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Chapter 1 : BMJ Best Practice

Inhibitors to Factor VIII: Treatment of Acute Bleeds Christine A. Lee MA, MD, DSc (Med), FRCP, FRCPath Emeritus Professor of Haemophilia Honorary Consultant Haematologist 2,3, Erik E. Berntorp MD, PhD Professor of Hemophilia 4 and.

Vasc Health Risk Manag. All rights reserved This article has been cited by other articles in PMC. Abstract The development of high-titer inhibitors to FVIII and less often to other coagulation factors are the most serious complication of hemophilia therapy and makes treatment of bleeds very challenging. At present, bypassing agents, such as factor eight inhibitor bypass activity FEIBA and activated recombinant factor VII rFVIIa are the only coagulation factor concentrates available for the treatment of bleeds in inhibitor patients. A significant number of patients report a better effect of one or the other of the products, and in a minority of the patients none of the products are particularly effective. The hemostatic efficacy of bypassing agents is not considered equal to that of coagulation factor replacement in patients without inhibitors by most physicians. An improvement in hemostatic efficacy may be achieved by optimizing the dosing of by passing agents. However, the lack of standardized and validated laboratory assays reflecting the hemostatic efficacy of the bypassing agents is an obstacle to this achievement. At present, the development of inhibitors is the most serious complication to the use of these concentrates in hemophilia care, and patients with inhibitors represent a major therapeutic challenge. Inhibitors may occasionally also develop in patients with mild or moderate hemophilia. Progressive and disabling joint disease is more prevalent in inhibitor patients than in non-inhibitor patients Leissinger et al An incidence of 0. Although the clinical phenotype of acquired hemophilia differs from that of congenital hemophilia, managing bleeds poses more or less the same challenges to the clinician. Inhibitors are measured with the Bethesda assay or its modifications, and titers are expressed in Bethesda units BU. The development of inhibitors is the most pressing concern in hemophilia care to day, and there is great interest in methods to reduce the risk of inhibitor development, improve on immune tolerance therapy regimens, treat bleeds, provide hemostasis during surgery and develop effective laboratory methods to assess bypassing therapy. In this review we will focus on the management of bleeds and the prevention of chronic joint disease. Treatment of bleeds Apart from the severity and location of the bleed, the characteristics of the inhibitor are the most important factors to consider in the management of a bleeding episode in a particular patient. Treatment options are dependent on the inhibitor titer as well as whether the inhibitor is low or high responding. A bleed in a low-titer, low-responder patient can usually be treated by standard factor concentrates, but much higher doses than in non-inhibitor patients have to be used to overcome the inhibitor. In general, standard factor concentrates, even in higher doses, are not effective in patients with high-titer inhibitors. Hemostatic agents with proven efficacy in the treatment of bleeds in inhibitor patients are presented in Table 1. However, only bypassing agents are currently available. PCCs have been shown to be less effective than aPCCs and to show a higher rate of adverse reaction Sjamsoedin et al ; Lusher et al ; Negrier et al Currently, PCCs are seldom used to treat inhibitor patients. The hemostatic actions of these agents are different and still not fully unraveled. Nevertheless, both products appear effective, safe and well tolerated, but clinical evidence from randomized, prospective trials comparing the two agents as a guide to their optimal use in inhibitor patients are still lacking. There are ongoing studies addressing this issue, but the final reports are still pending. Table 1 Coagulation factor concentrates with proven efficacy in hemophilia patients with high-titer inhibitors Factor concentrate.

