



# **Référentiel national de bon usage des Facteurs VIII**

 Agence française de sécurité sanitaire des produits de santé	<b>DENOMINATION COMMUNE INTERNATIONALE :</b> <b>FVIII de coagulation plasmatique</b>	
	<b>NOM COMMERCIAL :</b> <b>FACTANE®</b>	
 HAUTE AUTORITÉ DE SANTÉ	<b>LABORATOIRE EXPLOITANT OU TITULAIRE DE L'AMM :</b> <b>LFB BIOMEDICAMENTS</b>	
	Version : 1 Date : août 2008 Date de révision : Historique des modifications :	<b>Condition de prescription : PIH</b>

### I. Autorisation de Mise sur le Marché (AMM)

Cf Résumé des Caractéristiques du Produit (RCP)

### II. Situation temporairement acceptable

Protocole thérapeutique temporaire

- Sans objet



### III. Situation non acceptable

- Sans objet

NB : Deux situations sont considérées comme faisant partie de l'AMM :

- Prévention et traitement des accidents hémorragiques en situation chirurgicale et obstétricale chez les conductrices d'hémophilie A à taux bas de facteur VIII, quand la réponse à la desmopressine (Minirin®) est jugée insuffisante ou n'a pu être testée
- Maladie de Willebrand en association au Wilfactin avec déficit en facteur VIII < 40% dans toutes les situations pour lesquelles une correction rapide de l'hémostase est nécessaire

Par ailleurs, la perfusion continue correspond à une modalité d'administration dans l'indication définie par l'AMM ; elle n'a donc pas lieu d'apparaître dans les référentiels de bon usage hors-AMM.

 Agence française de sécurité sanitaire des produits de santé	<b>DENOMINATION COMMUNE INTERNATIONALE :</b> <b>FVIII de coagulation plasmatique</b> <b>OCTANATE® OCTAPHARMA FRANCE</b>	
	<b>DENOMINATION COMMUNE INTERNATIONALE :</b> <b>FVIII de coagulation recombinant</b>	
 HAUTE AUTORITÉ DE SANTÉ	<b>ADVATE® BAXTER</b> <b>HELIXANE NEXGEN® ZLB BEHRING BAYER</b> <b>KOGENATE BAYER® BAYER</b> <b>RECOMBINATE® BAXTER</b> <b>REFACTO® WYETH</b>	
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### I. Autorisation de Mise sur le Marché (AMM)

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### II. Situation temporairement acceptable

Protocole thérapeutique temporaire

- Induction d'un état de tolérance immune (AMM pour Factane®)

### IV. Situation non acceptable

Sans objet

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## FACTEURS VIII

### Induction d'un état de tolérance immune

**sous réserve qu'elle soit conduite par un centre de traitement de l'hémophilie, et que le patient soit inclus, soit dans un essai clinique (international ou national), soit dans le registre national mis en place par le Centre de Référence Hémophilie.**

#### 1. PROTOCOLE THERAPEUTIQUE TEMPORAIRE

*Le protocole temporaire de traitement nécessite de se référer au Résumé des Caractéristiques du Produit (RCP). Il est nécessaire d'informer le patient de ce que la prescription est faite hors-AMM sous la responsabilité du médecin prescripteur.*

#### Schéma d'administration

- A quel moment débiter une induction de tolérance immune (ITI) ?  
L'ITI doit être débutée aussi rapidement que possible après la détection de l'inhibiteur. Dans la majorité des cas, le moment le plus favorable est celui de la réponse primaire, quel que soit le titre de l'inhibiteur.

Lors d'une réponse immune secondaire, il est recommandé de différer l'ITI si le titre de l'inhibiteur est > 10 UB, jusqu'à ce que celui-ci retombe en dessous de 10 UB.

- Avec quel FVIII faut-il initier une ITI ?  
Tous les types de concentrés de FVIII sont susceptibles d'induire avec succès une tolérance immune. Cependant, l'ITI doit préférentiellement être initiée avec le concentré de FVIII qui avait été choisi pour traiter le patient et sous lequel le patient a développé l'inhibiteur.

- A quelles posologies faut-il initier une ITI ?  
Chez l'enfant faible répondeur avec un titre d'inhibiteur de 0,6 à 5 UB, un traitement régulier, avec des doses comprises entre 50 UI/kg 3 fois par semaine et 200 UI/kg/jour, est suggéré; si le titre devient supérieur à 5 UB, les modalités proposées pour les forts répondeurs sont applicables.

Chez le fort répondeur et en l'absence d'étude prospective et randomisée, on ne peut recommander aucun régime spécifique. Cependant, le titre historique de l'inhibiteur, considéré comme l'un des meilleurs facteurs prédictifs, est un élément d'orientation.

Le régime "faibles doses", 3 fois par semaine, est proposé pour de très jeunes patients avec un titre maximum d'inhibiteur < 40 UB.

Quel que soit l'âge du patient, si le pic historique de l'inhibiteur est > 200 UB, un régime " fortes doses " peut être proposé.

Si le pic historique de l'inhibiteur est > 50 UB et < 200 UB, et le titre à l'initiation < 10 UB, les différents régimes semblent donner des issues comparables, mais avec un délai d'autant plus long que la posologie en UI/kg/jour est faible.

Si le pic historique de l'inhibiteur a été > 50 UB et < 200 UB, et le titre à l'initiation de l'ITI > 10 UB, des posologies > 50 UI/kg/jour augmentent les chances de succès.

- Quelles modalités d'administration ?

La voie veineuse périphérique est recommandée chaque fois que possible. Les régimes "fortes doses" peuvent imposer une voie veineuse centrale, d'autant plus que toute interruption de l'ITI doit être évitée puisqu'elle peut conduire à l'échec.

- Quelle surveillance ?

Durant l'ITI, le titre de l'inhibiteur doit être évalué au minimum tous les mois jusqu'à ce que l'inhibiteur anti-FVIII ne soit plus détectable. A ce stade, la récupération du FVIII injecté doit être déterminée tous les mois jusqu'à normalité. Lorsque le régime est devenu prophylactique, la demi-vie doit être mesurée, à 72 heures d'une injection, et tous les 3 mois jusqu'à normalité.

- Réduction progressive des doses

Après disparition de l'inhibiteur et obtention d'une récupération normale, une réduction progressive des doses est appliquée aux régimes "fortes doses" ou "doses intermédiaires" journalières, avec des paliers mensuels. Le schéma suivant, 100 UI/kg/jour, puis 50 UI/kg/jour, puis 50 UI/kg tous les 2 jours, puis régime prophylactique 3 fois par semaine pendant au moins 1 an, est proposé, mais doit être adapté au cas par cas et selon les résultats des contrôles biologiques.

### **Contre-indications**

Hypersensibilité à l'un des constituants.

### **Sécurité d'emploi et mises en garde (cf RCP)**

Des réactions allergiques de type hypersensibilité peuvent survenir.

### **Traitement associé**

Aucune interaction médicamenteuse connue à ce jour.

### **Grossesse et allaitement**

L'hémophilie A étant très rare chez les femmes, on ne dispose pas de données sur l'utilisation du facteur VIII pendant la grossesse. Par conséquent, il faut évaluer le bénéfice de l'utilisation de facteur VIII au cours de la grossesse par rapport au risque pour la mère et l'enfant. Les facteurs VIII ne seront prescrits pendant la grossesse et l'allaitement qu'en cas de nécessité absolue.

Nous vous rappelons que tout effet indésirable grave ou inattendu doit être déclaré au Centre Régional de Pharmacovigilance dont vous dépendez (coordonnées disponibles sur le site internet [www.afssaps.sante.fr](http://www.afssaps.sante.fr) ou sur les premières pages du Vidal).

- Ce protocole temporaire de traitement est limité à une durée de 4 ans.

