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Original Article

Pharmacokinetics and pharmacodynamics of two antithymocyte globulins in treatment of pediatric aplastic anemia

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Abstract: Objective: To compare the pharmacokinetics and pharmacodynamics of antithymocyte globulins (ATGs) produced by two companies in the treatment of children with aplastic anemia (AA). Methods: Six children with acquired AA were divided into two groups. The patients in each group were treated with either R-ATG or F-ATG for 5 consecutive days. Venous blood samples were collected at time points of 0 h, 4 h, 8 h after infusion of ATGs on day 1, at the end of the infusion on day 2-5, and on d7, d21, d35, d60, d90. The plasma concentrations of ATG were measured by ELISA. Pharmacokinetic parameters of ATG was calculated using pharmacokinetics calculation software 3P97. The kinetics of peripheral absolute lymphocyte count (ALC) was monitored. The long-term efficacy was evaluated according to international standards. Results: The plasma concentration of both R-ATG and F-ATG peaked on day 3~4 after treatment with about 30~32 μg/ml, then fell gradually, reaching half of the peak level on day 21. The traces of ATG were still detectable on day 90. In addition, ALC in both groups declined significantly to a low level for a long time. No significant differences were observed between two groups in terms of the pharmacokinetic parameters and ALC. In an average follow-up period of 12 months, the total response rates (66.7%) in two groups were same. No treatment-related deaths or serious adverse reactions occurred during the treatment. Conclusion: Both R-ATG and F-ATG have similar characteristics in pharmacokinetics and pharmcodynamics in the treatment of children with AA.

Keywords: Pharmacokinetics, antithymocyte globulin, immunosuppressive therapy, aplastic anemia

Introduction

Antithymocyte globulin (ATG)-based immunosuppressive therapy (IST) was successfully used to treat aplastic anemia (AA), which has offered an effective alternative for treating severe aplastic anemia (SAA) patients who are unable to receive allogeneic hematopoietic stem cell transplantation (allo-HSCT), and significantly improved the long-term therapeutic effects, survival rate and life quality of SAA patients. As a result, IST has been widely adopted [1-4]. However, due to the lack of a reliable and convenient method to measure plasma ATG level, in spite of its nearly 40-year history in the treatment of AA, the pharmacokinetics of ATG during AA treatment has never been reported in domestic or abroad. Monitoring the plasma concentration and analyzing the major pharmacokinetic parameters during ATG treatment of aplastic anemia are of significant importance to the fully understanding of the pharmacological mechanisms of ATG, predicting the clinical efficacy, and preventing and managing the adverse reactions, as well as selecting drugs and adjusting doses for individualized therapy. Therefore, we established a method to measure the plasma the concentration of ATG and acquired the plasma concentration-time curve of ATG and other pharmacokinetic data in children under the treatment with AA.

Materials and methods

Data of cases

Six children with AA who met the diagnosis and classification standards recommended by the Guidelines for the Diagnosis and Management

Table 1. Basic information about cases and group assignment

Order	diagnosis	gender	age (years)	weight	ATG
1	VSAA	F	7	25	F-ATG (Freseniu)
2	SAA	F	3	12	R-ATG (Genzyme)
3	SAA	M	12	40	F-ATG (Freseniu)
4	SAA	M	8	26	R-ATG (Genzyme)
5	NSAA	M	4	25	F-ATG (Freseniu)
6	SAA	F	4	17	R-ATG (Genzyme)

*VSAA: very severe aplastic anemia; SAA: severe aplastic anemia; NSAA: non-severe aplastic anemia.

Table 2. Comparison of pre-treatment peripheral hemogram between F-ATGgroup and R-ATG group

