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ORIGINAL ARTICLE *Meeting report*

# The need for speed in the management of haemophilia patients with inhibitors

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**Summary.** Rapid control of bleeding is the key to reducing bleeding complications and thereby preserving joint and musculoskeletal function in haemophilia patients with inhibitors. However, this requires early diagnosis following the onset of bleeding and strategies for rapid treatment in an outpatient setting. Overarching themes on the need for speed in managing bleeds in haemophilia patients were examined by a panel of clinicians experienced in managing inhibitor patients and joint disease during the *Third Zürich Haemophilia Forum* on 8 May 2009. This report summarizes the opinions of the panel on how to achieve rapid bleeding control in inhibitor patients and areas that were identified by the panel for future research or as needing new consensus guidelines. The consensus was that home treatment should be established for haemophilia patients with inhibitors, as it is associated with a faster time to treatment, as well as improvements in the quality of life of patients and their carers. In addition, as improved haemostatic control now allows inhibitor patients to participate in a wider range of physical activities, specific guidelines are required on which types of sport and work are appropriate. It was agreed that clear, systematic approaches are needed for early diagnosis of joint and muscle bleeds in inhibitor patients, which could facilitate rapid treatment. There may be opportunities for exploiting new diagnostic techniques from osteoarthritis to enable earlier diagnosis of haemophilic arthropathy. Overall, it was concluded that greater emphasis should be placed on education and patients' psychological needs, to enable inhibitor patients to cope up more effectively with their disease.

**Keywords:** arthropathy, haemophilia, inhibitors, muscle bleed, quality of life, recombinant activated factor VII

## Introduction

The World Federation of Haemophilia (WFH) guidelines for the management of haemophilia recommend early assessment and treatment (within 2 h, if possible) of acute bleeds [1]. In haemophilia patients with inhibitors, rapid treatment of bleeding episodes has been associated with the most effective outcome, in terms of fast resolution of bleeding, and requires fewer doses of haemostatic product than late treatment [2]. Rapid bleeding control also limits the degree of joint destruction, as this is proportional to the duration of exposure to blood in the joint, as well as to the amount of blood deposited. In addition,

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1. **Rapid control of bleeding is the key to reducing bleeding complications and thereby pre-serving ...**
**Anchor Name: Treat early**
*[Agency FCB Halesway Olga Kooi]*

2. **recommend early assessment and treatment (within 2 h, if possible ) of acute bleeds [1 ]. In haemop...**
**Anchor Name: Salek 2011/pg95/col2/P1**
*[Elizabeth Piscetelli]*

production of a tight, well-structured haemostatic plug at the lesion site, which is therefore more resistant against premature proteolysis, is dependent on prompt correction of the rate of thrombin generation in haemophilia patients [3].

The overall objective of the *Third Zürich Haemophilia Forum*, held in May 2009, was to examine strategies for achieving rapid bleeding control in haemophilia patients with inhibitors in order to preserve their mobility and improve their well-being and quality of life. Topics covered ranged from the potential of new techniques for earlier diagnosis, to the benefits of current treatments for inhibitor patients, and clinical scenarios where new approaches are needed to facilitate prompt treatment (see Table 1). The key discussions among the meeting participants and their opinions on how to achieve rapid bleeding control in patients with inhibitors are summarized in this report.

## Early diagnosis of joint damage: new insights

Rapid diagnosis and treatment of joint damage is imperative, as the degree of cartilage damage caused by haemosiderin deposits increases over time. Haemophilic arthropathy develops following resorption of intra-articular blood by synovial tissue and accumulation of haemosiderin, which in turn triggers inflammation of synovial tissue, and consequent cartilage and joint damage. In addition, the balance of anabolic and catabolic factors is disturbed in cartilage destruction [4,5].

As the pathogenesis of haemophilic arthropathy and cartilage degeneration in osteoarthritis are similar (both low-grade synovitis), the panel recognized the potential benefits of extrapolating advances in diagnostics for osteoarthritis to haemophilic arthropathy. For example, nanostructure analysis of cartilage using atomic force microscopy, a technique investigated for osteoarthritis [6], may enable earlier morphological diagnosis of chondropathy and consequently haemophilic arthropathy than is possible using current histopathological tools [7]. However, this particular technique would require a biopsy. It was agreed in principle that new methods for presymptomatic diagnosis could potentially guide early initiation of prophylaxis to prevent further bleeding in selected patients with inhibitors, and thus limit joint damage, arthropathy progression, and direct and indirect costs associated with this condition.

