Prophylaxis in haemophilia should be life-long

Mike Makris

Department of Cardiovascular Science, University of Sheffield, Royal Hallamshire Hospital, Sheffield, United Kingdom

Haemophilia is an inherited bleeding disorder caused by deficiency of factors VIII or IX (FVIII/IX). Severe deficiency is associated with spontaneous bleeding into the joints and recurrent bleeding results in haemophilic arthropathy, disability and reduced quality of life. The bleeding is treated with intravenous FVIII/IX concentrate, which the majority of people with haemophilia self-administer at home. Although initially FVIII/IX was administered on demand once bleeding started, increasingly it is now being used prophylactically. In haemophilia, prophylaxis can be defined as the administration of clotting factor concentrate in anticipation of or to prevent bleeding.

Although prophylaxis is now considered the gold standard for the treatment of severe haemophilia in childhood and adolescence, its use in adulthood is more controversial but here I argue that prophylaxis should be the gold standard in haemophilia treatment for life.

Prophylactic treatment is the norm for deficiency states

There are many human diseases characterised by a deficiency of an essential protein/agent such as diabetes mellitus, diabetes insipidus, hypothyroidism, Addison's disease, pernicious anaemia, thalassaemia, growth hormone deficiency and many more. In all of these diseases, once diagnosed, the treatment is with regular replacement of the missing protein/agent rather than treating the condition episodically once a crisis develops. Even with incredibly rare disorders in which treatment is more expensive than in haemophilia, such as paroxysmal nocturnal haemoglobinuria, Gaucher disease and Fabry disease, prophylactic treatment is now becoming the norm. If the management of deficiency states in medicine is with regular replacement of the deficiency, why should haemophilia be different?

Prophylactic treatment is effective in children and adults

We now have high quality evidence from two randomised trials demonstrating the effectiveness of prophylaxis in childhood. In an American study, 65 boys with severe haemophilia A were randomly assigned before the age of 30 months to either prophylactic or enhanced episodic therapy with FVIII concentrate. By the age of 6 years, 93% of the boys on prophylaxis had normal joints on magnetic resonance imaging compared to 55% of those on episodic therapy. As expected, prophylaxis was associated with significantly fewer joint and total bleeds[1]. In an Italian study, 45 children with severe haemophilia A were also randomised to prophylactic versus on demand therapy. After a median of 82.5 months, and using an intention-to-treat analysis, children on prophylaxis had significantly fewer haemarthroses (0.20 versus 0.52 events per month) and fewer radiological abnormalities on plain film examination[2]. In a Cochrane Review, largely driven by the above two studies, the authors concluded that there was strong evidence that prophylaxis was more effective than on-demand therapy in preserving joint function in children with haemophilia[3].

The evidence that prophylaxis is effective is less strong in adults than it is in children but it is nevertheless convincing. In a study of patients aged 30-45 years who had been on demand therapy all their lives, Collins and colleagues compared a 6-month period of on demand therapy with 6 months prophylactic treatment using the same FVIII concentrate. The median number (range) of haemarthroses decreased from 15 (11-26) to 0 (0-3) whilst on prophylaxis[4]. Two randomised trials in adults with severe haemophilia A examining on demand versus prophylactic therapy, the SPINART and POTTER studies, are under way in the USA and Italy respectively[5].

*Blood Transfus 2012; **10**: 165-8* DOI 10.2450/2012.0147-11

The benefits of prophylaxis

Although the benefits of prophylaxis in preserving joint health are clear, the advantages are more widespread (Table I). The reduction in haemarthroses leads to reduced haemophilic arthropathy, reduced disability, reduced need for orthopaedic surgery and ultimately improved quality of life. Prophylaxis in patients with severe haemophilia who did not have inhibitors or human immunodeficiency virus infection and who were followed up as part of the Centre for Disease Control and Prevention Universal Data Collection project, was shown to halve the risk of intracranial haemorrhage[6]. Finally, by introducing low level prophylaxis early and avoiding danger signals, it has been suggested that it is possible to reduce the risk of inhibitor development in previously untreated patients. In a study from Bremen and Munich using this approach, only one low responding inhibitor was observed in 40 children with severe haemophilia A followed up for a minimum of 40 exposures[7,8].

