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Rabbit anti-thymocyte globulin for the prevention of acute rejection in kidney transplantation

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This report describes the results of 2 international randomized trials (total of 508 kidney transplant recipients). The primary objective was to assess the noninferiority of rabbit anti-thymocyte globulin (rATG, Thymoglobulin®) versus interleukin-2 receptor antagonists (IL2RAs) for the quadruple endpoint (treatment failure defined as biopsy-proven acute rejection, graft loss, death, or loss to follow-up) to serve as the pivotal data for United States (US) regulatory approval of rATG. The pooled analysis provided an incidence of treatment failure of 25.1% in the rATG and 36.0% in the IL2RA treatment groups, an absolute difference of −10.9% (95% confidence interval [CI] −18.8% to −2.9%) supporting noninferiority (noninferiority margin was 10%) and superiority of rATG to IL2RA. In a meta-analysis of 7 trials comparing rATG with an IL2RA, the difference in the proportion of patients with BPAR at 12 months was −4.8% (95% CI −8.6% to −0.9%) in favor of rATG. In conclusion, a rigorous reanalysis of patient-level data from 2 prior randomized, controlled trials comparing rATG versus IL-2R monoclonal antibodies provided support for regulatory approval for rATG for induction therapy in renal transplant, making it the first T cell–depleting therapy approved for the prophylaxis of acute rejection in patients receiving a kidney transplant in the United States.

KEYWORDS

autoimmunity, clinical research/practice, clinical trial, immunosuppressant – polyclonal preparations: rabbit antithymocyte globulin, immunosuppression/immune modulation, immunosuppressive regimens – induction, kidney (allograft) function/dysfunction, kidney transplantation/nephrology

Rita R. Alloway and E. Steve Woodle are co–first authors.

Abbreviations: BPAR, biopsy-proven acute rejection; CI, confidence interval; CMV, cytomegalovirus; FDA, US Food and Drug Administration; IL2RA, IL-2 receptor antagonist; ITT, intent-to-treat; MMF, mycophenolate mofetil; rATG, rabbit anti-thymocyte globulin; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

1 | INTRODUCTION

Induction immunosuppressive therapy in kidney transplantation is used to reduce the incidence and severity of acute rejection, delay the initiation of calcineurin inhibitors, and/or facilitate minimization of maintenance corticosteroid or calcineurin inhibitor therapy.[1,2] Induction immunosuppression has traditionally included T cell–depleting or non–T cell–depleting therapy.[3-5] Before the approval of rabbit anti-thymocyte globulin [rATG] in 2017, the non–T-cell–depleting monoclonal interleukin-2 (IL-2) receptor antagonists (IL2RAs) basiliximab and daclizumab (the latter was removed from the market in 2009) represented the only Food and Drug Administration (FDA)-approved induction agents for kidney transplant in the United States.[6]

Rabbit ATG was first approved in the United States in 1998 for the treatment of acute rejection in renal transplantation.[7] During the past 2 decades, rATG has become the most frequently used induction agent in kidney transplantation in the United States, comprising 56% of induction therapy in kidney transplant recipients. These considerations led to this reanalysis of the current trials to support FDA approval of rATG as an induction agent in renal transplantation.

The decision to reanalyze previously completed well-controlled clinical trials for regulatory approval was based on the assessment that equipoise did not exist to allow ethical conduct of newly designed prospective randomized trials for regulatory approval for an rATG induction indication. The broad use of rATG for induction, both off-label in the United States and on-label out of the United States, has set a standard of care in kidney transplantation. Despite compelling methodologic reasons for using placebo, a placebo-controlled trial would not meet international ethical guidance permitting the use of placebo controls because withholding treatment poses considerable risks to participants and a trial would require participants to forgo treatment they would otherwise receive in clinical practice.[8] Similar ethical concerns exist for randomized studies comparing rATG with basiliximab, which may expose participants to excessive risks of harm compared with clinical practice.

Our purpose is to report the reanalysis of data from 2 clinical trials that support the use of rATG in the prophylaxis of acute rejection in kidney transplantation. This report also provides additional insights into the efficacy, dosing, and safety profile to inform treatment decisions.