A further possibility discussed that may enable early diagnosis of joint disease was to monitor biomarkers, such as proinflammatory cytokines in synovitis [4,5,8]. The panel discussed that serum cartilage oligomeric matrix protein and urinary C-terminal telopeptide of type II collagen, which may reflect the severity of cartilage damage in haemophilic arthropathy [8], would be good candidate biomarkers. Interleukin-10 was also considered promising as it protects against blood-induced joint damage in haemophilic tissue *in vitro* [5].

The opinion of the panel was that future strategies for early diagnosis of haemophilic arthropathy could involve a move from tissue-based diagnosis to gene expression profiling of early tissue lesions, genomic or proteomic profiling of pathogenically relevant genes/gene products, and metabolome analyses. These techniques are already being used to examine non-haemophilic cartilage and other tissues [9–12]. Analysis of gene expression profiles in synovial tissue from healthy donors and patients with osteoarthritis has so far identified genes that are proinflammatory and involved in tissue destruction (e.g. bone morphogenetic protein-4, interleukin-1β, tumour necrosis factor-α) [12]. The value of these techniques for analysing blood, synovia and low-grade synovitis to diagnose tissue damage is currently under investigation. The consensus was that it would be interesting to explore further the potential of these techniques for accurate, early diagnosis of joint damage in haemophilia (Table 1). In addition, the panel speculated whether it might be possible to define a risk genotype for haemophilic arthropathy through identification of gene polymorphisms; these patients could then be treated more intensively.

## Benefits of rapid bleeding control in current practice

### *The importance of home treatment*

Although rapid haemostatic treatment may not reverse the early damage already caused by a bleed and associated inflammation, it can limit further damage. Home treatment is associated with a fast treatment onset [13], as well as improvements in quality of life (including greater participation in physical activities), reduced pain and disability, fewer hospitalizations and less time lost from work or school [14]. As such, the panel recommended that haemophilia patients with inhibitors should be treated at home, as this is more convenient and is the best modality for controlling joint bleeds quickly. In addition, through home treatment, patients also become empowered to take charge of their own care. It was considered critical, however, that patients and their families should receive education on the most

 

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**Table 1.** Summary of key conclusions from the Forum.

| Topic | Conclusions/recommendations |
|---|---|
| Potential new methods for accurate, early diagnosis of joint damage | Biomoarkers already identified for osteoarthritis may be promising for earlier diagnosis of haemophilic arthropathy |
| | Gene expression profiling for diagnosis or determining risk genotypes should be investigated further |
| | Additional research is needed to explore the application of these new techniques in the haemophilia field |
| The role of home treatment in inhibitor patients | No serious adverse events have been reported for inhibitor patients receiving home treatment |
| | Efficacy rates for home treatment with recombinant activated factor VII (rFVIIa) in inhibitor patients are high and consistent |
| | Home treatment facilitates rapid bleeding control and improves quality of life |
| | Patients/carers should be educated on home-treatment regimens |
| | Patients with inhibitors should treat mild/moderate bleeds at home |
| | Single dose regimen of rFVIIa (270 μg $kg^{-1}$) and room temperature stable formulation of rFVIIa may improve home treatment feasibility |
| | Additional data from 'real-life' use are needed |
| Unmet needs in the management of muscle haematomas | Rapid treatment of muscle haematomas is crucial |
| | More accurate diagnosis of muscle haematomas is needed |
| | Consensus, systematic approaches, incorporating knowledge from sports physiotherapy following muscle bleeds, are needed for treating muscle haematomas |
| Prevention of haemophilic pseudotumours by rapid treatment | Haemophilic pseudotumours are one of the most severe complications of inadequate treatment of recurrent bleeds |
| | There is no standard approach to managing pseudotumours |
| | Uniform treatment options and protocols are needed |
| Impaired growth and bone length development in inhibitor patients: requirements for further studies | Inhibitor patients may have delayed growth and physiological development vs. non-inhibitor patients |
| | Early and aggressive attempts are needed to minimize physiological disruption of development |
| | Growth and maturation of children and adolescents with haemophilia, particularly inhibitor patients, should be monitored |
| | Studies are needed to determine the underlying mechanisms for any growth and leg-length differences |
| The need for broader approaches to patient management | Haemophilia patients are now leading more 'normal lives', but this is dependent on a variety of factors being met |
| | Patient needs should be assessed by introducing screening tools such as standardized questionnaires and interviews into clinical practice |
| | Extended health-care teams are needed to take care of social and psychological aspects and to educate patients and their carers |
| Benefits of physical activities in haemophilia patients with inhibitors, and the need for guidelines on sporting activities | Physical activity clearly benefits all haemophilia patients, but is commonly restricted, most notably in inhibitor patients because of the fear of injury or bleeding |
| | Education is needed on the bleeding risks associated with particular physical activities/sports |
| | Specific guidelines are required for inhibitor patients, in particular, on which physical activities/sports are most appropriate and which should be avoided |
| | More data are needed on the efficacy of prophylaxis regimens in inhibitor patients to allow safe physical activities |
| Work-related bleeding and employment choices | Fast access to treatment may give patients more flexibility at work |
| | Changes in employment choices may place haemophilia patients at greater risk of work-related bleeds and injuries |
| | As there are no data on work-related injuries in patients with haemophilia, a questionnaire study could be useful |
| | Adequate haemostatic cover should be available at work |

