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PedNet

Haemophilia is a rare disease. In a large country such as France only 30-35 new patients are diagnosed yearly with severe haemophilia. In 2003, 29 haemophilia treatment centres (HTCs) in Europe, Canada and Israel started a collaborative project. The aim was to develop a large international registry in order to improve the knowledge on clinical problems in children with haemophilia. Presently, in total 31 HTCs from 16 countries are participating.
Clotting factor products are essential for the prevention of bleeding in haemophilia patients. The most serious side effect of treatment is the development of inhibitors. They occur in 25-30% of the children with severe haemophilia A. Several factors may be involved, among which the type of clotting factor product. New products are only marketed in the European Union after approval by the European Medicine Agency (EMA). Although the registration process requires clinical trials in children, at the moment of licensing only a small number of patients have used the new product. Consequently, the full assessment of the safety of a new product is not possible before marketing; it needs to be followed up while the product is used in more patients. So it is very important to collect additional patient data after a clotting product is brought onto the market.

The PedNet Haemophilia Registry

The PedNet Registry uses a web-based research database with the data from diagnosis onwards from all children diagnosed and treated in any of the participating centres. The privacy of the children is protected: the individual patient data are coded by the haemophilia centre and anonymously entered in the registry. Before a new patient is included, the parents are asked for informed consent. Obviously, for reliable research results it is very important that as many patients as possible are included into the database. Presently the inclusion percentage is more than 95%: we have detailed data of 1600 children with haemophilia A or B, over 900 of whom have severe haemophilia.
The PedNet Registry has developed into a rich resource enabling us to answer various research questions. Presently the main topics are: what influences the development of inhibitors; when should prophylaxis start; how prophylaxis should be dosed. The annual research program can be found on our website (www.pednet.nl).

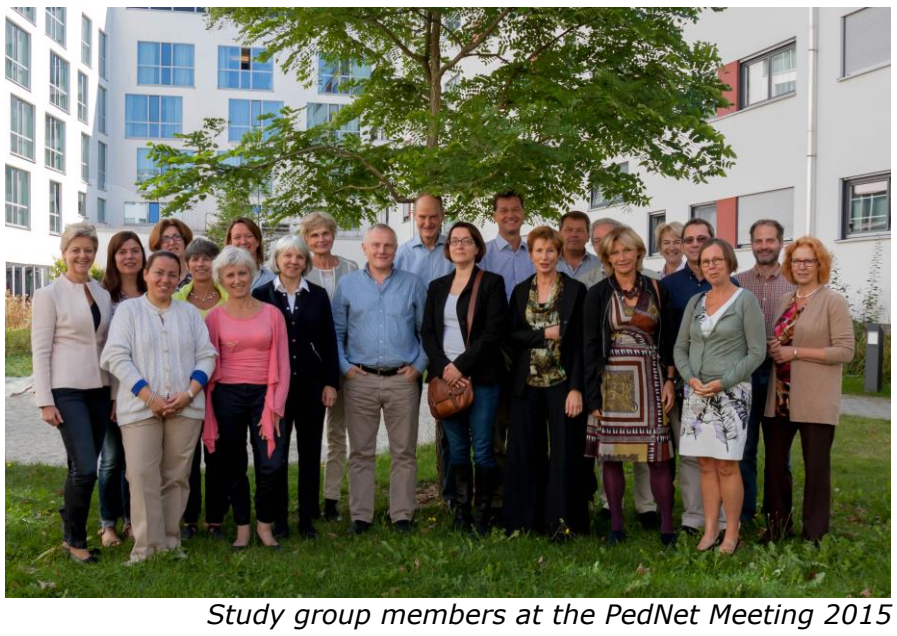
What did we learn from individual patients?

Sometimes, individual patients (‘case reports’) can increase our insight. To understand whether a different risk for inhibitors can be observed identical twins with severe haemophilia A are very interesting. These patients are discussed in our group of experienced doctors. We learned from them that intensive treatment for a bleeding might induce the risk for high titre inhibitors. Such differences in inhibitor behaviour between twins provides insight into the causes of inhibitor development. Consequently, when we can prevent high dosing, would it enable us to reduce the inhibitor risk?

The RODIN Study

Samantha Gouw, PhD graduate

The acronym RODIN stands for *Research Of Determinants of INhibitor development among previously untreated patients with severe haemophilia*. It was the first study based on the data of the PedNet Registry.



Study group members at the PedNet Meeting 2015

Why was the RODIN Study needed?

We needed to understand more about the factors influencing the risk of inhibitor development in children with severe haemophilia A. Today, in the Western world, the standard of care for patients with severe haemophilia is prophylaxis, which is the regular infusion of factor VIII, with the aim to enable patients to lead a normal life by preventing bleeds and joint damage. With prophylactic treatment, children with severe haemophilia A have a good quality of life with a life expectancy which is approaching that of other children. However, inhibitors can complicate this bright future. Inhibitors are antibodies produced by the child's immune system in a response to the infused factor VIII product. They bind to the product in the bloodstream and make it ineffective. Prophylaxis is not possible anymore and bleeds cannot effectively be treated with factor VIII product. Other clotting factor products are still available for treatment, but these are not nearly as effective as factor VIII. Inhibitor development typically occurs in young children within the first few years of treatment with factor VIII. They can disappear spontaneously or after specific treatment, but in some patients the inhibitors persist and cause life-long problems.
Fortunately not all children develop inhibitors, only about one in 3 to 4 children. We wanted to learn why some children with haemophilia develop inhibitors and others do not. With this knowledge preventive measures could be developed in the future for children with haemophilia.

PedNet Haemophilia Registry

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What was the goal of the RODIN study?

