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ORIGINAL ARTICLE

Analysis of infusion-site reactions in renal transplant recipients receiving peripherally administered rabbit antithymocyte globulin as compared with basiliximab

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Summary

Antithymocyte globulin rabbit (r-ATG) has been used for the treatment and prevention of acute rejection in renal transplant recipients (RTR). Current manufacturer recommendations for r-ATG dictate the need for administration through a high-flow vein (central line). Previous studies have shown peripheral administration of r-ATG to be safe; however, these studies suggest the co-administration of heparin and hydrocortisone and did not compare the infusion-site reaction rates to a control group. A retrospective analysis was conducted of adult RTR receiving r-ATG or basiliximab between January 2004 and October 2006. Each agent was administered through a dedicated peripheral line. The primary endpoint was the incidence of infusion-site reactions. Other endpoints included the need to replace the intravenous catheter and the incidence of systemic thrombosis within 1 month of transplantation. During the study period, 152 peripheral infusions of r-ATG and 92 peripheral infusions of basiliximab were administered. No difference in infusion-site reactions was noted between the groups. There was also no difference either in the need for peripheral line replacement or the rates of systemic thrombosis. Peripheral administration of r-ATG is safe and can be infused without concomitant heparin and hydrocortisone. This method of r-ATG infusion was shown to be as safe as peripherally administered basiliximab.

Introduction

Rabbit antithymocyte globulin (r-ATG) and equine antithymocyte globulin (e-ATG) are polyclonal antithymocyte agents available in the United States for use in solid organ transplantation [1,2]. Antithymocyte globulin (ATG) preparations have been used for decades in renal transplantation for induction therapy and treatment of cellular rejection [2–4]. It has been the standard practice that either of the ATG preparations when administered should be via central line in order to avoid thrombophlebitis, which is suggested to occur in 1% to 5% of patients treated, reportedly caused by peripheral infusion [5]. The manufacturers of both ATG formulations recommend that the agents be administered through a high-flow vein.

Three studies have demonstrated safe administration of the ATG preparations via peripheral infusion [6–8]. However, each of these studies utilized and recommended the concomitant administration of heparin and hydrocortisone mixed in the ATG infusion solution. One case series evaluating outcomes of peripherally administered r-ATG given without heparin noticed a high-rate of deep vein

thrombosis (DVT) [9]. None of these previously published reports have compared the incidence of r-ATG-induced infusion-site reactions to a control group [6–9].

At our institution, we have routinely administered r-ATG via peripheral infusion to patients, without the use of concomitant heparin and/or hydrocortisone in infusion solutions. This practice has helped avoid the need for placing and maintaining central lines and/or cannulating arteriovenous fistulas after renal transplantation. Although the use of hydrocortisone and heparin to infusate in patients receiving antibiotics, ATG and other high-protein solutions has been suggested to reduce the risk of phlebitis, the routine practice of combining these drugs cannot be recommended without trials that show clear benefit [6,10]. Possible risks associated with concomitant heparin include altered coagulation test results or increased risk of bleeding, heparin-induced thrombocytopenia (HIT) and the need to monitor for HIT [10]. We, in this article, review our inpatient experience in renal transplant recipients (RTRs) over a 2-year period, comparing peripheral vein infusion of r-ATG with that of basiliximab. Basiliximab is a chimeric monoclonal antibody used for induction in RTR [11,12]. The manufacturer of basiliximab states that the medication can be administered via any intravenous line, either central or peripheral [5]. The incidence of infusion-site reactions observed with basiliximab is low (<1%) and basiliximab administration has not been associated with thrombophlebitis or systemic thrombosis [5,11].

The main objective of this study was to determine the safety of peripherally administered r-ATG, given without concomitant heparin and hydrocortisone, as measured by the incidence of infusion-site reactions (i.e. erythema, induration, pain, swelling, thrombophlebitis, thrombosis), in comparison to a group of patients receiving basiliximab through a peripheral line.

Materials and methods

Study design

This is a single-center, retrospective study of a cohort of consecutive patients undergoing renal transplant. All RTRs, treated between the period January 1, 2004 and October 30, 2006, were identified for review. Individual infusions were assessed. The study was designed to include patients aged 18 years or older. Any infusion administered via a central line was excluded from the analysis.

This study was approved by our institutional review board as a retrospective analysis; therefore, informed consent was not required. Inpatient and outpatient medical records were reviewed for demographic data, transplant characteristics, infusion-site reactions and systemic thrombosis.

Patients and intervention

Ninety-one patients were included in this analysis and were divided into two groups depending on the medication administered, r-ATG ($n = 45$) or basiliximab ($n = 46$). Individual infusions were included for analysis only when there was clear documentation that the dose was given through a peripheral vein. Patients were not randomized into these treatments groups. Patients were chosen to receive a specific induction therapy agent based on our immunosuppressive protocols. In general, high-risk individuals [re-transplants, panel-reactive antibody (PRA) > 30, desensitized patients, African-Americans] and those receiving our rapid-steroid withdrawal maintenance regimen (i.e. corticosteroids withdrawn at 2 weeks) would receive r-ATG. However, some high-risk patients with a history of significant infectious diseases or malignancy would receive basiliximab. Low-risk patients (initial transplant, white or Asian descent) would receive basiliximab.