	F-ATG (X±SD)	G-ATG (X±SD)	t	P
RBC ($\times10^{12}$/L)	2.5767±0.42852	2.7500±0.13229	-0.669	0.540
HB (g/L)	76.0000±12.12436	75.3333±10.26320	0.073	0.946
WBC ($\times10^{9}$/L)	2.8000±0.96437	3.3667±3.05505	-0.306	0.775
Neu (%)	16.6667±9.86577	13.3333±5.03322	0.521	0.630
ANC ($\times10^{9}$/L)	0.5000±0.42000	0.3633±0.22811	0.495	0.646
Lym (%)	80.3333±8.62168	79.6667±9.50438	0.090	0.933
ALC ($\times10^{9}$/L)	2.1700±0.72381	2.8167±2.83592	-0.383	0.721
Ret (%)	0.8667±1.15470	0.3333±0.15275	0.793	0.508
ARC ($\times10^{9}$/L)	13.1533±31.40151	4.6233±7.25566	0.996	0.415
Plt ($\times10^{9}$/L)	16.6667±5.85947	13.3333±4.04145	0.811	0.463

of Aplastic Anemia as well as the IST therapeutic indications (5), were admitted for the ATG-based IST from November 2011 to May 2012. Congenital AA was eliminated for all patients by a comprehensive clinical observation as well as Mitomycin-Chromosome Breakage test. The recruited patients included 3 males and 3 females, aged 3 to 12 years with a median of 6 years old. One case was classified as very severe aplastic anemia (VSAA), 4 were severe aplastic anemia (SAA) and 1 was transfusion-dependent non-severe aplastic anemia (NSAA). Patients were assigned into two groups based on the order of their time of admission into the hospital. The 1st, 3rd and 5th patients were assigned into group 1, and group 1 patients received anti-human T lymphocyte globulin (F-ATG, Germany, Fresenius Company) treatment; the 2nd, 4th and 6th patients were assigned into group 2, and group 2 patients received rabbit anti-human thymocyte globulin (R-ATG, the United States, Genzyme Corporation) treatment. The general information of two groups of children who received R-ATG and F-ATG treatment are shown in **Table 1**. There was no significant difference in the pre-treatment peripheral hemogram between two groups (**Table 2**).

Clinical treatments

ATG treatment: The treatment regimen was: 3.5 mg/kg IV once a day for 5 consecutive days for R-ATG, or 5 mg/kg IV once a day for 5 days for F-ATG. Before the treatment was started an allergy test was conducted on the first day by administration of 5 mg R-ATG-F or 2.5 mg R-ATG-G dissolved in 100 ml saline solution to patients by slow IV infusion in 1 hour before treatment was started. ATG infusion was started right after the allergy test during which no adverse reaction had been observed. ATG was diluted with 500 ml saline solution and administered by IV infusion at a steady rate in 8 hours. In order to prevent anaphylaxis and serum disease, corticosteroid methylprednisolone was co-administered at 30 mg/m^2.d for 14 consecutive days. The dose of methylprednisolone was reduced gradually to 0 by day 30.

Adjuvant therapy: CSA (5 mg/kg.d) was taken orally with the plasma concentration maintained at 200~400 ng/ml. The patients received adjuvant therapy for at least 6 months. The treatment was maintained for 1 more year after the hemogram stabilized. Subsequently, the dose was gradually reduced by 10% of the initial dose every 3 months. At the same time, the patients orally took usual dose of androgens and conventional Chinese medicines.

Supportive treatment: As suggested by the Guidelines for the Diagnosis and Management of Aplastic Anaemia, platelet transfusion was given to the patient to keep the peripheral blood Plt level above 20×10^9/L during ATG treatment. When serum sickness occurred, methylprednisolone at 40 mg/m^2.d as well as appropriate antibiotics and platelet transfusion was administered. In case of an infection, potent broad-spectrum antibiotics and short-term granulocyte colony-stimulating factor (G-CSF) were given to patients.

Table 3. Criteria for response to IST in aplastic anemia

A. Response criteria for severe aplastic anemia (SAA)	
NR	Still severe
PR	Transfusion independent
	No longer meeting criteria for severe disease
CR	HB normal for age
	ANC >1.5×10^9/L
	Plt >150×10^9/L
B. Response criteria for non-severe aplastic anemia (NSAA)	
NR	Worse or not meeting criteria below
PR	Transfusion independence (if previously dependent)
	or doubling or normalisation of at least one cell line
	or increase of baseline HB of >30 g/L (if initially <60 g/L)
	or increase of baseline ANC of >0.5×10^9/L (if initially <0.5)
	or increase of baseline Plt of >20×10^9/L (if initially <20)
CR	Same criteria as for severe disease

NR: no response; PR: partial response; CR: complete response.

