Inhibitors in Haemophilia A – Ongoing Research and Clinical Practice

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Haemophilia A is the most common plasmatic bleeding disorder, caused by congenitally reduced activity of coagulation factor VIII (FVIII). Affected patients suffer from a more or less severe bleeding tendency, mainly in the joints, muscles and organs, which, untreated, leads to haemophilic arthropathy and high mortality. To date, there is no cure for the disease. So, the aim of haemophilia treatment is to prevent or treat bleeding episodes, mainly by substitution of the missing coagulation factor. During the last few decades, haemophilia treatment has reached a very high standard, at least in well-developed countries. Major milestones have been the development of safe and effective FVIII concentrates, either plasma-derived (pd) or recombinant (r), the introduction of prophylaxis and home self-infusion for patients with severe haemophilia A and the development of therapies for immune tolerance induction (ITI). Depending on the availability of sufficient amounts of FVIII, these therapeutic approaches can dramatically improve the situation of patients; at best, it is possible to almost normalise quality of life (QoL), social integration and life expectancy.

This progress and high standard of haemophilia therapy is a result of about 30 years of empiricism, clinical experience and scientific excellence, as well as clinical studies on reasonably small numbers of patients. Final prospective and controlled studies with large patient cohorts have the goal of moving such therapies from a well-justified to an evidence-based approach. As long as such evidence-based data are not available, clinical decisions for every single patient can be based only on long-term clinical and scientific experience and subjective opinion. This was also the case in the past, but nevertheless led to the development of safe and effective FVIII concentrates and the introduction of prophylaxis and home self-infusion in order to avoid haemophilic arthropathy. Today, inhibitor formation and treatment of patients with inhibitors are the main challenges of haemophilia therapy; again, long-term clinical and scientific experience is available, but there are only very few evidence-based data and no randomised controlled trials. What conclusions can be drawn from the existing clinical and scientific experience in order to find the best treatment for patients and to avoid or treat inhibitors?

Safe and Effective Factor VIII Products

In the late 1960s, FVIII concentrates became available. They were very well accepted, because due to the low volume of FVIII they allowed effective therapy for the first time. Unfortunately, in the 1970s and early 1980s product-related virus transmission, especially of hepatitis viruses and HIV, caused a major set-back in the young history of effective haemophilia therapy. Measures were taken to solve the problem, mainly by optimising the purification process, implementing steps for virus inactivation and establishing systems for quality assurance and quality control.

As early as the second half of the 1970s, a method to pasteurise the extremely unstable FVIII proteins was developed that effectively inactivated very high titres of enveloped viruses and high titres of non-enveloped viruses. The first pasteurised FVIII product was licensed in early 1981. Other manufacturers developed and implemented other inactivation procedures, for example the first dry-heat treatment (at 60°C for 72 hours), which later proved to be not very safe, or different methods using solvents and detergents (S/D). S/D methods very effectively inactivate enveloped viruses by destroying their outer lipid membranes, but in contrast to pasteurisation have no effect on non-enveloped viruses. Therefore, S/D inactivation had to be completed by a second complementary step with inactivation potential against non-enveloped viruses, for example a dry-heat treatment at very high temperatures. Effective virus-elimination and virus-inactivation steps have been implemented in the production process of all pdFVIII products for about 20 years, and no additional virus transmission has been observed with these products. In parallel, and with the aim of unlimited supply, technologies have been developed to produce human FVIII in cultures of genetically modified hamster cells.
Also, these recombinant technologies are based on biological systems, which generally are susceptible to pathogens. So, here again dedicated purification procedures, measures for virus inactivation and systems for quality assurance and quality control have been implemented, and no additional viral transmission has been observed with rFVIII products. Such advances in the manufacturing technologies of plasma-derived or recombinant products nowadays guarantee quality and a high margin of safety, and also ensure sufficient availability of modern concentrates for the management of people with haemophilia A.

