Summary and Conclusions

Treatment of Hemophilia A and B and von Willebrand Disease

A Systematic Review

Swedish Council on Health Technology Assessment

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Summary and Conclusions of the SBU Report:

Treatment of Hemophilia A and B and von Willebrand Disease

A Systematic Review

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In hemophilia A and B and von Willebrand disease, coagulation factors are absent or deficient. This impairs the capacity of the blood to coagulate and increases the risk of bleeding. The diseases are hereditary. If inadequately treated, hemophilia causes painful bleeding in joints and leads to disability. Bleeds can also occur in internal organs, e.g., the brain.

Hemophilia can be treated by replacing missing coagulation factors. The availability of coagulation factors has drastically reduced morbidity, and since the 1950s survival has increased from 15 years to nearly normal life expectancy.

In the past, patients were exposed to high risk of HIV infection and Hepatitis C transmitted via blood and blood products. Since the mid 1980s, concentrated coagulation factors have been produced by methods that have practically eliminated the infection risks. Nevertheless, several questions remain concerning optimum treatment, e.g., selecting the most appropriate dose and dosing strategy. Another question concerns the treatment of bleeding episodes (bleeds) in patients that have developed antibodies (inhibitors) that counteract the effects of factor concentrates.

SBU's Conclusions

- Concentrates of coagulation factors VIII and IX have good hemostatic effects on acute bleeding and during surgical intervention in patients with hemophilia A and B. As scientific evidence is limited, firm conclusions cannot be drawn about possible differences in the effects of different dosing strategies for acute bleeding and surgery. More studies of sufficient quality are needed to investigate the short-term and long-term effects of the different dosage strategies.

conclusions

- Preventive treatment (prophylaxis) initiated at a young age, i.e., before articular (joint) bleeding starts to appear, can prevent future joint damage. Due to a lack of studies, firm conclusions cannot be drawn regarding the optimum time to start treatment during infancy, or the optimum dose and dose interval. Another uncertainty is whether treatment should be discontinued or modified during adulthood in some patients. Such studies are difficult since the numbers of patients are small, and many years of follow-up are required to evaluate the progression of joint damage.

- In patients that have developed high levels of antibodies (inhibitors) against factor concentrates, acute bleeding can be inhibited by administering bypass agents, but it is difficult to predict the effectiveness of such treatment in individual cases. Prophylaxis with bypass agents probably has a favourable effect. When the antibody level has decreased, immunotolerance induction treatment – which usually involves daily administration of relatively high doses of factor concentrate – can halt the production of inhibitors. This means that patients can then be given normal prophylaxis and can be treated for bleeding by using normal factor doses. Treating inhibitor development is extremely demanding and costly. The available treatment options have been insufficiently assessed due to the limited group of patients and the subsequent difficulties in conducting appropriate studies.

- Patients with the more severe types of von Willebrand disease must be treated with factor concentrates that contain von Willebrand factor, and often factor VIII. The effects on acute bleeding and during surgery are good. At times, preventive treatment is necessary. Doses, dose intervals, and indications for factor concentrate treatment in von Willebrand disease have not been sufficiently studied, particularly as regards prophylaxis.

- Treating hemophilia and von Willebrand disease is expensive. The economic consequences of various treatment strategies have been insufficiently analysed due to the lack of studies on clinical effects.

- It is essential to create a national treatment register that includes defined quality indicators. Regarding the future, there is an obvious need for systematic and centralised follow-up of patients with hemophilia A and B and von Willebrand disease within the context of a national quality register aimed at documenting the short-term and long-term treatment effects.

SBU's Summary

Aim

This review aims to assess – from medical, economic, and ethical perspectives – different dosing strategies for replacement therapy using coagulation factor concentrates to treat patients with hemophilia A and B and von Willebrand disease.

The systematic literature review does not cover the safety aspects related to transmission of infections, or the risks for developing inhibitors (neutralising antibodies). The methods currently used for virus inactivation and virus reduction in producing plasma-based factor concentrates have been approved by European and U.S. drug authorities, and the products are considered to have a wide margin of safety. The transition to products manufactured by recombinant DNA methods has favourably altered the risks of blood contamination. An international debate is under way concerning the risks of inhibitor development, but evidence supporting the various opinions is deficient. Even a minor difference could have considerable medical and economic consequences.