2 | METHODS

2.1 | Pooled analysis of patient-level data from randomized trials

Two international, randomized, controlled trials that compared rATG (Thymoglobulin®; Sanofi Genzyme, Cambridge, MA) with basiliximab (Simulect®; Novartis Pharmaceuticals, Basel, Switzerland) (NCT00235300, "rATG versus basiliximab in renal transplant" referred to as the 1010 trial)[9] and with daclizumab (Zenapax®; Roche, Basel, Switzerland) (NCT00682292, "daclizumab versus rATG in high-immunologic-risk renal transplant recipients" referred to as the Tacrolimus Antibody Chimeric Induction [TAXI] trial)[10] as induction therapy in renal transplant patients have been reported previously. The 1010 trial recruited adult patients between May 2000 and March 2002 who were eligible candidates for renal transplants from deceased donors; eligibility was dependent on cold ischemia time and other transplant risk factors. Patients were excluded from the 1010 trial if they were already receiving immunosuppressive therapy before the transplant. The TAXI trial recruited adult patients between May 2001 and November 2005 who were eligible to receive a renal transplant from a deceased donor. Eligibility for the TAXI trial was also dependent on a current human leukocyte antigen-panel reactive antibody (PRA) ≥ 30%, a peak PRA of ≥ 50%, patients scheduled for a second renal transplant within 2 years of the first failure or a third or fourth kidney graft irrespective of HLA sensitization. The main exclusion criteria from the TAXI trial were receipt of a multiorgan or previous non-renal transplant.

The 1010 trial was designed to demonstrate superiority of rATG over basiliximab for a composite endpoint that included biopsy-proven acute rejection (BPAR), delayed graft function, graft loss, or death at 6 months posttransplant. The primary efficacy endpoint included the number of patients who failed treatment based on the composite quadruple endpoint up to 6 months. The TAXI study was designed to demonstrate noninferiority (with a noninferiority margin of 15%) of rATG over daclizumab for the occurrence of BPAR at 12 months posttransplant.

Briefly, the 2 trials included a combined total of 508 recipients of deceased donor kidney transplants, with the population in the TAXI trial being generally at immunologically higher risk for acute rejection compared with participants in the 1010 trial (>70% repeat transplants, higher PRAs). Maintenance immunosuppression in both trials included a calcineurin inhibitor (1010: cyclosporine; TAXI: tacrolimus, which was delayed in the rATG arm) as well as mycophenolate mofetil (MMF) and corticosteroids.

New statistical analysis plans for these previously reported randomized trials were developed with new prespecified analyses as agreed with the FDA with the common endpoint of treatment failure at 1 year. The FDA accepted that the composite quadruple endpoint of treatment failure including BPAR, graft loss, death, or patients lost to follow-up at 12 months posttransplant met their criteria.

The primary objective for the pooled analysis in the current study of the 1010 and TAXI trials was to assess the noninferiority of rATG versus IL2RAs for the composite endpoint, with a noninferiority margin of 10%. The determination of the noninferiority margin was based on the prospective, randomized, placebo-controlled studies included in the basiliximab and daclizumab package inserts.[11,12]

Each study was also evaluated separately by using the newly defined quadruple endpoint including a superiority test for rATG versus basiliximab in the 1010 study and a noninferiority test (with a margin of 15%) for rATG versus daclizumab in the TAXI study,

using the intent-to-treat (ITT) population. An analysis based on the time-to-event was performed using the Kaplan-Meier method for those patients who were lost to follow-up in the core pooled analysis.

Secondary efficacy and safety endpoints were analyzed using data from the individual trials and from the pooled data. The individual components of the composite endpoint and treatment-emergent adverse events (TEAEs) were assessed using 2-sided 95% CI of difference between treatment groups, which was based on normal approximation of binomial distribution, and *P* values were obtained by comparison of treatment groups using the Fisher exact test. Kaplan-Meier analysis was used to estimate event-free survival. The difference between treatment groups for the composite endpoint (rATG – IL2RA) and 2-sided 95% CI for the difference was obtained by use of the DerSimonian–Laird method.[13]

2.2 | Data collection

Efficacy and safety analyses were performed within each of the individual and pooled studies. The number of patients with missing data was not included in the denominator unless specified.

2.3 | Pooled aggregate analysis of data from randomized trials in the literature

A systematic review of the literature was carried out to identify randomized trials of rATG induction in kidney transplant (Figure 1). An initial search of EMBASE (1999-2014) was conducted to identify published human clinical trials that mentioned "kidney transplant" and "rabbit ATG" or "rabbit antithymocyte globulin" or "rATG" or "rabbit with ATG." All related reference articles in the English literature were included and reviewed.

