HEMOPHILIA CARE IN 2000S

Optimizing clotting factor replacement therapy in hemophilia: A global need

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Morbidity in hemophilia is predominantly related to musculoskeletal dysfunction consequent to damaged joints and soft tissue from repeated bleeding. The most critical aspect of the management of hemophilia therefore is the replacement of clotting factor concentrates (CFC) in ways that adequately prevent such bleeding and its complications [1]. In spite of the fact that CFCs have been available for over three decades, optimal ways to use them to achieve these ends have not been defined. While some models of replacement protocols that almost completely prevent bleeding have been described, the dosage used (5–9,000 IU/kg/yr) [2] and the associated costs are so high that they remain impractical in most parts of the world, even in many developed countries. More modest replacement protocols (2–4,000 IU/kg/yr) [3] with apparently similar long term musculoskeletal outcomes have also been described but systematic comparison between these two approaches particularly with regard to outcome over 3–4 decades remains to be done.

Current protocols for replacement therapy with CFC in hemophilia have several unresolved issues:

1. Is the aim preservation of normal joint architecture or maintenance normal overall musculoskeletal function? This is extremely important as the dosage that may be needed to achieve the former (if it is at all possible in the long term) may be much higher and often impractical than the latter approach.
2. Should treatment be started before or after the first (or the first two or three bleeds)? Should only joint bleeds be considered significant or subcutaneous bruises in little children also counted?
3. Do all patients with severe hemophilia need to be on regular prophylaxis? How should we identify 10–20% of patients with factor levels <1% who have clinically mild disease?
4. What should be the replacement protocol for prophylaxis? Is it necessary to maintain >1% levels at all times? Once initiated, till what age should prophylaxis be advised?
5. Should treatment be initiated with less frequent (even once a week) dosage and increased only for those who have breakthrough bleeds?
6. What should be the dose to treat breakthrough bleeds? Is there adequate data to support the dose of 25–40 IU/kg being commonly used at present? How many doses are needed? How many breakthrough bleeds are unlikely to change long term outcome and hence acceptable before intensification of prophylaxis regimen is needed?
7. What is the optimal dosage for hemostasis for surgery in hemophilia? There is a very large variation in the dosage used for similar procedures through out the world with apparently no significant difference in complications.
8. What are the optimal ways to induce tolerance in patients with different types of inhibitor profiles? Will the current studies be able to address the relevant issues?

Why is optimization necessary for replacement therapy with CFC in hemophilia? There could be several reasons. As for any pharmacologic therapy, the aim here too should be to use adequate and not excessive or inadequate dosage [4]. Venous access and the logistics of thrice a week therapy (as per current paradigms of intensive prophylaxis) in children below 2 years of age is not easy and results in significant inconvenience to the family and morbidity in the child [5]. From a pharmaco-economic point of view, the average cost of treating a person with hemophilia varies between $50–150,000 per year [6]. This is not
an insignificant amount anywhere in the world. While several economically sufficient countries are providing or attempting to provide care at this level (with a 2 to 3-fold difference in total CFC dosage/capita even among them), obtaining insurance for such costs has limitations. It is even more important therefore that such an approach be justified with suitable data. If not, not only is it inappropriate use of important resources but competing health care needs and demands may eventually impact on the sustainability of any program whose very basis is questionable. Some examples of this are already beginning to surface in different parts of the developed world.

The importance of these issues is even greater in economically less sufficient countries. Here, in the foreseeable future, the dosages described above are not likely to be used. It is therefore important that these countries generate data on long-term musculoskeletal outcome with different dosage in the range relevant to their practice [7]. This is completely lacking at present. It will be important to know whether there is a critical ‘minimum-dose phenomenon’ below which the extent of joint damage may be similar. It is possible that long-term outcome may only show significantly better results if dosages are above 500 or 1000 IU kg\(^{-1}\) per year and below that it may not matter whether it is 100 or 500 IU kg\(^{-1}\) per year even though the cost of providing CFC may be 5 to 10-fold different. Such information will be critical for health planners in deciding the minimum quantity of CFC to be provided if significant musculoskeletal morbidity is to be avoided.

It is therefore obvious that optimization of CFC replacement protocols is necessary all over the world. It is in the interest of patients, physicians and health care managers to ensure that large multi-center prospective studies are initiated to answer the relevant questions that will provide data for evidence based management of hemophilia.

References