appropriate home treatment, including the type(s) of haemorrhage to be treated at home and circumstances in which they should seek hospital advice (Table 1).

Although management of inhibitor patients presents more challenges than non-inhibitor patients, it does not obviate their participation in home-care programmes. Current options for home treatment of acute haemarthroses in inhibitor patients include recombinant activated factor VII (rFVIIa; NovoSeven®; Novo Nordisk, Bagsværd, Denmark) and plasma-derived activated prothrombin complex concentrate (pd-APCC; FEIBA®; Baxter Bioscience, Vienna, Austria). A recent systematic review of




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rFVIIa and pd-APCC in randomized trials reported efficacy rates of approximately 81–91% for rFVIIa (90 μg $kg^{-1}$ every 2–3 h or 1 × 270 μg $kg^{-1}$) and 64–80% for pd-APCC (50–85 IU $kg^{-1}$) 12 h after treatment initiation [15]. One of the studies directly comparing rFVIIa and pd-APCC, the FEIBA NovoSeven Comparative (FENOC) trial [16], showed that rFVIIa (2 × 90–120 μg $kg^{-1}$) and pd-APCC (1 × 75–100 IU $kg^{-1}$) had similar effects on joint bleeds overall, although some inhibitor patients expressed a preference for one of the bypassing agents, illustrating that different patients may respond better to one agent than the other. However, the FENOC study was not able to demonstrate equivalence between the treatments at the majority of timepoints.

Another important fact to address is the need for rescue medication as one might argue that despite early treatment and initial cessation of the bleeding, the occurrence of a re-bleed can worsen the situation. A more recent trial showed that 9.1% of patients receiving rFVIIa (3 × 90 μg $kg^{-1}$) required additional haemostatics within 9 h of dosing vs. 36.4% receiving pd-APCC (1 × 75–100 IU $kg^{-1}$) ($P = 0.069$) [17].

The importance of immediate treatment for inhibitor patients has been highlighted further by initial data for adult inhibitor patients from the HemoRec Registry suggesting that treatment of bleeds with rFVIIa within 2 h of bleeding onset may be even more effective than treatment given after 2 h (re-bleeds in 5.2% vs. 13.7% patients respectively) [18]. In addition, meta-analysis data suggested that treatment with rFVIIa may be associated with faster joint bleed resolution than pd-APCC because of higher efficacy levels at 12-, 24- and 36-h timepoints [19].

The panel emphasized that, to be noted as important, no serious adverse events have been reported in home-treatment trials [13,17,20,21]. In the studies of rFVIIa and pd-APCC reviewed by Knight *et al.* [15] the only significant adverse event reported was anamnestic response, which was identified in pd-APCC studies. In studies reporting adverse events other than anamnestic response, adverse event rates were <5% and serious adverse events, such as thromboembolic events, were reported in <0.5% of patients.

### *New options for rapid bleeding control in inhibitor patients*

Recent advances in rFVIIa therapy may be beneficial for inhibitor patients as they enable more convenient and rapid access to treatment, and thus bleeding control. The recent availability of a room-temperature-stable formulation of rFVIIa with greater stability up to 25°C and at differing temperatures [22], means that inhibitor patients can now carry their haemostatic therapy with them during their normal everyday life, enabling more immediate treatment.

The meeting participants agreed that data on treatment patterns, responses to therapy and any complications with new rFVIIa treatment paradigms should be collected by haemophilia treatment centres. In addition, 'real-life' clinical data on rFVIIa should be collected via patient registries (e.g. HemoRec [18]) (Table 1).

### *Unmet needs in the management of muscle haematomas*

An area of growing interest where improvements in treatment strategies are needed to achieve more rapid bleeding control and resolution is the management of muscle haematomas in inhibitor patients. Rapid treatment of muscle haematomas is crucial, but to date has received little focus as they represent only 10% of all bleeding events in haemophilia patients [23]. Expansion of bleeds in muscle compartments can, however, result in compression of nerves and vessels, with potentially life-threatening consequences. With insufficient treatment, recurrent muscle haematomas can cause loss of joint function, reduced range of motion, haemophilic pseudotumours and increased pressure in muscle compartments leading to ischaemic contractures.