Table I - The benefits of prophylaxis.

Fewer haemarthroses
Less arthropathy
Fewer muscle bleeds
Reduced chance of cerebral bleeding
Fewer hospital admissions
Less frequent monitoring
Less time off work
Less joint surgery
Better quality of life

What are the barriers against prophylaxis for life?

While prophylaxis in children is considered the gold standard, adult prophylaxis is still in its infancy and a number of potential barriers to its widespread use can be considered. Efficacy and safety are not important issues since the Collins study clearly showed a dramatic reduction in haemarthroses in adults receiving prophylaxis[4]. Recombinant concentrates do not transmit viral infections and in practical terms this is also the case with the currently used plasma-derived products which now undergo two different viral inactivation procedures[9]. Provided it is given at the appropriate dose, adult prophylaxis is effective[4]. Some reasons for the poor uptake of adult prophylaxis are the inconvenience and frequency of intravenous administration, as well as the cost of the clotting factor concentrate.

Overcoming the barriers

Ideally oral administration will improve uptake of prophylaxis but this is unlikely to be a reality in the near future. For the adult patient with poor venous access, the use of central venous access devices or the formation of a forearm fistula can improve the ease of administration.

Traditionally, prophylactic factor concentrate has been administered on alternate days/three times a week for haemophilia A and twice weekly for haemophilia B. The Canadian prophylaxis regimen which starts once weekly, and escalates depending on the number of bleeds has shown that for many patients less frequent prophylactic dosing may be sufficient. After a median of 4.6 years, 37%, 34% and 29% of the boys were on once a week, twice weekly and alternate daily prophylaxis respectively[10]. Furthermore it is possible that prophylaxis may not be required as frequently in adults as in children; in the Collins study, in which factor concentrations were measured before the next dose of prophylaxis, the median FVIII:C levels were 6.0 IU/dL at 48 hours and 4.0 IU/dL at 72 hours suggesting that less frequent or lower dose prophylaxis may be sufficient[4]. The use of pharmacokinetic profiling in every patient is likely to identify patients with very short or long FVIII/IX half-lives whose prophylaxis will need to be individualised[11]. Finally there are currently many clinical trials with new products that have extended half-lives, usually as a result of processes such as pegylation, or through the addition of the IgG1 Fc domain or albumin to the native clotting factor molecule[12]. If the initial optimism is realised, the era of once weekly prophylaxis may not be too far away, though this is likely to be easier to achieve with factor IX than factor VIII.

As in every aspect of the health service, cost containment is an issue, but this must not be used as the only reason against the introduction of adult prophylaxis in haemophilia. The unit cost of clotting factor concentrate varies throughout the world even for the same product. In the UK, for example, the cost of one specific recombinant product is less than half of what it is in France. Furthermore, in the UK recombinant products are 15-20% cheaper than plasma-derived products. The use of pharmacokinetic dosing may further reduce costs in patients who are prepared to infuse factor daily because in these individuals the weekly dose given daily is less than when given on alternate days or three times a week[11].

What happens in real life?

A recent survey organised by patients' groups in Europe examined the use of prophylaxis in people aged 20-35 with severe haemophilia and found an inverse correlation between time on prophylaxis and occurrence of major bleeds, presence of target joints and time off work. As expected, patients from Sweden who had spent the longest period on prophylaxis had the best preserved joints and best quality of life[13].

In practice, in Europe and North America prophylaxis is widely started in childhood but what happens on reaching adulthood is very variable[14]. In general, around one third of patients who start prophylaxis in childhood choose to stop it on reaching adulthood and of these one third eventually revert to regular adult prophylaxis (Table II).

