

Communication

Use of recombinant factor VIII Advate in paediatric patients

First steps in the Czech Republic

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Until gene therapy is available, the substitution therapy remains the basic therapeutic strategy in haemophilia. Currently, the efficacy and safety are the critical attributes of substitution products. Products insufficiently treated against blood-transmitted viruses became the reason of the tragedy which had affected virtually all haemophilic population in the 1980s. The proportion of HIV-positive patients treated in the USA and Europe before 1985 was up to 70%, and proportion of HCV-positive patients was approaching 100%. Before 1985 the concentrates untreated against viruses were used also in former socialistic Czechoslovakia to a limited extent. In 1985

when HIV antibodies started to be investigated in former Czechoslovakia, HIV positivity was detected in 7 paediatric patients with haemophilia out of the overall number of 200 children. Similarly, low number of children was HCV-positive.

The reason was that till 1986 most Czech haemophilic patients were treated with domestic CPAG and frozen plasma. Therefore, the isolation from Western countries and the limited availability of FVIII concentrates had protected our haemophilic population against catastrophic expansion of HIV and HCV infections. At present time no paediatric patient is HIV-positive, and the number of paediatric patients who have experienced viral hepatitis is also very low. Eight patients were affected (4% of paediatric haemophilic patients, 7 patients had hepatitis C, and 1 patient had hepatitis A – without any relationship to FVIII concentrates).

The modern FVIII and FIX concentrates have not been established in the treatment of haemophilic patients in CR until the velvet

revolution in 1989. Now most haemophilic children and virtually all adults are treated with highly purified plasma-derived FVIII and FIX concentrates. There is sufficiency of these products in CR, and they are fully reimbursed by reimbursement companies. Although treatment with these products is effective and safe, particularly the paediatric haematologists have been monitoring the current trend in Western Europe and USA, and struggle to establish treatment with recombinant FVIII products in their patients. The main reason for their effort is the excellent microbiological safety of the third generation recombinant product which contains no animal or human proteins. In addition, its safety has been further increased by the use of virucidal methods, therefore, from microbiological viewpoint it really represents the golden standard of current treatment. The Workgroup of paediatric haematologists is also convinced that the future of treatment of haemophilia and other diseases consists in the recombinant technology.

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Patients and methods

The situation in CR

In CR the recombinant FVIII (rFVIII) is currently 2.5-fold more expensive than highly purified plasma-derived products (pdFVIII). Therefore, full reimbursement of these products by reimbursement companies has not been enforced so far, and the recombinant products are reimbursed up to the level of reimbursement of plasma-derived products. Since it is apparent that financial means of public health insurance are insufficient to allow full establishment of the treatment with rFVIII in all paediatric haemophilic patients, the Workgroup for paediatric haemophilia in CR during negotiations with reimbursement companies has suggested at least the following elementary indication groups for their use:

- newborns with severe haemophilia A – PUPs,

- children with mild haemophilia A (e.g. for protection during a surgery),
- children returning from abroad where they have been established on the treatment with a recombinant product

Unfortunately, not even this proposal has been accepted by reimbursement companies so far, therefore, treatment with rFVIII is impossible in CR without dotation by others.

In CR there are currently 217 patients suffering from haemophilia below the age of 19 years:

- 119 patients with haemophilia A,
- 26 patients with haemophilia B.

6 patients (haemophilia A: 5 patients, haemophilia B: 1 patient) show a clinically significant inhibitor. They are monitored in eight regional centres, the largest centres are located in Prague, Brno and Ostrava. Approximately one third of these patients suffer from a severe form of haemophilia A. Most

patients are treated with pdFVIII, patients with the inhibitor are treated also with products FEIBA and NovoSeven.

We obtained the first experience in the treatment with rFVIII thanks to cooperation with Baxter which has been funding the treatment with the 3rd generation recombinant product Advate in 18 paediatric patients (►Tab. 1) from the whole of CR for three years.

Details on patients with inhibitors

- Advate consumption in 2008: 760 000 IU;
- efficacy and tolerability: excellent;
- treatment complications: none, except for the inhibitor.

Patient 1

O.P., 6. May 2004, Ostrava – haemophilia A, FVIII below 1.0% (PUP): The patient has been treated entirely with Advate. The first substitution was given at the age of 13 months, than relatively frequent substitution during the first year, on the average twice a month, due to articular and muscular haemorrhage. The inhibitor was detected on 2 January 2007 after 28 EDs, and after administration of 12 000 IU Advate overall. At subsequent check-ups of the inhibitor there was detected a further elevation of its level, the maximum titre of the inhibitor amounting to 9.8 BU was detected on 6 March 2007.