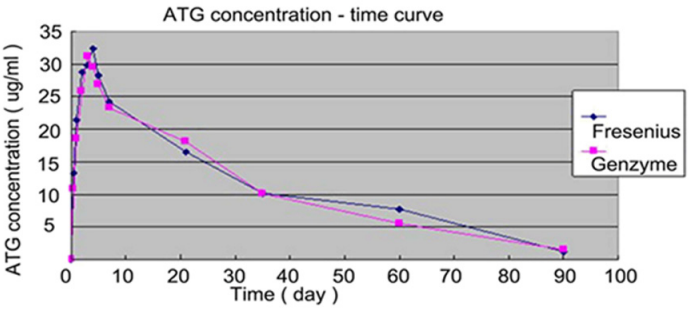

Figure 1. Change in plasma ATG concentration.

Determination of efficacy: The Camitta standard recommended by the Guidelines for the Diagnosis and Management of Aplastic Anaemia as shown in **Table 3** was adopted to determine the efficacy of ATG treatment.

ATG pharmacokinetic data detection

Sample collection: Venous blood samples of 2 ml were collected before, during and after ATG treatment, for a total of 12 time points: at 0 h, 4 h, 8 h on day 1; at the end of the infusion on day 2 to 5; and on d7, d21, d35, d60, d90 after treatment. During day 1 to 5, the venous blood was drawn from the contralateral arm of ATG infusion.

Quantitation of serum ATG concentration by ELISA assay: Serum ATG concentration was measured by using an ATG test kit (Shanghai research Biological Co. Ltd.) by following the manufacturer's instructions. Briefly, the 96 well plates were coated with a 1:2000 diluted monoclonal mouse anti-rabbit IgG antibody and blocked with 200 μl/well blocking solution at 4°C overnight. The serum samples were diluted 1:20 with PBS containing 0.1% BSA and added to the plates at 100 μl/well. Normal serum was used as negative control. The plates were incubated at 37°C for 2 hours to allow ATG to bind to the antibody immobilized on the plates. The plates were washed with PBS for 3 times and an HRP-labeled secondary goat anti-rabbit IgG polyclonal antibody, diluted with PBS containing 0.1% by 2500 fold, was added to the plates at 100 μl/well. The plates were incubated at 37°C for 1 more hour, and washed with PBS for 5 times. 100 μl TMB substrate was added to each well and the plates were incubated at room temperature for 30 min to allow color to develop. The color development was stopped by addition of 100 μl stopping reagent to each well. The absorbance at 450 nm was measured on a microplate reader (Model, Manufacturer?).

Pharmacokinetic parameter calculation: Based on plasma concentration data inputted, ATG pharmacokinetic parameters were calculated by using the practical pharmacokinetics 3P97 software.

Absolute lymphocyte count change detection

Absolute lymphocyte count (ALC) of peripheral blood lymphocyte was done on days 1 to 12, 15, 21, 28, and in the second and third months to compare the variation between F-ATG and R-ATG groups.

Statistical analyses

Data were analyzed by using Microsoft Excel 2007 and the SPSS17.0 statistical software and expressed as mean (X) ± standard deviation (SD). Non-parametric tests (Mann-Whitney and Kolmogorov-Smirnov test) were conducted to compare among groups. A *P*-value less than 0.05 indicates significant difference.

Table 4. R-ATG group plasma concentration values at various timepoints (μg/m)

Time	R-ATG (n=3)	F-ATG (n=3)	t	P
0 h	0	0		
4 h	10.80±0.96	13.25±4.90	0.850	0.443
8 h	18.51±1.95	21.38±8.25	0.586	0.589
d2	25.80±3.70	28.71±8.50	0.543	0.616
d3	31.17±4.07	29.84±3.49	0.431	0.689
d4	29.56±3.15	32.39±7.12	0.629	0.563
d5	26.92±3.24	28.23±3.14	0.503	0.641
d7	23.27±2.25	24.21±0.80	0.676	0.536
d21	18.05±5.84	16.50±0.83	0.455	0.673
d35	10.14±1.64	10.19±2.80	0.021	0.385
d60	5.55±1.91	7.74±3.59	0.064	0.510
d90	1.53±0.93	1.22±1.29	0.337	0.753

Results

Calculation of ATG concentration

The absorbance values for standard samples were analyzed using the software SPSS17.0 and a regression model was created by the software. The regression equation was: independent variables (y) =-0.398311+4.8850331 dependent variable (x), where the ATG concentrations of standard samples was independent variables, and the OD450 values for standard samples with the blank subtracted was dependent variables. The correlation coefficient (R) was 0.9992203. The lowest concentration of standard sample at which ATG was detectable was taken as the detection sensitivity.