## 2. ARGUMENTAIRE

Le développement d'inhibiteurs est la complication la plus fréquente du traitement substitutif par fractions coagulantes chez les hémophiles. L'induction d'une tolérance immune (ITI) chez les hémophiles constitutionnels ayant développé des inhibiteurs consiste à administrer des perfusions de facteur VIII à hautes doses jusqu'à disparition des anticorps anti-facteur VIII.

Selon les données descriptives 2005 du réseau FranceCoag, il existe environ 4000 patients hémophiles en France. Environ 450 d'entre eux (11%) ont développé des inhibiteurs au cours de leur prise en charge et 197 (5%) en présentaient encore lors de la dernière consultation. Les patients porteurs d'hémophilie A sévère sont les plus à risque de développer un inhibiteur (environ 25%) suivis des patients porteurs d'hémophilie A modérée et d'hémophilie B sévère (environ 7%). Environ un tiers des patients avec inhibiteur lors de la dernière visite (n=57/197) suivaient un traitement d'ITI.

Les recommandations britanniques (*UKHCDO ; 2006*), espagnoles (*Haya, 2001*), allemandes (*Brackmann ; 1999*), italiennes (*Gringeri ; 2005*) ainsi que des revues de la littérature (*Paisley, 2003 ; Kreuz, 2003 ; Mariani, 2003 ; DiMichele, 1998 ; Nilsson, 1993 ; Wight 2003*) rejoignent les conclusions du rapport de l'Afssaps (2006) sur le développement des inhibiteurs et prise en charge chez les patients hémophiles traités par facteur VIII ou IX d'origine plasmatisque ou recombinante. Ce rapport indique que l'induction d'une tolérance immune (ITI) éradique l'inhibiteur anti-FVIII chez plus de 80% des hémophiles A sévères et qu'il faut l'envisager chez tout patient ayant une hémophilie A sévère avec inhibiteur anti-FVIII confirmé. Le niveau de preuve repose sur des études non comparatives.

Trois registres concentrent les données principales : "The International Immune Tolerance Registry" (IITR), "The German registry of immune tolerance treatment", "The North American Immune Tolerance Registry" (NAITR). Ils ont permis de recueillir des données chez plus de 500 patients traités pour induction de tolérance immune, certains patients étant inscrits dans plusieurs registres. Le protocole de Malmö peut associer aux perfusions de facteur VIII l'administration de cyclophosphamide, d'immunoglobulines et/ou des séances d'immunoadsorption, le protocole de Bonn un traitement prophylactique par Feiba®.

L'obtention d'une ITI, qui permet de restaurer un traitement efficace par des concentrés de FVIII, réduit le risque de séquelles articulaires et améliore considérablement la qualité de vie du patient. L'ITI représente un investissement à long terme et son coût doit être comparé à celui du traitement d'un hémophile qui conserve un inhibiteur toute sa vie. Les alternatives thérapeutiques sont moins efficaces à ce jour pour prévenir le développement de l'arthropathie hémophilique et l'ITI évite des interventions orthopédiques particulièrement onéreuses chez un patient avec inhibiteur.

L'ITI doit être envisagée chez tout patient avec une hémophilie A sévère chez lequel un inhibiteur anti-FVIII est découvert et confirmé. L'évaluation doit analyser les facteurs influençant l'issue de l'ITI. Sont considérés comme des facteurs de bon pronostic :

- un titre d'inhibiteur < 10 UB lors de l'initiation de l'ITI,
- un pic historique avant l'ITI < 200 UB,
- un délai court entre la détection de l'inhibiteur et le début de l'ITI,
- l'absence de nouvelle injection de FVIII entre la détection de l'inhibiteur et le début de l'ITI,
- un jeune âge.

Dans 80% des cas, une ITI bien conduite permet l'éradication de l'inhibiteur et l'instauration de la prophylaxie thérapeutique recommandée dans l'hémophilie sévère.

Enfin concernant la non substitution des produits anti-hémophiliques, les termes de la circulaire relative à l'organisation des soins aux hémophiles (Circulaire DGS/DH/DSS n°97/142 du 24/02/1997) sont ici rappelés :

« ...Les différentes spécialités pharmaceutiques antihémophiliques (facteurs de coagulation recombinants ou dérivés du sang) ne sont pas équivalentes pour le traitement des malades....Elles sont utilisées à vie et prescrites en évitant l'alternance, sauf si la prescription médicale le précise, de façon à éviter notamment le risque majeur présenté par le développement d'anticorps inhibiteurs anti-facteurs VIII ou IX. De ce fait, il est impératif que les prescriptions des médecins qui prennent en charge des hémophiles soient strictement respectées.... ».

En conclusion, l'induction d'un état de tolérance immune est une situation temporairement acceptable, sous réserve qu'elle soit conduite par un centre de traitement de l'hémophilie, et que le patient soit inclus, soit dans un essai clinique (international ou national), soit dans le registre national mis en place par le Centre de Référence Hémophilie.

### **Registre national**

L'établissement et la coordination du registre national de suivi des inductions de tolérance immune sont assurés par le Centre de Référence Hémophilie, avec la collaboration des centres spécialisés dans le traitement de l'hémophilie (centres de compétence).

Il est prévu que ce registre national puisse être compatible avec l'infrastructure du Réseau FranceCoag - RFC - (InVS).

Le document de recueil d'informations est à demander à l'adresse mail suivante : [CRMH@chu-lyon.fr](mailto:CRMH@chu-lyon.fr).

Pour l'inclusion des patients dans le registre national « Tolérance Immune », contacter :

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### **Comité scientifique *ad hoc* Tolérance Immune**

Un comité scientifique *ad hoc*, sous l'égide du Centre de Référence Hémophilie est mis en place, afin de répondre aux situations suivantes :

- en cas de facteurs de mauvais pronostic, la décision d'induction de tolérance immune sera prise après concertation du comité scientifique *ad hoc* ;
- la décision d'interrompre une induction de tolérance immune sera prise après concertation du comité scientifique *ad hoc*, qui évaluera avec le(s) praticien(s) l'opportunité d'une éventuelle modification du

protocole thérapeutique (augmentation des doses de FVIII injecté, modification du rythme des injections, voire changement de produit). L'interruption de traitement pourra être envisagée dans les circonstances suivantes :

- réaction allergique grave au facteur VIII,
- échec au terme d'une induction de tolérance immune bien conduite pendant plus de 24 mois,
- non-observance du traitement conduisant à une administration trop irrégulière de FVIII.