Chapter 2 : FEIBA - About Haemophilia with Inhibitors Therapy

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Indeed, the efficacy of bypassing agents, i. In addition, the therapeutical response is unpredictable, with a relevant inter-individual and even intra-individual variability, and no laboratory assay is validated to monitor the efficacy and safety of the treatment. As a result, inhibitor patients have a worse joint status and quality of life compared to inhibitor-free subjects and the eradication of the inhibitor by immune tolerance induction is the preeminent therapeutic goal, particularly in children. However, over the last decades, treatment with bypassing agents has been optimised, allowing home treatment and the individualisation of regimens aimed at improving clinical outcomes. This review offers an update on the current knowledge and practice of the use of bypassing agents in haemophiliacs with inhibitors, as well as on debated issues and unmet needs in this challenging setting. Introduction The development of alloantibodies inhibitors that neutralise the clotting activity of exogenous coagulation factor F given as replacement therapy is currently the most serious complication of the treatment of haemophilia. Inhibitors develop in approximately one-third of previously untreated patients PUPs with severe haemophilia A i. The risk of inhibitor development then declines, becoming almost negligible in previously treated patients PTPs who have been exposed to FVIII concentrates for more than 50â€" days. The mechanisms responsible for inhibitor formation remain only partially understood, but studies in PUPs with severe haemophilia A have led to the identification of several risk factors, of both a genetic nature null mutations in the F8 gene, genotype of the major histocompatibility complex, polymorphisms of immunoregulatory genes, ethnicity and those which are treatment-related, which indicate a multifactorial pathogenesis, resulting from complex interactions between genetic and environmental influences [3 , 4 , 5]. The incidence of inhibitors is also lower in PUPs with haemophilia B, in whom they are often associated with large deletions in the F9 gene [10]. However, the management of patients with haemophilia B and inhibitors is further complicated by severe allergic reactions occurring in association with the administration of FIX-containing products in approximately half of patients [11]. The aetiology of such reactions is still unknown. Patients with LR inhibitors usually have fewer clinical problems because haemostasis can usually be ensured by saturating the inhibitor through the administration of higher doses of the deficient factor. By contrast, HR inhibitors rule out the use of standard on demand therapy and prophylaxis and, although bleeds are not more frequent than in patients without inhibitors [13], alternative haemostatic agents are required, which have poorer efficacy and safety profiles than factor concentrates. ITI treatment is recommended by international and national guidelines [16 , 17 , 18 , 19 , 20], the European principles of haemophilia care [21], and expert panels [22 , 23 , 24] for all patients with severe haemophilia A and HR inhibitors. Children with recent onset HR inhibitors are the main candidates, because early eradication can optimise the cost-utility ratio in a long-term perspective [25 , 26 , 27]. ITI should also be considered for patients in whom persistent LR inhibitors interfere with standard-dose prophylaxis or on-demand treatment [22 , 23 , 24]. However, ITI fails in about one third of patients; it takes a long time to be achieved in a substantial proportion of cases, and its availability is restricted in many areas due to its high cost. International groups of experts do not, therefore, recommend ITI for patients with haemophilia B with inhibitors [16 , 17 , 18 , 19 , 20 , 21 , 22 , 23 , 24]. However, data recently collected in Italy demonstrated the complete success of inhibitor eradication in four of five patients with severe haemophilia B with inhibitors treated with a low-dose ITI regimen [31]. Data on ITI in patients with non-severe haemophilia A are mostly anecdotal, and strong evidence supporting the systematic performance of ITI in such patients is therefore lacking [17 , 18 , 30 , 32]. However, a case series of 32 patients with mild haemophilia A demonstrated a potential effect of rituximab, an anti-CD20 monoclonal antibody, in eradicating inhibitors [33]. Nevertheless, most clinicians consider implementing ITI in patients with frequent bleeding, although there is no evidence in the literature supporting

