

Management of Haemophilia A-Inhibitor Patients: Clinical and Regulatory Perspectives

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Abstract Inhibitors to factor VIII (FVIII) are alloantibodies directed against epitopes able to neutralise FVIII procoagulant activity. They may render FVIII replacement therapy ineffective. They represent the most severe complication of haemophilia A. At least three mechanisms of FVIII neutralisation activity by anti-FVIII antibodies have been described: (1) steric hindrance; (2) recognition of neo-epitopes and (3) catalytic activity. The Nijmegen modification of the Bethesda is the recommended method for inhibitor surveillance. The occurrence of inhibitors is a relatively frequent and early event in previously untreated patients. Conversely, it is rare in previously treated patients. Therapeutic strategies for managing inhibitors include: inhibitor eradication, haemostatic management of bleeding episodes and/or surgery and supportive care. For high responding inhibitors, immune tolerance induction (ITI) is the strategy for achieving antigen-specific tolerance to FVIII. ITI success rate ranges commonly between 60% and 80%. For treatment of patients with high-titre, high-responding inhibitors, ‘by-pass’ therapy is generally recommended. Activated prothrombin complex concentrates represent the historically primary ‘by-pass’ treatment. Recombinant factor VIIa has also been widely used as a by-passing agent. Considering the small patient population,

it has to be considered that full immunogenicity data cannot be collected premarketing authorisation. Thus, stringent follow-up of patients in the post-authorisation phase is required.

Keywords Haemophilia A · FVIII inhibitors · Clinical management · Regulatory issues

Introduction

Inhibitors to factor VIII (FVIII) are alloantibodies directed against epitopes able to neutralise FVIII procoagulant activity. They may render FVIII replacement therapy ineffective. They represent the most severe complication of haemophilia A. They are polyclonal high-affinity IgG antibodies (IgG4, IgG3) reflecting an allogeneic immune response to the repeated administration of an exogenous FVIII protein. The risk of inhibitor development is higher in patients with severe haemophilia A (baseline FVIII plasma levels <1%) when compared to moderate or mild forms of the disease; the vast majority of anti-FVIII inhibitors appear within the 20 first cumulative exposure days (CED) to the product. The occurrence of inhibitors in previously untreated patients (PUPs) can be understood as an immune reaction against a foreign protein. In addition, it is also linked to patient specific factors such as the genetic defects leading to the absence of FVIII in plasma. Conversely, development of inhibitors in multi-transfused previously treated patients (PTPs) may reflect a neo-antigenicity of the product.

Inhibitors are directed against functional or non-functional epitopes. A majority of FVIII epitopes recognised by these antibodies do not participate in the function of FVIII. Using a functional assay to detect anti-FVIII

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antibodies, only ~25% of the antibody response is evaluated. For the same patients, inhibitor titre may vary a lot over time, highlighting that production of these alloantibodies by B lymphocytes and plasmocytes is a dynamic process.

Pathophysiology

At least three mechanisms of FVIII neutralisation activity by anti-FVIII antibodies have been described: (1) steric hindrance preventing FVIIIa interaction with thrombin or phospholipids; (2) recognition of neo-epitopes and (3) catalytic activity leading to FVIII hydrolysis.

Steric hindrance

Most FVIII inhibitors described so far neutralise the pro-coagulant activity of FVIII by blocking functional epitopes through steric hindrance [1]. FVIII epitopes that are targeted by inhibitors have been mapped, showing that they are mainly located in three major clusters delineated on the FVIII molecule: aminoterminal segment of the A2 domain on the heavy chain [2, 3], epitopes located in the A3 domain [4] and epitopes located in the C2 domain [5–7]. Inhibitors that bind to the heavy chain of FVIII prevent the cleavage of FVIII by thrombin and its subsequent activation [2, 8–10]. Light chain specific inhibitors prevent the interaction of FVIII with activated FIX [11] or phospholipids and/or von Willebrand factor (vWF) [5, 12–14].