The time-concentration curve of serum ATG concentration during treatment

As shown in **Figure 1**, the blood concentration of ATG raised quickly on the first day, with the highest concentration being seen at the end of transfusions (8 h). The concentration continued to increase and peaked (exceed 30 μg/ml) on day 3~4. The blood concentration of ATG started to fall slowly from day 5 to about 1/2 of the peak level (about 16~18 μg/ml) on day 21. Traces of ATG could still be detected on day 90. Interestingly, the peaking of blood ATG during the treatment was immediately followed by a steady decline which lasted for a long time, without an obvious plateau seen in between. The pharmacokinetics of F-ATG and R-ATG were compared by statistical analysis. As are shown in **Figure 1** and **Table 4**, no significant difference in the plasma ATG concentration between two groups was found at various time points.

Pharmacokinetic parameters

Based on the plasma drug concentration data, a two-compartment model was established by using the practical pharmarcokinetics 3P97 software. The major pharmacokinetic parameters, including distribution half-life (t1/2α), elimination half-life (t1/2β), area under the curve (AUC), volume of distribution (Vc), clearance (CLs), elimination rate constant (K10), transfer rate constants (K12, K21), rate constant distribution, rate constant elimination (A, B and α, β), were also derived. The measured values were used as peak concentration (Cmax) and time-to-peak (Tmax). As is shown in **Table 5**, no significant difference was found in major pharmacokinetic parameters including drug concentration and distribution data (t1/2α, Cmax, Tmax and Vc) and drug clearance related data (t1/2β, CLs, K10), between the R-ATG group and F-ATG group.

Peripheral lymphocyte counts changes after ATG treatment

The absolute lymphocyte counts (ALC) significantly declined after ATG treatment in all cases. The lowest counts were seen during day 2-8 and remained lower than normal for months after ATG treatment. As are shown in **Table 6** and **Figure 2**, no significant difference was found in ALC at various time points between the two groups.

Effectiveness and adverse reactions

Effectiveness: After ATG-based CIS treatment, 6 patients were followed up until February 2014. Complete response (CR) was achieved in 2 cases, partial response (PR) in 2 cases, and no response (NR) in 2 cases. Taken together, the total response rate was 66.7% (4/6). Each group had a NR patient, and these patients are still receiving component transfusion and supportive therapies.

Adverse reactions: Two patients developed fever, chills and other types of allergic reactions during the first 2 days of ATG treatment. When this occurred, ATG infusion was paused and

Table 5. Pharmacokinetic parameters of ATG

Parameters (unit)	Parameter value		P
	Genzyme (n=3)	Fresenius (n=3)	
A (μg/ml)	7.79±7.44	7.11±7.93	>0.05
A (L/d)	0.36±0.26	0.73±1.02	>0.05
B (μg/ml)	532.77±86.77	435.08±300.68	>0.05
B (L/d)	0.03±0.01	0.04±0.03	>0.05
t1/2α (d)	2.46±1.24	2.4±0.99	>0.05
t1/2β (d)	21.56±4. 53	22.75±3.67	>0.05
K10 (L/d)	0.03±0.01	0.06±0.04	>0.05
K12 (L/d)	0.05±0.06	0.37±0.63	>0.05
K21 (L/d)	0.31±0.20	0.34±0.36	>0.05
Vc (L)	0.53±0.05	0.61±0.27	>0.05
AUC (mg/L·d)	902.75±142.59	1004.1±142.75	>0.05
CLs (L/d)	0.02±0.01	0.03±0.02	>0.05
Cmax (μg/ml)	31.64±3.3	36.75±3.73	>0.05
Tmax (d)	3.67±1.15	3.33±1.15	>0.05