In the r-ATG group, a total of 152 peripheral infusions were evaluated (not all doses during a course of therapy were given via a peripheral line). The r-ATG was dosed at 0.75–1.5 mg/kg/day, depending upon the need for dose reductions resulting from thrombocytopenia and/or leukopenia. All doses were diluted in normal saline to a final concentration of 1 mg/ml, with no other additives. The initial r-ATG infusion was instructed to be given over 4–6 h, with subsequent doses to be infused over 2–4 h. The manufacturer of r-ATG recommends a more diluted final concentration (0.5 mg/ml) and for infusions to be completed over a longer period of time. However, it is our experience that our current concentration and infusion times are well tolerated. In the basiliximab group, a total of 92 peripheral infusions were evaluated. Basiliximab was administered at 20 mg/dose and it was reconstituted with 50 ml of normal saline. The recommended infusion time for basiliximab was 30–60 min. Both medications were administered through a dedicated peripheral line. The use of diphenhydramine and acetaminophen was allowed on a patient-to-patient basis for prevention of systemic infusion-related reactions.

Clinical definitions

A complete chart review, including evaluation of the intravenous (IV) placement documentation form used at our institution, was completed for all patients in this study. The IV documentation form serves as a tool for our hospital's phlebotomy and nursing teams to record and follow IV access sites and prompts nurses to record any infusion-site reactions that may occur. Although this form has not been externally reviewed for precision and

accuracy, it is used universally at our institution for monitoring of all IV infusions. Infusion-site reactions are well documented using this form, which includes a phlebitis rating scale ranging from zero (no pain, redness, swelling or induration) to four (pain with either redness or swelling, plus induration of greater than 3 inches). Nurses caring for transplant recipients receiving an antibody preparation are asked to perform frequent monitoring of these patients. When administering r-ATG, nurses are asked to monitor the patient during the initiation of the infusion, and again after 15, 60, 120, 240 and 360 min. When administering basiliximab, nurses are asked to monitor the patient during the initiation and conclusion (30 min) of the infusion. The nurses are asked to assess the infusion site for adverse events during these monitoring time points.

The IV documentation form, in conjunction with caregiver evaluations, was reviewed for any incidence of infusion-site reactions, which was the primary endpoint of this analysis. Infusion-site reactions are a composite endpoint that included the incidence of infusion-related pain, erythema, swelling, thrombophlebitis, thrombosis or induration. Each of these reactions were clearly documented and described in the patient charts. Secondary outcomes measures that were evaluated included the need for premature removal or replacement of the peripheral line and the incidence of systemic thrombosis [i.e. DVT, pulmonary embolism (PE), allograft thrombosis]. Other systemic effects seen with r-ATG administration such as chills, fever, leukopenia, and thrombocytopenia were not evaluated in this analysis.

Statistics

Sample-size estimation was based on the incidence of infusion-site reactions observed in previous reports (incidence of 5% with r-ATG and <1% with basiliximab) [5]. At a significance level $\alpha = 0.05$, 128 total infusions (85 r-ATG and 43 basiliximab) were needed to detect a difference in infusion-site reactions and achieve a power of 80%. Categorical variables were analyzed using the Fisher's exact test. The Student's *t*-test was used to compare mean values of continuous variables. Statistical analysis was performed using GraphPad InStat version 3.0 for Windows (GraphPad Software, San Diego, CA, USA).

Results

During the study period, 244 total peripheral infusions were evaluated (r-ATG = 152; basiliximab = 92). None of the infusions in either group were administered with concomitant heparin or hydrocortisone (or other additives). Patient baseline demographics data were similar between the two groups and are summarized in Table 1. One difference seen between the two groups was that a higher percentage of patients in the r-ATG group received their allograft from a deceased donor (62.2% vs. 39.1% with basiliximab; $P = 0.04$).

There were four (2.6%) infusions in four different patients associated with at least one infusion-site reaction in the r-ATG group and four (4.3%) infusions in four different patients in the basiliximab group [P = nonsignificant (NS)]. Analysis of the different types of infusion-site reactions revealed that pain (r-ATG = 2 vs. basiliximab = 2; P = NS) erythema (r-ATG = 2 vs. basiliximab = 2; P = NS) and swelling (r-ATG = 1 vs. basiliximab = 2; P = NS) occurred at similar rates in both groups. The severity of these adverse events were considered mild for both groups (severity rating score; r-ATG = 1.3 vs. basiliximab = 1.5; P = NS). In the patients that developed these infusion-site reactions, all subsequent doses continued to be administered through a peripheral line. Neither agent was associated with thrombophlebitis, thrombosis (localized) or induration. One of the patients in the r-ATG group required line replacement as compared with no such requirement from any of the patients receiving basiliximab (P = NS). Systemic thrombosis has been reported with r-ATG; thus we evaluated the rates of DVT, PE and allograft thrombosis within a month of transplantation. No cases of DVT or PE were seen, but allograft thrombosis did occur in two patients from each group (P = NS). As mentioned earlier, the use of diphenhydramine and acetaminophen was allowed on a patient-to-patient basis for prevention of systemic infusion-related reactions. Five of the 152 infusion of r-ATG and none of 92 infusions of basiliximab were given after premedication (P = NS). A summary of peripheral infusion-related complications is compiled in Table 2.