#### Effet des facteurs VIII dans l'induction de tolérance immune

Auteurs	Posologie	Critères d'évaluation et résultats
<i>The International Immune Tolerance Registry (IITR)</i> Mariani (1994 ; 1999)  Cohorte 1989-1997 <b>n=295</b>	4 régimes de doses différents	<b>Succès : 52.3%</b> (n=114/295)  Succès : Titre indétectable: n=114/295 (52.3%) Titre<10BU : 9.7% Titre>10BU : n=51 (23.4%)
<i>The North American Immune Tolerance Registry (NAITR)</i> DiMichele (2002)  Cohorte 1993-1999 <b>n=164</b>	4 régimes de doses différents	<b>Succès : 70%</b> (n=115/164)  - titre ≤1% : n =104 (87%) - OU taux FVIII nal : n=69 (56%) - OU ½ vie facteur nale: n=34 (28%) - OU conversion de fort à faible répondeur : n=12 (10%)
<i>The German registry of immune tolerance treatment</i> Lenk (1999; 2000)  Cohorte 1993-1999 <b>n=126</b>	FVIII: 200 à 300 UI/kg/jour.	- <b>Succès : 78.6%</b> (n=99/126)  - Succès : ITT à terme + taux + ½ vie FVIII n <sup>aux</sup> : n=99/126 (78.6%) - ITT à terme + titre inhibiteurs<2 BU, ↓½ vie FVIII + ↓ taux FVIII: n= 11/126 (8.7%) - Echec: n=16/126 (12.7%)
Oldenburg (1999) Suivi : 20 ans <b>n=60</b>	Protocole de Bonn	<b>Succès : 86.7%</b> Succès : ½ vie FVIII nale: n=52/60 (86.7%) Pas de rechute à long terme: n=52/52
Mauser-Bunschoten (1995) Suivi : 13 ans <b>n=24</b>	FVIII 25UI/kg tous les 2 jours	<b>Succès : 87%</b> ITI complète : Titre <2BU/ml + taux FVIII ≥50% de la normale + ½ vie FVIII≥6 heures + pas de réponse anamnesticque ITI complète : n=21 (87%)
Freiburghaus (1999) <b>n=16</b>	Protocole de Malmö	<b>Succès : 62.5%</b> (n=10/16) Succès : taux FVIII nal + ½ vie FVIII nal + pas de réponse anamnesticque
Battle (1999) <b>n=11</b>	FVIII de 50U/kg tous les 2 jours à 220 U/kg/jour	<b>Succès : 81.6%</b> (n=9/11) Succès : titre inhibiteurs indétectable et/ou taux FVIII nal avec ½ vie nale
Rothschild (1998) Cohorte : n=50 <b>ITI : n=8</b>	Recombinate : 2 régimes de doses différents	<b>Succès : 50%</b> ITI complète : Titre<0.6BU/ml+ taux FVIII à ≥66% de la normale + ½ vie FVIII≥6 heures ITI complète : n=4/8 (50%)
Orsini (2005) <b>n=8</b>	FVIII LFB (n=7), Factane (n=1) : 50 UI à 200 UI/kg/ j	<b>Succès : 87.5%</b> (n=7/8) Succès ITI : Titre <0.6BU/ml+ ↑FVIII ≥0.66 UI/dL par UI/kg et/ou ½ vie FVIII≥6 heures
Lusher (2004) <b>n=8</b>	Kogenate : 50 à 200 UI/kg/jour.	<b>Succès : 62.5%</b> (n=5/8) Succès : titre indétectable + taux FVIII nal
Scheibel (1987) <b>n=11</b>	FVIII 90 à 200 u/kg/jour	<b>Succès : 54%</b> (n= 6/11) Succès : titre indétectable+ taux FVIII nal ↓ titre à 0.4-1.4 BU/ml : 36% (n=4/11) Echec : 9% (n=1/11)
Kreuz (1995) n=21 Forts répondeurs (HR) : n=16/21 Faibles répondeurs (LR) : n=5/21	HR : FVIII 50-300 U/kg/j + FEIBA (n=11/16)  LR : FVIII 20-100 U/kg/2-3 j	<b>Succès : 90%</b> (n=19/21) Succès : titre indétectable + taux FVIII nal + absence de réapparition d'inhibiteurs sous prophylaxie

Auteurs	Posologie	Critères d'évaluation et résultats
Nilsson (1988) n=11	Malmö protocol	<b>Succès : 81%</b> (n=9/11) Succès : Titre indétectable

## Bibliographie

Les référentiels de la Juste prescription (AP-HP), des Pharmaciens de CHU et des Hospices Civils de Lyon ont été les documents de base du travail bibliographique.

La recherche bibliographique a été réalisée par interrogation systématique des banques de données Medline, Embase et Pascal. Elle a identifié préférentiellement les essais cliniques et les revues de synthèse publiés en langue française ou anglaise après janvier 1993.

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Pr VICAUT Eric, médecin de santé publique

La Commission d'AMM du 14 juin 2007 présidée par le Pr Daniel VITTECOQ n'a pas émis d'objection à ce référentiel, qui a également été visé par la Commission de la transparence de la HAS, présidée par le Pr Gilles BOUVENOT.

## Résumés- abstracts

Brackmann HH, Lenk H, Scharrer I, Auerswald G, Kreuz W. German recommendations for immune tolerance therapy in type A haemophiliacs with antibodies. *Haemophilia*. 1999 May;5(3):203-6.

Haemophilia A is the most common X-chromosomal-linked congenital bleeding disorder and is caused by decreased activity of blood coagulation factor VIII. Affected individuals develop a variable phenotype of haemorrhages, mainly into joints and muscles depending on the amount of the residual factor VIII. The exogenous factor VIII-substitution by plasma-derived or recombinant products are the only treatments either on demand or prophylactically. The most important complication of treatment is the development of inhibitors that affect about 20%-50% of the severe cases. These antibodies neutralize the therapeutic effect of factor VIII-concentrates, leading to recurrent bleeding episodes, progredient joint damages and sometimes life-threatening situations. The only chance for a complete and permanent eradication of the inhibitors in these patients is the induction of Immune-Tolerance (ITT) to substituted factor VIII by the application of high-doses of factor VIII. The treatment demands a strict compliance of the patient and a much higher effort of the physician, to non-compared inhibitor patients. Requirements for a consistent realization of the ITT to increase the successful outcome was carried out by German Haemophilia Center Directors.

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Brackmann HH, Gormsen J. *Lancet*. 1977 Oct 29; 2(8044):933. Massive factor-VIII infusion in haemophiliac with factor-VIII inhibitor, high responder. Abstract non disponible

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Brackmann HH, Oldenburg J, Schwaab R. Immune tolerance for the treatment of factor VIII inhibitors--twenty years' 'bonn protocol'. *Vox Sang*. 1996; 70 Suppl 1:30-5.  
Abstract non disponible

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DiMichele DM, Kroner BL; North American Immune Tolerance Study Group. The North American Immune Tolerance Registry: practices, outcomes, outcome predictors. *Thromb Haemost*. 2002 Jan;87(1):52-7.

The North American Immune Tolerance Registry was initiated to study of immune tolerance (ITT) in Canada and the United States with respect to: 1) therapeutic regimens in use for haemophilia A (HA) and B (HB) inhibitor patients; 2) therapeutic outcomes; 3) potential predictors of successful outcome and 4) complications of therapy. Data on 188 ITT courses was collected by questionnaire from 60 haemophilia centers from 1993-99. Among the completed courses, the overall success rate was 70% (115/164) for all HA and 31% (5/16) for all HB. Outcome parameters noted to be predictive of ITT success for all HA were 1) pre-ITT induction (p = 0.003), 2) ITT peak (p = 0.007) and 3) historical pre ITT peak (p = 0.04) inhibitor titres. An inverse correlation between total daily dose (units/kg/day) and success: (80% with under 50; 71% with 50-99; 73% with 100-199; and 41% with > or = 200, p = 0.01) was found. Outcome predictors

were not evaluable for HB, although adverse reactions to therapy, including nephrotic syndrome, and access complications were more common among failed courses. Infection most often complicated the use of access catheters. These results are discussed within the context of the international ITT registry and upcoming prospective ITT study.

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DiMichele DM, Kroner BL; North American Immune Tolerance Study Group. The North American Immune Tolerance Registry: practices, outcomes, outcome predictors. *Thromb Haemost.* 2002 Jan; 87(1):52-7.

The North American Immune Tolerance Registry was initiated to study of immune tolerance (ITT) in Canada and the United States with respect to: 1) therapeutic regimens in use for haemophilia A (HA) and B (HB) inhibitor patients; 2) therapeutic outcomes; 3) potential predictors of successful outcome and 4) complications of therapy. Data on 188 ITT courses was collected by questionnaire from 60 haemophilia centers from 1993-99. Among the completed courses, the overall success rate was 70% (115/164) for all HA and 31% (5/16) for all HB. Outcome parameters noted to be predictive of ITT success for all HA were 1) pre-ITT induction ( $p = 0.003$ ), 2) ITT peak ( $p = 0.007$ ) and 3) historical pre ITT peak ( $p = 0.04$ ) inhibitor titres. An inverse correlation between total daily dose (units/kg/day) and success: (80% with under 50; 71% with 50-99; 73% with 100-199; and 41% with  $\geq 200$ ,  $p = 0.01$ ) was found. Outcome predictors were not evaluable for HB, although adverse reactions to therapy, including nephrotic syndrome, and access complications were more common among failed courses. Infection most often complicated the use of access catheters. These results are discussed within the context of the international ITT registry and upcoming prospective ITT study.

