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Pilot study using tacrolimus rather than cyclosporine plus antithymocyte globulin as an immunosuppressive therapy regimen option for severe aplastic anemia in adults

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ABSTRACT

Severe aplastic anemia (SAA), which is considered to be an immune-mediated destruction of bone marrow stem cells with pancytopenia and hypoplasia, can be successfully treated with immunosuppressive therapy or hematopoietic stem cell transplantation (HSCT). Between January 2009 and December 2012, thirteen patients diagnosed with SAA were treated with tacrolimus plus rabbit antithymocyte globulin (ATG)-based immunosuppressive therapy (IST). The outcomes were then compared with our previous data for twenty-four patients administered with cyclosporine (CsA) plus rabbit ATG-based IST. All 37 cases accepted methylpredenisolone and recombinant human granulocyte colony-stimulating factor (rhG-CSF) from the first day that rabbit ATG was initiated. A total of 7 (54%) of the 13 patients in the tacrolimus group and 10 (42%) of the 24 cases in the ATG + CsA group achieved the criteria for complete response (CR); the partial response (PR) rate was 31% in the tacrolimus group and 33% in the ATG + CsA group. The median follow-up duration of the tacrolimus group and ATG + CsA group patients was 28 months and 27 months, respectively. Two patients in the tacrolimus group who were red blood cell- and platelet transfusion-dependent died, one of sepsis and the other of cerebral hemorrhage, whereas one patient died from serious infection on the 5th day after ATG was initiated in the ATG + CsA group. No clonal transformation to paroxysmal nocturnal hemoglobinuria (PNH) was observed in either group. Our data provide a possibility of using tacrolimus as part of an IST regimen for SAA in adults who have no opportunity of HSCT from human leukocyte antigen (HLA)-matched sibling donors.

Introduction

Severe aplastic anemia (SAA) is a life-threatening bone marrow failure disorder characterized by bone marrow aplasia and peripheral blood pancytopenia [1]. In most cases, the bone marrow failure is attributed to the autoimmune destruction of hematopoietic stem cells [2]. Patients diagnosed with SAA often die of infection, bleeding, or complications from severe anemia [3]. Immunosuppressive therapy (IST) and hematopoietic stem cell transplantation (HSCT) are currently the two major treatments for patients diagnosed with SAA [4,5]. In general, the outcomes of HSCT for SAA are better in children than in adults, accompanied with a better overall survival and fewer chances of graft-versus-host disease [6,7]. However, most patients diagnosed with SAA lack an HLA-histocompatible sibling; thus, IST is regarded as a primary consideration for the treatment of SAA. Antithymocyte globulin (ATG) plus cyclosporine (CsA) are administered as the standard IST [8].

As the most widely used IST for patients diagnosed with SAA, CsA has some troublesome effects that can lead to reduced therapy compliance, including hirsutism and gingival hyperplasia, along with such potential toxicity as nephrotoxicity and neurotoxicity, hypertension, electrolyte disturbance, and dyslipidemia [9]. Tacrolimus, a widely used calcineurin inhibitor, can be substituted for CsA in some cases, such as Acute Severe Colitis (ASC) [10], HSCT [11,12], and solid organ transplantation [13–15]. Additionally, Tacrolimus has a better bioavailability than cyclosporine and thus may be used for oral treatment, and its toxicity profile is appealing. However, fewer studies have been reported to support its use in adult SAA [10].

Here, we first describe the use of tacrolimus substituted for CsA as a uniform IST regimen in combination with ATG for the treatment of 13 adults diagnosed with SAA.

Materials and methods

Sample

A total of 13 newly diagnosed patients with SAA in our department from January 2009 to December 2012 were reviewed. The inclusion

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criteria were as follows: 1) patients of different ages were included who had not received immunosuppressive therapy protocols, such as CSA; 2) patients without past history of basic diseases of the heart, liver, kidney, and lung; 3) patients with active infections were excluded or completely controlled before the regular treatment was initiated; 4) HIV patients and pregnant and lactating women were excluded. The patients were confirmed as SAA according to the following criteria: 1) severe clinical manifestations and signs; 2) meeting at least two-thirds of the following hemogram-reticulocyte count ≤ 15,000/μl, absolute neutrophil count (ANC) ≤ 500/μl, and platelet count ≤ 20,000/μl; 3) seriously low hyperplasia bone marrow. Written informed consent was obtained from all patients, and the collection of clinical data was in accordance with the Declaration of Helsinki.

Treatment regimen

All 13 patients received a new IST regimen: tacrolimus combined with ATG was substituted for CsA plus ATG. Tacrolimus was used at a concentration of 0.1 mg/kg, with the final plasma concentration maintained at 8–12 ng/mL for at least one year. All patients gradually stopped the treatment with tacrolimus in the third year when their conditions were improving. However, one patient refused to stop the therapy with tacrolimus, even though his condition was well controlled; no obvious side effects were observed or influenced his quality of life during the follow-up observation. A skin test for rabbit ATG was performed to assess allergic hypersensitivity. Rabbit ATG was administered at a dosage of 3.5 mg/kg/day, with a duration of 5 days. Methylprednisolone was started on the first day and ATG was initiated and maintained at a dose of 1 mg/kg/day for 14 days to prevent serum sickness and then tapered down over the subsequent 7 days. Treatment with recombinant human granulocyte colony-stimulating factor (rhG-CSF) was considered as a supportive therapy at a dose of 5 mg/kg/day for a short course until the ANC achieved 500/μl. The concrete dosage and administration are shown in Table 1.

