Immune tolerance induction rescue with turoctocog-alfa in a poor risk haemophilia A inhibitor young child: the history of a success

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The development of alloantibodies against the replacement of Factor VIII (FVIII) is the major complication in haemophilia A treatment. The gold standard to eradicate inhibitors is the immune tolerance induction (ITI), but in some cases it fails requiring another immune tolerance, defined ITI rescue (ITI-R), using a different concentrate, even though it is still debated. We report a successful case of a poor risk (titre of inhibitor at start of ITI > 10 BU/ml, peak titre on ITI > 200 BU/ml, >2 years since the inhibitor diagnosis) haemophilia A child treated with a high-dose regimen (200 UI/kg/day) turoctocog-alfa after a failed first-line ITI with octocog-alfa lasting 29 months. At 22 months of ITI-R, the inhibitor titre was undetectable, the FVIII recovery was 74%, of the expected level and the FVIII half-life more than 7 h. A complete successful ITI-R was then achieved with turoctocog-alfa. *Blood Coagul Fibrinolysis* 29:000–000

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Case report

The development of alloantibodies against the Factor VIII (FVIII) concentrates is the major complication of haemophilia A treatment, causing difficulties in patient management, that results nonresponsive to standard therapies and in case of bleeding use of by-passing agents is mandatory to avoid severe complications. The gold standard to eradicate the inhibitors is the primary immune tolerance induction (ITI), but in some cases it fails, requiring another approach of treatment as the use of by-passing agents on prophylaxis, or the start of a new ITI, defined ITI rescue (ITI-R), with a different concentrate [1]. It is still debatable which replacement factor should be used in case of ITI-R. The recent UK guidelines in case of poor responder children (titre at start of ITI > 10 BU/ml, peak titre on ITI > 200 BU/ml) consider the FVIII dose increase, the introduction of plasma-derived FVIII with a high von Willebrand factor (pdFVIII/vWF) content and/or immunosuppression with rituximab as second-line therapy, whereas the use of recombinant FVIII (rFVIII) is recommended only in case of primary ITI, but no indications are given on its use in case of ITI-R [2]. The same data are confirmed in literature in which the few published cases on the use of rFVIII to eradicate the inhibitors in patients with congenital haemophilia are limited to primary ITI [3,4], but no exhaustive data are available on its use as second-line therapy.

We report a successful case of a poor risk haemophilia A child treated with turoctocog-alfa (Novo Nordisk® S.p.A. – Rome, Italy) after a failed first-line ITI with octocog-alfa.

Our young patient was born in 2011, and is suffering from severe haemophilia A (FVIII < 1%) with the intron 22 inversion, diagnosed at 6 months after a bleeding episode. The child started prophylaxis immediately after diagnosis with octocog-alfa 50 IU/kg/once a week. Five months later, after 20 exposure days to treatment, the young patient developed a high-titre inhibitor (16.32 BU/ml), without severe bleeding manifestations during the brief prophylaxis. The presence of these alloantibodies against FVIII led the physicians to start a primary ITI with the same concentrate used on prophylaxis. The ITI was started at the high-dose regimen of 200 IU/kg/day when the child was 22 months and the inhibitor titre was 3.10 BU/ml. One month after the start of ITI the inhibitor titre reached a peak of 426.2 BU/ml, and then dropped in the following months to 10.92 BU/ml. During this period of treatment the child reported only a few mild bleeding episodes (e.g., posttraumatic haematomas), treated with activated rFVII (rFVIIa) 90 μg/kg on demand. The therapy with this by-passing agent was subsequently modified into prophylaxis 90 μg/kg/three times a week when inhibitor titre increased to 120.3 BU/ml and also bleeding events increased (recurrent haematomas to lower limbs, haematoma to left elbow, and facial haematoma), many of which were spontaneous. Primary ITI lasted 25 months, but the inhibitor titre remained very high, maintaining a mean of 91.23 BU/ml. The ITI was then considered failed and stopped (Fig. 1).