2.4 | Dosing

Dosing of rATG varied across the trials described here and in the published literature. In the majority of trials, rATG was initiated intraoperatively, often before graft reperfusion, and was typically given at daily doses of 1.5 mg/kg for 4 to 7 days (longer in some trials).

2.5 | Safety

The incidence, nature, and severity of TEAEs in the 1010 and TAXI trials were monitored and assessed throughout the trials for all

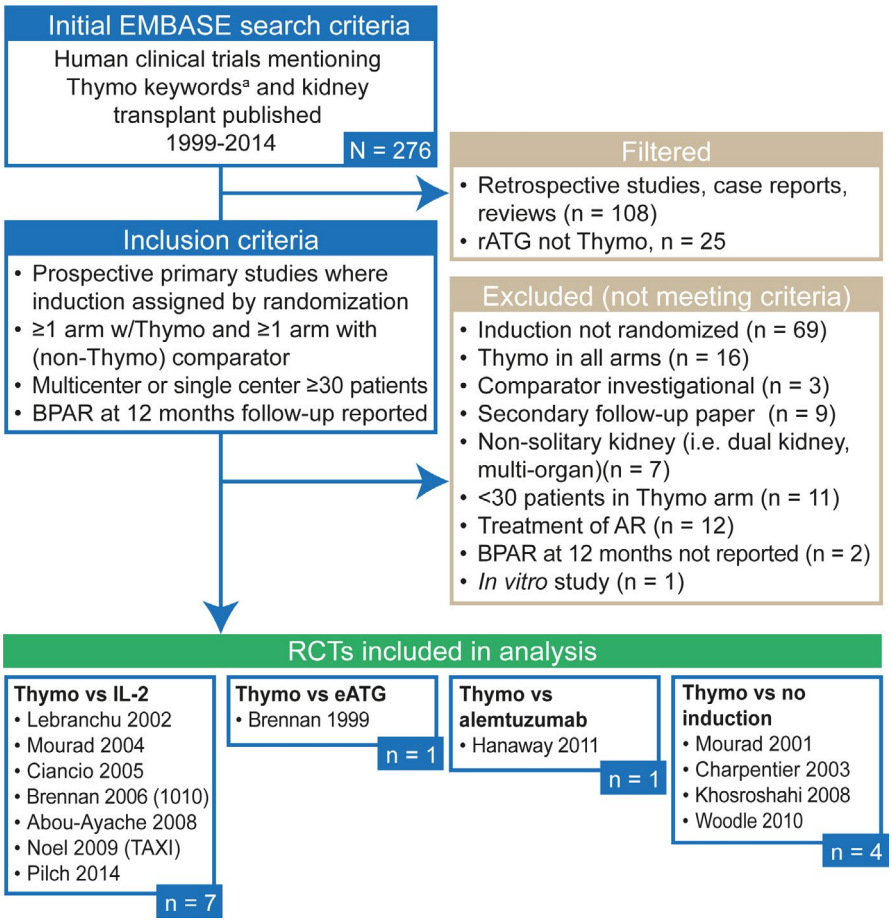

FIGURE 1 Systematic literature review: summary of study selection. AR, acute rejection; BPAR, biopsy-proven acute rejection; eATG, equine anti-thymocyte globulin; rATG, rabbit anti-thymocyte globulin; TAXI, "daclizumab versus anti-thymocyte globulin in high immunologic-risk renal transplant recipients." [a]Key words: kidney transplant; rabbit ATG, rabbit anti-thymocyte globulin; rATG, rabbit with ATG

patients who received ≥1 dose of study drug. Safety data were analyzed over 12 months posttransplant. The safety data collected in the TAXI study were restricted to serious adverse events (SAEs).

