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REVIEW

Prophylactic therapy in haemophilia

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SUMMARY

Clinical experience since decades and numerous retro- and, recently, also prospective studies clearly demonstrate that prophylactic treatment, albeit much more expensive, is superior to on-demand treatment regardless if outcome focus on number of joint- or life-threatening bleeds or arthropathy, evaluated by X-ray or MRI, or quality of life measured by general or hemophilia specific instruments. Optimal prophylactic treatment should be started early (primary prophylaxis) but various opinions exist on the dose and dose interval, depending on the objective of treatment in the individual patient which in turn is usually dependent on the resources in the health care system. Secondary prophylaxis, started later in childhood or in adults is beneficial but less cost-effective. This review covers proof of concept of primary prophylaxis in children and secondary prophylaxis in adults, comparisons between prophylaxis and on demand treatment as well as outcome measurers, health economics and future trends of prophylactic treatment of hemophilia.

Introduction and definitions

Haemophilia A and B are hereditary, X-chromosomal recessive disorders caused by deficiency or absence of coagulation factors VIII (FVIII) or IX (FIX) in the blood. Depending on the concentration of FVIII or FIX coagulant activity in blood, the disorders may be classified as severe (<1% of normal activity), moderate (1–4%) or mild (5–25%). Haemophilic arthropathy due to repeated joint bleeds is the major cause of morbidity in individuals with haemophilia. In patients with the severe form of the disease, i.e. FVIII or IX concentrations in plasma <0.01 IU/mL or <1% of normal, joint bleeding episodes may occur as frequently as 20–30 times/year[1,2] and, furthermore, life-threatening bleedings such as intracranial haemorrhage may occur. Therefore the main goal in the management of haemophilia should be 'prophylaxis', which in the field of hemophilia is the provision of regular infusions of FVIII or IX concentrates with the aim of preventing bleeding episodes and their pathological consequences. This contrasts with 'on-demand therapy', where infusions are given to treat an ongoing bleed.

However, there is no universal agreement on the definition of 'prophylactic therapy' and 'on-demand therapy' for haemophilia. The European PedNet group (The European Paediatric Network for Haemophilia Management) has suggested definitions of prophylaxis to reflect the variety of prophylaxis regimens implemented today (Table 1).[3,4] According to this definition, which has been widely used, primary prophylaxis can be a continuous therapy starting after the first joint bleed or before the age of two. Alternatively, primary prophylaxis can be a continuous treatment started before the age of two years in a patient without any previous joint bleed (i.e. initiated solely based upon age). The objective of secondary prophylaxis is to avoid progression of joint disease. Secondary prophylaxis can either be continuous long-term treatment started after two or more joint bleeds or after the age of two; however, secondary prophylaxis can also be an intermittent periodic prophylactic treatment. Similar definitions has been worked out by a Canadian group, Ota et al. (2007).[5]

However, definitions should not only reflect the ways in which prophylaxis is implemented, but also the ultimate clinical objective of such treatment. The objective of therapy in haemophilia can be mapped along a spectrum of treatment choices, as shown in Fig. 1. At one end, the goal is to prevent life-threatening bleeding and/or crippling haemophilic arthropathy. This can in most cases be accomplished with an on-demand treatment approach. On-demand therapy can also be used to prevent target joint formation by limiting patients to a set number of annual joint bleeds if the frequency and promptness of treatment is increased. Secondary prophylaxis is used to achieve a goal of maintaining patients below certain orthopaedic or radiologic scores for a defined age. Increasing the frequency and dose of prophylaxis generally also allows patients to participate in many of the normal activities of daily life, which can be an important goal for children and teenagers. Patients who receive prophylaxis at the high end of frequency and/or dose can even perform physical exercise on days when concentrate is administered. In Sweden, a nation with one of the longest history of prophylaxis therapy for patients with haemophilia, the dose is established to allow patients, especially children, to live a practically normal life and psycho-social development without

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Table 1
Definitions of prophylaxis treatment.[4]

Type of therapy	Definition
Primary prophylaxis A	Regular continuous treatment started after the first joint bleed and before the age of 2 years
Primary prophylaxis B	Regular continuous treatment started before the age of 2 years without previous joint bleed
Secondary prophylaxis A	Regular continuous (long-term) treatment started after two or more joint bleeds or at an age >2 years
Secondary prophylaxis B	Intermittent regular (short-term) treatment, because of frequent bleeds

