Immune Tolerance Therapy (ITI) in Children with FVIII Inhibitors: Progress Report

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Introduction

In up to 40% of cases, Hemophilia A (HA) treatment is complicated by the development of alloantibody inhibitors against FVIII, rendering the patient resistant to replacement therapy and thereby increasing the risk of unmanageable bleeding, particularly arthropathy and disability [1]. Inhibitors represent the most problematic and expensive complication of HA therapy. Bleeding episodes and surgical interventions in FVIII-recalcitrant patients require hospitalisation and alternative bypassing agents; either activated prothrombin complex (aPCC, FEIBA®) or recombinant FVIIa (rFVIIa, NovoSeven®) [2]. In 2003, the COCIS Study Group reported that administration of rFVIIa, mostly for orthopaedic surgery, accounted for over half the annual cost of treating high-responding inhibitor patients [3].
Inhibitors can be overcome through administration of high-dose FVIII during immune tolerance induction (ITI). Successful tolerisation with octanate® allows resumption of fully effective replacement treatment with a consequent improvement in patient quality of life [4]. ITI treatment with octanate®also improves the overall musculoskeletal status in both adults and children (5).
Since 2006, 30 children with inhibitors and poor-prognosis for ITI success have been treated with octanate® for ITI at seven Russian hemophilia treatment centers in the frame of the ongoing Observational Immune Tolerance Induction (ObsITI) study.
Seventeen of 30 poor prognosis inhibitor patients have been treated with octanate® for ITI at the Izmaylovskaya Clinical Children's Hospital in Moscow. Despite the stringent ITI success criteria, 14 patients completed the 36 months ObsITI study period with a high ITI success rate of 78% by the end of March 2011.
The objective of this study was to conduct a cost-of-care analysis to assess the consumption of octanate® in ITI in comparison with NovoSeven® and to quantify the average direct medical costs for the treatment of children with FVIII inhibitors.
An intraindividual cost comparison was performed between pre-ITI on-demand management with NovoSeven® for at least one year and the time period after the start of high-dose ITI with octanate®. Break-even point (BEP)* analysis was performed after completion of ITI therapy to estimate the number of years after which ITI treatment with octanate® becomes cost effective.
The comparative cost estimation for octanate® in ITI versus bypassing agent therapy may help to understand the determinants of both the clinical and economical outcome of treatment in patients with inhibitors and to assist in the decision making and reimbursement negotiations in order to provide the optimal therapy for the patient and an effective use of financial resources.

*(BEP) is measured as the number of years at which the cost of treatment with high-dose octanate® ITI, including prophylaxis after successful ITI and on-demand treatment with NovoSeven, are equal.

Patients, Materials & Methods

Treatment

octanate® is a human, native, highly purified, plasma-derived FVIII concentrate. FVIII in octanate® is physiologically bound to and protected by VWF. The concentrate contains VWF:RCo and FVIII:C in a ratio of ~ 0.4. It also undergoes two independent virus-inactivation procedures, i.e., solvent/detergent (S/D) treatment and terminal dry heat, and is approved in a variety of countries for the treatment and prophylaxis of bleeding in patients with HA. octanate® is also approved for ITI in Germany, Russia, Brazil and Colombia in patients with FVIII inhibitors.
As a general recommendation, ITI therapy with octanate® was to be conducted according to the Bonn protocol.

- low-responders (LR, inhibitor titre < 5 BU) received 50 – 100 IU octanate®/kg daily or every other day.
- high-responders (HR, inhibitor titre ≥ 5 BU) received 100 – 150 IU octanate®/kg every 12 hours.
- in the case of acute bleeding during ITI, rFVIIa or aPCC were additionally administered until the bleed had completely resolved.
- prophylactic treatment regimen of ≤ 50 IU octanate®/kg every second day after complete success was achieved