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DiMichele DM, Kroner BL. Analysis of the North American Immune Tolerance Registry (NAITR) 1993-1997: current practice implications. ISTH Factor VIII/IX Subcommittee Members. *Vox Sang.* 1999;77 Suppl 1:31-2.  
Abstract non disponibile

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Ehrenforth S, Kreuz W, Scharrer I, Linde R, Funk M, Gungor T, Krackhardt B, Kornhuber B. Incidence of development of factor VIII and factor IX inhibitors in haemophiliacs. *Lancet.* 1992 Mar 7; 339(8793):594-8.

The development of factor VIII:C inhibitors remains one of the most serious complications of repeated transfusion in patients with haemophilia A. The proportion of patients affected has been reported to range from 3.6% to 25%, but these figures have been derived mainly from retrospective data and from total numbers of known haemophiliacs instead of number at true risk. The assessment here is based on a prospective study, started in 1976, on the incidence of inhibitor development in haemophiliacs born after 1970 whose FVIII or FIX activity was 5% or less, and who had received replacement therapy at least once. 46 of 63 children with haemophilia A and 13 of 17 with haemophilia B fulfilled the enrollment criteria. Inhibitors developed only in haemophilia A patients who had previously been treated with FVIII products--inhibitor concentrations were high in 12 and low in 3. Inhibitors developed in 24% (15/63) of all haemophilia A patients, and in 52% (14/27) of those with severe disease. The incidence of inhibitor development for all haemophilia patients was 39.1 per 1000 patient-years of observation. All inhibitors were first detected when patients were aged 0.08-5.2 years. The cumulative risk was 33% at age 6 years. The findings indicate that previous reports have underestimated the risk of acquiring FVIII inhibitors. Prospective, standardised studies, especially in children, are needed for the assessment of the true risk of this complication.

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Freiburghaus C, Berntorp E, Ekman M, Gunnarsson M, Kjellberg B, Nilsson IM. Tolerance induction using the Malmo treatment model 1982-1995. *Haemophilia.* 1999 Jan;5(1):32-9.

The ultimate goal in the treatment of haemophilia patients with inhibitors is to eradicate permanently the inhibitor and induce tolerance. Here we summarize our experience at the Malmo centre regarding tolerance induction according to the Malmo Treatment Model. The protocol includes immunoadsorption if needed, neutralization of inhibitor and replacement with factor concentrates, cyclophosphamide intravenously for 2 days (12-15 mg kg<sup>-1</sup> bw) and then orally (2-3 mg kg<sup>-1</sup> bw) for an additional 8-10 days and intravenous gammaglobulin daily at dosages of 0.4 g kg<sup>-1</sup> bw for 5 days. This protocol has been applied in 23 haemophilia patients with inhibitors, 16 haemophilia A patients and seven haemophilia B patients. Altogether 36 attempts have been made to induce tolerance. Ten of the 16 haemophilia A (62.5%) and 6/7 patients with haemophilia B (86%) became tolerant after the treatment. The chances of success or failure are roughly equal, if the series is considered in a historical perspective. The data showed that the chances of success in tolerance induction with the Malmo protocol were best in those patients with low inhibitor titres, with relatively low historical inhibitory peak and with a long interval since the previous replacement therapy. This was especially true where no inflammatory state was present at the start or during tolerance induction. The advantage with this method compared to the high-dose regimen is that in the successful cases tolerance can be achieved within 3-4 weeks.

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Gringeri A, Mannucci PM; Italian Association of Haemophilia Centres. Italian guidelines for the diagnosis and treatment of patients with haemophilia and inhibitors. *Haemophilia.* 2005 Nov; 11(6):611-9.

The Italian Association of Haemophilia Centres reviewed and finally approved in November 2004 the new Italian Guidelines for the diagnosis and treatment of patients with clotting factor inhibitors. The recommendations have been based on the identification of levels of clinical evidence derived from the systematic review carried out in 2003 by the School of Health and Related Research, the University of Sheffield, UK, and further integrated by clinical studies published from 2003 to 2004. The Italian guidelines consist of six major domains concerning inhibitor definition,

epidemiology, risk factors, diagnosis, inhibitor eradication, management of bleeding episodes, in patients with congenital and acquired coagulation disorders, with 121 statements, 59 synthesis and 54 recommendations. We report here recommendations and open issues concerning the diagnosis and monitoring of inhibitors, inhibitor eradication and the management of bleeding in patients with haemophilia A and B.

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Gringeri A, Tagliaferri A, Tagariello G, Morfini M, Santagostino E, Mannucci P; The ReFacto-AICE Study Group. Efficacy and inhibitor development in previously treated patients with haemophilia A switched to a B domain-deleted recombinant factor VIII. *Br J Haematol.* 2004 Aug; 126(3):398-404.

There have been recent reports of unexpected poor efficacy of a B-domain-deleted recombinant factor VIII (BDD-rFVIII) in haemophiliacs, and inhibitor development in previously treated patients (PTPs) switched to BDD-rFVIII. The results of a 6-month prospective study of 25 PTPs and of a retrospective survey of 94 PTPs, all switched to BDD-rFVIII, were used to evaluate efficacy and inhibitor development. The prospective study showed that 89% of 362 bleeds were controlled by one to two infusions, reproducing the efficacy profiles of other recombinant products (rFVIII). One patient, previously treated with plasma-derived FVIII only, developed a high titre inhibitor (30 BU) after 5 days of exposure. The retrospective survey, carried out in the total Italian PTP population switched to BDD-rFVIII, involved 19 PTPs at higher inhibitor risk due to previous exposure of < or = 50 days and 75 PTPs at lower inhibitor risk due to previous exposure of > 50 days. One patient developed an inhibitor: he was a high-risk, severe PTP previously exposed to another rFVIII for 3 days only. Among the entire low-risk population of severe Italian PTPs switched to BDD-rFVIII (25 in the prospective study, 49 in the retrospective cohort) only one developed an inhibitor (1.3%). These data indirectly support the views that BDD-rFVIII is equivalent to other rFVIII in term of efficacy and inhibitor development. Copyright 2004 Blackwell Publishing Ltd

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Hay CR, Brown S, Collins PW, Keeling DM, Liesner R. The diagnosis and management of factor VIII and IX inhibitors: a guideline from the United Kingdom Haemophilia Centre Doctors Organisation. *Br J Haematol.* 2006 Jun;133(6):591-605.

The revised UKHCDO factor (F) VIII/IX Inhibitor Guidelines (2000) are presented. A schema is proposed for inhibitor surveillance, which varies according to the severity of the haemophilia and the treatment type and regimen used. The methodological and pharmacokinetic approach to inhibitor surveillance in congenital haemophilia has been updated. Factor VIII/IX genotyping of patients is recommended to identify those at increased risk. All patients who develop an inhibitor should be considered for immune tolerance induction (ITI). The decision to attempt ITI for FIX inhibitors must be carefully weighed against the relatively high risk of reactions and the nephrotic syndrome and the relatively low response rate observed in this group. The start of ITI should be deferred until the inhibitor has declined below 10 Bethesda Units/ml, where possible. ITI should continue, even in resistant patients, where it is well tolerated and so long as there is a convincing downward trend in the inhibitor titre. The choice of treatment for bleeding in inhibitor patients is dictated by the severity of the bleed, the current inhibitor titre, the previous anamnestic response to FVIII/IX, the previous clinical response and the side-effect profile of the agents available. We have reviewed novel dose-regimens and modes of administration of FEIBA (factor VIII inhibitor bypassing activity) and recombinant activated FVII (rVIIa) and the extent to which these agents may be used for prophylaxis and surgery. Bleeding in acquired haemophilia is usually treated with FEIBA or rVIIa. Immunosuppressive therapy should be initiated at the time of diagnosis with Prednisolone 1 mg/kg/d +/- cyclophosphamide. In the absence of a response to these agents within 6 weeks, second-line therapy with Rituximab, Cyclosporin A, or other multiple-modality regimens may be considered.