Prophylaxis and Home Self-infusion
Besides cerebral and other lethal organ bleedings, recurrent joint bleeds with resulting joint damage and disability are the main problems in haemophilia. One milestone in the history of haemophilia therapy occurred almost 30 years ago with the introduction of prophylactic treatment and home self-infusion for patients with severe haemophilia A in some treatment centres in Sweden and Germany. Empiricism and clinical experience led to the conviction that the joint problems could be reduced only by preventing spontaneous joint bleeds by applying prophylactic FVIII substitution. The excellent results of the first long-term follow-up studies supported this theory. Some years later, the US orthopaedic outcome study demonstrated with more than 500 patients that the most critical factor for a good orthopaedic outcome is the reduction of joint bleeds and that full-time prophylaxis is likely to produce the best orthopaedic outcome. At almost the same time, the relationship between number of joint bleeds and joint alterations was studied, demonstrating that even a small number of joint bleeds causes irreversible osteoarthropathic alterations leading to haemophilic arthropathy. The conclusion was that in severe haemophilia effective prophylaxis should be started before or at least immediately after the first joint bleed in order to prevent haemophilic arthropathy. In 2007, a prospective, randomised, controlled clinical trial proved with statistical significance that, in contrast to enhanced episodic treatment, prophylaxis can prevent joint damage and reduce the frequency of joint and other haemorrhages in young boys with severe haemophilia A. After more than 30 years of successful clinical practice, this study finally provided the evidence-based proof.

Development of Inhibitors
Today, the most serious complication of haemophilia treatment is the development of factor VIII inhibitors, which occurs in about 25% of children with severe haemophilia A. The risk for children with mild to moderate haemophilia is much lower – generally in the range of only a few percent. Inhibitors develop in response to replacement therapy, mostly within the first 20–30 exposure days (EDs). About half are high-responding inhibitors, which make classic substitution therapy impossible in cases of bleeding. A large number of patient-related and treatment-related parameters that potentially contribute to inhibitor development have been described. The patient-related factors, which have been relatively well investigated and therefore are well accepted, do not change throughout life. The most important are type of mutation, severity of disease, ethnicity, family history of inhibitors and other genetic risk factors influencing the immunological response. The situation is different for the treatment-related parameters, such as age at first exposure, number and severity of bleeds, intensity of FVIII treatment and type of FVIII product, because some of these parameters are not easy to define and all of them require careful prospective documentation that begins at the birth of the child. The documentation parameters, the methods and the patient cohorts must be defined very clearly, because even minor variations may lead to very different results. Not all published studies on inhibitor development have comparable protocols, so direct comparisons of study results have to be performed very carefully and are sometimes impossible. Good examples of this problem are the early studies on inhibitor epidemiology: some studies were prospective and others retrospective; some studies looked for the prevalence and others for the incidence of inhibitor development; some studies looked at previously untreated patients (PUPs) and others at previously treated patients (PTPs); some studies investigated all patients of a given cohort and others differentiated between severe, moderate and mild forms; some studies defined severe haemophilia as <1% FVIII and others as <2% FVIII of normal; some studies looked for all inhibitors and others only for the so-called ‘clinically relevant’ inhibitors; in some studies inhibitor measurements were taken regularly and in others only occasionally; and so on. The resulting and published inhibitor rates range from almost 0% up to 52%. More recent studies took these problems into account: the protocols were more similar and the results thus more comparable.

Patient-related Parameters
The patient-related parameters influencing inhibitor development can be investigated relatively easily, because they do not change throughout life and do not need long-term documentation. Some of these parameters – such as ethnicity, severity of the disease and family history of inhibitors – are related and are based on the genetics of the disease. Other parameters – such as immune-modulating factors or mutations in immune response genes – influence inhibitor formation in different ways. To date, the patient-related factors cannot be influenced by any therapy.

FVIII Gene Mutation
Different types of mutation of the FVIII gene causing haemophilia A have been described. Patients with major mutations, such as large deletions, non-sense mutations or intron-22 inversion, carry the highest risk of inhibitor formation, probably because these mutations cause the absence or severe truncation of the FVIII protein. Other mutations, such as missense and splice-site mutations, which result only in a loss of function rather than the absence of the FVIII protein, are associated with a relatively low inhibitor risk of <10%. This finding indicates that the presentation of a novel antigen to the immune system is the major driving force for inhibitor development.