Recognition of neo-epitopes

In the early 1990s, two clusters of inhibitors were observed in PTPs treated with plasma-derived products whose manufacturing process was changed, suggesting that a neo-antigenicity phenomenon occurred [15–17].

Catalytic activity

Lacroix-Desmazes et al. showed in patients with haemophilia A the development of FVIII-hydrolysing IgG able to inactivate the therapeutically administered factor VIII, and contributing, therefore, to the FVIII-inhibiting activity [18].

Inhibitor terminology and assessment criteria

PUPs, MTPs and PTPs

The FVIII and FIX subcommittee of the scientific and standardisation committee of the International Society of Thrombosis and Haemostasis (ISTH) expressed in 1999

[19] a position on the inclusion of PTPs and PUPs in the evaluation of new FVIII and FIX concentrates.

Considering that PUPs have a certain but undefined likelihood of inhibitor formation, they may be less appropriate in the evaluation of immunogenicity of new FVIII and FIX concentrates; PTPs with greater than 150 treatment exposure days (ED) generally considered to be tolerant to FVIII are therefore at low risk for inhibitor development. Taking also into account the relative rarity of PUPs, the ISTH subcommittee recommended that the analysis of immunogenicity of new concentrates should be performed in PTPs with greater than 150 treatment ED. However, inhibitors are more often observed in PUPs with severe haemophilia A. A new population called MTPs for minimally treated patients have been reported together with PUPs in some recent studies [20, 21]. These patients have received three to five exposure days to FVIII. The medical relevance of this new population has been discussed in the report of the European Medicines Agency (EMA) expert meeting on FVIII products and inhibitors development. Stating that this population was not well defined, the experts unanimously agreed not to combine data on MTPs with data on PUPs (EMA/CHMP/BPWP/123835/2006).

Low and high responders

Low responders have antibody titres <5 Bethesda units (BU), demonstrating a lack of anamnestic response on exposure to FVIII. They can be treated with high doses of specific factor replacement in order to obtain a saturation of the inhibitor. High responders have antibody titres ≥5 BU, demonstrating a brisk anamnestic response to FVIII. Therefore, they are not treatable with specific factor replacement [22].

Quantification methods

One Bethesda unit is defined as the amount of antibody that neutralises 50% of plasma FVIII activity. Titres ≥0.6 BU suggest the presence of an antibody directed against FVIII [23].

The Bethesda assay has been recommended as the standard method for measuring FVIII inhibitor titre [24]. However, the original Bethesda method may give false positive results, unrelated to the presence of an inhibitor, owing to a loss of FVIII activity caused by pH shift and/or reduced protein concentration in the incubation medium. The Nijmegen modification of the assay avoiding these problems [25] is the recommended method for pre-marketing authorisation studies for a new FVIII concentrate and also for its post-marketing surveillance. It is also recommended to perform the inhibitor assay in a centralised laboratory especially for pre-licensing studies.

Diagnosis and investigational analyses

Monitoring of inhibitor development should be started at the onset of treatment in order to obtain solid baseline data. Routine testing for inhibitors should be carried out on a regular basis. In particular, testing should be frequent in the early phases of substitution combining clinical and laboratory data. As seen earlier in this review, the occurrence of inhibitors is a relatively frequent and early event in PUPs. Conversely, it is rare in PTPs. Therefore, duration and follow-up should be differently defined for PUPs and PTPs and should be long enough to detect a possible occurrence of inhibitors. In PUP studies, all inhibitor risk factors as well as exposure days or period of exposure should be documented until at least 50 CED. In PTPs inhibitor risk factors are probably more therapy-related than patient-related (number of previous exposure days, product switch...).