2.6 | Meta-analysis

Trials in which rATG was compared with an approved comparator for induction (ie, basiliximab or daclizumab) were assessed in a meta-analysis for BPAR, graft loss, death, and, if available, a composite of these endpoints at 12 months posttransplant.[9,10,14-20] This meta-analysis provided information on a larger population of recipients with a broader immunologic risk of rejection than evaluated in other designated clinical trials. Aggregate data from the remaining randomized trials identified in the literature review comparing rATG with nonapproved comparators[15,17] or maintenance regimens without induction[21-24] were also evaluated for safety, efficacy, and dosing. The treatment effect was assessed by using the risk difference for each of the trials, and corresponding 2-sided 95% CIs were calculated by using normal approximation. When a weighted average across several studies or its corresponding CI was calculated, the inverse variance was used as the weight. For pooled analyses, a test for homogeneity was performed and the weighted averages of differences between treatment groups and 95% CI of the differences were calculated using the methods of DerSimonian and Laird.[13]

2.7 | Inclusion and exclusion criteria for the meta-analysis

2.7.1 | Inclusion criteria

Inclusion criteria included studies published in peer-reviewed journals and any identified unpublished manuscripts meeting the following conditions: prospective studies whereby (1) induction treatment was assigned by randomization, (2) studies had an active control treatment group that did not contain rATG, (3) patients had at least 12-month follow-up post kidney transplantation, (4) patients were recipients of a solitary kidney from a living or deceased donor, and (5) efficacy endpoints included at least 1 of the following: BPAR at 12 months posttransplant determined by either a central or a local pathologist; composite endpoint of BPAR, graft loss, or death at 12 months posttransplant; graft loss at 12 months posttransplant; death at 12 months posttransplant.

2.7.2 | Exclusion criteria

The following studies were excluded: (1) single-center studies with <30 patients treated with rATG, (2) rejection therapy trials (nonprophylaxis), (3) clinical trials with crossover design, and (4) retrospective studies, case reports, literature reviews, or meta-analyses or when results were only available from abstracts.

3 | RESULTS

3.1 | Pooled analysis of patient-level data

3.1.1 | Primary endpoint: quadruple composite endpoint in the trials at 12 months

Individual analysis

Each study was evaluated separately for the quadruple composite treatment-failure endpoint. Both trials achieved significance using the original statistical objective planned per protocol, with statistical superiority of rATG (24.8%) versus basiliximab (38.0%) in the 1010 trial (−13.1%, 95% CI 23.9% to −2.3%; $P = .0202$) and noninferiority of rATG (25.4%) versus daclizumab (33.6%) in the TAXI trial (−8.2%, 95% CI −19.9% to 3.6%) (Table 1).

Pooled analysis

In a pooled analysis of data from the 1010 and TAXI trials, the reported incidence of treatment failure was 25.1% and 36% in the rATG and IL2RA treatment groups, respectively. The estimated difference between the groups was −10.9% (95% CI −18.8% to −2.9%) supporting noninferiority of rATG to IL2RA (upper bound of the 95% CI below prespecified noninferiority margin), and there was a significantly lower treatment failure rate in the rATG group (upper-bound of the 95% CI below 0, Table 1) indicating that rATG was superior to IL2RA. Components of the composite endpoint were BPAR (11.8% versus 20.9%), graft loss (11.0% versus 10.3%), death (4.3% versus 4.0%), and loss to follow-up (3.5% versus 5.5%) for rATG versus IL2RA, respectively. Results for the composite endpoint were relatively consistent across various patient subgroups analyzed as shown in Figure 2A.

Time-based analysis of the 3 components of the composite endpoint (BPAR, graft loss, or death) using study as a stratification factor indicated that treating loss to follow-up as a nonevent did not alter the conclusions of the ITT analysis. Kaplan-Meier estimates of the event-free rates for BPAR, graft loss, or death within 12 months posttransplant pooled analysis of trials 1010 and TAXI are shown in Figure 2B (nominal P values from stratified log-rank test = .0121). Results for individual studies are shown in Figure 2C (nominal P value from stratified log-rank test: 1010: $P = .0298$; TAXI: $P = .1749$).

3.1.2 | BPAR at 12 months

When analyzed separately, 12-month BPAR rates were 12.8% versus 21.2% in the 1010 trial and 10.5% versus 20.7% in the TAXI trial for rATG and IL2RA, respectively (Table 2). The majority of BPARs occurred in the first 6 months posttransplant (25 of 30 BPARs in the rATG arms and 51 of 53 in control arms). In the pooled analysis, severe BPAR (grades IIb/III) occurred in 2.0% of rATG patients and 5.5% of patients in the IL2RA comparator arms. Similarly, 2.7% of patients in the rATG arms received antibody treatment for acute