Most information on the management of muscle bleeds in inhibitor patients is from case studies. However, a recent cross-sectional questionnaire study by Sørensen *et al.* evaluated current practice for managing muscle bleeds in patients with severe haemophilia A with and without inhibitors. The results showed that in most cases (68.2%), treatment was adjusted according to the location of the bleeding. However, protocols were not consistent across the 20 participating centres and/or were not being followed closely, as doses suggested for haemostatic intervention using FVIII (non-inhibitor patients) or bypassing agents (rFVIIa and pd-APCC; inhibitor patients) varied considerably. Notably, the study revealed room for improvement in the speed of treating patients with and without inhibitors as the maximum accepted time for obtaining haemostasis was, in most cases, <6 h (54.5%), but 13.6% of centres accepted 18–24 h [B. Sørensen, Unpublished data].

One of the obstacles identified by the panel that prevents prompt on-demand treatment of muscle haematomas in inhibitor patients is the difficulty in

 

recognizing whether symptoms are attributable to a muscle bleed or other causes. Distinguishing between muscle bleeds and other muscle conditions such as contusions or strains is not easy and accordingly it can delay the onset of appropriate treatment or increase the risk of over- or under-treatment. It was agreed that protocols and training are required on visualizing and diagnosing muscle bleeds to provide a better platform for starting haemostatic interventions earlier, and for monitoring bleed resolution.

More emphasis is also needed on optimizing haemostatic intervention (e.g. choice of factor, timing and duration of treatment, dosing regimen), and the use of concomitant and adjuvant therapy (e.g. physiotherapy) in haemophilia patients with inhibitors. In addition, patients should be educated on the benefits of faster (and prolonged) treatment. Approaches should also be broadened by incorporating methods used in sports physiotherapy to accelerate rehabilitation and prevent re-injuries. Finally, it was agreed that a model that can detect a muscle bleed and determine treatment efficacy would be informative (Table 1).

### *Reducing complications by rapid treatment: haemophilic pseudotumours*

Another issue discussed was the development of haemophilic pseudotumours, which, although only present in 1–2% of the patients with severe haemophilia, represent one of the most serious complications of inadequately treated frequent re-bleeding [24,25]. Critically, their development could be reduced by fast, effective haemostatic therapy soon after the onset of symptoms (and by treatment prolonged until clear resolution) (Table 1).

### *Impaired growth and bone length development in inhibitor patients*

In mature joints, haemophilia has a major detrimental effect on cartilage; as it exacerbates, joint function deteriorates. However, chronic synovitis in the immature joints of children causes hypertrophy of the epiphyseal growth plates and significant structural deficiencies may rapidly develop, resulting in bone hypertrophy, leg-length discrepancy and angular deformities [26].

The panel determined that little information is available on growth and bone length differences in haemophilia, apart from anecdotal cases (e.g. [27]). However, one small study showed a significant delay in skeletal maturation and puberty in children with a history of inhibitors (≥1 Bethesda Unit) vs. non-inhibitor patients. By 18 years of age, patients with inhibitors were also significantly shorter than non-inhibitor patients (mean height 170.0 cm and 177.1 cm, respectively; $P < 0.001$) [28]. There was general agreement that although these results suggested increased physiological disruption of development in inhibitor vs. non-inhibitor patients, they need to be confirmed and the underlying mechanisms explored. Nevertheless, early intervention was recommended to minimize delayed or abnormal physiological development and maturation of haemophilia patients. Further, the growth and maturation of children and adolescents with severe haemophilia, particularly those with inhibitors, should be carefully monitored (Table 1).

## Future challenges in the management of inhibitor patients

### *The need for broader approaches to patient management*

With advances in haemostatic control for inhibitor patients, the general consensus of the panel was that it is becoming increasingly practicable for haemophilia patients to lead more 'normal lives' (e.g. to participate in sports and have careers and families). As such, more emphasis is now needed on wider aspects of patient care beyond factor treatment so patients are able to cope more effectively with their disease in different, and potentially new, situations.

A commonly held view was that psychological approaches to the management of haemophilia patients are becoming increasingly important. Studies have shown that key factors influencing quality of life from the psychological perspective of adult patients with haemophilia include family, employment, health, education and leisure time [29,30]. In addition, results using the Haemophilia Well-Being Index, a patient report outcome measure developed from the patient's perspective, showed a significant correlation between poor well-being and the presence of chronic pain, severe haemarthrosis in the same joint, high number of bleeds in the last 6 months, problems with mobility/walking or self care, and poor health-related quality of life (EuroQoL-5D) [E. Remor, Unpublished data], all of which are common in inhibitor patients. These findings are consistent with a previous study of haemophilia patients [31].