In a 2006 survey in Canada of 2663 people aged over 18 years with haemophilia A and B, 53% of individuals with haemophilia A and 20% of those with haemophilia B were already on prophylactic treatment[10].

Table II - The frequency of discontinuation and restarting prophylaxis in adults with severe haemophilia.

Country	Number of patients discontinuing prophylaxis (%)	Number of patients restarting prophylaxis after discontinuation (%)
USA[18]	27/76 (36)	9/23 (39)
Europe[14]	92/218 (42)	26/92 (28)
The Netherlands[19]	18/58 (31)	0
Denmark[19]	10/22 (42)	Not available
Sweden[20]	3/42 (7)	Not available

Should all patients with severe haemophilia be on life-long prophylaxis?

Severe haemophilia is conventionally defined according to the ISTH definition as a FVIII/IX concentration of <1 U/dL[15]. It is well recognised, however, that the actual clotting factor concentration does not always correlate well with the frequency of bleeding in an individual. A number of groups have attempted to use the calibrated automated thrombogram to identify individuals at the extremes of the haemophilic population in terms of bleeding frequency, but these studies have given mixed results[16]. It is not possible at present to identify individuals who will bleed less (or more) frequently than the person with standard severe haemophilia. In practice, the frequency and severity of bleeding in an individual can only be defined clinically and it is, therefore, important that all patients keep good documentation of the treatments they self-administer. For those individuals with a mild phenotype who bleed infrequently on demand therapy, regular prophylaxis is unlikely to be acceptable or recommended; for those with very frequent bleeds, prophylaxis is likely to be offered by the majority of treaters in countries in which concentrates are readily available. For the majority of patients with standard severe haemophilia, however, adult prophylaxis should be the standard of care in the future as it will prevent bleeds, arthropathy and improve quality of life.

A pragmatic way forward

People with haemophilia are usually experts at managing their condition at home by self-administration of concentrate. Although it is said that administration of prophylaxis is inconvenient, it must be appreciated that this is the patient's not the treater's inconvenience. It would be reasonable to offer all adult patients with severe haemophilia the opportunity of trying prophylaxis for a fixed period before deciding whether, or not, it would be a long-term option. Patients should keep good records of bleeds on and off prophylaxis. In the author's experience, most patients who have taken part in clinical trials of adult prophylaxis have chosen to continue with the prophylaxis once the trial is over.

Ultimately, as the authors of the editorial to accompany Manco-Johnson's paper in the New England Journal of Medicine state, "The dilemma in managing haemophilia is not whether to use prophylaxis or episodic treatment but how to manage prophylaxis such that the optimal, most cost effective treatment is provided"[17]. Although the authors were referring to childhood prophylaxis, I believe the statement applies equally well to the adult situation and for the majority of patients with severe haemophilia prophylactic treatment for life should be the new gold standard of care.

Acknowledgement

This manuscript arose from a debate that took place at a symposium sponsored by Bayer Pharma AG at the ISTH 2011 meeting in Kyoto, Japan.

Conflicts of interest disclosure

Dr. Makris has acted as a consultant to CSL Behring and Novo Nordisk, and has received honoraria for lecturing or attending advisory boards for SOBI, Bayer, Pfizer, Novo Nordisk and CSL Behring.