Patients should be screened for inhibitors every fifth exposure day or every 3 months until the 20th exposure day, every 6±12 months thereafter, and prior to any surgical procedure [26]. Patients should also be screened for inhibitors when the frequency of bleeding increases or if the clinical or laboratory response to replacement therapy becomes poor. In addition, an estimation of FVIII recovery and/or half-life has to be conducted [27]. Moreover, a confirmatory test on a second, separately drawn sample should always be performed. This second sample should be taken prior to any change of treatment and shortly after the previous positive test (within a month).

Factor VIII recovery should be based upon the difference in FVIII concentration between a sample taken pre- and 30 to 60 min after infusion [27]. Half-life studies should be conducted after a wash-out period or when the FVIII or IX level has reached its baseline. A sample should be taken at 1 h, 4 h and at several points thereafter until the FVIII activity has fallen back to baseline [27].

How to assess inhibitor occurrence within a population?

In the past, studies assessing inhibitors used the prevalence which is the proportion of patients with inhibitors at a given time; nevertheless, this criterion does not take into account transient inhibitors which regress spontaneously over time, inhibitors that have been eliminated by an appropriate treatment, and also patients who possibly died because of a very severe inhibitor [28].

Owing to these limits, another criterion has been used: the incidence, which is the number of new cases of inhibitors occurring in a defined length of time, even if it is highly variable among studies. The main limit of studies using this parameter is the heterogeneity of cohorts which, for example, combine PUPs and MTPs.

It is difficult to compare clinical trials reporting data on inhibitor occurrence because of discrepancies in duration of follow-up of patients, dosing regimens, definition of severe haemophilia (baseline FVIII $\leq 2\%$ or $< 1\%$), patient characteristics (non comparable genetic background), methods of inhibitor testing, and use of central versus local laboratories. Frequency of inhibitor development in PTPs is difficult to assess since the methodology of post-marketing authorisation studies (PMS) reported so far is not strong enough to draw conclusions; accuracy of exhaustiveness of population studied as well as a comprehensive notification of all inhibitors including transient ones is often lacking. New risk management plans taking into account a rigorous screening of patients for both the numerator and the denominator are needed.

Epidemiology

The incidence rate of inhibitors in PUPs studies ranges from 2.7% to 36% (cf Table 1). In their systematic review, Wight and Paisley [29] report that large scale prevalence studies and registry data indicate that the overall prevalence of inhibitors in the haemophiliac population ranges between 5% and 7%. The prevalence among severe haemophiliacs (FVIII:C $< 1\%$) is substantially higher, being between 12% and 13%. They also report clear evidence that different FVIII preparations have different levels of immunogenicity. All studies in which patients have been treated with a variety of FVIII preparations have reported higher cumulative risks of inhibitor development than those in which patients were confined to a single preparation. A reduced incidence in patients treated with unique plasma-derived products remains, however, and linear regression analysis shows that this difference is independent of disease severity, study size or inhibitor testing frequency. Following factors could influence the incidence rate: severity of haemophilia, frequency of testing for inhibitors, ethnic origin, treatment and product used [30]. Incidence rates of inhibitors in PUPs and MTPs are summarised in Table 1. Inhibitor incidence varies among PUPs studies using recombinant FVIII products (rFVIII) between 10.5% and 31.6%. Nevertheless, Kreuz and Giangrande's studies include PUPs and an almost similar proportion of MTPs which is questionable [20, 21].

Regarding plasma-derived FVIII (pdFVIII) studies, inhibitor incidence varies from 2.7% to 28%. But for example, the Philipp' study used an immunopurified product devoid of co-purified plasma proteins such as vWF [31].