Table 6. Comparison of changes in ALC between the F-ATG and R-ATG groups

	F-ATG (X±SD)	R-ATG (X±SD)	t	p
D1	3.7367±2.60558	3.2400±1.51681	0.285	0.790
D2	0.4367±0.30665	0.4500±0.18028	-0.065	0.951
D3	0.6433±0.47078	0.4033±0.16743	0.832	0.452
D4	0.6400±0.38575	0.3367±0.22811	1.172	0.306
D5	0.7233±0.40204	0.2100±0.16523	2.046	0.110
D6	0.6933±0.46058	0.1667±0.05774	1.965	0.121
D7	0.6467±0.50846	0.2100±0.16523	1.415	0.230
D8	0.4233±0.19655	0.3000±0.18682	0.788	0.475
D9	0.4467±0.22480	0.2800±0.12124	1.130	0.322
D10	0.7100±0.64133	0.3033±0.26083	1.017	0.367
D11	1.2767±1.20981	0.3400±0.12166	1.334	0.253
D12	0.6633±0.31786	0.4400±0.15100	1.099	0.333
D15	0.9767±0.61452	0.9200±0.33645	0.140	0.895
D21	1.2667±0.87369	0.9900±0.20075	0.535	0.621
D28	1.2733±0.91659	1.0600±0.22716	0.391	0.716
2 m	1.5900±0.99454	1.1367±0.20648	0.773	0.483
3 m	1.2733±0.80351	1.2700±0.18083	0.0007	0.995

anti-allergy treatment was given to the patients. ATG infusion was resumed once the symptoms of allergy disappeared. 5 cases developed symptoms of serum sickness including fever, rash, or joint pain between day 10 and 14 of ATG treatment. These symptoms eased off in 1 to 3 days after corticosteroids treatment was given. 1 case developed pulmonary fungal infection 1 month after ATG treatment, which was controlled by antifungal therapy. None of the remaining 5 patients developed serious infectious or bleeding complications. No serious organ damage or death occurred during the ATG treatment.

Discussion

ATG is a purified antibody against human T lymphocytes, which can be produced by animals immunized with human thymocytes or T lymphocytes, such as rabbit, horse, pig, etc. Currently, the "immune-mediated" pathogenic mechanism by which abnormal function of T lymphocytes causes immune attack of bone marrow hematopoietic cells, leading to aplastic anemia, has become an international consensus [7-10]. ATG can ablate abnormal T lymphocytes via specific antibody-mediated cytotoxicity and reverse the "immune-mediated" pathogenic mechanisms in aplastic anemia. The total effectiveness of ATG in treating aplastic anemia can reach 80%, which has been evidenced by its 40 years of history of application in AA treatment. Therefore, the CIS therapy combining ATG with CSA has been recommended as the first-choice treatment for childhood SAA that can't accept allo-HSCT therapy and blood transfusion-dependent NSAA [5, 7]. Although ATG has been widely used in clinics, the pharmacokinetic study of ATG in AA treatment has not been reported yet.

Since ATG is produced in animals, it can trigger allergies, serum sickness and other adverse reactions in human body. In addition, due to its immunosuppressive effect, ATG can increase the risk of secondary infection. Besides, although much effort has been invested over the years in studies on potential factors that may affect the effectiveness of ATG, currently little is known about the prediction indicators for ATG effectiveness in individual patients. What's more, even when a response has been observed, the hematopoietic reconstitution and the degree of effectiveness can be uncertain in individual patients. Pharmacokinetic studies, however, will help understand the metabolic process of the drug in the body and lay foundations for further clarifying the mechanism of drug action and predicting