the choice of a specific ITI protocol [17 , 18 , 30 , 32]. Selecting the best treatment strategy by the use of these agents is of fundamental importance both for children waiting for ITI, in order to prevent the irreversible consequences of difficult-to-treat haemorrhages, and for patients who are not eligible for or who have failed to benefit from ITI, in order to lessen bleeding-related morbidity and improve the quality of life. Over the last decade, advances have been made in the management of bleeding with bypassing agents and prophylactic regimens are being increasingly used. Treatment of Acute Bleeding The treatment of acute bleeding in patients with an inhibitor should be tailored to the type and severity, the actual inhibitor level, and the anamnestic response LR or HR after exposure to the missing factor. Replacement treatment with FVIII or FIX concentrate is the ideal haemostatic approach [17 , 18], and still applies in the case of LR inhibitors which are commonly overcome with higher factor doses. The dose necessary to neutralise the inhibitor and increase the amount of FVIII or FIX to a haemostatic level varies widely and several dosing algorithms have been proposed [35 , 36]. The initial bolus must provide enough FVIII or FIX to neutralise circulating inhibitors, as well as the amount required to increase the clotting factor to haemostatic levels. Alternatively, a continuous infusion can be used, with the infusion rate adjusted on the basis of the circulating levels reached. Plasmaderived porcine FVIII was previously widely used in this setting, but is no longer available; however, a recombinant porcine FVIII has been developed [37] and is currently in clinical trials for use in congenital haemophilia A with inhibitors. A new formulation of rFVIIa includes sucrose and L-methionine, so that the product can be stored at room temperature before reconstitution. The consequent increase in thrombin generation enhances platelet aggregation, leads to the full activation of thrombin-activatable fibrinolysis inhibitor and FXIII, and ensures that a tight fibrin plug is produced [39]. The half-life of rFVIIa is 2. Its mechanism of action is multifactorial, although FII and activated FX are considered to be the most important components [41]. Thus, the high-dose regimen may be conveniently used, especially in children with venous access problems. However, some patients may respond better to rFVIIa or aPCC and, importantly, the same patient may have different responses to one product or to the other on different occasions, even when the bleeding episodes are similar. In another head-to-head, randomised controlled trial, by Young et al. The efficacy was assessed using a global response algorithm that took into account pain and mobility scores at 9 h after the start of treatment and the requirement for additional haemostatic agents rescue medication within the 9-h period of observation. No statistically significant differences were found in the global algorithm or in the pain and mobility scores measured separately. Overall, on the basis of the results of these two randomised controlled trials, a Cochrane Collaboration review concluded that there was no compelling evidence for the superior efficacy of one product over that of the other in the management of haemarthroses [43]. Studies on other types of bleeds have not been performed. However, the anamnestic response is usually transient, and does not affect the efficacy of the aPCC treatment. Other elements that may influence the choice between the two products include the infusion characteristics larger volumes but less frequent infusions with aPCC and, in haemophilia B patients, the avoidance of allergic reactions and anamnesis of the inhibitor, which can occur with aPCC use, because of the presence of FIX. In addition, it should be taken into consideration that bleeds unresponsive to intensive treatment with one or the other of the two bypassing agents used singly have been shown to be controlled by their use in combination or sequentially at short intervals [54]. In fact, the two products have been reported to have a synergistic effect in vitro [55] and in vivo [56]. Eleven sequential courses of bypassing therapy were recorded in a European survey of nine haemophiliacs, aged between 9 and 73 years old median 24 , whose bleeding, in five cases due to major surgery, was unresponsive to single therapy with one of the two bypassing agents [57]. Bleeding was successfully controlled within 12â€”24 h in all patients and treatment was discontinued after 1â€”15 days. No clinical adverse events were noted, but D-dimer levels increased significantly in three of the five patients in whom this parameter was assessed. Combination therapy with bypassing agents may, therefore, predispose to thrombotic complications and must only be used, after an appropriate risk-benefit assessment, as salvage therapy for a short period of time in a hospital setting, when other interventions have failed [17 , 18]. As regards the treatment of haemophilia B patients with a history of