Questions

The overriding questions have been:

- What are the short-term and long-term effects of different treatment strategies?

- What methods are available to treat hemophilia patients that have developed inhibitors against factor concentrates?

Background

The disease and its prevalence

Hemophilia results from an inherited deficiency in coagulation factor VIII (hemophilia A) or coagulation factor IX (hemophilia B). Hemophilia A and B are gender-related, hereditary, and affect males almost exclusively. One in 5 000 boys are born with the disease. In Sweden, approximately 1 000 patients have hemophilia, whereof approximately 300 receive regular treatment.

Coagulation factors are proteins produced in the liver. Deficiency in a coagulation factor means that the blood coagulates poorly, or barely at all. Hemophilia A and B has three grades of severity: severe, moderate, and mild. Bleeding risk is associated with the degree of severity. Usually, the first bleeds appear at 5 to 6 months of age with the severe type, and at 1 to 2 years of age with the moderate type. The bleeds can appear spontaneously, or following minimum trauma. In mild hemophilia, bleeding problems usually occur in conjunction with surgery and major injuries, and therefore some patients are diagnosed late in life.

Symptoms in severe and moderate hemophilia are more or less spontaneous bleeds in joints and muscles. Untreated, articular (joint) bleeding leads to an acute increase in pressure in the joints, accompanied by severe pain. Later, patients develop chronic joint

inflammation and degradation of articular cartilage, leading to stiffness, impaired motion, and chronic pain. Without adequate medication, hemophilia can result in serious mobility-related disabilities. Patients with hemophilia are also at risk for other types of serious bleeding, e.g., cerebral or gastric hemorrhage.

Von Willebrand disease (VWD) is also hereditary and can affect both men and women since the gene is not in the sex chromosomes. The disease results from deficient or impaired function in a protein called von Willebrand factor (VWF), which is produced in the vascular walls. Von Willebrand disease presents mainly as bleeding in the mucus membranes. Approximately 1 000 patients in Sweden have von Willebrand disease. The few patients that have the severe type also suffer from articular bleeding, leading to chronic joint damage and disability similar to that in patients with severe/moderate hemophilia.

Treatment

Patients with hemophilia and the more severe types of von Willebrand disease are treated with the coagulation factor or factors they lack. This treatment approach is usually referred to as replacement therapy. The implication is that patients can become symptom free, similar to the situation with other diseases involving deficiency-related symptoms (e.g., insulin dependent diabetes, vitamin B12 deficiency, hypothyroidism).

With the introduction of highly purified concentrates in the 1970s, treatment of hemophilia patients became easier and more common, but in the 1980s the new concentrates were found to transmit HIV and hepatitis C. These two catastrophic situations shifted the focus toward the care of affected patients and the development of safe products, weakening the momentum for the other types of treatment studies. New studies began after year 2000, but many of them have yet to be completed.

Two types of factor concentrates are currently used to treat hemophilia A and B, plasma-derived or recombinant coagulation factor concentrates. Optimum dosing of factor concentrate is an important question. Internationally, practices vary widely due to tradition, costs, and limitations in the scientific data. The comparison between prophylaxis and on-demand treatment is also important, particularly as regards the long-term out-comes in hemophilia patients. For many years, all patients in Sweden with severe hemophilia have been offered preventive treatment. From an international perspective, however, definitions and perceptions vary regarding dosing practices and when to start prophylactic treatment. Hence, this is another matter that must be analysed. Mild hemophilia A can be treated with desmopressin, a synthetically produced hormone-like (vasopressin) agent that affects blood coagulation by quickly and briefly increasing the concentration of factor VIII and von Willebrand factor in blood.