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Hay CR; The 2000 United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO). The 2000 United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) inhibitor guidelines. *Pathophysiol Haemost Thromb.* 2002;32 Suppl 1:19-21.

The UKHCDO inhibitor guidelines address the diagnosis and management of patients with haemophilia A, haemophilia B and acquired haemophilia. Recommendations are based on best current practice as reflected in the published evidence base. Many current treatment strategies are based on uncontrolled observations highlighting the need for well designed controlled studies.

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Hay C, Recht M, Carcao M, Reipert B. Current and future approaches to inhibitor management and aversion. *Semin Thromb Hemost.* 2006 Jun;32 Suppl 2:15-21.

Immune tolerance induction (ITI) is the most common approach used to eliminate inhibitors that develop in hemophilia A patients following exposure to factor (F) VIII therapy. ITI generally requires ongoing long-term exposure to factor replacement therapy using FVIII or FIX. Although plasma-derived products have been the mainstay of ITI therapy in the past, recent data indicate that high-purity (i.e., recombinant) rFVIII products are probably equally effective. For patients who have failed to respond to ITI treatment, or for those at high risk to do so, immunosuppressive therapy may be helpful. Rituximab has demonstrated a possible clinical benefit in hemophilic and nonhemophilic patients developing FVIII inhibitors, but benefit in those with congenital hemophilia and inhibitors has not been established and more extensive clinical studies are needed. More recently, research on reducing the incidence of inhibitor development has included mutagenizing key epitopes of the FVIII antigenic molecule to alter its immunogenicity without affecting biological activity, as well as induction of tolerance by gene therapy with immunodominant A2 and C2 domains of FVIII presented by B cells as immunoglobulin fusion proteins.

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Haya S, Lopez MF, Aznar JA, Batlle J; Spanish Immune Tolerance Group. Immune tolerance in haemophilia patients with inhibitors: the Spanish Registry. *Haemophilia*. 2001 Mar;7(2):154-9.

We present a retrospective study of immune tolerance treatment (ITT) carried out in 42 Spanish haemophilic patients. Most of the patients were high responders (39/42), with a median maximum titre of 67 Bethesda units (BU) (range 6-2984). The median inhibitor titre at the start the ITT was 11 BU (range 1-256 BU) and the median age of the patients was 7 years (range 0-57). The mean factor dosage was 140 IU kg bodyweight<sup>-1</sup> day<sup>-1</sup> (range 25-500). In most of the ITTs, plasma-derived factor concentrate of intermediate and high purity was used. The inhibitor was eradicated in 26/38 (68%) of the patients who completed the treatment and two patients changed their status from high to low responders. Multivariate logistic regression analysis showed that three significant variables were associated with the highest probability of success: (i) the use of low factor doses for ITT (< or = 100 IU kg<sup>-1</sup> day<sup>-1</sup>); P = 0.0106; 95% CI 0.000289-0.342); (ii) a titre of < 10 BU at start of ITT (P = 0.0286; 95% CI 0.00253-0.7189) and (iii) a lower maximum titre (P = 0.0214; 95% CI 0.98-0.9994).

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Kreuz W, Becker S, Lenz E, Martinez-Saguer I, Escuriola-Ettingshausen C, Funk M, Ehrenforth S, Auerswald G, Kornhuber B. Factor VIII inhibitors in patients with hemophilia A: epidemiology of inhibitor development and induction of immune tolerance for factor VIII. *Semin Thromb Hemost*. 1995;21(4):382-9.

Factor (F) VIII inhibitor development remains one of the most serious complications in the treatment of hemophilia A. Former and recent studies on inhibitor development revealed that patients with severe hemophilia A and positive inhibitor family history are at highest risk of developing an inhibitor. Comparison of recent inhibitor incidence studies on previously untreated patients indicate that the risk of inhibitor development under treatment with recombinant FVIII concentrates is comparable to the inhibitor incidence under FVIII substitution by plasma-derived concentrates. However, longer observation periods are necessary to draw final conclusions. Since inhibitor development may result in inefficacy of FVIII concentrates in the treatment of severe bleedings, the induction of immune tolerance (IT) is still of main concern. Various regimens to induce IT by application of FVIII concentrates have been conducted up to now. Success rate appears to be influenced by low to high responder status, number of exposure days before onset of treatment, and dosage of therapeutic regimen. Especially, discontinuation of IT therapy seems to be associated with failure of therapy. Taking into account available data on IT therapy, we recommend early onset of a high dosage regimen in high responder patients as soon as possible after inhibitor detection, as this is associated with higher success rate and shorter elimination time.

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Kreuz W, Ettingshausen CE, Auerswald G, Saguer IM, Becker S, Funk M, Heller C, Klarmann D, Klingebiel T; GTH PUP Study Group. Epidemiology of inhibitors and current treatment strategies. *Haematologica*. 2003 Jun;88(6):EREPO4.

The development of inhibitors is currently one of the most serious complications in the treatment of hemophilic children. Prospective studies of previously untreated patients (PUP) showed that up to 52% of patients with severe hemophilia A developed inhibitors during the first 50 exposure days (ED) (>100 for outliers). Inhibitor development is influenced by the type of hemophilia, the severity and the type of mutation. No significant differences in inhibitor incidence were found in prospective studies conducted with plasma-derived or recombinant products. However, no comparative study has been finished yet. A still ongoing prospective, multi-center PUP-study initiated by the German, Austrian and the Swiss Society of Thrombosis and Hemostasis Research (GTH) foresees the direct comparison of different types of concentrates with regard to inhibitor development. Preliminary results (update February 2002) show a slightly higher inhibitor development (p=0.08) in severely affected hemophilia A patients treated with recombinant factor (F) VIII concentrates. However, the groups are very small and statistically reliable statements cannot be made at the moment. In case of inhibitor development rapid inhibitor elimination and immune tolerance induction (ITI) is the preferred way to reduce the high risk of bleeding episodes. In this respect, various therapeutic regimens, such as the administration of high doses of FVIII twice daily (Bonn protocol), or lower doses three times weekly (van Creveld protocol), have been attempted. Elimination of inhibitors from plasma by immune adsorption followed by immune suppression (Malmo protocol) has also been used. The influence of the type of concentrate used for ITI has never been investigated comparatively. A longitudinal study of ITI at our center showed a significantly decreased success rate since the introduction of high purity plasma derived and recombinant FVIII products using the Bonn protocol. In inhibitor patients who showed an unsatisfactory response to treatment with FVIII concentrates with very little or no VWF the change to concentrates containing high amounts of von Willebrand factor (VWF) increased success rates up to 90%. These observations raise the question of whether VWF plays an important role in the induction of immune tolerance. 2003 Ferrata Storti Foundation

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Lenk H; ITT Study Group. The German Registry of immune tolerance treatment in hemophilia--1999 update. *Haematologica*. 2000 Oct; 85(10 Suppl):45-7

As of 1999, the German registry of immune tolerance treatment in hemophilia has received reports on 146 patients who have undergone this therapy from 25 hemophilia centers. In 16 of the reported patients treatment is ongoing. Therapy has been completed in 126 patients of all groups with hemophilia A; most of them are children. In 78.6% of hemophilia A patients full success was achieved, 8.7% finished with partial success, and in 12.7% ITT failed. Statistical analysis demonstrates that interruptions of therapy have a negative influence on success. The inhibitor titer has the highest predictive value for success or failure of therapy. A high maximum titer as well as a high titer at start of treatment were related to a low success rate. Other variables such as exposure days and time interval between inhibitor detection and

start of ITT were not statistically significant. Four patients with hemophilia B have also completed therapy, only one of them with success.