Despite a significant number of comparative cohort studies conducted in PUPs reported so far, comparison of the incidence of inhibitors induced by plasma-derived

Table 1 Clinical trials in PUPs

Author	Product	Nb patients	Baseline FVIII	% inhibitor
Recombinant				
Gouw 2007 [78]	rFVIII	236	<2%	28%
Kreutz 2005 [21]	Kogenate® FS	37 PUPs	<2%	13.5%
		23 MTPs	<2%	17.3%
Luscher 2005 [79]	Refacto®	101	<2%	31.6%
Lusher 2004 [80]	Kogenate®	65	<2%	29%
Giangrande 2002 [20]	Kogenate® FS	19 PUPs	≤1%	10.5%
		12 MTPs	≤1%	16.6%
Rothschild 1998 [81]	Recombinate®	50	<1%	28%
Bray 1994 [82]	Recombinate®	71	≤2%	23.9%
Plasma derived				
Gringeri 2006 [83]	Emoclot®	31 PUPs	14 pts <1%	9.6%
		68 MTPs	17 pts=1 to 5%	
Philipp 2001 [31]	Monoclate®	30	57 pts <1%	5.8%
			11 pts=1 to 5%	
Goudemand 1998 [84]	FVIII-LFB®	72	18 pts <1%	23%
Yee 1997 [85]	BPL8Y	37	12 pts=1 to 5%	
Guerois 1995 [86]	FVIII-LFB®	56	<1%	11.1%
Addiego 1993 [87]	Pd FVIII	89	<2%	2.7%
Addiego 1992 [88]	Hemofil®	23	<1%	9%
Plasma derived versus recombinant				
Gouw 2007 CANAL [34]	rFVIII	181	<1%	28%
	Pd FVIII	135	≤3%	8.7%%
Chalmers 2007 [37]	rFVIII	172	<2%	29%
	Pd FVIII	132	<2%	21.5%
Goudemand 2006 [35]	Recombinate® or Kogenate®	86	≤1%	27%
	FVIII-LFB	62	≤1%	14%
Ettinghausen 2006 [36]	rFVIII	47	<1%	31%
	Pd FVIII	57	<1%	11%
Kreuz 2002 [33]	rFVIII	21	ND	36%
	Pd FVIII	51	ND	21%
Mauser-Bunschoten 2001[32]	rFVIII	22	11 pts <1%	19%
	Pd FVIII	59	10 pts=1to 5%	
			35 pts <1%	35%
			16 pts=1 to 5%	
			<1%	9%
			<1%	17%

ND: not defined

versus recombinant products remains highly controversial [32–37]. In order to address this issue on an evidence-based approach, Mannucci and colleagues proposed the design of the forthcoming study called Study on Inhibitors in Plasma-Product-Exposed Toddlers. It is a prospective, controlled (open-label) and randomised clinical trial [38]. It will compare the immunogenicity of pdFVIII products containing vWF (pdVWF-FVIII) with that of rFVIII products by determining the frequency of inhibitor development in PUPs and MTPs less than 6 years of age. Prophylaxis or on-demand regimens will be chosen by the clinician according to local guidelines and patient preferences. The screening assessment will be done by a central laboratory, and patients will be followed up until 50 EDs or 6 months.

Risk factors

Several patient-related factors and products-related factors have been associated with the risk of inhibitor development.

Patient-related factors

Occurrence of inhibitors correlates with genetic abnormalities underlying the disease: 35% of patients with large gene deletion in the FVIII gene, gene inversion and stop mutations have a high risk of developing an inhibitor, whereas inhibitors occur in 5–7% of patients with missense mutations and small deletions in the FVIII gene [39]. These anti-FVIII responses are also linked to the genetic

background such as ethnic origin, and familial history of inhibitor or to the immunological status such as age at the first treatment and the intensity of treatment. Some HLA haplotypes may confer either a weakly increased or decreased inhibitor risk [40, 41]. On the other hand, associations with cytokine genes have been studied as well as gene polymorphism: for example, Astermark and colleagues showed a strong association between an allele of the promoter of *IL-10* gene and the risk of developing an inhibitor [42].

Product-related factors

Product characteristics may also play a role in inhibitor development such as type of FVIII concentrate (recombinant or plasma-derived products) or purity of FVIII products (presence or absence of vWF).