Most patients with the mild form of von Willebrand disease do not need treatment except in cases of surgery and trauma. An exception would be untreated women with von Willebrand disease, since blood loss associated with menstruation can lead to blood deficiency. The primary treatment for mild von Willebrand disease is tranexamic acid, which reduces blood loss from menstruation and bleeding problems after minor surgery. Another drug is desmopressin, which can temporarily increase the amount of von Willebrand factor and is occasionally used to complement tranexamic acid in surgery and profuse menstruation.

With more severe forms, concentrates containing von Willebrand factor, and usually factor VIII, must be administered in addition to tranexamic acid.

Inhibitors (neutralizing antibodies) against factor concentrate

Treatment of hemophilia can become more complicated with the development of inhibitors against factor concentrates, which in most cases neutralise the effects of factor VIII and factor IX agents. Inhibitors appear in 20 to 30 percent of the patients. In approximately half the number of patients, the levels are low and the inhibitors usually disappear after a period of "enhanced" prophylactic treatment. Others have high levels of inhibitors (high titres) that completely neutralise the administered factor concentrates, and they have no effect. The inhibitors usually appear within the first 10 to 30 treatment doses. To inhibit bleeding, these patients are administered treatment with recombinant factor VIIa (rFVIIa) or activated prothrombin complex concentrate (aPCC), so-called "bypass products". Without these agents, even minor bleeds could become lifethreatening. The treatment goal in these patients is to eliminate the formation of inhibitors through immunotolerance induction, which involves daily administration of relatively high doses of factor concentrate. This treatment method has been used in Germany and Sweden for approximately 30 years with apparently good effects in most cases, but at a very high cost. Studies in this area are difficult to conduct, but a couple is in progress. Acute hemorrhaging causes severe pain and must be treated.

Only recently have randomised trials been published on treatment in patients with inhibitors. Prophylaxis to prevent acute hemorrhaging in inhibitor patients is in its early stages, but several smaller studies have been published, and others are under way.

Method for Systematic Review of the Literature

SBU's assessment methods include a systematic review of scientific studies in the subject area. In this context, systematic refers to identifying and assessing the quality of all relevant scientific studies that address the question.

The literature reviews cover several phases: identifying, selecting, and assessing the quality of studies, and finally synthesising the information and rendering a collective judgement. This report has been compiled by a panel of 10 experts representing different specialties. Five external experts and the SBU Scientific Advisory Committee reviewed the final report.

Based on the questions addressed by the project, a systematic database search was conducted in PubMed, NHSEED, Cochrane Library, EMBASE, and other relevant databases. The literature search covered all studies in the field published from 1985 up to the spring of 2010, with a supplementary search in October 2010 (reported separately).

Inclusion criteria

In the initial phase of the review, the following criteria were used to select relevant publications:

– The study must address patients with hemophilia A and B, with and without inhibitors, and patients with von Willebrand disease (VWD) of all ages treated with recombinant or plasma-derived factor VIII or factor IX concentrates, recombinant coagulation factor VIIa, activated prothrombin complex concentrate or factor concentrate containing von Willebrand factor (VWF) and factor VIII (FVIII).

– The study must report on one or more of the following effects: quality of life, articular bleeding, number of factor concentrate infusions for hemostasis, life-threatening hemorrhages, other bleeding, tolerance development (measured as the absence of inhibitors), inpatient days, resource utilisation (orthopaedics, surgery, sick leave/disability pension, school absenteeism).

– Primarily, treatment studies should be randomised controlled trials (RCT), or secondarily, controlled prospective studies. If studies of this type are not available, non-randomised studies without controls may be reviewed.

– At least 5 to 20 patients per study group (trial groups and control groups) depending on diagnosis.

– Health economic studies must address both costs and effects, be relevant to Swedish conditions, and include comparisons with the best alternative. Preferably, effects should be measured in quality-adjusted life-years.

– The article must be written in English, Swedish, Danish, or Norwegian.

Quality appraisal

At least two individuals in the project group, independently, evaluated the structured abstracts of articles found in the database search. The inclusion criteria listed above were used in evaluation. All articles that any of the reviewers found to be relevant were retrieved in full text format. Using the inclusion criteria, the same individuals (independent of one another) reviewed the articles. Articles that none of the reviewers found relevant were excluded. The included articles were carefully reviewed using SBU's standard checklists to determine the extent to which the studies met the quality criteria, e.g., study

design, study population, outcome measures, and the analytical methods used. Based on this information, the reviewers rated study quality and relevance as high, medium, or low.