Immediately an ITI-R was started with turoctocog-alfa 200 UI/kg/day, without washout period before this new

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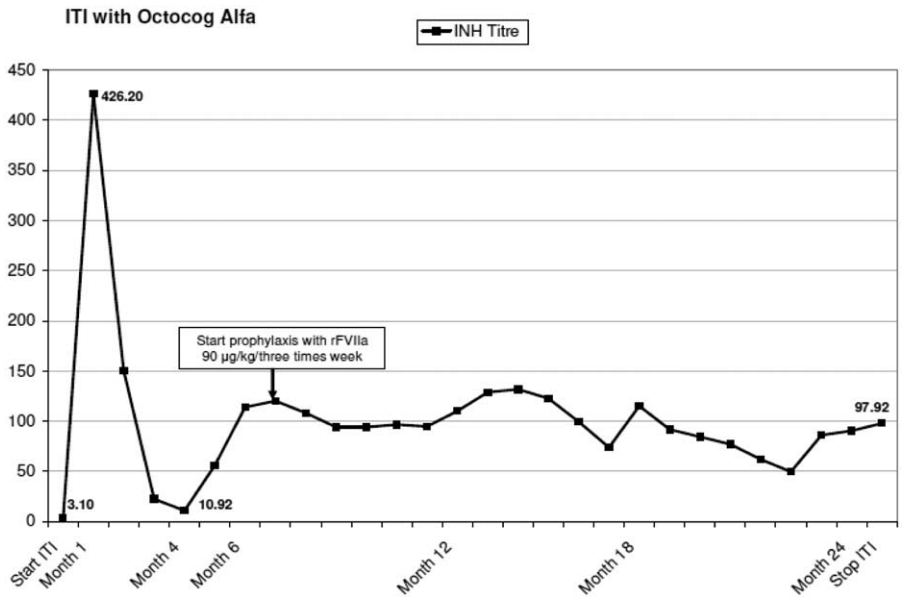
Fig. 1



Primary immune tolerance induction with octocog-alfa failed after 25 months. INH, inhibitor; rFVIIa, recombinant FVII activated.

treatment, and at the onset of ITI-R the inhibitor titre was 97.92 BU/ml. Prophylaxis with rFVIIa three times a week to control bleeding events was maintained and the inhibitor peak reached 105.6 BU/ml after 1 month of treatment with turoctocog-alfa. In the following months inhibitor titre progressively decreased, showing a single unexpected rise after 9 months of treatment, and reaching a peak of 88.0 BU/ml, afterwards the titre began to fall again and the prophylaxis with rFVIIa was reduced to 90 µg/kg/twice a week, and then definitively stopped at the 18th month of treatment when inhibitor disappeared (Fig. 2). Planned controls in the following months confirmed the absence of alloantibodies. At 22 months FVIII recovery was 74% of the expected level and FVIII half-life more than 7 h. ITI-R with turoctocog-alfa reported a complete response (CR), according to the criteria of the international guidelines on ITI [5].

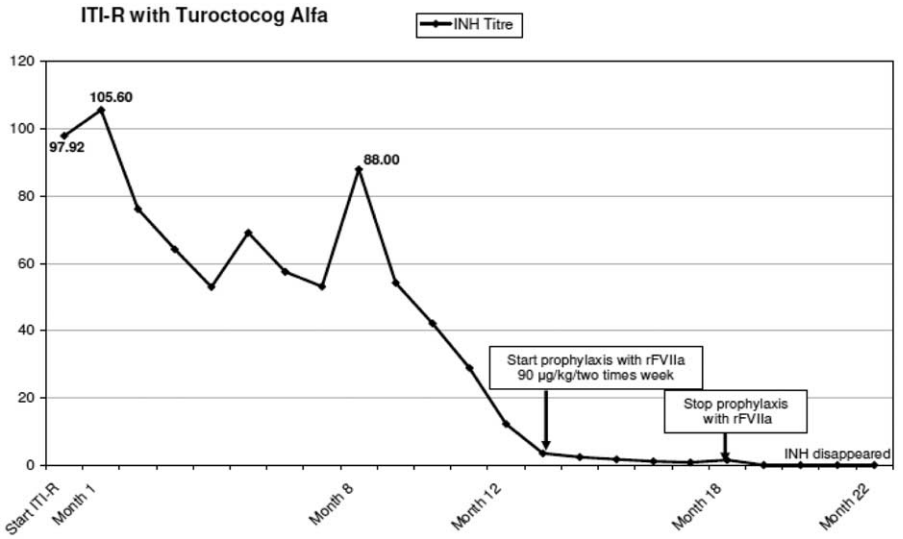
Turoctocog-alfa is a new rFVIII with a truncated B domain and a high degree of tyrosine sulphation, similar to plasma-derived FVIII concentrates. Six fully sulphated tyrosin sites are present in the human molecule of FVIII, but only the sulphation of tyrosine at amino acid 1680 is important for binding to the vWF. The affinity to vWF would be reduced five-fold, if this sulphation is absent [6]. The role of vWF in the success of immune tolerance induction is reported in several studies in which the patients were treated with pdFVIII/vWF concentrates both in the first and second-line therapy. In a German study published in 2001 by Kreuz *et al.* [7], the total rate of success of ITI using pdFVIII/vWF was 87–91%, higher than with rFVIII; the same result was obtained in the last year in the OBSITI study in which 79.8% of patients reached a complete or a partial success [1]. The efficacy of these concentrates to eradicate alloantibodies is proven, but the pathophysiological mechanism with which it occurs is still unclear, and an immunomodulatory role of vWF has been hypothesized, but not completely confirmed.