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Ljung R, Petrini P, Lindgren AC, Tengborn L, Nilsson IM. Factor VIII and factor IX inhibitors in haemophiliacs. *Lancet*. 1992 Jun 20;339(8808):1550.  
Abstract non disponible

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Lusher J, Abildgaard C, Arkin S, Mannucci PM, Zimmermann R, Schwartz L, Hurst D. Human recombinant DNA-derived antihemophilic factor in the treatment of previously untreated patients with hemophilia A: final report on a hallmark clinical investigation. *J Thromb Haemost*. 2004 Apr;2(4):574-83.

BACKGROUND: Development of recombinant factor VIII (rFVIII) replacement therapy represents a milestone in the treatment of hemophilia A. OBJECTIVE: The objective of this long-term, multicenter study was to assess the safety, efficacy and rate of inhibitor formation of rFVIII (Kogenate) in the treatment of hemophilia A in a group of previously untreated patients (PUPs). PATIENTS AND METHODS: Between January 1989 and October 1997, 102 evaluable patients (mean age 3.9 years) were treated with rFVIII as sole therapy for prophylaxis against bleeding or for hemorrhage. Patients with mild hemophilia were treated for > or =2 years, while those with moderate or severe hemophilia were treated for > or =5 years or 100 exposure days. RESULTS: All patients responded well to therapy, so that 82% of bleeding episodes required a single infusion for treatment. Only four mild drug-related adverse events were recorded during the study for an overall rate of 0.03% (4/13 464 infusions). No viral seroconversions were observed. The inhibitor incidence in PUPs with severe hemophilia was 29% (19/65). Overall, inhibitory antibodies developed in 21 patients (20.6%). Inhibitor titers were low (<10 Bethesda Units) in nine of the 21 patients despite continued episodic treatment with rFVIII and transient in eight patients receiving episodic treatment (seven low titer, one high titer). Eight high-titer inhibitor patients were treated with immune-tolerance induction therapy; five had successful outcomes. CONCLUSIONS: The observed incidence of inhibitor formation is similar to studies of PUPs receiving plasma-derived FVIII. These results demonstrate the safety and efficacy of rFVIII in long-term treatment of hemophilia A.

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Mariani G, Ghirardini A, Bellocco R. Immune tolerance in hemophilia-principal results from the International Registry. Report of the factor VIII and IX Subcommittee. *Thromb Haemost*. 1994 Jul;72(1):155-8.

40 Hemophilia Centers from the USA, Canada, Europe and Japan referred to the International Registry 204 patients with haemophilia A, treated by Immune Tolerance (IT) Protocols over the past two decades because of the presence of an inhibitor to FVIII. 82% of the patients were high responders, while IT was started with low levels of inhibitor (< 10 BU) in most (57.3%) of the cases. 69 patients (33.8%) were given the highest FVIII dosage (> or = 200 IU/kg/day), 71 (34.8%) intermediate dosages (50- < 200) and 64 (31.4%) the lowest dosages (< 50). Of 158 patients persevering with treatment long enough to judge the outcome thereof, 107 (67.7%) achieved tolerance, 12 (7.6%) had a partial response, while 39 (24.7%) did not respond. Multivariate logistic regression analysis showed that two variables were independently associated with the highest probability of success: the use of high dose protocols (> or = 100 IU/kg/day) (p < .0001) and the presence of low levels of inhibitor (< 10 BU) at enrollment (p = .004). The Kaplan-Meier inhibitor-free survival curve showed that tolerance is longlasting: only 1 out of 107 patients relapsed and the longest documented tolerant patient has been inhibitor-free for 16 years. 129 hemophiliacs were HIV Ab-negative at enrollment; of the 118 HIV-screened after the treatment, 18 (13.9%) were found to be HIV Ab-positive. IT can indeed modify the natural history of inhibitors to FVIII in hemophilia.

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Mauser-Bunschoten EP, Nieuwenhuis HK, Roosendaal G, van den Berg HM. Low-dose immune tolerance induction in hemophilia A patients with inhibitors. *Blood*. 1995 Aug 1;86(3):983-8.

In patients with hemophilia A and inhibitory alloantibodies against factor VIII, various dosage schedules are used to obtain immune tolerance. In this study, we have evaluated the results of 13 years of low-dose immune tolerance induction and factors that are predictive of a positive result. The effect of immune tolerance induction in relation to age at inhibitor development, number of exposure days, age at start of therapy, maximum inhibitor titer, factor VIII products involved, and virologic status were determined. We evaluated 24 patients with severe hemophilia A and inhibitors who were treated with regular infusions with low-dose (25 U/kg every other day) factor VIII to obtain immune tolerance. In 21 of 24 patients (87%), immune tolerance induction was successful. The response time was determined by two factors: the highest inhibitor level and the age at inhibitor development. In patients with maximum inhibitor levels of less than 40 Bethesda units (BU)/mL, immune tolerance was obtained sooner than in patients with inhibitor levels exceeding 40 BU/mL (P = .005). Patients in whom an inhibitor developed before the age of 2.5 years also tended to have a quick immune response (P = .014). Immune tolerance with low-dose factor VIII is often successful in hemophilia A patients with inhibitors. Young children and patients with maximum inhibitors of less than 40 BU/mL show a relatively rapid response.

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Nilsson IM, Berntorp E, Freiburghaus C. Treatment of patients with factor VIII and IX inhibitors. *Thromb Haemost*. 1993 Jul 1;70(1):56-9.  
Abstract non disponible

Nilsson IM, Berntorp E, Zettervall O. Induction of immune tolerance in patients with hemophilia and antibodies to factor VIII by combined treatment with intravenous IgG, cyclophosphamide, and factor VIII. *N Engl J Med.* 1988 Apr 14;318(15):947-50.

The development of antibodies to factor VIII is a serious complication of the treatment of patients with hemophilia A. We successfully induced immune tolerance in patients with such antibodies with a new treatment protocol, which combined factor VIII, cyclophosphamide, and high-dose intravenous IgG, followed by regular prophylactic treatment with factor VIII. This protocol has now been used in 11 patients with hemophilia A, of whom 9 had a strong antibody response. When the initial concentration of antibodies exceeded 3 Malmo inhibitor units (corresponding to about 10 Bethesda units) per milliliter, treatment was preceded by adsorption of antibody to protein A. After two to three weeks of the combined treatment, factor VIII coagulant antibodies had disappeared in 9 of the 11 patients; in 8 of these 9 patients the half-life of infused factor VIII had normalized. The tolerant state appears to be stable after a median of 30 months. Two patients did not respond to the treatment. Because earlier treatment with factor VIII and cyclophosphamide or with factor VIII and IgG had been ineffective in these patients, our experience suggests that all three components of the protocol are required for the successful induction of tolerance to factor VIII.

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Oldenburg J, Schwaab R, Brackmann HH. Induction of immune tolerance in haemophilia A inhibitor patients by the 'Bonn Protocol': predictive parameter for therapy duration and outcome. *Vox Sang.* 1999;77 Suppl 1:49-54.

The treatment of inhibitors is one of the most challenging fields in haemophilia care. The present study reports the results of 60 haemophilia A inhibitor patients treated according to the 'Bonn Protocol' and evaluates predictors for the duration and outcome of therapy. Successful immune tolerance could be achieved in 52 patients (86.7%) while the therapy failed in eight patients (13.3%). The immune tolerance achieved was longlasting in all 52 patients, with no inhibitor relapse in up to 20-years follow-up. The course of ITT was influenced by several factors. Interruptions of treatment during the ITT course led to a substantial prolongation of ITT duration (median 39.9 months vs 14.1 months in continuously treated patients). Infections of intravenous central lines appeared to be frequently coincided with ITT prolongation and sometimes even ITT failure. Further negative predictors towards the ITT duration were high inhibitor titres at enrollment or during ITT. There was also a tendency towards longer ITT duration in patients exhibiting the prevalent intron 22 inversion. As a consequence of our data treatment interruptions and infections of intravenous central lines should be avoided during the course of ITT. Furthermore our data suggest, that ITT should be started at low inhibitor titres preferably with a high factor VIII dosage protocol.