Environmental factors

Environmental risk factors for inhibitor development investigated include: breast feeding, age at first FVIII exposure, treatment intensity, type of product used, product switching, mode of administration of FVIII and concomitant infection or vaccination.

A small influence of breast-feeding has been suggested but not fully demonstrated [43]. Santagostino et al. [44] suggested that there was an inverse relationship between age at first FVIII exposure and inhibitor risk. Goudemand et al. [35] found a threefold difference in inhibitor risk between the oldest and youngest age at first exposure ($p=0.031$). The CANAL study also showed a highly significant association between early age at first exposure and increased risk of inhibitor development [45].

It seems that a first episode of intense treatment (≥ 5 days) and/or surgery predispose to an increased risk of inhibitor development [45].

Therapeutic approaches: clinical guidelines

Therapeutic strategies for managing inhibitors can be divided in three parts: (a) inhibitor eradication, (b) haemostatic management of bleeding episodes and/or surgery and (c) supportive care.

Inhibitor eradication

Given the inhibitor-associated morbidity, antibody eradication is the main goal of inhibitor management. Immune tolerance induction (ITI) is the only proven strategy for achieving antigen-specific tolerance to FVIII. It is a very long term (months to years) of uninterrupted exposure to

FVIII to “tolerise” the immune system. Its precise mechanism of action remains unclear even if memory B lymphocytes eradication seems to play a prominent role [46]. The first protocols were reported almost 30 years ago [47]. The current knowledge comes mainly from observational studies [48–54] and registries [55–57]. ITI success rate ranges commonly between 60% and 80%; success is defined as both an undetectable inhibitor titre (≤ 0.6 BU), and normalised FVIII pharmacokinetics (PK, plasma recovery $\geq 66\%$ of expected, and a half life ≥ 6 h), determined following a 72 h FVIII exposure-free period (58)). Once a successful ITI is achieved, long term FVIII prophylaxis is commonly instituted. The International ITI (I-ITI) study defines ITI partial success as a reduction in inhibitor titre to ≤ 5 BU, unaccompanied by both normalisation of FVIII PK and treatment-limiting anamnesis over a prolonged observation period [59]. The I-ITI also defines ITI failure by either of two criteria: (1) failure to attain the definition of success within 33 months of uninterrupted ITI or (2) failure to demonstrate a progressive 20% reduction in inhibitor titre over each successive 6-month period of uninterrupted ITI [56, 58, 59].

There is today no controlled comparison of regimens currently used and there is no agreement on the optimal regimen to use; nevertheless, collaborative international studies are currently ongoing (RESIST study) [60].

Inhibitor titre at the onset of ITI is the most reliable predictor of success; titres <10 BU/ml correlate with a high success rate. Titres >10 BU/ml are associated with a 43% success within 15 months [26]. There is no clear demonstration that a low historical peak prior to ITI, an early start after inhibitor detection, or high dose of FVIII influence the outcome of ITI.

Factor VIII product type and purity is a highly controversial issue: a possibly higher efficacy of plasma-derived products containing vWF has been suggested by a retrospective analysis of the Frankfurt cohort [61]; This team reported a high success rate (91%; 19/21) with intermediate purity products and a low success rate (29%; 4/14) with high purity FVIII; a switch to plasma-derived vWF containing products was successfully reported in eight out of ten patients. These historical comparisons were not confirmed by the North American or the International Immune Tolerance Registries [56, 57]. Nevertheless, a possible role of vWF remains a matter of basic and clinical research. In addition, vWF was shown in vitro to reduce the binding [62] and the inhibitory activity of anti-FVIII IgG to FVIII [63, 64].

Management of bleeding episodes

Three criteria must be taken into account to determine the treatment of an acute bleed: (1) the severity of the bleed, (2)

the current inhibitor titre and (3) a previous anamnestic response.

