Infection: One patient

Fourteen percent (3/21; one LR, two HR) of the patients who received pdFVIII developed inhibitors, compared with 22% (22/99; 6 LR, 16 HR) who received rFVIII, and 21% (3/14; one LR, two HR) who was switched FVIII products in the first 50 EDs.

There was no difference for inhibitor development between the plasma-derived and recombinant products (p= 0.7) or the development of high-titre inhibitors between the groups (p=0.96).

In addition, there was no difference at the inhibitor rate between the first and second generation of rFVIII.



- **In conclusion;** no statistically difference was observed in the development of inhibitors between patients treated with plasma-derived FVIII and RFVIII. However, our study population was small, retrospective and non-randomized. Multicenter, randomized, clinical trials are needed to solve these challenging problems.

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