Bleeding phenotype and clinical management of children with severe Hemophilia A and inhibitors: a follow-up cohort study

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Background

- Inhibitor development is the main complication of replacement therapy in children with severe hemophilia A, because it renders prophylaxis unfeasible and the management of bleeding episodes difficult. Clinical research in the last decade has been focused on the identification of potential risk factors for inhibitor development, that represented the main endpoint of several studies.
- On the other hand, little is known on the clinical behaviour of this patient population in terms of bleeding phenotype, bleeding frequency, management of bleeds after inhibitor development.
- Moreover, the vast majority of children who develop clinically relevant inhibitors undergo immune tolerance induction (ITI) treatment in order to eradicate them. However, although used since almost 40 years, ITI treatment still need to be optimized.
- High success rates can be achieved with different regimens, however time to success and treatment-related morbidity may be influenced by treatment schedule as shown by the International ITI Study.
- The main aim of ITI is to restore standard replacement therapy and allow prophylaxis in order to prevent recurrent bleeds especially into joints and avoid chronic degenerative arthropathy, however the time needed to achieve tolerance is often long enough to let joint bleeds occur and joint damage is a common feature in children with inhibitors.

Hypothesis/Aim of the study

✓ To describe the bleeding phenotype of children with severe hemophilia A after inhibitor development

✓ To describe the outcome of ITI in an unselected cohort of children with severe hemophilia A and inhibitors

Study Design

✓ This study was designed as a satellite study of the CANAL/RODIN cohort studies in the frame of the European Pediatric Network (PedNet) that included previously untreated patients with severe hemophilia A and followed them up until inhibitor development or the achievement of 75 or 50 exposure days (EDs).

✓ In this study all children from CANAL and RODIN cohorts who developed clinically relevant inhibitors are included and a 3 year follow-up period since inhibitor development will be evaluated.

Materials and Methods

✓ Data collection will pertain 3 main periods: the period between inhibtor development and ITI start, the period of ITI accomplishment and the period between ITI completion and end of the 3-year follow-up

✓ Data on inhibitor titers, bleeding frequency, type and site of bleeding, treatment of bleeding episodes and any other treatment strategy will be collected for each of the aforementioned periods. Details on ITI regimens will be collected as well.

Results

✓ Demographic data are available from 267 children of whom 180 developed high-responding inhibitors.

✓ Inhibitors developed at a median age of 1.3 years (IQR: 0.9-1.7) after a median of 14 EDs (IQR: 9-19).

✓ The median inhibitor titer at diagnosis was 2.5 BU/ml (IQR: 1-13.5) and the median historical peak was 16 BU/ml (IQR: 3-70).

✓ Eighty-six children started ITI during the 3 years follow-up period; the median time elapsed between inhibitor development and ITI start was 4 months

✓ In 49 children who completed ITI the median duration of treatment course was 11 months.

✓ The analysis of data on bleeding phenotype and treatment of bleeding episodes is underway.

Perspectives

✓ The results from this large cohort study will improve knowledge on bleeding phenotype and bleeding management in children with severe hemophilia A complicated by newly diagnosed inhibitors and will provide information on ITI performance in the field practice in this patient population

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