

Severe anaphylactic reaction following anti-thymocyte globulin administration in a pediatric stem cell transplantation patient

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Abstract

We present a case of a severe reaction after anti-thymocyte administration despite premedication and strict adherence to administration guidelines during the conditioning regimen. Due to the severity of the adverse drug reaction, we believe that this case should be reported.

Keywords

Stem cell transplantation, anti-thymocyte globulin, pediatrics, infusion reaction

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Introduction

Rabbit anti-human thymocyte globulin (ATG-T) (Thymoglobulin[®], Genzyme Europe, The Netherlands) is the purified fraction of rabbit-derived polyclonal antibodies against human thymocytes.¹ It is used as an immunosuppressive agent (mostly acting on T-lymphocytes) in solid organ transplantation and in allogeneic hematopoietic stem cell transplantation (HSCT) to reduce the severity of acute en chronic graft-versus-host-disease.^{1,2}

Infusion-associated reactions (IAR) may occur following the administration of ATG-T as soon as from the first or second dose. Clinical manifestations of IARs include fever, chills, rigors, nausea/vomiting, diarrhea, hypotension or hypertension, malaise, rash, urticaria and/or headache. These reactions are usually mild and transient and can be managed with reduced infusion rates and/or medications. Serious and in very rare instances, fatal anaphylactic reactions have been reported.^{1–4}

In addition, IARs consistent with cytokine release syndrome (CRS) have been reported,¹ although rarely severe and potentially life-threatening. According to post-marketing reports, severe CRS has been associated

with cardiorespiratory dysfunction (including hypotension, acute respiratory distress syndrome, pulmonary edema, myocardial infarction, tachycardia and/or death).

To reduce the incidence and severity of IARs, close compliance with the recommended dosage and infusion time (minimum 6 h into a high-flow vein) is mandatory.¹ Premedication with corticosteroids, paracetamol and/or an antihistamine is highly advised. During the entire infusion, patients should be carefully monitored.

Severity and frequency of toxicities are highest during the first infusion and diminish with each subsequent day.⁴

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We present a case of a severe reaction after ATG-T administration despite premedication and strict adherence to administration guidelines during the conditioning regimen.

Case presentation

A 5-year-old Caucasian boy was treated for hemophagocytic lymphohistiocytosis (HLH) according to the protocol of the HLH Study Group (HLH 2004) consisting of dexamethasone, cyclosporine and etoposide. Due to relapse of HLH after stop of therapy, an allogeneic HSCT was performed. The patient received ATG-T (Thymoglobulin®) at a dose of 2.5 mg/kg (batch numbers C2262H16, C2262H10) intravenously on day -4 (minus 4) of the conditioning regimen. Concomitant medications were treosulfan (14 g/m²) and fludarabine (30 mg/m²). Premedication consisted of paracetamol (15 mg/kg) and methylprednisolone (2 mg/kg). Corticosteroids were administered 30 min prior to the administration of ATG-T, according to the hospital's protocol. No test dose of ATG-T was administered.

The patient received the prescribed dose of ATG-T into a high-flow vein, gradually increasing the infusion rate. During the first hours of administration, the patient developed headache, tachycardia and fever. The infusion rate was decreased, and the patient symptoms disappeared. About 14 h after start of the infusion and 1 h after stop of the infusion, and despite hyperhydration, the patient became severely hypotensive requiring transfer to the pediatric intensive care unit. Extensive fluid resuscitation (60 ml/kg crystalloids,

20 ml/kg colloids and 15 ml/kg Packed Red Cells) and vasoactive support (norepinephrine up to 0.5 µg/kg/min and epinephrine up to 0.1 µg/kg/min) were required. Because of refractory shock, hydrocortisone substitution therapy was started. Multiple organ failure (oliguria and coagulation disorder—INR 2.4) and severe lactic acidosis (lactate up to 58 mg/dL) were noted. Shock reversal was obtained within 6 h after admission and vasoactive support could be weaned (epinephrine within 24 h, norepinephrine within 48 h).