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Orsini F, Rotschild C, Beurrier P, Faradji A, Goudemand J, Polack B. Immune tolerance induction with highly purified plasma-derived factor VIII containing von Willebrand factor in hemophilia A patients with high-responding inhibitors. *Haematologica.* 2005 Sep;90(9):1288-90.

We retrospectively evaluated the efficacy of immune tolerance induction (ITI) in a homogenous cohort of eight patients with constitutive severe hemophilia A with high-responding factor VIII (FVIII) inhibitors using Facteur VIII-LFB/Factane, a highly purified FVIII concentrate containing von Willebrand factor (VWF).

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Paisley S, Wight J, Currie E, Knight C. The management of inhibitors in haemophilia A: introduction and systematic review of current practice. *Haemophilia.* 2003 Jul;9(4):405-17.

Haemophilia is the commonest bleeding disorder in the UK, affecting approximately 5400 people, almost all of them male. In haemophiliacs, reduced levels, or absence, of factor VIII (FVIII) cause bleeding episodes, typically into joint spaces or muscles. Haemophilia is generally treated with exogenous FVIII. However, in some haemophiliacs, therapeutically administered FVIII comes to be recognized as a foreign protein, stimulating the production of antibodies (inhibitors), which react with FVIII to render it ineffective. Alternative treatment strategies then have to be used to manage bleeding episodes. In addition, strategies have been developed to attempt to abolish inhibitor production through the induction of immune tolerance. A systematic review was undertaken of current international practice for the clinical management of haemophilia A patients with inhibitors to FVIII, concentrating on literature published from 1995 onwards. Although it can be difficult to determine what constitutes current practice, current guidelines indicate that immune tolerance induction is seen as desirable, with the choice of regimen dependent on patient characteristics, familiarity with regimens and cost. Various approaches, based on similar factors, are used to control bleeding episodes.

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Rothschild C, Laurian Y, Satre EP, Borel Derlon A, Chambost H, Moreau P, Goudemand J, Parquet A, Peynet J, Vicariot M, Beurrier P, Claeysens S, Durin A, Faradji A, Fressinaud E, Gaillard S, Guerin V, Guerois C, Pernod G, Pouzol P, Schved JF, Gazengel C. French previously untreated patients with severe hemophilia A after exposure to recombinant factor VIII : incidence of inhibitor and evaluation of immune tolerance. *Thromb Haemost.* 1998 Nov;80(5):779-83.

Fifty French previously untreated patients with severe hemophilia A (factor VIII < 1%), treated with only one brand of recombinant factor VIII (rFVIII), were evaluated for inhibitor development, assessment of risk factors and outcome of immune tolerance regimen. The median period on study was 32 months (range 9-74) since the first injection of rFVIII. Fourteen patients (28%) developed an inhibitor, four of whom (8%) with a high titer (> or = 10 BU). All inhibitor patients but one continued to receive rFVIII either for on-demand treatment or for immune tolerance regimen (ITR). Among these patients, inhibitor was transient in 2 (4%), became undetectable in 6 and was still present in 6. The prevalence of inhibitor was 12%. Presence of intron 22 inversion was found to be a risk factor for inhibitor development. Immune

tolerance was difficult to achieve in our series despite a follow-up period of 16 to 30 months: immune tolerance was complete in only one out of the 3 patients undergoing low dose ITR and in one out of the 5 patients with high dose ITR.

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Roussel-Robert V, Torchet MF, Legrand F, Rothschild C, Stieltjes N. Factor VIII inhibitors development following introduction of B-domain-deleted recombinant factor VIII in four haemophilia A previously treated patients. *J Thromb Haemost.* 2003 Nov;1(11):2450-1.  
Abstract non disponible

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Scheibel E, Ingerslev J, Dalsgaard-Nielsen J, Stenbjerg S, Knudsen JB. Continuous high-dose factor VIII for the induction of immune tolerance in haemophilia A patients with high responder state: a description of eleven patients treated. *Thromb Haemost.* 1987 Dec 18;58(4):1049-52.

Eleven severely affected haemophilia A patients (aged 6-42 y) with F VIII:C inhibitor (high responders) were treated with high-dose F VIII in order to eliminate the inhibitors. The patients comprise Danish high responder patients treated during the period 1977-1985. In all patients the inhibitors decreased significantly. In six, the inhibitor apparently disappeared (detection limit 0.4 Bethesda Units per ml) (BU/ml), in four patients a low level inhibitor of 0.4-1.4 BU/ml persisted. One patient is still on high-dose schedule. The duration of high-dose treatments ranged from less than one month up to 18 months. In all patients the tendency to spontaneous bleedings vanished when a measurable VIII:C level appeared in the post-infusion sample. The inhibitor suppression has allowed for extensive physical training and rehabilitation orthopaedic surgery. The patients are now able to conduct a normal haemophilic life on self-administered prophylactic doses of F VIII.

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Wight J, Paisley S, Knight C. Immune tolerance induction in patients with haemophilia A with inhibitors: a systematic review. *Haemophilia.* 2003 Jul;9(4):436-63.

In some patients with haemophilia A, therapeutically administered factor VIII (FVIII) comes to stimulate the production of antibodies (inhibitors) which react with FVIII to render it ineffective. As a result, FVIII cannot be used prophylactically and patients become liable to recurrent bleeds. There are two elements to the management of patients with inhibitors: the treatment of bleeding episodes, and attempts to abolish inhibitor production through the induction of immune tolerance. This paper reports a systematic review of the best available evidence of clinical effectiveness in relation to immune tolerance induction (ITI) in patients with haemophilia A with inhibitors. Owing to the lack of randomized controlled trials on this topic, broad inclusion criteria with regard to study design were applied in order to assess the best available evidence for each intervention. As a result of the clinical and methodological heterogeneity of the evidence, it was not appropriate to pool data across studies; instead, data were synthesized using tabulation and qualitative narrative assessment. The International Registry provides the most reliable estimate of the proportion of successful cases of ITI [48.7%, 95% confidence interval (CI) 42.6-52.7%]. The duration of effect is unclear, but relapses appear to be infrequent. The International Registry shows a rate of relapse of 15% at 15 years. The comparative effectiveness of different protocols is uncertain, as no trials have been undertaken which compare them directly. However, the evidence suggests that the Bonn protocol may be more effective than the Malmo or low-dose protocols. There is no good evidence that immunosuppressive drug regimens are effective.

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Yee TT, Pasi KJ, Lilley PA, Lee CA. Factor VIII inhibitors in haemophiliacs: a single-centre experience over 34 years, 1964-97. *Br J Haematol.* 1999 Mar;104(4):909-14.

A retrospective study of the natural history of factor VIII inhibitors in haemophilia A patients experienced in a single comprehensive haemophilia centre over three decades is reported. 431 haemophilia A patients of all severities have been followed-up for a total of 5626 patient-years. The frequency of inhibitors was 10% in the severe haemophilia A patients and 37% occurred in children <10 years. The majority of the patients received several products before developing the inhibitors. 59% of patients had <50 exposure days and 48% were high responders (>5 BU). An 8-year (1987-95) inhibitor-free period was seen during which all previously untreated patients were treated with an intermediate-purity factor VIII concentrate. A moderate haemophiliac with a missense mutation that has not been described in association with inhibitor is reported. Six HIV-positive patients preserved their antibody response to factor VIII even at the advanced stage of their disease.

