Disorders of Hemostasis

Immune tolerance induction with highly purified plasma-derived factor VIII containing von Willebrand factor in hemophilia A patients with high-responding inhibitors

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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The development of factor VIII (FVIII) inhibitors is still one of the most serious complications for hemophilia patients, especially those who are high-responding.[1] One of the recognized therapies for overpowering high-responding inhibitors involves permanent inhibitor suppression, which may be achieved by immune tolerance induction (ITI). FVIII concentrates containing von Willebrand factor (VWF), the physiological FVIII stabilizing protein, have been proposed to treat hemophilia A patients with FVIII inhibitors.[2] The rationale for their use is based on experimental observations showing that VWF protects against FVIII inactivation by FVIII antibodies,[3] which were confirmed in a mouse model of FVIII immunization, since the absence of VWF carried an increased risk of eliciting FVIII inhibitors.[4] Even though the influence of VWF-containing FVIII concentrates in ITI can only be ascertained through a double-blind randomized study, it is of paramount importance to continue to fuel this very important debate with new observations.

The study drug is a very highly purified plasma-derived FVIII concentrate (Facteur VIII-LFB) prepared by ion exchange chromatography and including solvent-detergent virus inactivation by the Laboratoire Français du Fractionnement et des Biotechnologies (LFB, Les Ulis, France). Its main characteristics are specific activity exceeding 150 IU of FVIII/mg of protein, and 14-20 IU of VWF/ml. As a consequence, all FVIII molecules are found as complexes bound to VWF. Detailed characteristics of the product have been previously published.[5] Since January 2001, this product is nanofiltered and is manufactured under the name of Factane® by LFB.

To be included in the study, patients had to fulfill the following criteria: constitutive severe (<1% FVIII) hemophilia A, with high-responding FVIII inhibitors (peak titer ≥5 BU),[6] and an initial intention ITI attempted using the study drug. The medical files of 11 unrelated patients were recorded. They were collected from six hemophilia units in France. A telephone enquiry was performed in the last quarter of 2002 to locate centers in which patients had

Table 1. Main data of the patients.

Patient	Molecular defect	Age at 1st FVIII infusion	Age at 1st PRBC infusion	Age at inhibitor detection	CED at inhibitor detection	Age at inhibitor treatment	Pre-product	ITI Inhibitor titer (BU) 1st	Max	Pre-ITI	ITI regimen (dose IU/kg)	Time to <1BU	Final values	ITI duration
1	inv int 22	9 mo.	1 yr mo. (gastr. ulc.)	1 yr	9	1 yr 3 mo	Kogenate®	48	52	12	230/d×11 d 100/d×6/7 d×4 mo 100/d, 3/7 d×3 mo	93 d	I<0.3 R=1.1 $T_{1/2}$=7.2	5 mo.
2	R2163H	2 d	4 yr 3 mo.	4 yr 3 mo.	81	4 yr 3 mo	Factor VIII LFB	clinical diagnosis	21	ND	50/d×28 d 50/2 d×9 mo	ND	I<0.3 R=1.3 $T_{1/2}$=7.0	7 mo.
3	inv int 22	8 yr 10 mo.	8 yr 10 mo.	9 yr	33	24 yr 6 mo	Factor VIII LFB	1	30	<0.3	50/d×36 d 50/2 d×110 d	ND	I<0.3 R=2.2 $T_{1/2}$=8.0	4.8 mo
4	inv int 22	8 mo.	8 mo.	10 mo.	28	1 yr 8 mo	Factor VIII LFB	24	24	8.5	50/d×81 d 50/2 d×156 d 50/3 d×351 d	75 d	I<0.3 R=1.7 $T_{1/2}$=6.4	1 yr.
5	inv int 22	8 mo.	–	8.5 mo.	7	9 mo	Factor VIII LFB	0.85	14.5	14.5	150 IU/kg/d×2mo 200 IU/kg/d×12mo 110 IU/kg/d×3mo 75 IU/kg/d×1mo 50 IU/kg/d×2mo	–	I=0.8 R=1 $T_{1/2}$=5	3 yr.
6	inv int 22	1 yr 1 mo	1 yr 9 mo. (ICH)	1 yr 10 mo.	21	3 yr 1 mo	Factor VIII LFB	0.85	52	0.5	100/d×5 mo 66/d×2 mo 66/2 ×4 mo	142 d	I<0.3 R=1.8 $T_{1/2}$=7	4.7 mo.
7	inv int 22	6 mo	9 mo. (ICH)	9 mo.	10	11 mo	Factor VIII LFB	5	20	3.8	150/d×8 mo 150/2 d×1.5 mo 90/2 d×4 mo 40/2 d×10 mo	216 d	I<0.3 R=1.0 $T_{1/2}$=ND	1 yr 11 mo.
8	inv int 22	4 mo	4 mo. (ICH)	5 mo.	16	1 yr 9 mo	Factor VIII LFB	8.5	500	4	115 /d×50 d 130/d×3 d 130 6/7 d×94 d 200 3/7 d×5 mo	176 d	I<0.3 R=2.0 $T_{1/2}$=17.0	10 mo.
Mean	–	1 yr 7 mo	2 yr 7 mo	2.3 yr	25.6	4.8 yr	–	12.6	89.2	6.2	–	140 d	–	12 mo.
Median	–	8 mo	1 yr 3 mo	10.5 mo	18.5	1.7 yr	–	5	27	4	–	142 d	–	8 mo.