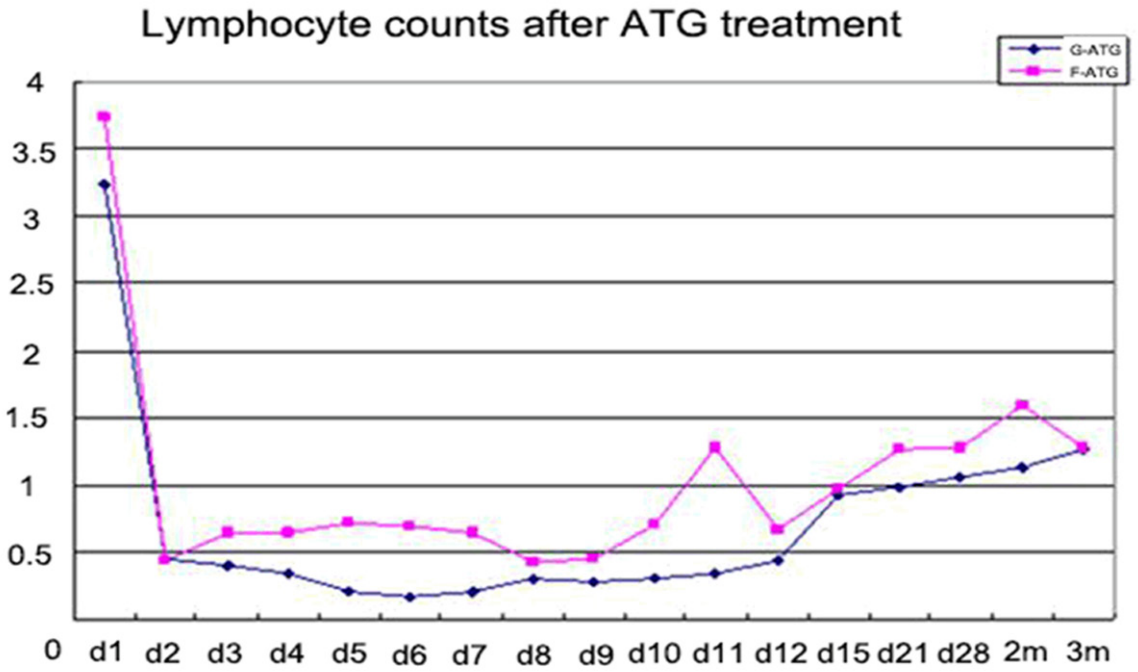

Figure 2. Lymphocyte counts after ATG treatment.

efficacy and adverse reaction in individual patients.

ATG preparations currently used in Mainland China include F-ATG (Fresenius) and R-ATG (Genzyme). This study used a double antibody sandwich ELISA method to determine the se-r um concentration of ATG. After repetitive experiments, we found that this method had high specificity for both brands. Additionally, the inter-batch and intra-batch variances were small by our measurement using this method, suggesting that the results by this method were reproducible and reliable.

This study revealed that the ATG concentration in plasma raised quickly after ATG treatment, and peaked on day 3-4, but was cleared slowly, with the concentration declined to ½ of the peak value by day 21, which matches the elimination half-life (t1/2β) of 21 to 22 days that was shown in pharmacokinetic analysis, and is comparable to the half-life of 16-24 day for human immunoglobulin. ATG was readily detected on day 90 after treatment, suggesting that ATG can remain in the body and function for a long time. R-ATG and F-ATG were produced by immunization of rabbit with human thymocytes and T-cell leukemia cells (Jurkat) respectively. Although the sources of the immunogens were different, T lymphocytes share almost identical antigen determinants with Jurkat cells. Therefore, both have been successfully applied in the treatment of aplastic anemia, or the pre-treatment for hematopoietic stem cell transplantation [11, 12].

Horse-ATG was used recommended for use as the first choice treatment for aplastic anemia. However, due to the difficulty in the supply of horse-ATG, rabbit-ATG has gradually replaced horse-ATG and gained the status as the first choice in the recent years [5]. In Mainland China, the supply of ATG has not been reliable. It was not unusual that only one brand (R-ATG or F-ATG) was available in a certain period in recent years. To our relief, our data showed that no significant difference was found in terms of effectiveness, pharmacokinetics and side effects between R-ATG and F-ATG.

In this study, no treatment-related death or serious adverse event occurred in patients receiving ATG treatment, indicating that the current ATG dose is safe and tolerable. However, due to the small size of cases in this study and a short period of follow-up, further studies in the future would be needed, and the relationship between pharmacokinetic parameters and efficacy or adverse effects also requires further study with larger case number. Despite of this, we have successfully established a simple and

reliable method to quantitate plasma ATG in patients plasma concentrations and pharmacokinetic successfully, which has laid a solid foundation for future in-depth research.

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Disclosure of conflict of interest

None.

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