The B domain truncated of turoctocog-alfa seems to be unrelated to procoagulant activity of FVIII. Moreover the fusion sequence of the B domain truncation was created to avoid the formation of new potential T-cell epitopes that can lead to inhibitor development [6].

With this background and considering that the infusion volumes of recombinant factors are smaller than plasma-derived favouring the compliance to treatment of the child and his parents, we have chosen to try an ITI-R with turoctocog-alfa. Our young patient was considered to have a poor prognosis factor for ITI success: the historical inhibitor peak reached more than 400 BU/ml, the inhibitor titre when primary ITI failed was more than 90 BU/ml, and the time from inhibitor diagnosis was more than 2 years. Usually, in these cases a second-line therapy with pdFVIII/vWF is considered the gold standard by the paediatric international guidelines [2], but parents refused the use of these products. We chose turoctocog-alfa because it has similar characteristics to plasma-derived concentrates, especially due to its sulfatation and therefore its higher affinity to vWF, which can mimic the pdFVIII/vWF products.

According to the Bonn protocol, high-dose regimen 200 UI/kg/day was started without a previous washout

Fig. 2



Immune tolerance induction rescue with turocotocog-alfa that reached a complete response after 22 months. INH, inhibitor; rFVIIa, recombinant FVII activated.

after the primary failed ITI, and with a very high inhibitor titre. This choice was performed because no confirmed data or specific guidelines and recommendations are available about the washout period needed between two consecutive ITI. In a recent review [8] that compares all published reports and registries on use of a pdFVIII with a high vWF content both, in the primary and rescue ITI, in case of second-line therapy 43% of poor risk patients achieved a success, but no indications were recorded about the transition from one ITI to another.

As reported in different published studies the rate of complete primary ITI success with rFVIII varies, from 25 to 100%; this high variability is due to a regimen of treatment, definition of ITI success, and the features of each treated patient. The risk of failure is then always present especially in case of patients with poor prognostic factors for ITI response. In our child, primary ITI with octocog-alfa failed after 25 months of treatment, but without the inhibitor titre ever dropping below 10 BU/ml. The constant presence of a high-titre inhibitor resulted in the occurrence of many haemorrhagic events that required the introduction of rFVIIa treatment, making the therapy more complex and the patient less compliant.

International guidelines [2] suggest the use of plasma-derived products with high vWF in case of second-line therapy due to the immunomodulatory role of vWF, but van Velzen *et al.* [9] affirmed that the data synthesis of pooled meta-analysis of 13 studies did not support the hypothesis that vWF-containing products have higher success rates of ITI than non-vWF containing products, although however in this review the success rate of ITI-R with pdFVIII/vWF was 75%.

Following all previous reported considerations we decided to start an ITI-R in our young patient at high-dose regimen with turoctocog-alfa. Successful ITI is defined by the international guidelines [5] as an undetectable inhibitor titre (<0.6 BU/ml), a FVIII recovery at least 66% of the expected level and a FVIII half-life at least 7 h. In our case, a CR was achieved after 22 months of treatment.

Based on these results, it is our opinion that turoctocog-alfa can be an effective option for the ITI-R, it presents a pharmacokinetic profile comparable with octocog-alfa [10], but its molecular characteristics such as the new fusion sequence of B truncation and the posttranslational tyrosin sulphation makes this molecule more similar to plasma-derived products than other rFVIII. Turoctocog-alfa was proved to be very effective in reaching a successful ITI also in a poor risk haemophilia A inhibitor child, and its recombinant origin guarantees in addition to effectiveness the safety of being free from any residual infection risk.

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All of the authors meet the International Committee of Medical Journal Editors criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given final approval of the version to be published.

Conflicts of interest

There are no conflicts of interest.

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