The aim of the RODIN study was to identify risk factors for inhibitor development in patients with severe haemophilia A.

How many children participated in the RODIN study?

Over 600 children with severe haemophilia A have participated in the RODIN study. This makes the RODIN study the largest ever study in children with severe haemophilia A. We need information on such large numbers of children in order to get insight into of the causes of inhibitor development.

What did the RODIN study teach us?

We focused on three main questions:

1. Does prophylaxis have any effect on the risk to develop inhibitors?
From the RODIN study we learned that prophylaxis *decreases* the risk of inhibitor development. The current haemophilia care guidelines state that prophylaxis is the standard of care and should be started in young children before frequent joint bleeds occur. The findings of the RODIN study do not give any reason to modify this recommendation.

2. Does high dosed factor VIII treatment for bleeds and surgery affect this risk?
In the RODIN study we found that factor VIII treatment for large bleeds and surgery *increases* the risk of inhibitor development. It may therefore be beneficial to attempt to avoid large bleeds and surgery in young children with severe haemophilia A, for example by starting early prophylaxis and if possible delaying surgery.

3. Does the type of factor VIII product influence this risk?
There are two sources of factor VIII products: human blood donors, providing so-called plasma-derived products, and artificially produced factor VIII, so-called recombinant products. There was no difference in risk between the use of factor VIII products produced from donated human blood or with recombinant techniques. An unexpected finding, however, was that one specific brand of recombinant factor VIII product seemed to carry a higher risk of inhibitor development. This observation was confirmed by studies in France and the UK. Further analyses are now performed by the European Medicine Agency (EMA). Your child's haemophilia doctor can inform you further on this matter.

More information on, and publications of the PedNet study group can be found on our website:
http://www.pednet.nl

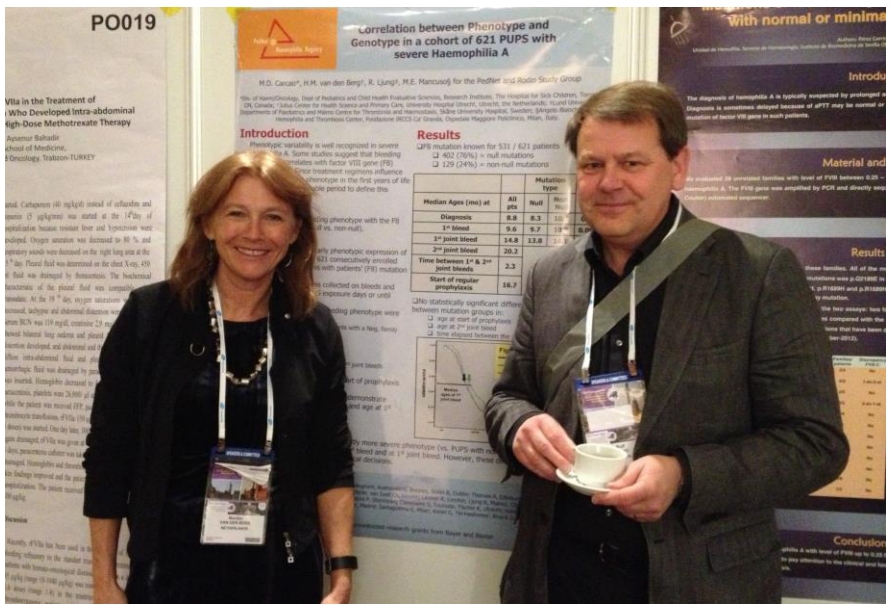
Other satellite studies performed with data of the PedNet Registry

1. Inhibitor studies
- A study on the endogenous (genetic) and exogenous (treatment-related) determinants of inhibitor development;
- A study on inhibitor incidences for both high-titre and low-titre inhibitors over time;
- We have developed a prediction model for inhibitors;
- The 3 year follow-up data for patients with inhibitors diagnosed in the PedNet registry will be analysed soon.

2. Perinatal studies
- A study on the optimal mode of delivery for children with haemophilia.

3. Studies on the haemophilia phenotype
- A study on the correlation between genotype (hereditary factors) and phenotype (outcome) in haemophilia;
- We compare the bleeding phenotypes of haemophilia A and haemophilia B.

5. Other side effects of haemophilia and its treatment
- A study on the outcome and management of central venous lines (Port-A-Cath) as a means of factor VIII delivery in young children;
- A study on the frequency of intracranial haemorrhages in children on prophylactic treatment.



The PedNet Registry would never have been possible without your cooperation as parents and care givers of the children. We thank you on behalf of the whole study group for your ongoing collaboration and willingness to help collect the data of treatment and bleedings. Only with enough reliable data we are able to understand more about haemophilia and improve the lives of the children.

Marijke van den Berg and Rolf Ljung
Principal investigators

Participating centres in the PedNet Registry
Århus, Denmark; **Athens**, Greece; **Barcelona**, Spain; **Birmingham**, UK; **Bonn**, Germany; **Bremen**, Germany; **Dublin**, Ireland; **Edinburgh**, UK; **Frankfurt** (Goethe & Mörfelden-Walldorf), Germany; **Genova**, Italy; **Glasgow**, UK; **Graz**, Austria (until September 2015); **Helsinki**, Finland; **Leuven**, Belgium; **London**, UK; **Madrid**, Spain; **Malmö**, Sweden; **Marseille**, France; **Milan**, Italy; **Montreal**, Canada; **Munich**, Germany; **Paris**, France; **Seville**, Spain; **Stockholm**, Sweden; **Tel Hashomer**, Israel; **Toronto**, Canada; **Toulouse**, France; **Utrecht**, The Netherlands; **Valencia**, Spain; **Vienna**, Austria; **Wabern**, Switzerland.