Low-titer inhibitors in children with severe hemophilia A: real-life data from the REMAIN study

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Background: the development of neutralizing anti-Factor VIII (FVIII) antibodies (referred to as inhibitors) is a rare but challenging complication of replacement therapy in children with severe hemophilia A (SHA). Low-titer inhibitors (i.e., peak titer always < 5 BU/mL) may be transient and disappear without any modification to treatment strategy; however, immune tolerance induction treatment has been used to eradicate persistent antibodies. Data on the natural history, the clinical impact and the management of low-titer inhibitors are still limited.

Aim: This study is aimed at describing the natural history and management of low-titer inhibitors in a cohort of ***260 children*** with severe hemophilia A *followed-up for at least 3 years* after inhibitor development.

Methods: The REMAIN study is a satellite of the PedNet Registry including children with severe haemophilia A (FVIII<1 IU/dL) born between January 1990 and December 2009 who developed clinically relevant inhibitors. Previously untreated patients were consecutively recruited from 31 haemophilia treatment centers in 16 countries. Clinical data were collected from medical records and laboratory data retrieved from local laboratories. ***Immune tolerance induction*** (ITI) was defined as regular FVIII infusions given at least 3 times weekly at a minimum dose of 45 IU/kg/infusion.

Results:

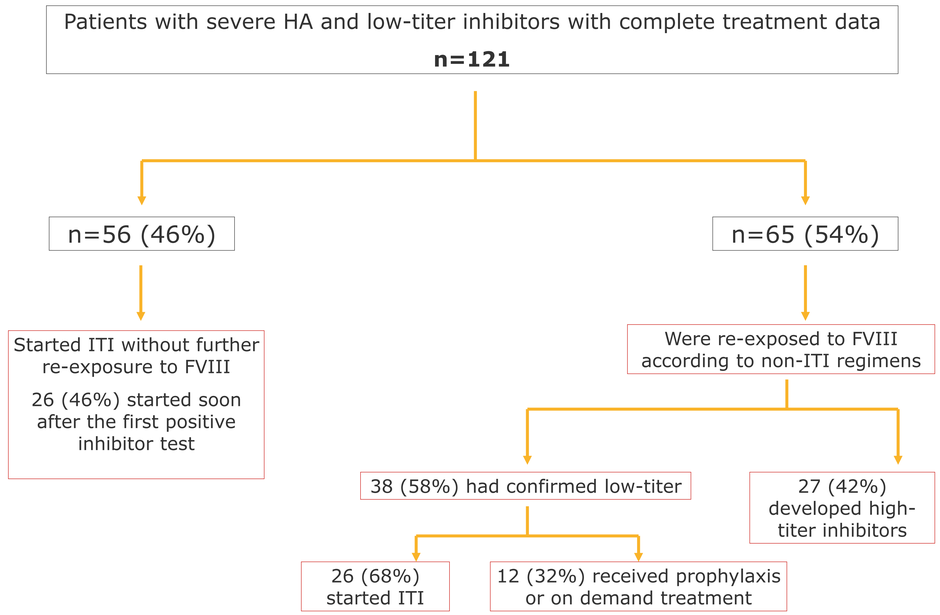
- Median inhibitor titer at diagnosis: ***1.1 BU/mL*** (IQR: 0.8-2.0)
- A second positive inhibitor test was obtained prior to start any treatment in 97 (76%) after a median of 8 days (IQR: 2-24)
- Complete treatment data were available for 121/127 (95%) children (see Figure)
- From the whole group, 100 (79%) reached a persistently negative inhibitor titer during the 3-year follow-up period: 82 received ITI and 18 prophylaxis or on demand treatment with FVIII
- In our cohort of unselected children with severe hemophilia A and low-titer inhibitors a high proportion of patients (65%) underwent ITI during the follow-up period.
- Analyses on treatment outcome and bleeding phenotype are underway.

Based on inhibitor titer at diagnosis

127 (49%) had low-titer

Based on inhibitor peak reached during the 3-year follow-up period

69 (26%) maintained low-titer upon FVIII re-exposure



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