Low responders (persistently low-titre inhibitor <5 BU/ml) can be treated with large doses of FVIII, since they are not exposed to an anamnestic response and the likelihood that large doses of FVIII will saturate the antibodies is significant and will provide an excess of FVIII to achieve haemostasis. Human FVIII concentrates are the treatment of choice for haemorrhages of low-responder patients, and also in severe haemorrhages of high-responder patients who have a low inhibitor titre at that moment.

DDAVP may play a role in the management of patients with mild haemophilia and inhibitors. If the antibody reacts only with the therapeutic FVIII and leaves the patient's FVIII activity unaffected, DDAVP may be effective [65].

For treatment of patients with high-titre, high-responding inhibitors, 'by-pass' therapy is generally recommended. Activated prothrombin complex concentrates represent the historically primary 'by-pass' treatment. Activated recombinant factor VII is another useful option of by-pass therapy. Porcine FVIII is not yet available for common use; a recombinant product is under clinical investigation. On the basis of limited evidence, inhibitor removal by plasmapheresis with or without immunoadsorption, can be used as a second line treatment for patients with high-titre inhibitors when other approaches have failed [66].

The main active components of prothrombin complex concentrate (FEIBA) are activated factor X and activated prothrombin. The largest observational study on the use of FEIBA is a retrospective multicentre French study where an 82% efficacy was reached [67]. The more frequent doses employed vary between 50 and 200 IU kg⁻¹ day⁻¹.

Recombinant factor VIIa (rFVIIa) has been widely used as a by-passing agent. It could act on activated platelets in a tissue factor-independent manner. It has also been shown that an enhanced thrombin generation by rFVIIa not only accelerates clot formation but also inhibits fibrinolysis since it activates the thrombin activable fibrinolytic inhibitor. Nevertheless, a large variability of antifibrinolytic potential of rFVIIa exists between patients [68]. It may explain why this product is not equally efficient in all patients, leading to high doses protocols. The licensed dose or dosing regimen for NovoSeven® (rFVIIa) is 90 µg/kg given up to every second hour [69]. However, treatment with a single, large, bolus dose of NovoSeven® has been reported to provide rapid relief of pain and an absence of adverse events, thus reducing the duration of treatment, especially in paediatric patients [70]. Optimal rFVIIa dosing was evaluated in a crossover dose comparison (270 versus 90 µg/kg).

As highlighted by Acharya and colleagues regarding by-pass therapy, it is important to consider that: (1) no single product is optimal for the treatment of bleeding at all times and under all circumstances; (2) the optimal dose and

dosing schedule is not well defined for any by-passing agent; (3) no direct comparison study of APCCs and rFVIIa efficacy in all clinical settings has yet been completed; (4) the potential for musculoskeletal or surgical prophylaxis with these agents still needs to be explored [22].

Whether these two by-passing agents are clinically equivalent was investigated in the FENOC study [71]. It was designed to test equivalence of the products in the treatment of joint bleeding. It showed that FEIBA® and NovoSeven® appear to exhibit a similar effect on joint bleeds, although the efficacy between products is rated differently by a substantial proportion of patients.

Both products have a good safety record even if thrombo-embolic events are reported for both of them.

Finally, interest has focused recently on selective B-cell depletion using Rituximab a humanised monoclonal antibody to B cell CD20 antigen. Case report data seemed to indicate a beneficial effect in acquired haemophilia [72]. However, the number of successful case reports in severe haemophilia A is extremely limited [73]. This therapeutic option remains experimental. Products commonly used in the management of bleeding episodes and their main characteristics are summarised in Table 2.

Supportive care

As young children represent the majority of patients treated by ITI, venous access is a critical issue. A central venous catheter device is often used even if infection complication rate is higher than 50% during ITI [74]. The use of an arteriovenous fistula has been suggested as an alternative. However, practical issues must be solved prior to large scale use [75]. Conventional measures used for non-inhibitor patients may also be considered such as immobilisation, cold application, compression or antifibrinolytic agents.