The anaphylactic shock (grade 4 according to Common Toxicity Criteria for Adverse Events)⁵ was attributed to the use of ATG-T. The patient was administered broad-spectrum antibiotics (amikacin, piperacillin-tazobactam and vancomycin), but blood cultures remained negative. Microbiological control of the infusion bag with ATG-T confirmed sterility of the infusion.

The postponed remaining ATG-T administrations were with delay performed on day -4, day -3 and day -1 (minus days) of the HSCT conditioning regimen, again with premedication (paracetamol, corticosteroids), gradually increased rate of administration and strict monitoring of the patient. No reactions reoccurred.

The patient scored 8 on the Naranjo probability scale indicating a probable causality of ATG-T as the drug causing the reaction⁶ (Table 1).

Discussion

Infusion of ATG-T during conditioning for allogeneic HSCT is associated with several practical issues for

Table 1. Naranjo score of probability.

Question for assessment of adverse drug reaction	Answer	Score
1. Are there previous conclusive reports on this reaction?	Yes	+1
2. Did the adverse event appear after the suspected drug was administered?	Yes	+2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	Yes	+1
4. Did the adverse reaction reappear when the drug was re-administered?	No	-1
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	No	+2
6. Did the reaction reappear when a placebo was given?	Do not know	0
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	Do not know	0
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	Yes	+1
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	Yes	+1
10. Was the adverse event confirmed by any objective evidence?	Yes	+1
Final result		8

physicians, pharmacists and nursing staff and is an area for continued improvement.⁷

Although ATG-T administration is usually uneventful, the most common complication being fever, IARs may occur following the administration as soon as the first or second dose. However, these IARs are usually mild and transient and can be managed with reduced infusion rates and/or medications. We present a patient with anaphylactic shock related to the use of ATG-T infusion during conditioning regimen for HSCT.

The life-threatening reaction with refractory shock required admission to the pediatric intensive care unit and resulted in postponement of the further ATG treatment. The occurrence of the anaphylactic reaction, despite pretreatment with paracetamol and corticosteroids highlights the importance of close follow-up and monitoring during ATG-T administration, even when premedication is administered.

Pharmacological strategies for optimal administration of ATG-T and prevention of IARs are not well documented in the literature, and many protocols for administration are available worldwide. The Summary of Product Characteristics (SPC) recommends premedication with antipyretics, corticosteroids and/or antihistamines in order to decrease both the incidence and severity of these adverse reactions and mentions a total infusion time of not less than 6 h.¹

Corticosteroids were used as part of the pretreatment. However, there are reports on pretreatment use of corticosteroids that have been shown to be ineffective in prophylaxis of severe anaphylaxis and even increase the severity of these reactions.⁸ Other protocols advise the use of an antihistaminic.⁷

According to the SPC, severe, acute IARs are consistent with CRS, the latter being attributed to the release of cytokines by activated monocytes and lymphocytes.¹ HLH is known as an aggressive and life-threatening syndrome of excessive immune activation.⁹ It is not clear if persistent activation of macrophages and cytotoxic lymphocytes in our patient might have led to excessive cytokine production after the administration of ATG-T.

Hypersensitivity (allergy or anaphylaxis) to rabbit proteins, or any component of the formulation is mentioned as official contra-indication.¹ As the presence of rabbit antigens could have caused the severe reaction in the patient, a follow-up discussion with the parents of the patient was performed but revealed no previous exposure to pet rabbits.

As advised by the manufacturer, a skin test was not performed, because of the poor predictive value for anaphylactic reactions.¹⁰

The pharmacovigilance department of Sanofi was informed about this case.

Conclusion

This case highlights the careful use and administration of ATG-T during conditioning regimens as well as the need for strict monitoring. Optimal premedication methods to prevent or reduce infusion-related reactions associated with the use of ATG-T are warranted.

Declaration of conflicting interests

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