Clinical Experience of Alpha 1 Antitrypsin (AAT) Treatment in Pediatric Patients with Primary Immunodeficiencies Facing to Steroid Refractory (SR) Acute Intestinal Graft versus Host Disease (aGvHD)

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Abstract

Background: The only curative therapy for many primary immunodeficiencies is HSCT. aGvHD is a serious and potentially fatal complication of HSCT with an incidence of nearly %50. Furthermore, involvement of the lower gastrointestinal (LGI) tract is associated with a poor prognosis. Unfortunately, there isn't consensus about second-line therapies for steroid-refractory (SR) aGvHD. Alpha 1 Antitrypsin (AAT) is one of the second-line therapies. There isn't a study in pediatric population with acute SR-GvHD in the literature. **Method:** We retrospectively evaluated data of 3 patients that received AAT as second-line therapy for acute SR-GvHD. **Results:** Each patients' response to treatment was unique. P1 had a complete response beginning with the third dose of the treatment. P2 showed a partial response to the treatment after the second dose. Despite 8 doses of the treatment, P3 did not achieve remission. **Conclusion:** AAT may play a promising role in the treatment of severe and refractory aGvHD in children, without causing an additional immune suppression in opposite to agents which were placed in guidelines. Further studies are warranted with AAT for pediatric population.

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Alpha 1 Antitrypsin (AAT) Treatment in Pediatric SR aGvHD

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Abstract:

Background: The only curative therapy for many primary immunodeficiencies is HSCT. aGvHD is a serious and potentially fatal complication of HSCT with an incidence of nearly %50. Furthermore, involvement of the lower gastrointestinal (LGI) tract is associated with a poor prognosis. Unfortunately, there isn't consensus about second-line therapies for steroid-refractory (SR) aGvHD. Alpha 1 Antitrypsin (AAT) is one of the second-line therapies. There isn't a study in pediatric population with acute SR-GvHD in the literature.

Method: We retrospectively evaluated data of 3 patients that received AAT as second-line therapy for acute SR-GvHD.

Results: Each patients' response to treatment was unique. P1 had a complete response beginning with the third dose of the treatment. P2 showed a partial response to the treatment after the second dose. Despite 8 doses of the treatment, P3 did not achieve remission.

Conclusion: AAT may play a promising role in the treatment of severe and refractory aGvHD in children, without causing an additional immune suppression in opposite to agents which were placed in guidelines. Further studies are warranted with AAT for pediatric population.

Keywords: Alpha 1 Antitrypsin (AAT), GvHD, pediatric, primary immunodeficiency.

KEY MESSAGE:

The article provides information about a novel treatment- Alpha 1 Antitrypsin in pediatric patients with steroid-refractory acute intestinal graft versus host disease.

INTRODUCTION:

Allogeneic hematopoietic stem cell transplantation (HSCT) is a curative therapy for certain primary immunodeficiencies. Acute graft-versus-host disease (aGvHD) is a serious and potentially life-threatening complication of HSCT that can occur in about half of the patients, with lower gastrointestinal (LGI) tract involvement in about 30%. First-line treatment is generally consisting of high-dose corticosteroids but nearly %30 of patients is unresponsive.[1, 2] Steroid refractoriness is associated with poor prognosis and unfortunately, there isn't consensus about second-line therapies for steroid-refractory (SR) aGvHD.[3]

Alpha 1 Antitrypsin (AAT) is a novel experimental therapy as a second-line treatment.[3] In murine models, it's shown that AAT can suppress GvHD development and provide an alternative treatment for existing GvHD.[4,5] In literature, limited number of studies[6-10] are available. There are also recruiting clinical trials both for prevention (NCT03805789) and primary treatment (NCT04167514) of GvHD. However, only one clinical trial (NCT03805789) has participants aged >12 years and there is no published data about its use in children. In this study, we aimed to report our clinical experience with AAT treatment in the pediatric population.