Regulatory perspective

In Europe, Health authorities are fully consistent with ISTH recommendations with pre-marketing studies performed exclusively in PTPs [19]. Therefore, a pre-licensing study assessing inhibitor occurrence in a limited PTP number is combined with mandatory post-marketing studies and risk management plans. In the USA, the acceptability criteria of "ruling out of a true inhibitor rate of >5.6%" for a new product have been chosen. The need for harmonisation of the requirements between EU and USA is often highlighted taking into account the limited size of patient population available. Nevertheless, new statistical strategies adapted to small population could be used as suggested in the *ad hoc* EMEA guideline (CHMP/EWP/83561/2005). Since children

Table 2 Management of bleeding episodes

Products	Indications	Limits
DDAVP	Mild haemophilia with inhibitor	No cross reaction between inhibitor/patient's FVIII
Human FVIII	Low titre inhibitors <2 BU/ml: increased doses of human FVIII	FVIII is reserved for life and limb threatening emergencies (for risk anamnestic response)
Porcine FVIII	Not yet available for common use currently in clinical trials	
PCCs	Effective in about 50% of haemarthroses	
aPCCs	More effective than PCCs RR: 52% to 80–90%	Isolated episodes of thromboembolism myocardial infraction, DIC aPCC contains FVIII → anamnestic response
	Active moiety: aFX and thrombin	
	Half-life: 4–7 h	
rFVIIa	A dose of 90 µg/kg controls ~70–90% bleedings	Costly if long period
	Dose ranging effect (high RR of mega-doses 300 µg/kg)	Cases of myocardial infraction/stroke/DIC
	Short half-life	

may respond differently from adults, children under the age of 6 should also be studied separately. In Europe, there is no requirement for specifically studying PUPs. Data related to PUPs are, however, included in the core Summary of Products Characteristics when available. European recommendations coming from an EMEA review on inhibitors (EMEA/CHMP/BPWP/123835/2006) elicited by rFVIII are listed below: (1) Pharmacovigilance planning is recommended for all rFVIII products; (2) there is a need to establish standardised requirements for pre- and post-marketing studies to ensure comparable safety data on inhibitor development in PUPs and PTPs treated with rFVIII products (harmonisation at an international level is desirable to achieve this aim) (3) the value of patient registries as a source of data on incidence of inhibitors should be further explored.

Clinical investigation of pdFVIII and rFVIII products: the example of the current European Notes for Guidance (CPMP/BPWG/198/95 rev.1 and CPMP/BPWG/1561/99)

Prior to marketing authorisation, a PK trial should be performed in at least 12 immunocompetent subjects suffering from severe haemophilia. Efficacy, safety and immunogenicity data are required from 50 PTPs (≥ 150 ED, aged >12 years) with residual FVIII levels $\leq 1\%$. Immunogenicity data should be based on follow-up over a period of ≥ 50 ED or 6 months. Inhibitor titre should be monitored at baseline and every 3 months using the Nijmegen modification of the Bethesda assay. Treatment of PUPs should be documented and should not be initiated before data on 50 ED from 20 PTPs included in the clinical trials are available. This Note for Guidance is currently under revision: The main evolutions are: (1) a definition of severe haemophilia A restricted to patients with FVIII plasma levels $<1\%$; (2) a new schedule of immunogenicity screening and (3) more detailed requirements for PMS studies (CPMP/BPWG/198/95 rev.2 and CPMP/BPWG/1561/99 rev.1).

2003 Food and Drugs Administration (FDA) workshop on FVIII inhibitors

The FDA encouraged manufacturers of recombinant products to put data from product development and clinical trials into the public domain. The current FDA approach is to assess efficacy and safety in PTPs (defined as >150 ED) rather than in PUPs. A PK comparative study versus equivalent recombinant product should be conducted. Eighty PTPs should be studied for 50 ED to be able to permit the detection of one inhibitor while ruling out by statistical analysis a true inhibitor rate of $>5.6\%$ (report of the workshop available from www.fda.gov/cber/minutes/fctrviii112103t.htm). As in Europe, paediatric studies are preferred over PUPs studies and are required as a phase IV commitment although the protocol should be approved prior to licensure.