Severity of the Disease
The severity of the disease, as well as the risk of inhibitor formation, is strongly correlated with the underlying FVIII mutation. Major mutations cause severe forms of haemophilia and at the same time
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**Immune Modulation**

Other immune-stressing factors such as infections, inflammatory processes and concomitant diseases may activate the immune system, modulate the immune response and increase the inhibitor risk.

**Treatment-related Parameters**

In addition to the genetic risk factors, there must be also environmental or treatment-related risk factors, because discordant monozygotic twins have been described. Treatment-related parameters have not been as extensively investigated as patient-related factors; reasons for this include that some of them are not easy to define and all of them require careful prospective documentation, ideally beginning at the birth of the child. As a consequence of different definitions and documentation protocols, very different results on the influence of treatment-related parameters have been published, leading to controversial discussions. Careful analysis of study details is necessary before comparing results and drawing conclusions.

**Age at First Treatment**

Several authors have described a higher inhibitor incidence of up to 41% in children starting replacement therapy before six months of age. However, the cumulative inhibitor risk decreases rapidly when therapy is started later, and was in the range of only 12–18% when the first FVIII infusion was given after one year of age.

**Intensity of First Treatment**

The intensity of the first replacement therapy may be an independent risk factor for inhibitor formation. Traumatic muscle bleeds, which require intensive replacement therapy, activate the immune system and modulate cytokine levels. Under these activated conditions, the infusion of large amounts of potentially immunogenic FVIII is more likely to induce inhibitor formation than under non-activated conditions. Early intensive treatment with high doses of FVIII appears to be an independent risk factor for inhibitor development. This theory is supported by reports of inhibitor development during surgery even in patients with milder forms of haemophilia.

**On-demand Treatment versus Prophylaxis**

Bleeding episodes activate the immune system and modulate levels of regulatory immune elements such as cytokines. Under such activated conditions, on-demand treatment with exposure of FVIII is, at least theoretically, more likely to induce inhibitor formation than prophylactic substitution under non-activated conditions. Indeed, more and more studies provide evidence that in severe haemophilia A and with similar patient groups in terms of ethnicity, mutation and age at first treatment, on-demand treatment induces about twice as much inhibitor development than prophylaxis. Bolus on-demand treatment represents a real risk factor for inhibitor development, while prophylactic treatment has a protective effect, even in children with mutations that are high-risk for inhibitor development.
Continuous Infusion
In the 1990s, continuous infusion of FVIII concentrates, mainly during and after surgical interventions, became widespread because this mode of administration avoids the risks of peak and trough levels obtained with bolus injections and reduces the amount of concentrate needed. However, some reports of de novo inhibitors in patients with a long history of FVIII exposure or in patients with mild haemophilia have raised the question of whether this mode of administration represents an additional risk factor for inhibitor development, at least during surgery, which itself is a stress situation for the immune system.28 To date, the situation is not clear and more data are needed.

Type of Factor VIII Product
In the last 15 years several studies have investigated the influence of the type or brand of FVIII concentrate on inhibitor development in PUPs.2,30 Due to great differences in design and patient population, the studies resulted in a large range of inhibitor incidences. Nevertheless, a systematic analysis of the published data could demonstrate a general trend.31 Patients treated with a single pdFVIII product had a lower cumulative inhibitor incidence (0–12.4%) than those treated with a single rFVIII concentrate (36.0–38.7%). Even if the differences in study design and study population do not allow a direct comparison of these numbers, the lower incidence in patients treated with pdFVIII remains when only high responders are considered and can be shown to be independent of the severity of the disease, the study size or the frequency of inhibitor testing.32 In contrast to the generally higher inhibitor rates in PUPs treated with rFVIII in the 1990s, a more recent prospective study with a sucrose-formulated rFVIII product in PUPs and minimally treated patients revealed a relatively low inhibitor incidence of only 15%,22 although the genetic and environmental background of the patients showed a typical risk profile for severe haemophilia A.33 Figure 1, a summary of the analysed studies,32,34–44 shows the cumulative inhibitor incidences in PUPs treated with a single pdFVIII or a single rFVIII product.