The panel recommended that screening tools such as standardized questionnaires and interviews should be introduced into clinical practice to assess patients' needs and beliefs and thus help to detect early effects




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on patient well-being and anticipate future problems. In addition, physicians should place greater emphasis on educating, and thereby empowering, patients (and their parents or relevant others) to take control of their haemophilia and thus improve their well-being and ability to deal with different situations. One approach to address this would be to extend healthcare teams to include psychologists and social workers, to provide early comprehensive and effective therapy addressing the broad range of issues faced by patients (Table 1).

### *The need for physical activity in haemophilia patients with inhibitors*

The benefits of physical activity (including physiotherapy) are clear for all haemophilia patients: being overweight overloads the joints. There is evidence that non-inhibitor patients who exercise regularly exhibit fewer bleeds and have functional abilities similar to their non-haemophilic peers [32,33]. Notably, in haemophilia, physiotherapy is the basis for all physical activities and is not restricted to post-surgical rehabilitation. Despite this evidence, physical activity is frequently restricted because of the fear of injury or bleeding. In the Italian COCHE study, 56.7% of adult non-inhibitor patients always or often had to refrain from sports, 75.5% always or often had to refrain from soccer and only 15.4% participated in sports as much as their peers [34]. Furthermore, the panel advised that the fear of injury or bleeding plays a major role in limiting the participation of inhibitor patients in physical activities.

The WFH recommends that the choice of sport should reflect the individual's resources; however, sports entailing high risk for trauma should be avoided [1]. The panel supported WFH recommendations for regular physical exercise from the first years of life to improve endurance, flexibility, strength and coordination, and agreed that any sporting activities need to be individualized to match the patient's physical and psychological abilities. The panel also agreed that it is still unclear which physical activity/sport is most appropriate for a given patient with inhibitors as guidelines on the risks of injury associated with different activities are not sufficiently tailored to haemophilia complicated by inhibitors [35].

The panel concluded that sport, particularly via organized programmes, plays an important psychological role in enhancing self-esteem, with children with inhibitors learning how to manage their personal abilities and recognize their limits. Physicians and patients must, however, be aware of bleeding complications during leisure sports, which are much higher for adults than for adolescents [36]. Currently, the quality of life of inhibitor patients is impaired by their limited participation in daily activities, including sports. In contrast, the availability of prophylaxis, with adjusted regimens according to the specific activities, is enabling non-inhibitor patients to participate in a wider range of activities. The efficacy of prophylaxis in inhibitor patients still needs to be proven [37], so they can also participate more fully, and hence experience improved quality of life in the future (Table 1).

### *Work-related bleeding in haemophilia patients*

To date, patients with haemophilia have primarily been employed in sedentary, often more subservient, work to prevent work-related injuries. Providing fast access to treatment will give patients more flexibility at work, with participation in more active jobs increasing their self-esteem. The panel proposed that data (via questionnaire) are needed on work-related injuries in haemophilia patients so that jobs associated with inappropriately high risks of injury can be avoided and proper indications can be given for treatment and prophylaxis (Table 1).

## Conclusions and future issues for inhibitor patients

There was a broad agreement among the meeting participants that rapid treatment and thereby control of bleeding is advantageous to haemophilia patients with inhibitors, as it can reduce complications such as joint bleeds and thus prevent arthropathy, preserve mobility and improve quality of life. In addition, the consensus was that home treatment with more user-friendly concentrates and devices for administration had successfully facilitated faster treatment onset and provided more flexible treatment regimens for inhibitor patients.

A further commonly held view was that the possible application in the future of techniques to diagnose bleeds soon after the onset of bleeding may allow more rapid initiation of therapy. In addition, more research and strategic approaches are needed to enable rapid diagnosis, treatment and monitoring of muscle haematomas in inhibitor patients.

New challenges faced by inhibitor patients and their physicians include the need for specific data on bleeding risks associated with a wider range of physical activities and types of work, so that




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evidence-based recommendations can be made regarding appropriate and inappropriate activities. The panel also highlighted the increasing need to take into account aspects of patient care beyond factor replacement, including psychological issues, concluding that haemophilia care teams should be broadened to include psychologists and social workers, who can provide expert guidance on patient well-being and quality of life. It was also widely perceived that more importance should be placed on educating inhibitor patients (and their carers) so that they feel more in control of their disease and are more aware of the need for speed in managing their bleeds.

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[no notes on this page]