METHODS:

We retrospectively evaluated data of 3 patients that received AAT as second-line therapy for acute SR-GvHD. Patients had undergone allogeneic HSCT from related or unrelated donors with reduced-intensity conditioning regimens (RIC) and had developed acute GvHD unresponsive to high dose steroids. Steroid refractoriness is defined as progression in GvHD within 3–5 days of starting the treatment or an incomplete response by 7–14 days. All patients' GvHD status was classified by Glucksberg criteria.[11] Endoscopic and colonoscopic examinations were performed and intestinal GvHD was proven by biopsies for all patients. All patients had received multiple second-line therapies before AAT administration.

Treatment protocol:

Written informed consent was obtained from all parents and permission was taken from the health authority for off-label use. Patients received an initial loading dose of human plasma-derived AAT intravenously (IV) at 90 mg/kg followed by 60 mg/kg (P1, P3) and 30 mg/kg (P2) (depending on drug availability) IV every other day for 7 doses, total 8 doses.[6] Serum AAT levels were measured at 24 and 48 hours after the infusion

of AAT. Also, regulatory T cells (CD4+ CD25+FoxP3+ lymphocytes) were assessed by flow cytometry after the first, fourth and eighth doses.

PATIENTS:

Patient 1:

A two-year-old boy, first and the only child of non-consanguineous parents was diagnosed as SCID due to IL2RG mutation at 8 months with a severe CMV pneumonia treated at ICU. Since a matched donor was not available in the family, he underwent unconditioned haploidentical transplantation from his father at 16 months. However, a primary graft failure occurred and seven months later he retransplanted from an HLA 10/10 matched unrelated donor (MUD) following an RIC regimen consisting of Treosulfan (42g/m^2), Fludarabine (150mg/m^2) and ATG (20mg/kg). CSA was preferred for GvHD prophylaxis. On post-transplant 7th day, grade I skin aGvHD was detected that Methylprednisolone 2mg/kg/day was added to the treatment. Since aGvHD of the skin did not respond to corticosteroid but progressively exaggerated, infusions (3 x) of mesenchymal stem cells and MMF were initiated followed by tacrolimus which was then switched to sirolimus. On post-transplant 63rd day, during the steroid tapering schedule, severe diarrhea (>2000cc/day) and subsequently melena and fresh intestinal bleeding occurred. A Grade IV GvHD was revealed by endoscopic and colonoscopic biopsies. Generalized ulcers were found in the whole colon; however, the area of bleeding could not be detected. Coagulation parameters were normal with insignificant thrombocytopenia (platelet levels ranging from 50 to 120x10^9/L). However, erythrocyte transfusion twice a day was required to maintain haemoglobin level. Oral budesonide and one additional mesenchymal stem cells infusion were added to the treatment. Furthermore, he did not respond to Tocilizumab (2x) (recombinant humanized anti-interleukin-6 receptor (IL-6R) monoclonal antibody) which was given in every two weeks.[12-13] Severe and several immunosuppressive agents refractory intestinal GvHD was controlled by 8 doses of alpha1-antitrypsin.(Table 1) After third dose of alpha1-antitrypsin treatment, although diarrhea started to resolve, intestinal bleeding persisted that Ankaferd Blood Stopper (a haemostatic powder approved in Turkey) [14] initiated orally (2 ml via nasogastric tube, twice a day for 7 days). After 4 days of treatment, frequency and the amount of intestinal bleeding substantially decreased while completely resolved following the first week. His oral intake increased subsequently and he went home on post-transplant 139th day.