Table 1. Baseline demographic data and transplant donor type.

	r-ATG [*n* = 152 infusions (45 patients)]	Basiliximab [*n* = 92 infusions (46 patients)]	*P*-value
Age (years; mean ± SD)	55.5 ± 14.9	50.7 ± 12.5	0.10
Weight (kg; mean ± SD)	74.8 ± 14.0	76.3 ± 16.5	0.64
Gender (Male, %)	24 (53.3)	29 (63)	0.40
Transplant donor type			
Living donor (%)	17 (37.8)	28 (60.9)	0.04*
Deceased donor (%)	28 (62.2)	18 (39.1)	

r-ATG, antithymocyte globulin rabbit.
*Statistically significant difference.

Table 2. Complications associated with peripheral infusions.

	r-ATG	Basiliximab	*P*-value
Infusions associated with infusion-site reactions (%)	4/152 (2.6)	4/92 (4.3)	0.48
Pain (%)	2/152 (1.3)	2/92 (2.2)	0.63
Erythema (%)	2/152 (1.3)	2/92 (2.2)	0.63
Swelling (%)	1/152 (0.7)	2/92 (2.2)	0.56
Thrombophlebitis (%)	0/152 (0)	0/92 (0)	–
Thrombosis (%)	0/152 (0)	0/92 (0)	–
Induration (%)	0/152 (0)	0/92 (0)	–
Mean infusion-site reaction severity score (0–4; mean ± SD)	1.3 ± 0.5	1.5 ± 0.6	0.63
Premature removal or replacement of IV line (%)	1/152 (0.7)	0/92 (0)	1.00
Systemic thrombosis (DVT, PE or allograft thrombosis) within 1 month of transplantation (%)	2/45 (4.4)	2/46 (4.3)	1.00
Patients administered premedication with acetaminophen and diphenhydramine (%)	5/152 (3.3)	0/92 (0)	0.16

r-ATG, antithymocyte globulin rabbit; IV, intravenous; DVT, deep vein thrombosis; PE, pulmonary embolism.

Discussion

Manufacturer's instructions dictate that r-ATG be administered via high-flow vein, typically a central line. Institutions have previously reported on the successful use of peripheral r-ATG protocols [6–8]. However, to our knowledge, this is the first study to examine the incidence of infusion-site reactions of peripherally administered r-ATG, when compared with basiliximab. In addition, this is the first analysis to report on peripherally administered r-ATG without concomitant heparin and hydrocortisone.

Our study found no difference in infusion-site reactions between peripherally administered r-ATG and that of basiliximab. Among the r-ATG group, 91.1% of patients received the medication without infusion-site complications. The four r-ATG infusions associated with infusion-site reactions were mild and there were no reports of serious adverse events such as thrombosis or thrombophlebitis. The incidence of systemic thrombosis was low in both groups.

The early removal of central venous catheters is advantageous in the immunocompromised host, as these lines increase the risk of infection. Although we did not explore the pharmacoeconomic advantages of peripherally administered r-ATG, we speculate that this practice may permit early hospital discharge and thus shorten overall length of stay and decrease costs. Historically, peripherally infused r-ATG is administered concomitantly with heparin and hydrocortisone and this practice is not without risks. Heparin use may increase bleeding risk, alter coagulation tests and lead to HIT. Thrombocytopenia occurs in greater than 35% of patients receiving r-ATG [5]. When r-ATG is co-administered with heparin, the etiology of any decrease in platelets may be more difficult to diagnose and may delay appropriate treatment.

We acknowledge the limitations of our study. Data was collected at a single center and done so in a retrospective manner. Resulting from the nature of the data collection, adverse effects may be prone to under-reporting. Documentation of infusion-site reactions, the primary endpoint, is somewhat subjective and is subject to inter-observer variability. The IV documentation form that we utilize has never been tested for precision and accuracy. Also, during this analysis we were unable to evaluate the total infusion duration times of the r-ATG.

Given this analysis, we conclude that r-ATG may be safely administered via peripheral vein, without concomitant heparin and hydrocortisone. The early removal of central venous catheters and the lack of need to administer with concomitant medications may decrease overall hospital costs and medication-related adverse events.

Authorship

ALE, KR and SG: participated in research design. ALE, KR, SKM, AKC, SGT and SG: participated in the writing of the paper. ALE, AKC and SG: participated in the performance of the research. ALE, SKM, AKC, SGT and SG: participated in data analysis.

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