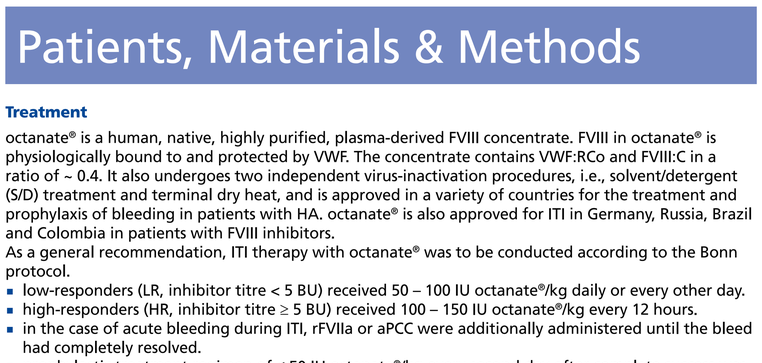
Efficacy assessments
ITI success was determined by the fulfillment of three criteria: *(I)* inhibitor titre < 0.6 Bethesda Units, *(II)* incremental *in vivo* recovery ≥ 80% of 1.5% per IU/kg body weight reference and *(III)* FVIII half-life ≥ 7 hours. According to the criteria fulfilled, patients achieved the following: *partial response (I), partial success (I, II), complete success (I, II, III) or failure.* Following complete success, patients received prophylaxis with octanate® every second day. The success criteria defined in the ObsITI study are more stringent than the consensus criteria (inhibitor titre < 0.6 BU, FVIII:C IVR ≥ 66% and FVIII:C $t_{½}$ ≥ 6 hours) agreed by the European Haemophilia Therapy Standardization Board (EHTSB) in 2006, which were also used in the recently halted I-ITI study [6,7].
17 poor prognosis inhibitor patients have been recruited into the ObsITI study and were administered octanate® for ITI at the Izmaylovskaya Clinical Children's Hospital in Moscow. Efficacy analyses are reported here for the subset of completers (those with complete success or achievement of 36 months of treatment, or the investigator's decision to finish ITI treatment [n = 14]).

Utilization of resources and related costs

In order to evaluate the utilization of resources and related cost of treatment of severe hemophilia patients with inhibitors in Russia, the following approach was used:
Potential study subjects were drawn from the pediatric center at the Izmaylovskaya Clinical Children's Hospital in Moscow who were diagnosed with severe or moderate hemophilia with FVIII inhibitors and who had been or were currently being treated with octanate® for ITI in the frame of the ongoing ObsITI study. All patients were prospective patients undergoing or having undergone ITI treatment with octanate® from the initiation of the research study in December 2005 up until the end of March 2011.
Data were collected by reviewing each patient's medical and pharmaceutical records:

- pre-ITI phase management with NovoSeven® for at least one year before the start of ITI was collected retrospectively
- high-dose ITI treatment with octanate® relates to *prospective* patients undergoing or having undergone ITI treatment with octanate® from the initiation of the research study in December 2005 up until the end of March 2011.
- direct medical costs were calculated by multiplying resources absorbed by their unit cost. This included the cost of therapy with haemostatic agents calculated on the basis of bodyweight and hospitalizations because of bleeding. The average wholesale price for haemostatic agents was obtained from www.zakupki.gov.ru

Figure 1. A schematic representation of the analysis

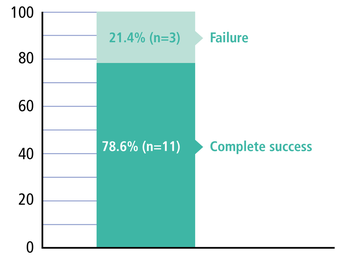


Results

ITI outcome

- Treatment with octanate® led to *complete ITI success* in 78% of patients (11/14) in 8.3 months (range 5.2-17), **Figure 2**
  - all patients were Caucasian, male, with a median age of 6.2 years old at the start of ITI (range 2.7-16.4), diagnosed with severe HA (FVIII:C ≤ 1%; n=10) or moderate HA (> 1% FVIII:C ≤ 5%; n=4) with FVIII inhibitors.
  - all patients (n=14) were HRs
  - 71% of patients (4/14) were treated with octanate® for ITI according to the Bonn Protocol
  - the median inhibitor titre at baseline was 12.4BU, range 2-9736 BU

Figure 2. 78% ITI success rate in children treated with octanate® (n=14)



- 86% of the patients (2/14) had at least one of poor-prognostic factors for ITI failure
  - 6 of 14 patients (43%) >7years of age at the ITI start
  - 6 of 14 patients (43%) with an inhibitor >2years after inhibitor diagnosis
  - 4 of 14 patients (28%) with a historical peak inhibitor titre of >200 BU
  - 7 of 14 patients (50%) >10 BU at the start of ITI

- The median annual number of bleeding episodes before and during ITI with octanate®decreased from 17 to 5 (70.5%) in patients who successfully completed ITI, **Figure 3**

- During ITI with octanate®, 90% of the bleeding episodes were resolved without need for bypassing therapy and with no change in octanate® ITI dose. Only 1 from 9 patients was treated with rFVIIa to resolve bleeding episodes during ITI with octanate®, **Figure 4**.

