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Comparison of dexamethasone and anti-D immune globulin for immune thrombocytopenia purpura in children

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ABSTRACT

Different therapeutic options in children with immune thrombocytopenic purpura include observation alone, periodic treatment with corticosteroids, intravenous immunoglobulin (IVIG) or anti-D, chronic administration of immunosuppressive agents, and splenectomy.
Preference of the type of therapy depends on the degree of thrombocytopenia and clinical bleeding manifestations. Dexamethasone is safe but its side effects are the main disadvantages for its usage. Anti-D is more expensive than dexamethason but the side effect is rare and not dangerous and response to treatment is assessed in approximately 3 days after infusion.

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Introduction

Immune thrombocytopenic purpura (ITP) is an immunologic and hematologic disorder characterized by antiplatelet antibodies that lead to immune-mediated platelet destruction by the reticuloendothelial system (RES) (1). Chronic immune thrombocytopenic purpura (chronic ITP) develops in 20% of acute ITP in children (2). Treatment of ITP in children is considered appropriate with platelet count of 10×10^9 /l with mild purpura or platelet count of 20×10^9 /l with mucosal bleeding (2).

Depending on the degree of thrombocytopenia and clinical bleeding, in children with ITP therapeutic options

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include observation, periodic treatment with corticosteroids, intravenous immunoglobulin (IVIG) or anti-D, chronic administration of immunosuppressive agents, and splenectomy (1).

Anti-D

Rho(D) immune globulin (WinRho) was developed in 1972 at the Winnipeg Rh Institute using the Hoppe and colleagues. RhoD immune globulin was FDA approved for the treatment of ITP in patients that nonsplenectomized and D+ in 1995 (5).

Despotovic et al. showed the efficacy of intravenous immune globulin (IVIG) in children with ITP at a dose of 50 to 75 mg/kg. Based on the mechanism of action, a small amount of extravascular hemolysis is known to be an expected consequence of treatment, which has been good tolerated in the majority of otherwise healthy and no anemic recipients (5).

Shagholi et al. divided patients in two groups, one group received single dose of anti-D at dose of 75 mg/Kg intravenous, during 3-5 minutes and another group received IVIG 1 g/Kg for two consecutive days, as a 6 to 8 hours continuous infusion and 24 hours interval. The response in IVIG group (98%) was more significant than anti-D group (76%). After 7 days, the platelet counts of all patients in IVIG group were more than 20,000/μL while in anti-D group 12% had platelet counts below 20,000/μL (3).

Alfy et al. randomized 34 patients with chronic ITP (18 boys and 16 girls) and recurrent bleeding episodes. The patients were divided into two subgroups. Group A given anti-D as an intravenous bolus in a dose of 50 mg/kg over 4-5 mins. Repeated doses of anti-D were given every 3-4 weeks to 12 patients in a dose of 50 mg/kg and group B received IVIG in a dose of 250 mg/kg for 2 consecutive days. On day 3, 33.3% of group A versus 37.5% of group B, and on day 7, 66.6% of group A versus 75% of group B patients demonstrated a good response (platelet count 150×10^9 /l and /or doubling of baseline platelet count) (2).

The most commonly used administration route was IV injection. IV anti-D doses between 25 and 50 mg/kg were used in six studies (6-11).

Bussel et al. started with 10 mg/kg increasing to 25 mg/kg per day until either platelet count was $>20\times10^9$ /l or hemoglobin decreased 2 g/dl or more. Average total dose is 52 mg/kg (30-150 mg/kg). Andrew et al. also used repeated IV anti-D administration (25-55 mg/kg) until platelet count rose up to 150×10^9 /l (12). Several studies used doses up to 100 mg/kg (13-17). A positive dose response relationship has been demonstrated in both chronic ITP and acute ITP (15).

However, doses exceeding 75 mg/kg were associated with higher risk of severe intravascular hemolysis and acute renal failure (12).

Dexamethason

In 1994, Andersen selected ten referred patients who had persistent idiopathic thrombocytopenic purpura after undergoing at least two standard therapies and were treated with six cycles of dexamethasone (40 mg per day for 4 sequential days every 28 days). He reported that oral dexamethasone in pulse therapy was associated with durable responses in 10 adults with chronic ITP (18).