severe reactions to FIX-containing concentrates, it is generally advised that their bleeds be treated with rFVIIa [17 , 18 , 29 , 58]. In patients unresponsive to this drug and those who are not candidates for FVIII replacement therapy, bleeding episodes can be treated or prevented with bypassing agents [17 , 18 , 32], although some clinicians prefer to use rFVIIa, with the aim of avoiding anamnestic responses to further exposure to FVIII. Regarding safety, the administration of activated factor concentrates in patients with inhibitors has been associated, albeit rarely, with thrombotic complications, including deep vein thrombosis, pulmonary embolism, disseminated intravascular coagulation, and myocardial infarction [60 , 61 , 62 , 63 , 64]. It is believed that the thrombotic risk is related to the dose of the bypassing agents used, the duration of treatment, and the combination of other risk factors, such as hepatic, cardiovascular, and metabolic disorders, prolonged bed-rest, active infections, and surgery which increases the likelihood of patients developing thrombotic events. The concomitant use of antifibrinolytics and thromboprophylaxis is still under discussion in this setting. The rationale for the concomitant use of bypassing agents and tranexamic acid is to exploit a potential synergistic effect and increase clot stability [65]. Tranexamic acid is generally used in association with rFVIIa, whereas it was not often used with aPCC in the past, because of concerns about the risk of thromboembolic complications. However, a recent literature review of studies and individual case reports showed that the concomitant use of aPCC and tranexamic acid during dental procedures, orthopaedic surgery, gastrointestinal bleeding, epistaxis, and cerebral haemorrhages was safe, well-tolerated, and effective, and no thrombotic complication was reported [66]. Nevertheless, additional randomised controlled studies are warranted in order to confirm these findings. Thus, currently, tranexamic acid should be considered in all patients with inhibitors, irrespective of the bypassing agents used, but should be used with caution in association with aPCC. The association of tranexamic acid is especially useful for the management of mucosal bleeds [17 , 58]. Local measures, such as thrombin or fibrin glue, may improve haemostasis and should be considered in patients with persisting bleeding complications that may be controlled by the use of such adjunctive therapy [67]. Finally, regarding the use, still debated, of thromboprophylaxis during treatment with bypassing agents, this strategy could be considered in patients who receive concomitant intensive treatment with bypassing agents during ITI when the inhibitor has been reduced to low levels, but not completely eradicated, especially in patients with comorbidities or risk factors associated with a high risk of thrombotic complications. Monitoring Therapeutic Efficacy of Haemostatic Treatment No laboratory assay is currently validated either to monitor the efficacy of bypassing agents, or to determine their optimal dose. Both thromboelastography TEG and the thrombin generation assay TGA may offer some information relevant for the treatment of individual subjects [68 , 69]. These laboratory tests have shown that ex vivo responses to both bypassing agents are dose-dependent. However, so far, no routine laboratory test has been found suitable for monitoring the efficacy and safety of these drugs in routine clinical practice [70 , 71]. Moreover, the well-recognised, relevant variability in the clinical phenotype among patients with severe haemophilia, as well as in the clinical responses to the bypassing agents, is reflected by variations in the results of in vitro assessments of haemostatic interventions. Such a treatment approach offers the possibility of an early intervention, but clinicians and patients should appreciate that in order to obtain the best response from treatment with bypassing agents, the bleeding must be recognized early and the treatment, which should be adequate in terms of dosing, timing, and number of infusions, needs to be initiated promptly. Moreover, such an approach requires that patients and their caregivers are educated very thoroughly on how to evaluate the efficacy of the treatment and recognize the onset of adverse events [

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The most significant complication of treatment in patients with hemophilia A is the development of alloantibodies that inhibit factor VIII activity. In the presence of inhibitory antibodies, replacement of the missing clotting factor by infusion of factor VIII becomes less effective. Once.

Hypersensitivity to the product or any of the components. Acute thrombosis or embolism including myocardial infarction. As with any intravenously administered plasma product, allergic type hypersensitivity reactions may occur; patients should be informed of the early signs of hypersensitivity reactions. When medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections. Administration of FEIBA to patients with inhibitors may result in an initial anamnestic rise in inhibitor levels. The treatment of hemophilia bleeding with limited resources. World Federation of Hemophilia. Guidelines for the management of hemophilia. Factor eight inhibitor bypass activity FEIBA in the management of bleeds in hemophilia patients with high-titer inhibitors. Vascular Health and Risk Management. Suggestions for the management of factor VIII inhibitors. Journal of Thrombosis and Haemostasis. The use of factor eight inhibitor by-passing activity FEIBA immuno product for treatment of bleeding episodes in haemophiliacs with inhibitors. A randomized comparison of bypassing agents in hemophilia complicated by an inhibitor: Prophylactic treatment with activated prothrombin complex concentrate FEIBA reduces the frequency of bleeding episodes in paediatric patients with haemophilia A and inhibitors. Differential response to bypassing agents complicates treatment in patients with haemophilia and inhibitors. A systematic approach to controlling problem bleeds in patients with severe congenital haemophilia A and high-titre inhibitors. US National Hemophilia Foundation. Luu H, Ewenstein B. FEIBA safety profile in multiple modes of clinical and home-therapy application.

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Chapter 5 : FEIBA - Managing Bleeds During ITI

Preparations of human factor VIII (FVIII) sometimes are appropriate for management of acute bleeding in patients with haemophilia A and an inhibitor to FVIII. The most common use is in patients.

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Claude Negrier, M.D., Ph.D., who have hemophilia A without factor VIII inhibitors. had been receiving episodic treatment with factor VIII to receive a subcutaneous maintenance dose of.