Inv int 22: inverted intron 22; PRBC: packed red blood cells; gastr. ulc.: gastric ulcer; ICH: intracerebral hematoma; CED: cumulative exposure days to FVIII; BU: Bethesda units/mL; ND: not determined; I: inhibitor titer (BU); R: FVIII activity recovery (IU/dl per IU/kg); $T_{1/2}$: half life (hour). Patient 1 was switched to Factane® for ITI because of shortage of Kogenate®. Initial inhibitor titer was not available for patient 2. Inhibitor presence was diagnosed clinically based on treatment inefficacy. ITI was started after an acute bleeding episode treated with saturation of FVIII antibodies. Therefore, the titer at ITI onset was not determined. Patient 3's inhibitor was undetectable when ITI was initiated because of a compressive hematoma of the hand, that required FVIII associated with high doses of corticosteroids; no subsequent inhibitor re-increase was observed. Patient 7 received a first injection of Kogenate® and was treated thereafter with Facteur VIII LFB.

undergone ITI with the study drug. In each center, we checked that all the patients were recruited. Monitoring was carried out by a hematology fellow in four centers and by sending standardized case-report forms to the remaining two.

ITI success was defined as an FVIII antibody titer <0.6 BU and FVIII recovery ≥0.66 IU/dL per IU/kg and/or a half-life ≥6 hours.[7] Partial success was defined as a titer >0.6 but with <1 BU, making treatment with FVIII instead of FEIBA® or NovoSeven® possible.

Three patients were excluded: one had baseline FVIII levels of 7%, one had received recombinant FVIII at the initiation of ITI, and one had no follow-up information. Therefore, eight patients were evaluated. Seven patients were treated with Facteur VIII-LFB and patient 1 received Factane®.

The relevant data for the eight patients are reported in Table 1. The cohort was highly homogenous. All patients but one were Caucasian, seven of the eight had an inverted intron 22, and ITI was performed with the same drug.

The response to treatment was completely successful in seven (87.5%) of our eight patients and led to the complete disappearance of FVIII-inhibiting activity with a median ITI duration of 8 months; treatment was partially successful in patient 5 who relapsed after becoming inhibitor-free, albeit with a low titer allowing treatment with FVIII concentrates. Since all eight patients had resumed FVIII treatment, either on demand or as prophylaxis, we can consider that the study drug was able to obtain 100% successful ITI.

These results may be compared with those of a previously published French cohort of hemophilia A patients treated with one brand of recombinant FVIII. The cohort comprised seven patients with high-responding inhibitors. ITI was completely successful in one patient, partially successful in another, failed in one and was ongoing in four with a follow-up ranging from 16 to 30 months.[7]

The suggestion of using FVIII preparations containing VWF for ITI referred to intermediate purity FVIII.[2] Notably, we were able to show here that highly purified plasma-derived FVIII containing VWF is also effective for ITI.

The mechanisms responsible for successful ITI are still being discussed. However, it has recently been shown that high doses of FVIII could induce memory B-cell apoptosis instead of their differentiation into antibody-secreting plasma cells.[8] Since isolated FVIII is degraded approximately twice as efficiently as FVIII-VWF complexes via the low density lipoprotein receptor-related protein,[9] VWF might contribute, through prolonged high FVIII levels and a modulation of FVIII immunogenicity,[4] to the efficacy of ITI. These properties can provide a rationale for preferring a highly purified plasma-derived FVIII stabilized with VWF for second-line ITI in patients with recombinant-FVIII ITI failure or relapse, as previously suggested.[10]

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Key words: immune tolerance, hemophilia A, factor VIII inhibitor, von Willebrand factor.

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