There are four studies comparing the effect of pdFVIII and rFVIII on inhibitor incidence in PUPs with haemophilia A. Three are retrospective – the French cohort study,44 the UK cohort study45 and the CANAL study46 – and one is prospective – the GTH PUP Study.30 The French cohort study retrospectively evaluated 148 PUPS with severe haemophilia A, 62 of whom received a pdFVIII product stabilised by von Willebrand factor (VWF) and 86 of whom received a full-length rFVIII concentrate. Under comparable treatment regimens and regardless of other risk factors, 11% of the patients receiving pdFVIII and 31% of those receiving rFVIII developed an inhibitor (p=0.049). The UK cohort study retrospectively evaluated 348 children with severe haemophilia A. All of them had more than 50 EDs. Information on the product used for initial management was available for 304 of them. Inhibitors developed in 27% (47/172) of those PUPs initially treated with rFVIII and in 14% (18/132) of those treated with pdFVIII (p=0.009).46 The recently published multicentre CANAL study, which retrospectively documented treatment details of 316 PUPS with severe haemophilia A born between 1990 and 2000, did not find a significant difference between the two product types. However, it must be mentioned that this study looked only for so-called ‘clinically relevant inhibitors’, excluded 15 inhibitors that were by definition of the study protocol not seen as clinically relevant, did not require regular or frequent inhibitor testing, did not repeat any inhibitor measurements in a central laboratory for confirmation and accepted that about one-third of the patients switched to another product (mainly from pdFVIII to rFVIII) after a median of five exposure days.46 Together, these protocol details may very well explain why this study failed to demonstrate a difference. The fourth study comparing the risk of inhibitor development between the two product types and requiring frequent inhibitor testing is the prospective multicentre GTH PUP Study, initiated 15 years ago by the German, Austrian and Swiss Society of Thrombosis and Haemostasis Research. More than 330 PUPS have been enrolled into this study, but the final analysis of the results is not yet available.

In conclusion, the trend towards a lower inhibitor risk with pdFVIII products could be confirmed by at least two of the three completed comparative studies. The potential reasons for such a difference are unclear. One explanation could be differences in the applied purification and virus inactivation methods. Also, the content and amount of bound VWF seems to play an important role,26 as bound VWF protects FVIII from endocytosis by antigen-presenting cells.48 A protective effect of VWF could also be demonstrated in a haemophilia A mouse model, where the immunogenicity of VWF-containing products was much lower than that of VWF-free concentrates.49 Another important difference between the two product types could be the ratio between FVIII antigen and activity, as well as the content of FVIII that cannot bind to VWF.50 In plasma-derived products, the FVIII:Ag/FVIII:C ratio is almost 1, whereas recombinant products contained approximately 25% more antigen than activity; also, the content of FVIII unable to bind to VWF was quite low in plasma-derived products, but in the range of 20% of the antigen in recombinant products. Non-complexed FVIII presents epitopes to immune-competent cells, which are covered in VWF-bound FVIII. Accordingly, a possible correlation between the antigen surplus and the higher immunogenicity of rFVIII products can be considered.30 One possible explanation for the lower inhibitor incidence with the sucrose-formulated rFVIII product42 might be that the VWF-binding capacity is increased and the content of free FVIII is minimised by the improved purification process used for this product. In addition to the various effects of VWF, other proteins such as tumour necrosis factor (TNF)-α or transforming growth factor (TGF)-β, which may be present in plasmatic but not in recombinant products, may have protective or immune-modulating effects.50