Study quality, evidence grading, and conclusions

Outcome data from studies that met the basic quality requirements were compiled for each of the questions. The quality ratings of the scientific literature were then compiled as a basis for grading the strength of the evidence (Facts 1). In each chapter, appraisal of the evidence is based solely on studies found to have high or medium quality and relevance. Hence, the strength of the evidence expresses the collective scientific support for a conclusion, i.e., how many studies of medium or high quality support the conclusion. The strength of the evidence is indicated within parenthesis in the text below.

Facts 1 Study Quality, Relevance and Evidence Grading.

Study quality refers to the scientific quality of an individual study and its capacity to answer a specific question in a reliable way.

Evidence grade refers to the assessed strength of the collective body of scientific evidence and its capacity to answer a specific question in a reliable way. SBU uses an international evidence grading system called GRADE. Study design is the primary factor considered in the overall assessment of each outcome measure. Secondary factors that can increase or decrease the strength of the evidence include: study quality, relevance, consistency, transferability, effect size, data precision, risk of publication bias, and other aspects, e.g. the dose-response relationship.

Evidence grades – four levels

Strong scientific evidence (⊕⊕⊕⊕)
Based on high or medium quality studies with no factors that weaken the overall assessment.

Moderately strong scientific evidence (⊕⊕⊕○)
Based on high or medium quality studies with isolated factors that weaken the overall assessment.

Limited scientific evidence (⊕⊕○○)
Based on high or medium quality studies having factors that weaken the overall assessment.

Insufficient scientific evidence (⊕○○○)
Scientific evidence is deemed insufficient when scientific findings are absent, the quality of available studies is low, or studies of similar quality present conflicting findings.

The stronger the evidence, the lower the likelihood that new research findings would affect the documented results within the foreseeable future.

Conclusions
SBU's conclusions present an overall assessment of benefits, risks, and cost effectiveness.

Obviously, the grades chosen to indicate the strength of the conclusions cannot be interpreted as ultimate truth. Nevertheless, conclusions based on strong scientific evidence should provide more concrete guidance than conclusions based on weaker evidence. It is important to note that when the scientific evidence is graded as being insufficient, this does not necessarily mean that a given method has no effect.

Basic Conditions for Treatment

In Sweden, treatment with coagulation factor concentrate has increased survival of patients with severe hemophilia from approximately 15 years to nearly normal life expectancy. Knowledge of the molecular biological mechanisms and the pathophysiology underlying hemophilia forms the foundation for clinical treatment. Clinical outcomes show that treatment has marked effects and extends survival. However, since these positive results have not been documented in scientific studies, it is difficult to grade the evidence in accordance with SBU's standard methodology. It seems logical to assume that treatment of hemophilia and von Willebrand disease is effective since it involves replacement of a single, deficient factor.

Presented below is a summary of treatment methods that are based on clinical experience and involve the use of coagulation factor concentrates.

Treatment with coagulation factor concentrate

Using factor VIII to treat bleeding resulting from hemophilia A has the following effects: hemostasis, reduced pain, and improved mobility. The improvements appear within a few hours. Usually a single treatment is sufficient to achieve a lasting effect. Side effects from current factor concentrates are few and mild, apart from inhibitor development.

Using factor IX concentrate to treat acute bleeding resulting from hemophilia B is effective, and similar to the situation in treating hemophilia A. Occasionally, treatment of hemophilia B can lead to an allergic reaction, particularly if inhibitors are present at the time.

Regular administration of factor VIII concentrate for severe hemophilia A – starting at an early age before the first episode of articular bleeding – has good protective effects against articular bleeding and development of joint damage later in life. Since hemophilia B is less prevalent than hemophilia A, the scientific evidence is even more limited as regards regular replacement therapy. However, available studies suggest a similar, positive effect.

Clinical experience and observational studies suggest that replacement therapy with coagulation factor concentrate has effects that enable surgical intervention. Common procedures include knee and hip arthroplasty.