- To date, 7 of 8 patients who successfully completed ITI are on regular prophylactic treatment with octanate® and another patient is about to start prophylactic treatment and no relapses have been reported so far.

Figure 3. Median number of bleeding episodes per year before and during ITI with octanate® in successfully tolerized patients (data available for n= 9HRs)*.

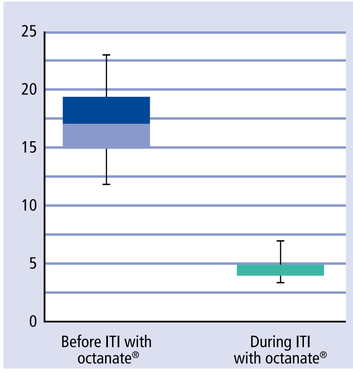
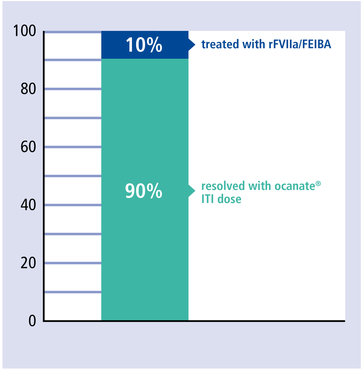


Figure 4. Bleeding episodes during ITI in successfully tolerized patients (data available for n= 9HRs).



*During ITI with octanate®, the number of bleeding episodes in 2 patients with failed ITI was reduced by 1.8-fold and 1.4-fold, respectively.

On-demand treatment of bleeding episodes with rFVIIa before ITI with Octanate®

Table 1. Data used in on-demand treatment of bleeding episodes with rFVIIa (data available for n=8 HRs),

Scenario 1	mean (range)
Body weight (kg);	36 (14-82)
Number of bleeding episodes per year	17 (12-23)
Single dose rFVIIa, (µg/kg bw)	120
Number of infusions per treatment day	2
Number of treatment days per bleeding episode	6 (5-8)
Number of hospitalisation days per year	19 (12-32)

ITI with octanate® following prophylaxis with octanate® after successful ITI

Table 2. Data used in ITI with octanate® followed prophylaxis with octanate® after successful ITI (data available for n=8 HRs)

Scenario 2	mean (range)
Initial daily ITI dose, (IU/kg bw)	230.0 (53.6-304.0)
ITI treatment duration until complete success	11.2 (6.1-17.0)
Number of bleeding episodes per year	5.3 (3-7)
Prophylactic octanate® dose, (IU/kg bw)	46.8 (41.6-50.0)
Number of octanate® infusions for prophylaxis per week	3.3 (2.5-3.5)
Number of hospitalisation days per year	0

- Figures **5A-5H** represent the individual costs during 10 years and the BEP per patient according to the on-demand treatment of bleeding episodes with NovoSeven® (blue line) and ITI with octanate® including prophylaxis with octanate® after successful ITI (green line).

