INHIBITOR ELIMINATION IN A HIGH TITER HAEMOPHILIA A PATIENT DURING LONG-TERM PROPHYLAXIS WITH aPCC (FEIBA®)

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Introduction and objectives

The development of inhibitors is one of the most serious complications to replacement therapy with factor (F) VIII, affecting approximately 30% of severe haemophilia A patients.

Immune tolerance induction (ITI) is an effective therapeutic approach to eradicate inhibitors and to enable regular FVIII administration for prophylactic reasons or in case of bleeds/surgery. Different protocols which are based on the regular administration of FVIII reveal success in 60-80%.

For the patients with persisting inhibitors treatment outcome becomes poor due to the rapid development of haemophilic arthropathy and long-term disability under on-demand treatment with bypassing agents (BPA), i.e. aPCC (FEIBA®, Baxalta (now part of Shire) or rFVIIa (NovoSeven®, NovoNordisk).

The proven benefits of FVIII prophylaxis in severe haemophilia A patients without inhibitors provide the rationale for the usage of BPA prophylactically in patients with FVIII inhibitors.

Prophylactic use of BPA revealed a significant reduction of bleeds [1,2,3] as well as prevention of bleeds and haemophilic arthopathy if started during early childhood, e.g. immediately after ITI failure [4,5].

We report about a patient with severe haemophilia A who developed a high-titer inhibitor, failed high dose ITI, continued with prophylaxis with aPCC (FEIBA®) and who achieved complete immune tolerance to FVIII.

Methods and Materials - Case report

We report about a 21-yr-old man with severe hemophilia A (FVIII<1%), who developed a high titer inhibitor at the age of 1.2 years after 17 exposures to FVIII (rFVIII; on-demand treatment). FVIII gene defect: intron 22-inversion

- Inhibitor titre 1.9 Bethesda Units – BU/ml

Immune tolerance induction courses (ITI)

Two consecutive high dose ITI courses according to the Bonn protocol using recombinant factor (F) VIII (first ITI course) and von-Willebrand-factor (VWF)-containing FVIII (second ITI course) (100 IU FVIII/kg i.v. every 12 hours) as well as BPA prophylaxis during ITI (50 U FEIBA®/kg i.v. twice daily) failed.

- Inhibitor titre at start of first ITI < 5 BU/ml (1.9 BU/ml)
- Age at start at first ITI 1,3 years
- Peak inhibitor titre during ITI 180 BU/ml
- During ITI the patient experienced no joint bleed.
- No CVL infection during ITI
- No interruption of ITI
- Duration of ITI 2.2 yrs
- Inhibitor titre when ITI was stopped: 23 BU/ml

Prophylaxis with BPA (aPCC, FEIBA®)

- Started immediately after ITI failure at the age of 3 yrs
- Dose: 80 U FEIBA® kg^{-1} three times a week (TIW) then increased to daily applications since age of 6 years (qd)
- Inhibitor titre at start of FEIBA® prophylaxis: 23 BU/ml
- No inhibitory anamnestic response after introduction of FEIBA® prophylaxis
- Duration of FEIBA® prophylaxis: 17.9 years
- Bleeds during BPA prophylaxis
  - Annual joint bleed rate (AJBR) 0.2
  - Other major bleeds: muscle bleed right arm
- HJHS of 1 at the age of 21 years
- Negative inhibitor titre during BPA prophylaxis
- BPA prophylaxis with FEIBA® well tolerated

Low dose ITI – re-exposure to FVIII

After 18-years of effective prophylaxis we decided to expose the patient to FVIII again since his inhibitor titer remained negative for several years.

aPCC was discontinued and the patient received 50 IU VWF-FVIII kg^{-1} every other day. No adjunctive therapy, such as immunosuppressive agents have been used.

Results

From the first re-exposure to FVIII concentrate the response to FVIII was normal and FVIII trough levels >1% have been measured repeatedly in between the prophylactic doses. Inhibitor titre was constantly negative.

During an observation period of now 9 months the inhibitor titer remained negative and pharmacokinetic parameters stayed normal suggesting complete immune tolerance.

- No inhibitor relapse during 9-months follow-up
- FVIII response: 1.6-1.8% FVIII:C rise per IU FVIII administered
- FVIII half-life: 8.2 hours
- FVIII trough levels >1% at 48-hours intervals after prophylactic dose of 40 IU FVIII/kg
- No break-through bleeds during prophylaxis

Discussion

Prophylactic use of aPCC (FEIBA®) is used for prevention / reduction of bleeds in patients with haemophilia and persistent inhibitors.

Since FEIBA® contains trace amounts of FVIII, anamnestic response is observed in a substantial number of patients , particularly during on demand therapy. However, anamnestic response is not associated with an increased bleeding tendency. Titres usually drop to baseline BU within 3-6 months [5,6]. Some patients even might reach a continuously negative inhibitor titre during long-term FEIBA® prophylaxis, as we could observe in our cohort [4,5].

Re-exposure to FVIII concentrate showed complete tolerance in our patient for currently 9 months. Similar cases have been reported after long-term FEIBA® prophylaxis in high titre inhibitors in haemophilia A who failed previous ITI [7] and haemophilia B [8].

Inhibitor elimination due to FEIBA® prophylaxis might occur in a small proportion of patients. Further investigations, i.e. exposure to FVIII in those patients who reach negative inhibitor titres can be considered.

Conclusions

Long-term prophylaxis with aPCC was an effective tool to prevent recurrent bleeds and the development of hemophilic arthropathy and lead to complete inhibitor elimination in our patient.

References

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