Patient 2:

A thirteen-year-old girl (born to consanguineous parents) was diagnosed as leaky SCID due to Artemis mutation at 4 years, after multiple hospitalizations due to recurrent fever, diarrhea and bronchitis. She was referred to our centre for HSCT but unfortunately, she had conglomerate cervical lymphadenopathies on the admission. Excisional biopsy revealed marginal zone B cell lymphoma. She received 13 doses of Rituximab treatment leading to remission. Since a matched donor was not available in the family, she transplanted from an HLA 10/10 matched unrelated donor (MUD) following an RIC regimen consisting of Rituximab (375 mg/m^2), Treosulfan (42g/m^2), Fludarabine (150mg/m^2) and ATG (40mg/kg) at age of fourteen. CSA and MMF were preferred for GvHD prophylaxis. On post-transplant 21st day, severe diarrhea (1900 cc/day) and subsequently faecal occult blood occurred. A Grade IV GvHD was revealed by endoscopic and colonoscopic biopsies. Methylprednisolone (2mg/kg/day) and oral budesonide treatments were started. However, diarrhea was persistent and didn't respond to treatment, so CSA was switched to tacrolimus, infusions(x3) of mesenchymal stem cells and Tocilizumab (x1) were added to treatment respectively. Despite of all these intensive treatments, diarrhea persisted, so we decided to use AAT. After two doses of AAT, diarrhea started to resolve and the steroid tapering schedule was started. During steroid taper, after five doses of AAT, moderate transaminase elevation (AST: 241 IU/ml, ALT: 413 IU/ml) was detected as a possible side effect of the drug. We discontinued the treatment for a week until normal transaminase levels were achieved. During this period, a flare-up in diarrhea occurred and necessitated an additional dose of Tocilizumab. Subsequently, we completed AAT to 8 doses but even total 5 doses of Tocilizumab could resolve her GvHD on the 130th day. (Table 2)

Patient 3:

A ten-year-old girl (born to consanguineous parents) was diagnosed as DOCK8 deficiency due to atopic dermatitis, food allergies (egg and milk), elevated Ig E levels and elder brother's DOCK8 diagnosis at 6 months old. Although she was on regular IVIG treatment and antibiotic prophylaxis, she experienced multiple bronchitis, otitis and sepsis even disseminated BCG infection (an abscess in the right popliteal fossa with bilateral inguinal and axillary lymphadenopathies, fever, and weight loss). She also had comorbidities like esophageal papillomas, esophagitis, hepatic fibrosis, choledochal cysts, bronchiectasis and pulmonary nodules. Because of her elder brother's complicated transplantation course and the unavailability of a matched donor, she couldn't be transplanted. Finally, we decided to transplant her from her haploidentical father because of her severe malnutrition, recurrent sepsis episodes, non-healing skin wounds, chronic diarrhea, cryptosporidium infection and EBV viremia. She was transplanted following an RIC regimen consisting of Rituximab (375 mg/m^2), Treosulfan (42g/m^2), Fludarabine (150mg/m^2) and ATG (20mg/kg) at age of ten years and eight months. Tacrolimus, MMF (iv) and Post-transplantation Cyclophosphamide were preferred for GvHD prophylaxis. Her transplantation course was also challenging from the outset. On the post-transplant first day, she had catheter sepsis due to Klebsiella pneumonia requiring extended anti-microbial therapy. On the 11$^{\text{th}}$ day, diarrhea occurred due to cryptosporidium parvum. On the 14$^{\text{th}}$ day, a widespread maculopapular rash appeared. Skin biopsy revealed Grade 2 acute skin GvHD. Methylprednisolone (2 mg/kg) and subsequently infusions of MSC (x4, weekly) were added to treatment During steroid taper, on the 30$^{\text{th}}$ day, diarrhea with epigastric pain and vomiting occurred supporting intestinal GvHD. Endoscopic and colonoscopic biopsies revealed Grade IV GvHD. Because of her infectious background, we decided to use oral budesonide and AAT. Although she received 8 doses of AAT, bloody diarrhea occurred. Tocilizumab (x1) was added to the treatment. (Table 3) Unfortunately, she had septic shock due to pancreatitis requiring multiple inotropes and had respiratory distress, so she was transferred to ICU on the 78$^{\text{th}}$ day. During follow-up in ICU, her clinical status was deteriorated, she was intubated on the 85$^{\text{th}}$ day with TAMOF diagnosis. Despite all intensive treatments (plasma exchange, haemodialysis, an additional dose of MSC, etc.), she passed away on the 102$^{\text{nd}}$ day.

