

# Haemophilia

## What is haemophilia?

Haemophilia is an inherited disorder of blood clotting. The bleeding of individuals with haemophilia is prolonged, due to a defect or a deficiency of clotting factors normally present in the blood. Haemophilia A, which is the most common form and affects about 80 per cent of people with haemophilia, is caused by the deficiency of Factor VIII. Haemophilia B is due to a lack of Factor IX.

Haemophilia varies in severity, and this variability is related to the amount of clotting factor present in the blood. The more severe the disorder is, the earlier in life the signs of abnormal bruising or bleeding are observed. Minor trauma can result in extensive tissue bleeding.

Apart from bruising, haemorrhages into joints are the most common feature of the disease. Bleeding into muscles is also common and may occur after injury, or spontaneously. If such haemorrhages are improperly managed, they will result in crippling musculoskeletal deformities.

## Who does haemophilia affect?

As the genetic codes of Factors VIII and IX are both located on the human X chromosome which also determines the gender of an individual, haemophilia A and B affect males almost exclusively. Haemophilia occurs in about one in 5,000 male births and is found in all populations.

According to this level of incidence, 400 boys with haemophilia are born in Europe each year. Altogether, there are more than 22,000 European patients with haemophilia A and B. The deficiency is passed on by women who usually have no bleeding problems.

## Present treatments:

Haemophilia is a life-long condition for which, at present, there is no cure. However, with the development of comprehensive care and the provision of preparations containing clotting factors, it is possible for people with even severe forms of haemophilia (whose Factor VIII or Factor IX levels are less than one per cent of the average value of the unaffected population) to control bleeding and live near-normal lives.

Treatment must be given as soon as possible after the onset of bleeding. Factor concentrates are also used prophylactically on a planned regular basis to prevent recurrent haemorrhage, e.g. before physiotherapy and other exercise programmes. Today, the transfusion of Factor VIII concentrates is done under medical supervision at a hospital or haemophilia centre, at home by parents to treat their child or by the person with haemophilia himself.

**Haemophilia is an inherited disorder where the blood does not clot properly. Only men are affected. Once a crippling or even fatal condition, the pharmaceutical industry has introduced preparations to control bleeding and allow many patients to lead near normal lives.**



In January 2004, the European Commission approved a plasma-derived Factor IX concentrate, for continuous intravenous infusion which will help patients maintain a minimum and predictable level of Factor IX.

Factor concentrates are either produced from the plasma in blood donations, or synthetically by recombinant genetic engineering. For haemophilia A, the treatment of choice is viral attenuated or recombinant Factor VIII concentrate.

The newer preparations, unlike previous products, do not use the blood protein albumin as an ingredient, but rather a combination of sugars, amino acids and salts to stabilise human factor VIII. This should completely eliminate the former potential risk for transfusion of any blood-borne infectious agents.

The products fall into three categories: (i) recombinant products; (ii) monoclonal antibody purified products; and (iii) intermediate- and high-purity Factor VIII products, which are also used to treat a rare bleeding disorder called von Willebrand Disease.

For haemophilia B, the treatment of choice is a highly purified viral inactivated Factor IX concentrate. In the early 1980s, transmission of infectious particles through the preparations was a major problem. Since then, a series of inactivation procedures, such as heating and ultra-filtration, has been introduced into the manufacturing process and has dramatically lessened the risk of transmitting infectious diseases, such as hepatitis B and human immunodeficiency virus. Nowadays, with the introduction of recombinant factor therapies, this risk has become a theoretical one.

Between 20 and 30 per cent of severely affected haemophilia A patients develop inhibitors against Factor VIII. This is due to the reaction of the patient's immune system which recognises the clotting factor given to them as a foreign substance and forms antibodies against Factor VIII. Such inhibitors complicate the treatment of bleeding episodes.

The factor VIII antibodies responsible for inhibitor activity are heterogeneous and in some patients do not inhibit or only minimally inhibit porcine factor VIII. Thus, a high-purity porcine factor VIII preparation may control bleeding in such patients. Several other treatment methods are available by which the resistance to therapy can be overcome in most patients with inhibitors. In such a case, specialised haemophilia centres are usually consulted.

In mild (Factor VIII level between six and 50 per cent) or moderate (Factor VIII level between one and five per cent) forms of haemophilia A, the synthetic vasopressin analogue DDAVP can be used in the form of a highly concentrated nasal spray, which acts by releasing Factor VIII stores. Antifibrinolytic agents may also be prescribed. They slow the natural breakdown of blood clots and are particularly useful in bleeding in the mouth and tooth socket.

Newly diagnosed people with haemophilia should be vaccinated against hepatitis A and B.

### **What's in the development pipeline?**

The worldwide total demand for Factor VIII lies between 250 and 500 grammes of protein every year. The highest priority of research is devoted to the development of a non-plasma source for the manufacturing process of Factor VIII and Factor IX preparations. New preparation methods in cell cultures of gene-modified yeasts and bacteria are being investigated.

Another experimental approach would lead to transgenic animals, such as goats or sheep that synthesise human clotting factors and secrete them in their milk ("pharm-

ing"). Until now, the successful secretion of high levels of such factors and their purification remains to be demonstrated.

Research is also concentrating on new treatment avenues for haemophilia patients with inhibitors. The objectives are either to develop tolerance or to influence the person's immune system. Through this intensive and co-operative effort will eventually come the knowledge needed to treat this problem more effectively and, most importantly, to prevent it altogether.

### The longer-term future

Researchers have identified key amino acids with the potential to change the performance of the entire protein if they are replaced in the molecular structure of human factor VIII. The goal is to develop gains-of-function in factor VIII proteins that are superior to the natural version.

These more potent forms are not likely to occur naturally, since they would theoretically result in excessive clotting. In patients with hemophilia, however, enhanced clotting may be desirable.

The ultimate research goal of haemophilia therapy is to become totally independent from blood donations. For a person with haemophilia, gene therapy would allow continuous synthesis of a normal protein to correct the deficiency *in vivo*. The resultant protein synthesis would be comparable to a cure.

A variety of approaches for transferring genes for Factors VIII and IX are being investigated. No single technique has emerged as superior, but considerable progress has been made in factor expression, which has led to considerations of clinical trial development for both factors. Within the past few years newly-found vectors, i.e. geneferries, have provided sufficiently encouraging results to allow consideration of clinical trials in humans.



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