Treatment with recombinant factor VIIa and activated prothrombin complex concentrate (bypass therapy), has effects on acute bleeding and enables surgical intervention in hemophilia A and B patients with inhibitors. Retrospective observational studies have shown good effects. Nevertheless, therapeutic failure is possible. Clinical data suggest that response to treatment can vary among individuals and between the two agents available on the market. Although the scientific evidence is based mainly on retrospective clinical studies without controls, the reported effects are pronounced and clinically relevant.

Results from case series show that immunotolerance induction treatment with factor concentrates can be effective in up to 80 percent of hemophilia A patients with inhibitors, and in most cases the results are permanent. Clinical experience indicates that treatment should be started early in childhood, when a child with

hemophilia develops inhibitors. The situation regarding hemophilia B is less certain.

Treatment with factor concentrate containing von Willebrand factor (VWF) and factor VIII has effects on acute bleeding in patients with von Willebrand disease who do not respond adequately to desmopressin, and in patients with type 3 von Willebrand disease. Similar effects have also been observed with concentrates mainly containing von Willebrand factor alone.

Clinical experience and observational studies suggest that replacement therapy with coagulation factor concentrate containing von Willebrand factor (VWF) and factor VIII has effects that enable surgical intervention in patients that do not respond to desmopressin. Similar effects have also been observed with concentrates mainly containing von Willebrand factor alone. Often in acute situations, however, extra factor VIII has also been administered.

Evidence Graded Results

This report aims to present the scientific evidence underlying different dosing strategies for coagulation factor concentrate in treating patients with hemophilia A, hemophilia B, and von Willebrand disease.

Summarised below are the results from studies that meet the inclusion criteria. In most instances the studies are non-randomised and do not include control groups.

Treatment of hemophilia A and B

- The scientific evidence is insufficient to determine if there are any differences in effects between recombinant and plasma-derived factor concentrates in replacement therapy for hemophilia A and B.

- The scientific evidence is insufficient to determine if there are any differences in effects between different dosing strategies in replacement therapy with coagulation factor concentrates. Results from one randomised trial, supported by results from several non-randomised studies, suggest fewer joint bleeds and fewer major bleeds in prophylactic replacement therapy compared to on-demand treatment. Furthermore, regular administration of factor VIII starting from early childhood, before the onset of joint bleeds, in patients with severe hemophilia has protective effects against joint damage.

- The scientific evidence is insufficient to determine whether the risk of developing inhibitors against coagulation factors is more, or possibly less, for the prophylactic treatment compared with that seen in the treatment only when necessary on-demand.

- The scientific evidence is insufficient to determine if there are any differences in the long-term effects (>6 years of follow-up) of different treatment regimens in hemophilia A and B. Clinical experience and the results from retrospective, observational studies suggest that early prophylactic treatment yields better results than on-demand treatment, but this should be confirmed by prospective, longitudinal studies.

- The scientific evidence is insufficient to determine which doses and dosing intervals are the most effective when using factor concentrates as replacement therapy to inhibit and/or treat bleeding during surgery.

Treatment of patients with inhibitors

- The scientific evidence is insufficient to determine the effects of treating acute bleeds with the bypass agents, recombinant coagulation factor VIIa and activated prothrombin complex

concentrate. Observational studies suggest that treatment is superior to no treatment.

- The scientific evidence is insufficient to assess the effects of prophylactic treatment using recombinant coagulation factor VIIa and activated prothrombin complex concentrates to prevent bleeds in patients with hemophilia A and B with inhibitors.

- The scientific evidence is insufficient to appraise the effects of immunotolerance induction using factor VIII or IX concentrates during a given period when the aim is to eliminate antibody formation (inhibitors) against factors VIII and IX in hemophilia patients with inhibitors. Scientific evidence is lacking on immunotolerance induction in treat-ing inhibitors against factor IX.