Immune Tolerance Induction
The treatment of patients with inhibitors is challenging. Particularly for those patients with high-responder inhibitors (>5 Bethesda units [BU]), prophylactic treatment with FVIII is impossible, and even after the introduction of bypassing agents – mainly activated prothrombin complex concentrates (aPCCs) and recombinant activated factor VII (rFVIIa) – severe bleedings may be difficult to control. Because morbidity, mortality and treatment costs are high,1,51 the ultimate goal of inhibitor treatment is to permanently eradicate the FVIII antibody and to restore normal prophylactic treatment. The only proven way to achieve this goal is to induce immune tolerance to FVIII.52,53 Different protocols for ITI have been developed: long-term high-dose FVIII treatment (BonnFrankfurt protocol),44 long-term low-dose FVIII treatment (Van-Creveld protocol)54 or combined treatment with several extracorporeal immune adsorptions, immune suppression with cyclophosphamide, intravenous gammaglobulins and high-dose FVIII (Malmö protocol).54
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Table 1: Summary of Success Rates of Immune Tolerance Induction Performed with Plasma-Derived Factor VIII or Recombinant Factor VIII at the Haemophilia Treatment Centres in Frankfurt, Bonn and Bremen.

<table>
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<tr>
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<th>Frankfurt</th>
<th>Bonn and Bremen</th>
<th>Frankfurt, Bonn and Bremen</th>
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<tbody>
<tr>
<td>Before 1990–1993</td>
<td>pdFVIII 91%</td>
<td>pdFVIII 87%</td>
<td>pdFVIII 88%</td>
</tr>
<tr>
<td></td>
<td>(19/21)</td>
<td>(44/51)</td>
<td>(63/72)</td>
</tr>
<tr>
<td>After 1990–1993</td>
<td>pdFVIII 100%</td>
<td>pdFVIII 82%</td>
<td>pdFVIII 83%</td>
</tr>
<tr>
<td></td>
<td>(21)</td>
<td>(23/28)</td>
<td>(25/30)</td>
</tr>
<tr>
<td>pdFVIII</td>
<td>rFVIII 29%</td>
<td>rFVIII 43%</td>
<td>rFVIII 36%</td>
</tr>
<tr>
<td></td>
<td>(4/14)</td>
<td>(6/14)</td>
<td>(10/28)</td>
</tr>
<tr>
<td>rFVIII → pdFVIII</td>
<td>rFVIII → pdFVIII</td>
<td>rFVIII → pdFVIII</td>
<td></td>
</tr>
<tr>
<td>80% (8/10)</td>
<td>No data</td>
<td>80% (8/10)</td>
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pd = plasma-derived; r = recombinant; FVIII = factor VIII.

The ITI success rates published by experienced centres are in the range of 60–91%, while the success rates from a larger number of centres documented in the ITI registries and from a European survey on ITI practice are lower – in the range of 40–78%.1

Parameters have been identified that may influence the outcome of tolerance induction.3,5,17 Titre at onset of tolerance induction, time between inhibitor detection and start of tolerance induction, interruption of the treatment, when to stop ITI, dosage of FVIII product and type of FVIII product seem to be the most important parameters. However, our knowledge about the success of ITI and the parameters that influence outcome is mainly empirical and derives from the experience of only a few bigger treatment centres3,5,17,53,58,59 and from three larger registries of patients who have undergone ITI. Many questions are still open and need larger studies in order to generate more evidence for current treatment practice.

**Titre at Onset of Tolerance Induction**

When to start ITI is one of the open questions that need further data. On the one hand, several studies with smaller cohorts and all retrospective registries indicate that the success rate is highest when the inhibitor titre at start of ITI is below 10BU.1 As a consequence, the majority of treaters prefer to defer the start of ITI until the inhibitor titre is <10BU, treating the patient with bypassing agents only during this phase. On the other hand, the European survey on ITI practice revealed that one-third of centres nevertheless start ITI immediately after diagnosis and independent of the inhibitor titre.1 It is not known whether the overall ITI success rates in these centres are lower, but the time until tolerance is achieved is shorter; this may be of major importance, because the time spent living with an inhibitor is also the time when critical bleeding situations can occur.

**Time Between Inhibitor Detection and Start of Tolerance Induction**

This question correlates very closely to the question above. In general, ITI should be initiated as early as possible after inhibitor detection, because living with an inhibitor, especially a high-responding inhibitor, is critical for the patient. Severe bleedings are often not easy to control and in emergency situations adequate treatment may not be available.51 On the other hand, there are data suggesting better ITI success when the treatment is started after the titre has decreased below 10BU.1 Further studies are necessary to provide a clear answer to this question. Until then, the treater has to decide when to start ITI by taking the individual situation of the patient and his or her own experience into account.