Component blood transfusion was performed according to the personal characteristics, as follows: red blood cells (RBCs) were transfused when Hb ≤ 50 g/L and platelet transfusions were performed at a count ≤ 10×10^9/L with the presentation of bleeding or fever. Preventive administration against fungal infections was conducted when ANC ≤ 0.3×10^9/L and treatments against common infections with antibiotic drugs were necessary with fever.

Effect evaluations

The endpoint was defined according to the responses exhibited after 12 weeks of tacrolimus treatment. The following criteria should be fulfilled for a complete response (CR), ANC > 1.5×10^9/L, hemoglobin > 100 g/L, and platelet counts > 100×10^9/L. A partial response (PR) was considered when the hemogram no longer satisfied the criteria for SAA but was still insufficient to meet the criteria for CR. The concrete criteria were defined as follows: the ANC count increased to more than 0.5×10^9/L, the hemoglobin level increased to more than 80 g/L, and the platelet count was greater than 20×10^9/L or independent of platelet transfusions. No response (NR) was defined as still transfusion dependent or satisfying the criteria for SAA. Death was classified according to the longest follow-up period. The incidence of paroxysmal nocturnal hemoglobinuria (PNH) clones was examined by the flow cytometric analysis of CD55- and CD59-expressing neutrophils or red blood cells.

Table 1
Summary of tacrolimus plus ATG based-IST regimen.

	Dose	Route	Frequency	Duration
Tacrolimus	0.1 mg/kg	IV/PO	BID	Days 1– > 365[a]
ATG	3.5 mg/kg	IV	Qday	Days 1–5
Methylpredenisolone	1 mg/kg	IV	Qday	Days 1–14
G-CSF	5 mg/kg	IM	Qday	Day 1 until ANC > 500

IST: immunosuppressive therapy; ATG: antithymocyte globulin; IV: intravenously; PO: by mouth; BID: twice-daily; Qday: once-daily; G-CSF: granulocyte colony-stimulating factor; IM: intramuscular injection; ANC: absolute neutrophil count.
[a] The final plasma concentration of tacrolimus should be maintained at 8–12 ng/mL for one year at least.

Statistical analysis

The median values and frequencies for the categorical data were described by descriptive analyses. Estimates of the survival functions were calculated using the method of Kaplan and Meier. The analyses were performed using SPSS version 17.0 for Windows (SPSS, Inc., Chicago, IL).

Results

Thirteen patients with SAA diagnosed between 2009 and 2012 who had no opportunity for HSCT underwent tacrolimus-based IST. All of these patients were compared to a previous study on ATG + CsA-based IST at our institution between 2004 and 2011, a study of 24 SAA patients who all accepted a standard treatment of combined ATG and CsA [16]. The median age of the confirmed patients in the tacrolimus group was 26, and the median observation time of these cases was 844 days (range: 108 to 1335 days).

Of the 13 cases, 7 (54%) patients in the tacrolimus group achieved the criteria for CR compared to 10 (42%) of the 24 cases in the ATG + CsA group, a group for which the median follow-up was 27 months. Basic information, the follow-up observation time, responses, and efficacy outcomes are shown in Table 2 for the tacrolimus group. The median follow-up among the cases of CR in the tacrolimus group was approximately 975 days. Compared to 8 (33%) patients achieving the criteria for PR in the ATG + CsA group, 4 (31%) patients met the criteria for PR in the tacrolimus group. The total effective rate of tacrolimus treatment in 13 patients was 85% (Fig. 1). During follow-up, two patients in the tacrolimus group died, one of sepsis and one of cerebral hemorrhage, 108 days and 806 days later, respectively, and both were red blood cell and platelet transfusion dependent. In addition, one patient died from serious infection on the 5th day after the initiation of ATG therapy in the ATG + CsA group.

One patient showed a slightly transient hyperkalemia and recovered when the dosage of tacrolimus was adjusted. Gingival hyperplasia was observed in an additional patient during the long-term maintenance therapy with tacrolimus. In our previous ATG + CsA group, prior to the ATG + CsA-based IST, 18 (75%) cases of fever were reported, including 10 with definite infection foci, and broad-spectrum antibiotics were immediately initiated in all 18 cases. A total of 18 patients were diagnosed with fungal infection, including one patient with combined pulmonary tuberculosis after IST. The patients gradually achieved remission after standardized anti-infective therapy was administered. In addition, perianal abscess still occurred in 2 patients with ATG + CsA therapy, even though all strictly continued with 1:5000 potassium permanganate sitz bath. Data on other common complications, such as hirsutism and serum creatinine, were not recorded in the present study. Neither group showed relapse nor clonal transformation. Due to the small sample size, a meaningful statistical analysis was not performed on these data.

Discussion

As a standard initial IST for SAA in adults, horse ATG and CsA results in hematologic recovery in 60% to 70% of patients and has shown excellent long-term survival responses in a few large prospective studies in the United Stated, Europe, and Japan [5,17–21]. These findings compare favorably with the total effective rate of 75% based on our initial reported experience with CsA-based IST in adult SAA [16]. The present study