Figure 5A. Patient 1, HR

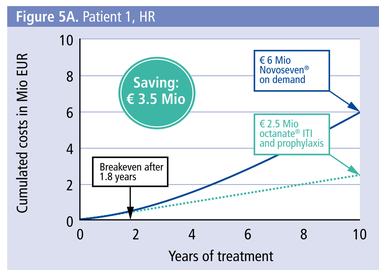


Figure 5B. Patient 2, HR

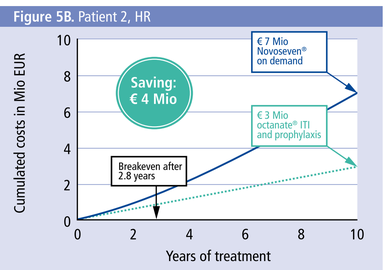


Figure 5C. Patient 3, HR

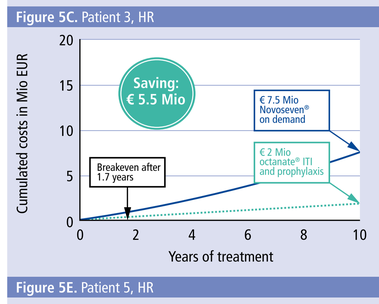


Figure 5D. Patient 4, HR

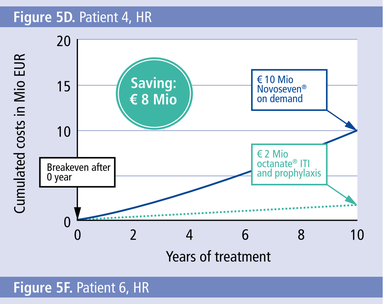


Figure 5E. Patient 5, HR

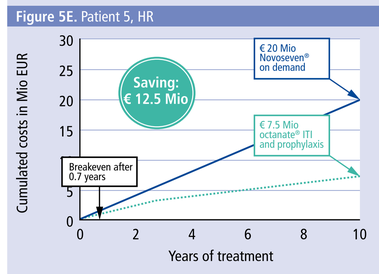


Figure 5F. Patient 6, HR

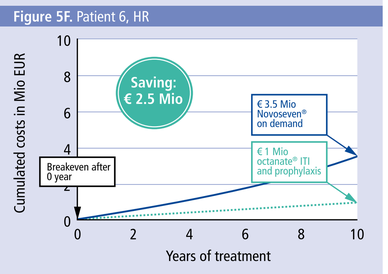


Figure 5G. Patient 7, HR

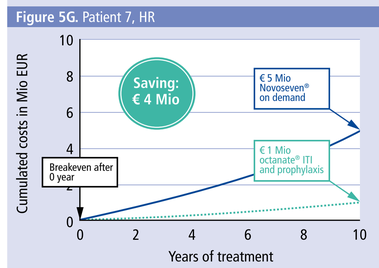
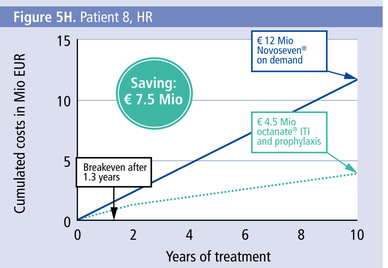


Figure 5H. Patient 8, HR



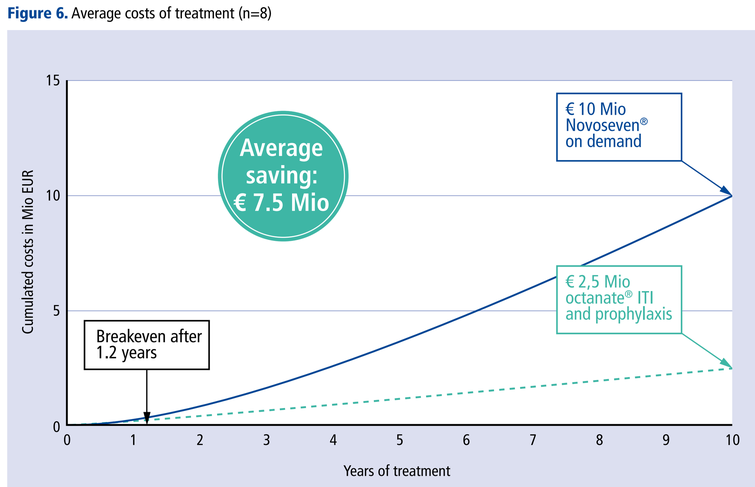
Cumulated NovoSeven® on-demand — Cumulated octanate® ITI HD+ prophylaxis

- **Figure 6** and **Table 3** represent the average cost and the BEP for all patients according to the on-demand treatment of bleeding episode with NovoSeven® (blue line) and with octanate® including prophylaxis with octanate® after successful ITI (green line).

Table 3. Average costs and the BEP

	mean (range)
Treatment with high-dose octanate® ITI including prophylaxis after successful ITI over 10 years, € million,	2.5 (1-5.5)
On-demand treatment with NovoSeven® over 10 years, € million	10 (3.5-25)
Estimated savings over 10 years, € million	7.5 (2.5-12.5)
BEP, year of treatment	1.2 (0-2.8)

Figure 6. Average costs of treatment (n=8)



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Conclusions

- Despite the stringent success criteria, octanate®, along with the high-dose Bonn Protocol, has led to complete ITI success rates in 11 of 14 (78%) children with high-responding inhibitors and poor ITI prognostic factors:
  - During ITI treatment with octanate®, bleeding frequency, hospitalization rates as well as administration of expensive FVIII-bypassing agents were significantly reduced in all patients.
  - The number of bleeding episodes was reduced 3.4-fold in median during ITI with octanate® in successfully tolerized patients.
  - During ITI with octanate® 90% of the bleeding episodes were resolved without need for bypassing therapy and with no change in octanate® ITI dosage.
- Successful tolerization with octanate® allows resumption of fully effective replacement treatment with a consequent improvement in the patients' quality of life [8] and an estimated average saving per patient over 10 years of €7.2 million.
- The BEP analysis resulted in 1.2 years on average.

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