Treatment of von Willebrand Disease

- The scientific evidence is insufficient to determine if the incidence of bleeds differs between long-term prophylactic therapy compared to treatment only in conjunction with bleeding when concentrates containing von Willebrand factor and factor VIII (FVIII) are used in patients with von Willebrand disease. The scientific documentation consists of retrospective studies. Prophylactic treatment, particularly for type III von Willebrand disease, probably has good effects, and larger studies are under way to address this.

- Experience concerning regular prophylaxis during long-term indicates a reduced incidence of joint damage and improved quality of life. However, the scientific evidence is insufficient, and further studies are needed.

- Scientific studies that illuminate possible differences between various concentrates containing von Willebrand factor and factor VIII (FVIII) are lacking, as regards their effects of treatment on bleeding.

- Scientific studies that illuminate possible differences between dosing strategies for concentrates containing von Willebrand factor and factor VIII are lacking, as regards their effects on bleeding.

Economic aspects

- The scientific evidence is insufficient to determine which dosing strategy, i.e., on-demand or prophylaxis, is the most cost-effective in treating hemophilia.

Ethical aspects

Treatment, particularly for hemophilia, raises a range of ethical issues due to the high costs involved. Previously, the risk of blood contamination was high. Today, this risk is thought to be so low that it is no longer weighed into the indications for administering factor VIII or IX concentrates. Given the widespread use of recombinant products, it is assumed that such risks have been eliminated. To some extent, plasma-based products are still used in treating von Willebrand disease and patients with inhibitors. The risk for developing inhibitors is high, and can constitute an ethical problem in treating small children from families with previous occurrence of inhibitors. Since patients with hemophilia now reach old age, they are also affected by common disorders such as cardiovascular disease, cancer, and dementia. Managing these problems in relation to bleeding disorders has several ethical and medical implications that have not been studied. An ethical analysis is necessary in each individual case to enable well-grounded decisions about treatment and care.

Summary and Discussion

This therapeutic area is unique since the diseases are rare and the clinical outcomes cannot be fully evaluated for many years, perhaps decades. Because of this situation, and the fact that contemporary regulations for clinical trials create major financial obstacles in comparing products, it becomes difficult to implement studies yielding high-grade evidence. Hence, well-executed studies are lacking.

No longitudinal studies have compared different types of factor concentrates. One of the reasons is that no scientific evidence is available to suggest that it would be possible to show any differences in effects in the comparatively small and heterogeneous group of patients available for study. Moreover, concentrates have advanced rapidly in recent years, which does not allow the decades needed for follow-up studies of individual product brands. Hence, we must rely on observational studies where treatment varies over time.

Studies often use two measures to determine the effects on bleeding, the number of infusions needed to stop articular bleeding, and a subjective rating of effects (where definitions can vary between studies). More recent studies often show how patients or parents rate the effects. For instance, the effects of a factor concentrate injection on articular bleeding could be rated as: *excellent*, *good*, *moderate*, or *no response*. The definition of *excellent* usually includes a combined assessment of pain and swelling. Hence, an *excellent* effect might be greatly reduced pain and swelling, e.g., within eight hours, and one infusion could be sufficient. *Good* response usually signifies that pain and swelling have not subsided substantially within eight hours, and a second infusion is administered, leading to markedly reduced pain and swelling. *Moderate* response could mean that a third injection is required after a further eight hours, and *no response* suggests that the treatment is comparable

to no treatment. Evaluation of treatment effects on acute articular bleeding becomes substantially more difficult when the natural course of a bleed is uncertain. Increased pressure during an ongoing bleed eventually helps stop the bleeding. Moreover, pain arising from an inflammation can be difficult to distinguish from any concurrent hemorrhaging.

In the absence of objective, generally accepted, evidence-based methods to identify and document treatment effects, most treatment providers accept the method of defining good treatment effects as marked reduction in pain and swelling, combined with the number of infusions needed.

Assessment of treatment effects, expressed as the number of infusions needed to stop a bleed, or subjective ratings such as *excellent*, *good*, etc have limitations when it comes to comparing outcomes of studies in different patient groups – in part, because previously untreated patients, usually small children, do not have joint damage. Hence, the results are not fully comparable to those from studies in older, previously treated, patients. Slightly older patients with joint damage probably have another course of symptoms and are more difficult to treat than patients with bleeds in a structurally normal joint.