On 14 March 2007 ITI with Advate was initiated, at the beginning of treatment a long-term central venous catheter was inserted under protection with NovoSeven. Within the ITI, 100 IU Advate/kg body weight were administered once daily until 6 June 2007 (for 3 months), when the inhibitor level dropped to 0.7 BU. Further, 100 IU Advate/kg body weight were given every other day for next two months till 14 September 2007 when the check-up investigation of the inhibitor still showed the level of 0.7 BU. With regard to the good clinical condition and absence of haemorrhage, the patient was switched to 100 IU Advate/kg three-times a week, and after additional month of treatment (on 24 October 2007) the dose of Advate was further decreased to 55 IU/kg three-times a week.

On 28 January 2008, i.e. after 10 months of treatment, the inhibitor level was 0.6 BU with

Tab. 1 Czech patients receiving Advate

patients	number	18 (Ostrava 10, Brno 3, Praha 2, Olomouc 2, Plzen 1)
	age	3 months to 17 years, in average: 4.5 years, 10 children below 3 years
	PUPs	9 patients
	PTPs	9 patients
form of haemophilia	severe	12 patients
	moderate	5 patients
	mild	1 patient
therapeutic approach	on demand	11 patients
	prophylactic	7 patients
	home treatment	7 patients
	administration at physician's office	11 patients
duration of Advate administration		1–39 months, in average: 20 months
inhibitor patients	1 (O.P.)	9.8 BU; inhibitor eliminated by ITI
	2 (M.K.)	2.0 BU, transitory, untreated, inhibitor spontaneously disappeared
	3 (Z.P.)	0.8 BU, transitory, untreated, inhibitor spontaneously disappeared

a very good recovery and FVIII half-time. On 21 March 2008 the infected central venous catheter was removed under protection with Advate at higher doses, on 21 April 2008 new central venous catheter was inserted under the same protection, and long-term prophylactic treatment with Advate 500 IU (approx. 26 IU/kg) three-times a week was initiated.

At follow-up tests in July and October 2008 the inhibitor remained negative, the patient is virtually without any haemorrhage, and feels very well.

Patient 2

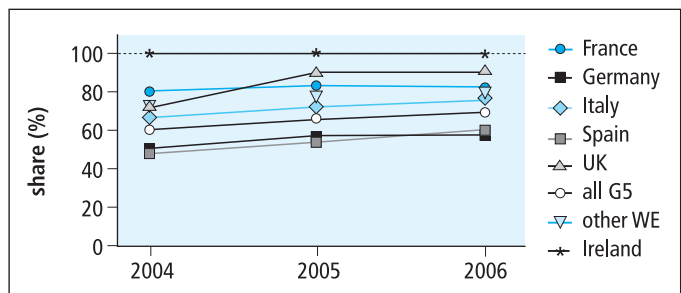
M.K., 26 December 2006, Ostrava – haemophilia A, FVIII 1% (PUP): Bleeding to the right kidney and adrenal gland after birth, during the first eight days of life 3250 IU Advate were administered overall in 8 EDs. Bleeding stopped, the patient was without difficulties.

Within laboratory tests in April 2007 the inhibitor 1.0 BU was detected. In addition, several haemorrhages to muscles and joints occurred, and responded well to the substitution with Advate at usual doses. Advate was administered for the last time on 19 June 2008, the last check-up investigation of the inhibitor was performed on 25 September 2008 – 0.8 BU.

Patient 3

Z.P., 9 June 1999, Plzen – haemophilia A, FVIII below 1% (PTP): The substitution therapy was initiated at the age of 10 months with Immunate, he used to bleed approximately

Fig. 1
Recombinant FVIII usage in Europe: market trends



twice a month to joints and muscles, at the age of 17 months a long-term prophylactic treatment with Immunate three-times a week was started. After 12 months the prophylaxis had been stopped on request of his parents, he continued in on-demand substitution twice to three-times a month. The inhibitor had been checked continuously, always with negative results. After approximately 285 EDs of Immunate he was switched to Advate in December 2007, the inhibitor was negative before the first administration. After 12 doses of Advate in March 2008 the inhibitor was 0.8 BU, however, his response to the treatment with the same product was very good. He continued in the same dosage.

In June and September 2008 the check-up investigations of the inhibitor were negative.

Conclusions

Recombinant products represent unambiguous technological progress, and are very likely to increase the safety of haemophilia treat-

ment. It is evidenced by their growing consumption, particularly in paediatric patients, in all developed countries (► Fig. 1) which have recommended recombinant products as the treatment of choice. The higher incidence of the inhibitor reported in some publications has not been fully confirmed till this time, and, in addition, the 3rd generation recombinant products appear to be less immunogenic compared to products of previous generations. The lower volume of the product after dissolution is also advantageous for paediatric use.

Our limited experience in the treatment with rFVIII Advate is very good, and we are going to struggle to include the recombinant products among fully reimbursed routine treatment of haemophilia. CR is not a rich country, but at the same time it is not poor, and it has a long tradition of quality treatment of haemophilia, thus, it should proceed to gradual implementation of recombinant products at least in PUPs.

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