In daily practice, the clinically most significant and relevant inhibitors occur in PUPs. An important issue in the treatment of PUPs is the choice between pdFVIII or rFVIII product i.e. the weighing of the potential risks of transmission of infectious agents versus the risk of inhibitor development. Therefore, investigation of inhibitor development in PUPs treated with pdFVIII compared to rFVIII product is often presented as the highest priority. To study this aspect in an evidence-based approach, a randomised controlled clinical trial has been suggested but difficulties to use this design must be highlighted: small patient population, choice of the product, dose regimen design (prophylaxis versus on demand) [38]. It has to be noted that in some EU countries randomised controlled trials comparing pdFVIII to rFVIII products are not feasible as only rFVIII products are used.

Previous experience with the occurrence of two clusters of inhibitors in PTPs treated with two modified pdFVIII products showed no abnormal product immunogenicity

during the clinical pre-licensing phase, while the first inhibitors occurred post approval (detected 18 months after market introduction for one of the products; most patients had more than 100 ED).

Based on this experience and considering the small patient population, it has to be considered that full immunogenicity data could not be collected pre-authorisation. Thus, limited stringent follow-up of patients in the post-authorisation phase is required.

Conclusion and future perspectives

As stated by the EMEA experts group (EMEA/CHMP/BPWP/123835/2006) reliable information on the incidence of inhibitor development in PTPs cannot be obtained only from post-marketing spontaneous reports. There is a need to standardise the requirements, definitions and methods in pre-and post-marketing as well as in observational studies with PTPs and PUPs. Considering the low patient numbers the need for international collaboration has to be highlighted together with the use of methodological clinical trials designs adapted to small populations.

Duration and follow-up are important parameters to compare the FVIII inhibitor incidence in clinical studies. There is a strong need for harmonisation within clinical trials with pending issues: (1) how long should the duration and follow-up period be and how should it be defined, based on exposure days or years? (2) What are the most appropriate laboratory parameters which should be monitored and in which intervals and (3) what recommendation regarding prophylaxis, treatment on-demand, FVIII plasma level, inhibitor measurement?

In this perspective, Post-marketing data represent a major part of inhibitor investigation for a new FVIII product. As mentioned by Lassila and colleagues [76], post-marketing studies should be supervised by a group of clinicians, with the aim of standardising the methodology and implementation; the use of direct electronic transfer of data would enhance the access to information. A risk management plan should be considered for a new product or when a modification to an already approved product is introduced, taking the known genetic and environmental risk factors of inhibitor development into account as well as the severity of this inhibitor.

As pharmacovigilance surveillance becomes also a key tool in inhibitor assessment there is a high need for registries, or large observational studies, with an accurate reporting of adverse events. The most precise recommendation for inhibitor patients management come from physicians' organisations especially the United Kingdom Haemophilia Centre Doctors' Organisation [26, 27]; similarly French

physicians provided guidelines for the management of inhibitor patients on behalf of the French agency for medicinal products (AFSSaPS report on development of inhibitors in haemophiliacs patients treated with plasma-derived or recombinant FVIII or FIX available on www.afssaps.sante.fr). In addition, North American physicians have published recommendations in this setting [57, 77].

All these recommendations are highly consistent and provide a reliable set of recommendations.

This review shows that researchers, clinicians, health authorities and pharmaceutical companies make lots of effort for the management of inhibitor issue; a better harmonisation of the action devoted to this issue is mandatory to increase significantly the knowledge and further improve daily practice for inhibitor patients.

Acknowledgement The authors are grateful to Stephanie Grenot for her technical assistance

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