Successful Immune Suppression Followed by Immune Tolerance Induction in a Factor IX patient who had developed an Anaphylactic Reaction to Factor IX.

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OBJECTIVES

A life threatening complication in a small number of Hemophilia B patients is an anaphylactic reaction to Factor IX replacement therapy. Once an anaphylactic episode has occurred major therapeutic problems arise for the Hemophilia B patient.

A treatment plan of immune suppression followed by immune tolerance therapy was developed for a 14 year old (2010) who had an anaphylactic reaction to factor 9 replacement therapy . It involved pre-treatments with Rituximab, the use of Mycophenolate, and a gradual reintroduction of Factor IX (plasma derived). This treatment option resulted in no anaphylactic reactions.

1. Correct factor IX deficiency and rehabilitate a 14 year old boy with severe Hemophilia B and an anaphylactic reaction to Factor IX.

2. Devise a protocol for the administration of Immune Suppression followed by Immune Tolerance Therapy (ITT) to Factor IX

3. Decrease cost of treatment with factor VIIa (> $5,300,000 Can / yr) (€ 4,121,947 Euros)

METHODS

A treatment plan of immune suppression followed by immune tolerance therapy was developed.
NOTE: Doses and schedule available on request

1. **Immune Suppression therapy**
   a. Rituximab cocktail given weekly for weeks 1-4. This included premedication's consisting of acetaminophen 650 mg, Diphenhydramine 25 mg and Methyl prednisone 100 mg followed by the gradual infusion of Rituximab to a total of 525mg.
   b. Mycophenolate 300mg given daily (days 1-52)
   c. Dexamethasone 16.8 mg BID (days 9-11, 24-27,45-48)
   d. IVIG 1 gm/kg (50gm) (days 12, 13, 47, 48)
   e. Sulfa/Trimethoprin 200mg/40mg, 3 times weekly for 4 weeks

2. **Immune Tolerance Induction with factor IX (Immunine, plasma derived)**
   a. Doses of factor IX starting at .01units/kg and increasing to 18 units/kg (days 1-7)
   b. Factor IX ~5000 units daily (days 8-33) then Factor IX ~4000 units daily (Aug 2010 - Nov 2011)
   c. Every other day therapy started in Nov 2011 with ~4000 units and gradual worked down to maintenance dose of ~3000 units every other day (present dose being used).

3. **Lab follow up**
   a. Factor IX, aPTT and inhibitor levels
   b. Liver function, kidney function, TSH, IgE
   c. Urinalysis

Figure 1

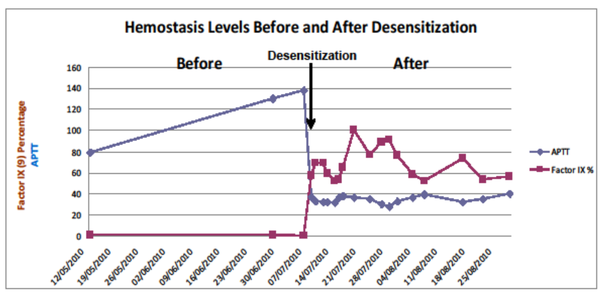


Figure 2

URINALYSIS						
Dates	Protein Urine g/l	Ketones Urine mmol/L	Glucose Urine mmol/L	Urobilinogen Urine mmol/L	Bilirubin Urine mmol/L	Hemoglobin Urine mmol/L
Sept-9-2010	Negative	Negative	Normal	Normal	Negative	Negative
Oct-2-2010	0.25	0.5	Normal	Normal	Negative	Negative
Nov-8-2010	0.25	0.5	Normal	Normal	Negative	Negative
Jan-10-2011	Negative	Negative	Normal	Normal	Negative	Negative
June-30-2011	0.75	0.5	Normal	70	17	Negative
July-18-2011	Negative	Negative	Normal	Normal	Normal	Negative
Sept-30-2011	0.25	0.5	Normal	Normal	17	Trace

Figure 3

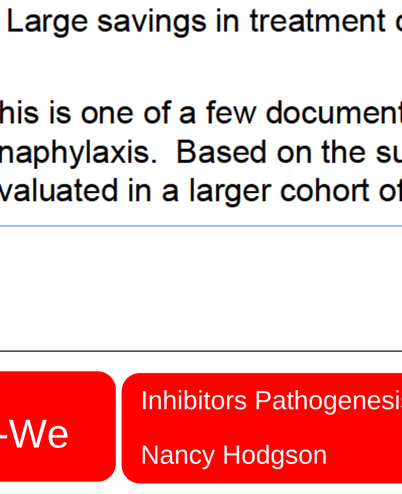
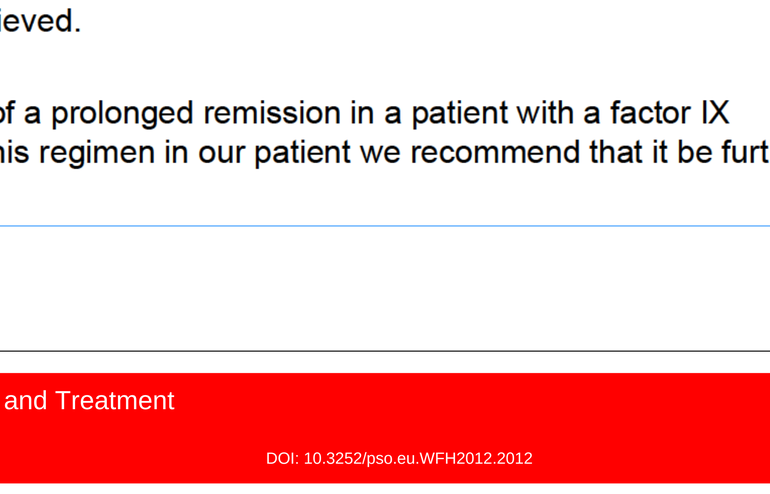


Figure 4



RESULTS

1. Immediate normalization of aPTT and factor IX. (see Figure 1)

2. No anaphylaxis.

3. No toxic effects to kidneys. (see Figure 2)

4. Better attendance at school and as a result better interaction with peers. Prior to Immune Suppression followed by Immune Tolerance Therapy the 14 year old boy attended only 14 days of school for the school year of 2009-2010. For the school year 2011-2012 the 14 year old boy's attendance is almost comparable to what you would expect for any other 14 year old boy who has hemophilia B.

5. Less bleeds and off of opiates as a result. (see Figure 3)

6. When comparing the costs of the 12 months prior to the Immune Suppression followed by Immune Tolerance Therapy to the 12 months after (see Figure 4), a savings of $5, 879, 434 Canadian (€4, 559, 114 Euros) is calculated.
   The resulting average cost savings/month following the Immune Suppression followed by Immune Tolerance Therapy was $ 489, 953 Canadian (€ 381, 049 Euros).

CONCLUSIONS

1. Treatment with a drug Immunosuppression regimen to eliminate an anaphylactic reaction to factor IX with slow induction is feasible.

2. On going every other day therapy with factor IX can keep the immune reaction to factor IX under control.

3. Plasma derived factor IX is effective in this condition.

4. Return to an almost normal life for this condition is possible.

5. Large savings in treatment can be achieved.

This is one of a few documented cases of a prolonged remission in a patient with a factor IX anaphylaxis. Based on the success of this regimen in our patient we recommend that it be further evaluated in a larger cohort of patients.

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Saskatchewan Bleeding Disorders Program (SBDP) which consists of Hematologists, Nurses, Physiotherapist, and Social Worker.

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