Acknowledging these reservations, the method of documenting treatment effects in most studies nevertheless enables the analyst to weigh the studies together. As a general conclusion, we could say that treatments with contemporary factor concentrates, whether recombinant or plasma-derived, have very good effects on pain and swelling from articular bleeds when the doses are adjusted for weight and type of hemorrhage. One or two doses are often sufficient to stop a bleed.

Treatment of acute bleeding in hemophilia A varies by country when it comes to choosing doses and the intervals between doses.

Similar variation is found in prophylactic therapy since opinions vary about dosing, the time to start treatment, and the age to which prophylaxis should continue. There is much to suggest that it is good to start prophylaxis early, before the onset of joint damage (primary prophylaxis), i.e., probably before the first or second articular bleed, and it should continue until adulthood. Even in adulthood, the fundamental problem of hemophilia remains (i.e., lack of a factor in blood), making patients prone to bleeding and exposing them to life-long risk of severe and life-threatening hemorrhaging. For this reason, it would be natural to extend prophylactic therapy into adulthood. More studies are needed to optimise and individualise prophylactic treatment, although such studies would require lengthy follow-up and would be difficult to perform.

Observational studies, primarily in Europe (but especially in Sweden and the Netherlands), have addressed the long-term effects that treatment of hemophilia A and B with regular replacement therapy (prophylactic treatment), from childhood to adulthood, has on the development of joint damage. The results show that the treatment has god effects and hence, it would be considered unethical, in Europe today to conduct a study with better design. In North America, where hemophilia treatment with prophylaxis has received less attention, randomized trials were permitted as late as year 2000 which from a European perspective exposed small children to unnecessary harm.

Patients that develop inhibitors are difficult to treat. Acute bleeds can be treated with bypass therapy, and two different products with fundamentally different modes of action are available. Treatment is costly, and the hemostatic response is difficult to predict. Only a few comparative studies are available. They suggest that effects vary by product and individual. Early treatment in the course of hemorrhaging appears to have decisive effects. Better studies are needed to assess the doses, dose intervals, and long-

term effects on joint damage. This applies especially to prophylaxis. Studies are under way.

Several different treatment models address immune tolerance, but all are associated with high costs. Most of the models only involve factor administration, although some add immune suppression. Since controlled trials are difficult to implement, the information currently available comes from register studies, observational studies, and case series. Studies in progress should eventually provide some guidance for cost-effective dosing and selection of factor concentrates, depending on the content of factor VIII and von Willebrand factor. Regarding hemophilia B, treatment for immunotolerance has been insufficiently studied and involves further difficulties due to the risk for allergy and development of nephrotic syndrome.

Comparing the studies is difficult because of variations in agents, doses, dose intervals, and definitions of tolerance development. Most of the retrospective analyses independently found that tolerance developed in 70 to 80 percent of the cases, regardless of agent type and dosing. Basically this coincides with available register data, as described above. The European immunotolerance register also indicates that high daily doses yield relatively better treatment results. Further studies and data are needed to confirm these findings.

A smaller percentage of patients with von Willebrand disease report little or no effect from treatment with desmopressin and are therefore dependent on replacement therapy with concentrate containing von Willebrand factor. Since von Willebrand factor, in addition to thrombocyte activation, is also the carrier protein for factor VIII (FVIII), patients with more severe forms of von Willebrand disease also have low FVIII even though their ability to produce FVIII is intact. Most of the concentrates used in treating von Willebrand disease contain both von Willebrand factor

and FVIII, and immediately increase both of these factors in plasma. The ratio between von Willebrand factor and FVIII varies among different products. Since the concentrates have not been compared, it is difficult to document the importance of the different contents in von Willebrand factor. Moreover, qualitatively, von Willebrand factor varies in the products.

The studies described in the report are retrospective or prospective observational studies without controls and present low-grade evidence. Using concentrates to treat von Willebrand disease is relatively new, and concentrates are reported to consistently yield very good results with few side effects.