**Interruption of the Treatment**

The immunological interactions during ITI are not very well known. However, it is clear that these reactions are very complex and should not be interrupted.1 Single cases have been reported that show that the inhibitor can reappear or that the titre can increase again when ITI is interrupted or stopped before tolerance is achieved. For the same reason, disturbance of the treatment by any immunologically stressful situation should be avoided; these include surgical interventions, vaccinations or other therapies influencing the immune system.

**When to Stop Immune Tolerance Induction**

ITI therapy should not be stopped before the inhibitor is permanently eradicated, because otherwise there is a high risk of inhibitor reappearance. The criteria for permanent eradication and successful ITI are undetectable inhibitor level (OBU), normal recovery and normal half-life. The critical parameter for normalisation of FVIII half-life is normalisation of 12-hour recovery. Repeated assessments of 12-hour recovery over six to eight weeks are needed to confirm normalisation before reducing FVIII dosage. A continuous reduction of about 10% of the initial ITI dosage should then be started, initiated with the evening doses. If 12-hour recovery remains normal, dosages can be further reduced by about 10% every two to four weeks, alternating evening and morning doses. When the daily dosage has been reduced to 50% of the initial ITI dosage, the total dose should be given once daily. Thereafter, dosage and frequency should be slowly tapered down to a normal prophylactic treatment.52

**Dosage of Factor VIII Product**

One of the most controversial outcome parameters is the optimal FVIII dose regimen for successful ITI. While the international ITI registry demonstrated a significant advantage of a high-dose regimen (200IU/kg/day), which correlates very well with the long-term experience of many European treatment centres, some other studies – and also the North American ITI registry – cannot confirm this result or even report an inverse relationship.4 The International Immune Tolerance Study, a multicentre, prospective, randomised trial of ‘good-risk’ patients with severe haemophilia A and inhibitors, was initiated in 2002 to definitively determine the influence of FVIII dosing on ITI success.50 The study hypothesis is that FVIII dosage in this good-risk population will not influence the overall ITI success rate, but will have an impact only on the time needed for tolerance induction and on morbidity. Even if this hypothesis can be confirmed by the study, this result can be seen as an advantage for the high-dose regimen because longer treatment time and higher morbidity are crucial disadvantages for patients.

**Type of Factor VIII Product**

Currently, the question of which is the superior type of FVIII product for ITI is the most debated question in this field. Common practice has been to start ITI with the same product that induced the inhibitory response. In the 1970s, 1980s and early 1990s, this was pdFVIII products, which contain VWF as a natural complex partner. During that time, the first large ITI studies according to the Bonn protocol were conducted, with success rates of 85–90%.5,54 After the introduction of ultra-high-purified pdFVIII or rFVIII products – which
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contain no or almost no VWF – and their use in otherwise unchanged tolerance therapies, the success rates decreased dramatically to 30–45%. Similar observations were made in several German treatment centres.47,61 The patients who failed immune tolerance with ultra-high-purified FVIII products were then switched to VWF-containing pdFVIII products (VWF:RCo/FVIII:C >0.3); in a second course of ITI, 80% of them could achieve tolerance.47,51 The published success rates of the treatment centres in Frankfurt, Bonn and Bremen are combined and summarised in Table 1.