References

1) Manco-Johnson MJ, Abshire TC, Shapiro AD et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. N Engl J Med 2007; **357**: 535-44.
2) Gringeri A, Lundin B, von Mackensen S et al. A randomized clinical trial of prophylaxis in children with hemophilia A (the ESPRIT Study). J Thromb Haemost 2011; **9**: 700-10.
3) Iorio A, Marchesini E, Marcucci M, et al. Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B. Cochrane Database Syst Rev 2011; **9**: CD003429.
4) Collins P, Faradji A, Morfini M, et al. Efficacy and safety of secondary prophylactic vs. on-demand sucrose-formulated recombinant factor VIII treatment in adults with severe hemophilia A: results from a 13-month crossover study. J Thromb Haemost 2010; **8**: 83-9.
5) Tagliaferri A. Awaiting evidence-based recommendations on prophylaxis in adult patients. Haemophilia 2011; **16**: 955.
6) Witmer C, Presley R, Kulkarni R, et al. Associations between intracranial haemorrhage and prescribed prophylaxis in a large cohort of haemophilia patients in the United States. Br J Haematol 2011; **152**: 211-6.
7) Auerswald G, Bidlingmaier C, Kurnik K. Early prophylaxis/FVIII tolerization regimen that avoids immunological danger signals is still effective in minimizing FVIII inhibitor developments in previously untreated patients - long-term follow-up and continuing experience. Haemophilia 2012; **18**: e18-20.
8) Kurnik K, Bidlingmaier C, Engl W, et al. New early prophylaxis regimen that avoids immunological danger signals can reduce FVIII inhibitor development. Haemophilia 2010; **16**: 256-62.
9) Keeling D, Tait C, Makris M. Guideline on the selection and use of therapeutic products to treat haemophilia and other hereditary bleeding disorders. A United Kingdom Haemophilia Center Doctors' Organisation (UKHCDO) guideline approved by the British Committee for Standards in Haematology. Haemophilia 2008; **14**: 671-84.
10) Blanchette VS. Prophylaxis in the haemophilia population. Haemophilia 2010; **16** (Suppl. 5): 181-8.
11) Collins PW, Fischer K, Morfini M, et al. Implications of coagulation factor VIII and IX pharmacokinetics in the prophylactic treatment of haemophilia. Haemophilia 2011; **17**: 2-10.
12) Pipe SW. Hemophilia: new protein therapeutics. Hematology Am Soc Hematol Educ Program 2010; 203-9.
13) Noone D, O'Mahony B, Prihodova L. A survey of the outcome of prophylaxis, on-demand or combined treatment in 20-35 year old men with severe haemophilia in four European countries. Haemophilia 2011; **17**: e842-3.
14) Richards M, Altisent C, Batorova A, et al. Should prophylaxis be used in adolescent and adult patients with severe haemophilia? An European survey of practice and outcome data. Haemophilia 2007; **13**: 473-9.
15) White GC 2nd, Rosendaal F, Aledort LM, et al. Definitions in hemophilia. Recommendation of the scientific subcommittee on factor VIII and factor IX of the scientific and standardization committee of the International Society on Thrombosis and Haemostasis. Thromb Haemost 2001; **85**: 560.
16) van Veen JJ, Gatt A, Makris M. Thrombin generation testing in routine clinical practice: are we there yet? Br J Haematol 2008; **142**: 889-903.
17) Roosendaal G, Lafeber F. Prophylactic treatment for prevention of joint disease in hemophilia -cost versus benefit. N Engl J Med 2007; **357**: 603-5.
18) Walsh CE, Valentino LA. Factor VIII prophylaxis for adult patients with severe haemophilia A: results of a US survey of attitudes and practices. Haemophilia 2009; **15**: 1014-21.
19) van Dijk K, Fischer K, van der Bom JG, et al. Can long-term prophylaxis for severe haemophilia be stopped in adulthood? Results from Denmark and the Netherlands. Br J Haematol 2005; **130**: 107-12.
20) Astermark J. When to start and when to stop primary prophylaxis in patients with severe haemophilia. Haemophilia 2003; **9** (Suppl. 1): 32-7.

Arrived: 10 November 2011 - Revision accepted: 16 December 2011
Correspondence: Mike Makris
Sheffield Haemophilia and Thrombosis Centre
Royal Hallamshire Hospital
Glossop Road
Sheffield, S10 2JF, United Kingdom
e-mail: m.makris@sheffield.ac.uk