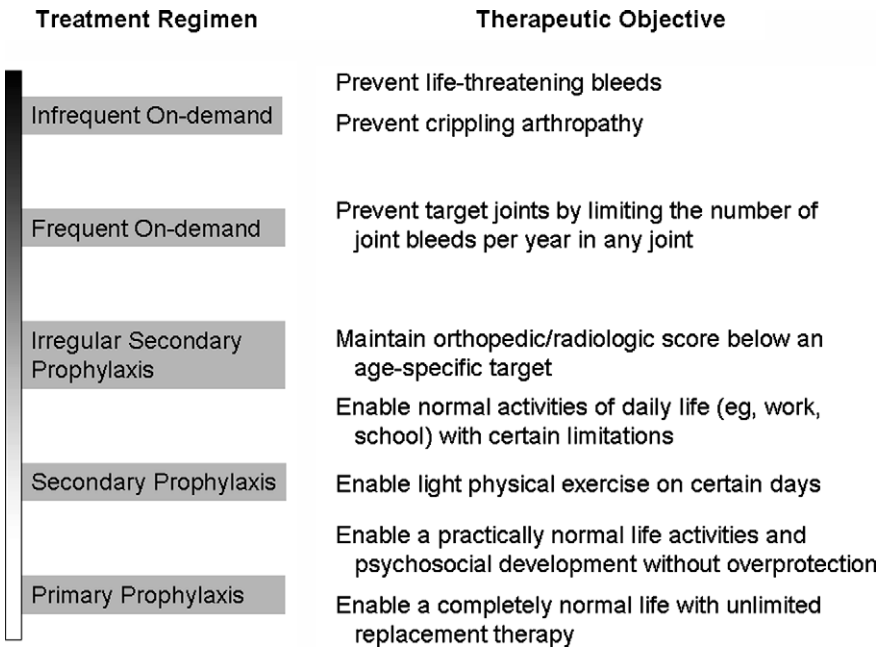

Fig. 1. Spectrum of hemophilia treatment regimens and the therapeutic objectives.

over-protection. We have yet to achieve the extreme of a completely normal life, as would be accomplished by unlimited replacement therapy that can be easily administered by the patient. Hope for a cure to haemophilia currently rests with gene therapy.

The choice of a treatment goal depends on both national healthcare priorities and available resources within the healthcare system for the treatment of patients with haemophilia. Consequently, there remains much variation in the implementation of prophylaxis worldwide.[6] Thus, for each patient, the treating physician should decide on the goal of treatment and the most appropriate therapeutic regimen to accomplish that goal within the limitations of the healthcare system.

Experience and evidence for prophylactic treatment

Prophylaxis was pioneered for haemophilia A in the late 1950s and in haemophilia B in the early 70s in Sweden by Nilsson and colleagues.[7–9] At the time, factor VIII (FVIII) was not always available in sufficient amounts and the doses given were small compared with today's norms. Moreover, many patients who received prophylaxis had already developed arthropathy prior to prophylaxis initiation. Despite these limitations, Nilsson et al.[7] reported the most comprehensive experience of prophylaxis up to the date comprising 60 patients in 1992, demonstrating that prophylactic treatment protect patients from the development of hemophilic arthropathy. In the youngest group of patients, aged 3–12 years who had received 25–40 IU/kg three times weekly for hemophilia A and twice weekly for haemophilia B, virtually no bleeds were seen and the orthopaedic and radiologic joint scores were zero, i.e. without abnormalities. In the oldest group, comprising 25 patients born 1960–1974, despite that they had received less intensive treatment with 10–20 U/kg every 3–5 days and started their prophylaxis at a higher age than the younger patients, they were still in a very good condition and differed strikingly from patients who had received no prophylaxis at all. This study demonstrated that the greatest impact on outcome was the introduction of regular treatment compared to on-demand and that the results could be further improved by earlier start of prophylaxis and higher doses. Over the years the Malmö protocol (sometimes called 'full-dose prophylaxis') has been refined and is currently 20–30 U/kg every other day in haemophilia A and every third day in haemophilia B.[10,11]

The Netherlands also have a long history of prophylactic treatment published in several papers.[12–14] In 2001, van den Berg et al.[14] published a study including patients born between 1974 and 1991 who were under the age of 6 when they first attended the clinic. In the oldest group, born between 1974 and 1979, the start of prophylaxis was postponed until after 5–10 joint bleeds had occurred and dosages of FVIII or FIX ranged from 5 to 10 IU/kg 2–3 times per week for hemophilia A and 15–20 IU/kg 1–2 times per week for hemophilia B.

Patients born between 1980 and 1985 were given prophylaxis after 2–5 joint bleeds had occurred. At 10–20 IU/kg 2–3 times per week for hemophilia A and 20–30 IU/kg twice a week for hemophilia B, the dosage used in this group was higher than for the older patient group. In the youngest patient group, born 1985–1991, prophylaxis was initiated after 1–2 joint bleeds or when more than 2 other bleeds per month required treatment