The conclusion from these findings is that the type of concentrate has an impact on the outcome of ITI, and that VWF-containing FVIII products can induce immune tolerance in about 80% of patients in whom ultra-high-purified products failed. Two mechanisms have been suggested by which VWF may support ITI. The binding sites of FVIII for VWF are in the A3 and C2 domains, which are also major epitopes against which FVIII antibodies are directed. By masking these epitopes, VWF may be able to block inhibitor binding by steric hindrance and thus increase FVIII activity in the circulation. Second, VWF may protect the infused FVIII from rapid degradation and so prolong antigen presentation to immune-competent cells.46,51 Parallel to these clinical studies, several in vitro studies demonstrated that inhibitors with C2 specificity are less reactive against VWF-bound FVIII products and result in higher recovery compared with ultra-high-purity plasma-derived or recombinant products.62–64 The clinical findings and the in vitro studies strongly support the theory that in a relatively high number of inhibitor patients VWF-containing FVIII concentrates are more effective in terms of achieving immune tolerance than high-purity plasma-derived or recombinant products. The use of VWF-containing FVIII products is recommended in several ITI guidelines as rescue therapy in case of ITI failure with an ultra-pure FVIII product.1,3,5,10 However, more and more treaters use pdFVIII concentrates even as first choice in ITI in order to take advantage of the higher success rate, avoid unnecessary inconvenience and risks for young patients, avoid losing time and avoid the costs of ITI failures. To consolidate this clinical approach, further clarify the beneficial role of VWF in ITI and establish final recommendations for ITI, data from well-controlled studies are necessary. Several such studies are ongoing – the International Immune Tolerance Study (start date 2002), the RESIST Study (start date 2009) and the ObsITI-Study (start date 2005) – but results will be available only in several years’ time.

Conclusions

Modern haemophilia treatment has reached a very high standard. In most European countries, the aim of treatment is not only to treat bleeding episodes but also to prevent serious bleedings, especially into the joints, in order to avoid haemophilic arthropathy and permanent disability. In some countries the goals of treatment are even higher. In Germany, for example, the directors of the haemophilia treatment centres agreed on a treatment consensus that defines normal social integration of patients and an almost normal QoL as the highest goals of treatment.61 Achieving these goals is very challenging, especially for paediatric haemophilia treaters, because non-optimal treatment in childhood and youth will impair patients for the rest of their lives. However, what is optimal treatment in haemophilia care? There are only very few treatment options that have been proved by prospective, controlled trials. Most haemophilia treatment practice is based on empirical findings and research and studies with small numbers of patients. So, the only way to make optimal treatment decisions is to study the literature and to rely on long-term clinical experience and the scientific expertise of leaders in the field. In the past, this approach meant that important advances – such as the development of safe and effective FVIII products and the introduction of prophylaxis and home self-infusion – could be achieved long before appropriate studies could provide statistical evidence. In the case of a newly diagnosed haemophilic boy, this would mean that the treating physician has to talk intensively to the parents and explain very patiently all of the details, because only well-informed parents will have the necessary understanding and compliance. The treater has to document the bleeding history of the family and perform all necessary laboratory tests and, if possible, also mutation analysis. In case of severe haemophilia, prophylactic treatment has to be discussed with the parents and initiated immediately after, or even before, the first joint bleed. Fortunately, prophylaxis is an evidence-based treatment option introduced to avoid joint damage, and the data basis is good enough to convince parents. Parents have to learn the infusion technique, because the full benefit of prophylaxis can be achieved only by utilising home infusion or self-infusion.

Next, the pros and cons of the different types of FVIII product have to be discussed in detail. If the boy has a mutation with a high inhibitor risk, the family has an inhibitor history or there are any other additional risk factors predisposing to inhibitor development, the preferred use of a pdFVIII product can be discussed. If the boy develops an inhibitor, the parents must be informed about the additional risks and the treatment strategy in case of bleedings, and they must be convinced to agree to ITI to get rid of the inhibitor and the permanent bleeding risk. The parents must be informed that it is common practice to start the therapy with the same product that led to the development of the inhibitor. However, depending on the product that led to the development of the inhibitor, the question of optimal product type for ITI has to be discussed. For this decision, the parents need to know that there is no proof, but good reason to believe, that with VWF-containing pdFVIII concentrates the success rate of ITI is probably higher, the risk of failure is lower and the time until inhibitor eradication is shorter. This also means that the time of intensive therapy and of increased bleeding risk for the boy is shorter. Similar considerations can be made for the question of ITI dosing. As yet, there is no proof that a high-dose regimen leads to a better outcome, but there are enough data showing that the time until tolerance induction is shorter with a high-dose protocol, which must be seen as an advantage. If all of the necessary treatment decisions throughout the patient’s life are made with the intention of finding the optimal solution, there is a good chance that the highest goals for haemophilia treatment will be reached.