The treatment of a 4-day pulse of oral dexamethasone (40 mg) given once daily and repeated monthly for a total of six cycles has been reported by Andersen. Several studies using pulse oral dexamethasone were undertaken in children. Unfortunately, this regimen has not been confirmed in prospective controlled studies with the early high expectation. In a study of 11 children with chronic ITP, we observed a

partial response in 3 cases and a complete response in only 1 case (19).

Steroid therapy was one of the cornerstones in acute ITP, but cannot suggest as a conntinuous maintenance therapy in chronic ITP because of significant short and long term side effects (20).

Advantage

Treatment with Anti-D has three routes of administration including infusion of in vitro opsonized erythrocytes, intramuscular injection, and subcutaneous injection. In vitro opsonized erythrocytes seemed as effective as standard IV anti-D (12). Anti-D is less expensive and can be used in outpatient condition without hospitalization but it is not useful for patients with negative rhesus antigen (Rh) factor and splenectomy (3). Subcutaneous (SC) administration of anti-D seems to offer the same efficacy as intravenous administration but with fewer side effects (21). Formulations other than oral prednisone, such as high-dose oral dexamethasone or oral methylprednisolone, have been proposed to achieve long-term remission (22).

Disadvantage

Anti-D was not use in urgent bleeding because of delay to response. Given the considerable toxicity of the regimen and the lack of solid evidence that the pulse cyclic dexamethasone treatment is associated with clinically significant long-term partial or complete remissions, has fallen out this treatment approach of favor, and is now used infrequently as second-line therapy in children with chronic ITP (23).

Treatment effect

Approximately, 60% Rhesus positive, non-splenectomized children with chronic ITP experienced increased platelet count to 20×10^9 /l within 3 days after IV anti-D (12). Zimmerman et al. reached that the mean increase in platelet count between day 0 and day 7 was $96\pm106\times10^9$/l, but did not statistically significant (1).

Alfy et al. revealed that the response to anti-D peaked on days 7 and 14. Difference in platelet increments observed between anti-D and low dose IVIG on days 14 and 21 was not statistically significant. The response rate decreased significantly in 3-4 weeks after infusion (2).

A randomized trial in chronic ITP children showed a significantly high platelet count after IVIG compared to IV anti-D on day 3 and 7 after treatment. The overall impression is that the dose of IVanti-D up to 50 mg/kg raises the platelet count at a slightly slower pace than IVIG (12).

Adverse effects

Despotovic et al. and several other studies showed that a decrease in hemoglobin (Hb) concentration of 0.5 to 2 g/dL over the 3 to 7 days after RhIG infusion occured in the majority of treated patients. This amount of hemolysis is typically well tolerated, with recovery to baseline counts usually within 3 weeks after administration (1).

Other generally mild and transient infusion-related side effects such as headache, fever, chills, and vomiting have been reported in 3%–15% of patients, which are lessened or alleviated with the routine use of premedications such as acetaminophen, diphenhydramine, corticosteroids, and if necessary, ondansetron (5).

DIC, acute respiratory failure, hemolysis and renal failure are very rare. All patients without prior renal insufficiency regained normal renal function. Two children experiencing renal impairment had symptoms of Epstein–Barr virus infection (5).

Conclusion

A single dose of 50 mg/kg IV anti-D

increased platelet count to 20×10^9/l within 3 days in approximately 60% of children. Intravenous anti-D seems safe in classic childhood ITP with fewer side effects than IVIG. However, hemolysis and renal failure may be of concern in some cases but it is not for cases that has good Hb and normal function of kidneys. It means that patients reach renal failure and hemolysis when they have previous history of renal diseases or have lower hemoglobin or anemic pretreatment.

Subcutaneous administration may be an interesting alternative, but further investigation is needed. Dexamethasone is a safe and not expensive drug to treat these patients but physicians are not intrested to use it because of its long-term side effects.

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Conflict of Interest

The authors declare no conflict of interest.

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