Some believe that prophylactic treatment of von Willebrand disease is justified, particularly for type 3 von Willebrand disease. International studies of higher quality are in progress.

To summarise, the use of concentrates to treat some types of von Willebrand disease is shown to have good clinical effects in relation to acute hemorrhages, surgery, and long-term prophylaxis. The various concentrates now available differ in content and have not been studied comparatively in terms of clinical effects. Evidence-based guidelines are lacking, and the assessments of indications, doses, and dosing intervals need to improve.

Uncertainties and the need for research

Greater knowledge and more research is needed on methods for treating hemophilia

Hemophilia and the more serious types of von Willebrand disease are rare disorders. Current treatment strategies are based mainly on more or less well-controlled observational studies. The trends suggested by these studies are easily subject to different interpretations and opinions. Current treatment principles are based mainly on “best clinical practice” and, to a lesser degree, on evidence-

based medicine. For several reasons it is difficult, if not impossible, to implement large, well-controlled, prospective, longitudinal studies. Such studies are extremely expensive since often they must be conducted in several countries to recruit a sufficient number of patients.

Several areas can be identified where we lack real knowledge, and where better studies are needed (but nevertheless are difficult to perform).

As regards hemophilia, more research is needed in several areas, including the following:

Prophylaxis in patients that have not developed inhibitors
- When should treatment be started?
- Should prophylactic treatment be stopped, and if so, when?
- Dose regimen
- Long-term evaluation of joint diseases
- Health economy

Inhibitors
- Impact of heredity and environment on the risk of developing inhibitors
- Protocols for immunotolerance induction treatment
- Prophylaxis in bypass treatment
- Health economy

Factor concentrates
- Improved pharmacokinetic features with longer biological half-life
- Increased potency
- Development of products or tools to avoid intravenous injections and replace them with alternate routes of administration (subcutaneous, inhaled, oral).

The clinical problems concerning von Willebrand disease are somewhat different. Here, the inhibitor problem is not as great as it is in hemophilia, but also less research is available. Regarding von Willebrand disease, the following areas can be emphasised:

- At what plasma levels of factor VIII and von Willebrand factor is treatment with factor concentrate required, i.e., when is treatment with desmopressin insufficient to achieve hemostasis?

- The clinical importance of heterogeneity in von Willebrand factor concentrate?

- Prophylaxis in von Willebrand disease; indications and dosing?

- Products used to treat von Willebrand disease remain plasma-derived. There is a need for products manufactured via recombinant DNA methods, as is already the case with hemophilia. One such product is undergoing clinical trials, but its utility remains to be proven.

Implementing a national treatment register with defined quality indicators is a high priority. A systematic and centralised means of following up patients with hemophilia A, B, and von Willebrand disease is needed within the context of a national quality register aimed at documenting short- and long-term treatment effects. Potentially, treatment could be improved by optimising dosing in accordance with better evidence on the pharmacokinetics of the agents, which could lower the consumption of factor concentrates while maintaining satisfactory treatment effects.

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SBU Evaluates Health Care Technology

Below is a brief summary of the mission assigned to SBU by the Swedish Government:

- SBU shall assess healthcare methods by systematically and critically reviewing the underlying scientific evidence.
- SBU shall assess new methods as well as those that are already part of established clinical practice.
- SBU's assessments shall include medical, ethical, social and economic aspects, as well as a description of the potential impact of disseminating the assessed health technologies in clinical practice.
- SBU shall compile, present and disseminate its assessment results such that all parties concerned have the opportunity to take part of them.
- SBU shall conduct informational and educational efforts to promote the application of its assessments to the rational use of available resources in clinical practice, including dental care.
- SBU shall contribute to the development of international co-operation in the field of health technology assessment and serve as a national knowledge centre for the assessment of health technologies.

Treatment of Hemophilia A and B and von Willebrand Disease

The report on Treatment of Hemophilia A and B and von Willebrand Disease from the Swedish Council on Health Technology Assessment (SBU) is a systematic review of the scientific literature in the field.

This document presents the summary and conclusions of the full report approved by SBU's Board and Scientific Advisory Committee.

The full report is available at www.sbu.se

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