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Yee TT, Lee CA. Is a change of factor VIII product a risk factor for the development of a factor VIII inhibitor? *Thromb Haemost.* 1999 May; 81(5):852.  
Abstract non disponible

**Situations hors-AMM  
pour lesquelles  
l'insuffisance des données  
ne permet pas d'évaluer  
le rapport bénéfice/risque**

**Facteurs VIII**

**Maladie de Willebrand sévère avec allo-anticorps anti-facteur Willebrand, dont le titre élevé ne permet pas l'utilisation de facteur Willebrand**  
**Maladie de Willebrand acquise sévère**

- **Maladie de Willebrand sévère avec allo-anticorps anti-facteur Willebrand, dont le titre élevé ne permet pas l'utilisation de facteur Willebrand**

Le développement d'un allo anticorps anti VWF chez les patients atteints de Maladie de Willebrand de type 3 (la moins fréquente des formes de maladie de Willebrand constitutionnelle) est un événement particulièrement rare. Moins de 5 patients par an sont concernés par cette situation en France.

L'injection de concentrés en facteur Willebrand (notamment sous forme de dérivés plasmatiques) dans cette situation peut entraîner des réactions d'intolérance de type anaphylactique (Mannucci, 1987). Il n'existe aucune alternative thérapeutique documentée dans cette situation. Toutefois il peut être utile de traiter ces malades par des concentrés en FVIII ne contenant pas de Facteur Willebrand (échappant ainsi à l'effet inhibiteur anti facteur Willebrand) pour élever la concentration en FVIII (en situation chirurgicale notamment). Il existe ainsi quelques cas rapportés dans la littérature de malades de ce type traités par FVIII recombinants.

Compte tenu du très faible nombre de patients concernés, nous ne disposons d'aucune étude clinique. Il est considéré que cette situation ne relève pas d'un PTT.

L'administration de facteurs VIII dans cette situation doit être discutée au cas par cas et conduite par un centre de traitement spécialisé dans le traitement des maladies hémorragiques sous couvert de l'avis du centre national de référence de la Maladie de Willebrand (cf annexe). Toute prescription, par exception, devra être justifiée dans le dossier médical du patient.

Les concentrés de FVIII totalement dépourvus de facteur Willebrand sont Refacto<sup>®</sup>, Kogenate Bayer<sup>®</sup> et Helixate Nexgen<sup>®</sup>.

#### Facteur VIII dans la maladie de Willebrand sévère avec allo-Ac anti-facteur Willebrand

Auteurs	Type d'étude	Posologie	Critères d'évaluation	Résultats
Rothschild (1996)	<b>n=2 (3 et 8 ans)</b> <i>abstract</i>	Dose FVIII : 9 à 19 UI/kg/h	Evolution clinique. Taux FVIII Titre AC anti-vWFRCo	<b>Succès hémostase</b>  - taux FVIII >60% lors chirurgie - efficacité des FVIII purs à distance des hémarthroses sans relance des AC anti-vWFRCo.
Boyer-Neumann C (2003)	<b>n=1 (29 ans)</b> <i>lettre</i>	Dose FVIII : 100 IU/kg puis 35 UI/kg/h	Evolution clinique Taux FVIII	<b>Evolution en 2 temps :</b> 1 : Succès hémostase taux FVIII : 60% lors d'une césarienne 2 : Reprise saignements et passage au Novoseven
Franchini et al. (2008)	<b>N=1 (35 ans)</b> <i>Lettre</i>	Dose FVIII 100 UI/kg puis 30 UI/kg/h	Evolution clinique	<b>Succès hémostase lors de 8 épisodes hémorragiques survenus en 11 ans (1994-2005)</b>

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- Franchini M, Gandini G, Giuffrida A, De Gironcoli M, Federici AB. Treatment for patients with type 3 von Willebrand disease and alloantibodies: a case report. Haemophilia, 2008; 14:645-646.

- **Maladie de Willebrand acquise sévère**

Dans le cas des maladies de Willebrand acquise liées à la présence d'un auto anticorps anti facteur Willebrand ou à un autre mécanisme d'élimination du Facteur Willebrand, il peut aussi être utile de traiter ces malades par des concentrés en FVIII contenant pas ou peu de Facteur Willebrand (échappant ainsi à l'effet inhibiteur anti facteur Willebrand) pour élever la concentration en FVIII (en situation chirurgicale notamment). La présence de quantités très faibles de Facteur Willebrand ne risque pas d'induire un effet de relance anamnestic de l'anticorps chez ces malades (à la distinction de la situation précédente). La totalité des concentrés de FVIII recombinants peuvent ainsi être utilisés dans cette situation (Kogenate®, Helixate®, Refacto®, Recombinate® et Advate®).

Compte tenu du très faible nombre de patients concernés (estimé à moins de 5 par an), nous ne disposons d'aucune étude clinique. Il est considéré que cette situation ne relève pas d'un PTT.

L'administration de facteurs VIII dans cette situation doit être discutée au cas par cas et conduite par un centre de traitement spécialisé dans le traitement des maladies hémorragiques sous couvert de l'avis du centre national de référence de la Maladie de Willebrand (cf annexe). Toute prescription, par exception, devra être justifiée dans le dossier médical du patient.

## ANNEXE

### CENTRE DE REFERENCE DE LA MALADIE DE WILLEBRAND

<b>Nom de la maladie ou du groupe de maladies rares prise(s) en charge</b>	<b>Maladie de Willebrand (formes héréditaires graves)</b>
<b>adresse du centre 1</b>	Pr. Agnès VEYRADIER Service d'Hématologie Biologique Hôpital Antoine Bécclère 157 rue de la Porte-de-Trivaux 92140 Clamart Cedex Tel : 01 45 37 43 05 (42 95) Email : <a href="mailto:agnes.veyradier@abc.ap-hop-paris.fr">agnes.veyradier@abc.ap-hop-paris.fr</a> Fax : 01 46 32 40 55
<b>adresse du centre 2</b>	Pr. Jenny GOUDEMANT Unité d'Hémostase Clinique et Biologique Institut d'hématologie –Transfusion Hôpital Cardiologique Bd du Pr Leclercq 59037 LILLE Cedex Tel : 03 20 44 48 45 Email : <a href="mailto:j-goudemand@chru-lille.fr">j-goudemand@chru-lille.fr</a> Fax : 03 20 44 68 50

<b>Nom, prénom du médecin* coordonnateur et spécialité médicale exercée:</b>	<b>Professeur Agnès VEYRADIER</b> Hématologie biologique
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<b>Nom des sites composant le centre</b>	<b>Nom, adresse de la structure de rattachement du site</b>	<b>Nom, prénom des médecins* dirigeant le site et spécialité médicale exercée</b>
- Service d'Hématologie Biologique	<b>CHU de Clamart</b> Hôpital Antoine Bécclère 157 rue de la Porte-de-Trivaux 92140 Clamart	<b>Pr VEYRADIER Agnès</b> Hématologie biologique
- Institut d'Hématologie	<b>CHRU de Lille</b> Hôpital Cardiologique Boulevard du Pr Leclercq 59037 Lille	<b>Pr GOUDEMANT Jenny</b> Hématologie biologique
- UF du Laboratoire d'Hématologie	<b>CHU de Nantes</b> Centre Régional de Traitement de l'Hémophilie et des Maladies Hémorragiques 30 bd Jean Monnet 44093 Nantes Tel : 02 40 08 74 68 Fax : 02 40 08 42 59	<b>Dr TROSSAERT Marc</b> Hématologie biologique Mel : marc.trossaert@chu-nantes.fr
- UF d'Hémostase du service d'Hématologie biologique - UF Centre de Traitement des Hémophiles du service d'Hématologie biologique	<b>CHU de Bicêtre</b> Hôpital de Bicêtre 78 rue du Gal Leclerc 94276 Le Kremlin-Bicêtre Tel : 01 45 21 21 21 Fax : 01 45 21 20 06	<b>Dr. DREYFUS Marie</b> Hématologie biologique Mel : marie.dreyfus@bct.ap-hop-paris.fr <b>Dr LAMBERT Thierry</b> Hématologie biologique Mel : thiery.lambert@ bct.ap-hop-paris.fr
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