RESULTS:

Each patients' response to treatment was unique. P1 had a complete response beginning with the third dose of the treatment. P2 showed a partial response to the treatment after the second dose. Despite 8 doses of the treatment, P3 did not achieve remission. All patients' serum AAT levels were in normal ranges before the treatment. Only P1's serum AAT level increased gradually and was found to be the highest after the final dose. Other patients' serum AAT levels didn't change during treatment. (Table 4) Distinctly, there was an increase in the proportion of CD4+ CD25+FoxP3+ lymphocytes in all of the patients.

DISCUSSION:

The only curative therapy for many primary immunodeficiencies is HSCT. aGvHD is a serious and potentially fatal complication of HSCT with an incidence of nearly %50. Furthermore, involvement of the lower gastrointestinal (LGI) tract is associated with a poor prognosis.[1, 2]

Based on murine studies, aGvHD pathophysiology is thought to include neoangiogenesis, intestinal tract infiltration by innate myeloid cells (neutrophils and monocytes), innate and adaptive immune responses triggered by sterile damage-associated molecular patterns (DAMPS) and pathogen-associated molecular patterns (PAMPS).[15] Also since the early 1980s, the intestinal injury in aGvHD had been identified to cause protein-losing enteropathy characterized by faecal AAT elevation. [16,17]

AAT is a circulating 52-kDa glycoprotein that is produced mainly by the liver. [4] It acts as an endogenous serine protease inhibitor, inhibits neutrophil elastase and protects especially lung and liver tissues from destruction.[4,7,9] Plasma-derived and recombinant AAT are devoid of antielastase activity, but recently, its anti-inflammatory, immunomodulatory and tolerogenic features have been identified; it decreases the production of pro-inflammatory cytokines (IL-6, IL-8, TNF-a, IL-1ß), increases differentiation and maturation of Foxp3+ regulatory T cells (Tregs).[6,7,9]Because of these features, it was a candidate for GvHD treatment. After successful treatment of GvHD in murine models [4,5], clinical trials with humans have begun.

Clinical trials revealed different results. In the first phase 1/2 clinical trial [6], AAT was used as the first-line therapy after corticosteroids and the overall response rate (ORR) was found 66% (8/12 patients) with a 33% complete response rate (CRR). In another phase 2 study with 40 patients, confirming the first trial, ORR and CRR were 65% and 35%, respectively.[7] AAT serum levels and proportion of Tregs were found elevated in both studies. In another study [8], AAT was used both as a first-line (4/7) and a subsequent line (3/7) of therapy in seven patients. Unfortunately, none of the patients achieved a CR. This was attributed by the authors to the fact that all patients had grade III-IV GvHD. In a recent study, AAT was used as both a first-line (6/16) and a subsequent line (12/16) of therapy in 16 patients.[9] ORR was 44%, CRR was 27%. Similar to the previous studies, serum AAT levels were elevated, though the proportion of Tregs was decreased. All of our patients received AAT as a subsequent therapy and had various responses. Differently from the literature, only one of our patients (P1) had elevated serum AAT levels, despite in all of them, proportions of Tregs were found elevated.

As SR-aGvHD is a major cause of mortality after HSCT, there are studies with pre-emptive treatment with AAT, too. [10]Unfortunately, in a recently published study, AAT wasn't found to improve GvHD outcomes.[10] There are recruiting clinical trials both for prevention (NCT03805789) and primary treatment (NCT04167514) of GvHD with AAT. We hope that further studies both with children and adults will help to overcome the disease.

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CONFLICT OF INTEREST:

The authors have no conflicts of interest to disclose.

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