TABLE 1 Analysis of the composite endpoint – occurrence of any one of the following: biopsy-proven acute rejection (BPAR; grade I–III), graft loss, death or loss to follow-up – within 12 months posttransplant (ITT population)

Parameter	Rabbit ATG	Control	Difference (95% CI[a])	P[b]
1010	**Rabbit ATG N = 141**	**Basiliximab N = 137**		
Endpoint	35 (24.8%)	52 (38.0%)	−13.1% (−23.9% to −2.3%)	.0202
BPAR	18 (12.8%)	29 (21.2%)	−8.4% (−17.2% to 0.4%)	.0780
Graft loss	11 (7.8%)	13 (9.5%)		
Death	6 (4.3%)	6 (4.4%)		
Loss to follow-up[d]	7 (5.0%)	11 (8.0%)		
TAXI	**Rabbit ATG N = 114**	**Daclizumab N = 116**		
Endpoint[c,d]	29 (25.4%)	39 (33.6%)	−8.2% (−19.9% to 3.6%)	
BPAR	12 (10.5%)	24 (20.7%)	−10.2% (−19.4% to -0.9%)	.0452
Graft loss	17 (14.9%)	13 (11.2%)		
Death	5 (4.4%)	4 (3.4%)		
Loss to follow-up[e]	2 (1.8%)	3 (2.6%)		
Pooled	**Rabbit ATG N = 255**	**IL2RA N = 253**		
Endpoint[d]	64 (25.1%)	91 (36.0%)	−10.9% (−18.8% to −2.9%)	
BPAR	30 (11.8%)	53 (20.9%)	−9.2% (−15.6% to −2.8%)	.0057
Graft loss	28 (11.0%)	26 (10.3%)		
Death	11 (4.3%)	10 (4.0%)		
Loss to follow-up[e]	9 (3.5%)	14 (5.5%)		

[a]Two-sided 95% confidence interval of difference between treatment groups (rabbit ATG – control) was based on normal approximation of binomial distribution.
[b]*P*-values obtained by comparison of treatment groups (rabbit ATG – control) using Fisher exact test.
[c]The difference between treatment groups (rATG - IL2RA) and 2-sided 95% CI for the difference was obtained by the DerSimonian–Laird method.[1]
[d]TAXI trial was a noninferiority study, the confidence interval approach was used to decide inferiority/noninferiority of the composite endpoint. *P* values were not available and therefore were not calculated for the pooled analysis.
[e]Loss to follow-up is defined as not having BPAR (grade I-III), graft loss, or death within 12 months posttransplant, at the last evaluation

rejection, whereas 9.1% of comparator patients received antibody treatment for rejection.

3.2 | Long-term follow-up data

Data from long-term follow-up of both core trials have been published. Five-year data on patients from the TAXI trial (n = 210) and 5- and 10-year data from the US patients in the 1010 trial (n = 183) have been previously described.[25-27]

In comparison with basiliximab, treatment with rATG resulted in significantly lower 5-year incidences of acute rejection and acute rejection requiring antibody treatment (15% versus 27%, *P* = .03 and 3% versus 12%, *P* = .05, respectively).[25] Patients treated with rATG compared with basiliximab also had a significantly lower incidence at 5 years of the composite endpoint (acute rejection, graft loss, and death; 37% versus 51%, respectively, *P* = .04).[25] Treatment with rATG was also associated with a significantly lower rate of BPAR at 5 years compared with daclizumab (14.2% versus 26.0%, *P* = .035, respectively).[26]

At 10 years posttransplant, the composite endpoint (freedom from acute rejection, graft failure, or death) was higher with rATG compared with basiliximab (32.6% versus 24.0%, respectively, *P* = .09).[27] The incidence of acute rejection at 10 years posttransplant was lower with rATG compared with basiliximab (21.0% versus 30.9%, respectively, *P* = .07). However, these studies found no meaningful differences between the rATG and basiliximab groups for graft survival or patient survival at 10 years.[27]

3.3 | Comprehensive literature review

A search of EMBASE from 1999 to 2014 identified 276 publications (Figure 1). These publications included > 13,000 rATG-treated patients and found similar results supporting the findings of the core clinical trials. Results of this extensive literature review concluded that BPAR rates were numerically lower in patients who received rATG for the prophylaxis of acute rejection, that rATG reduces BPAR compared with no antibody induction,[22,24] and that BPAR with rATG is less

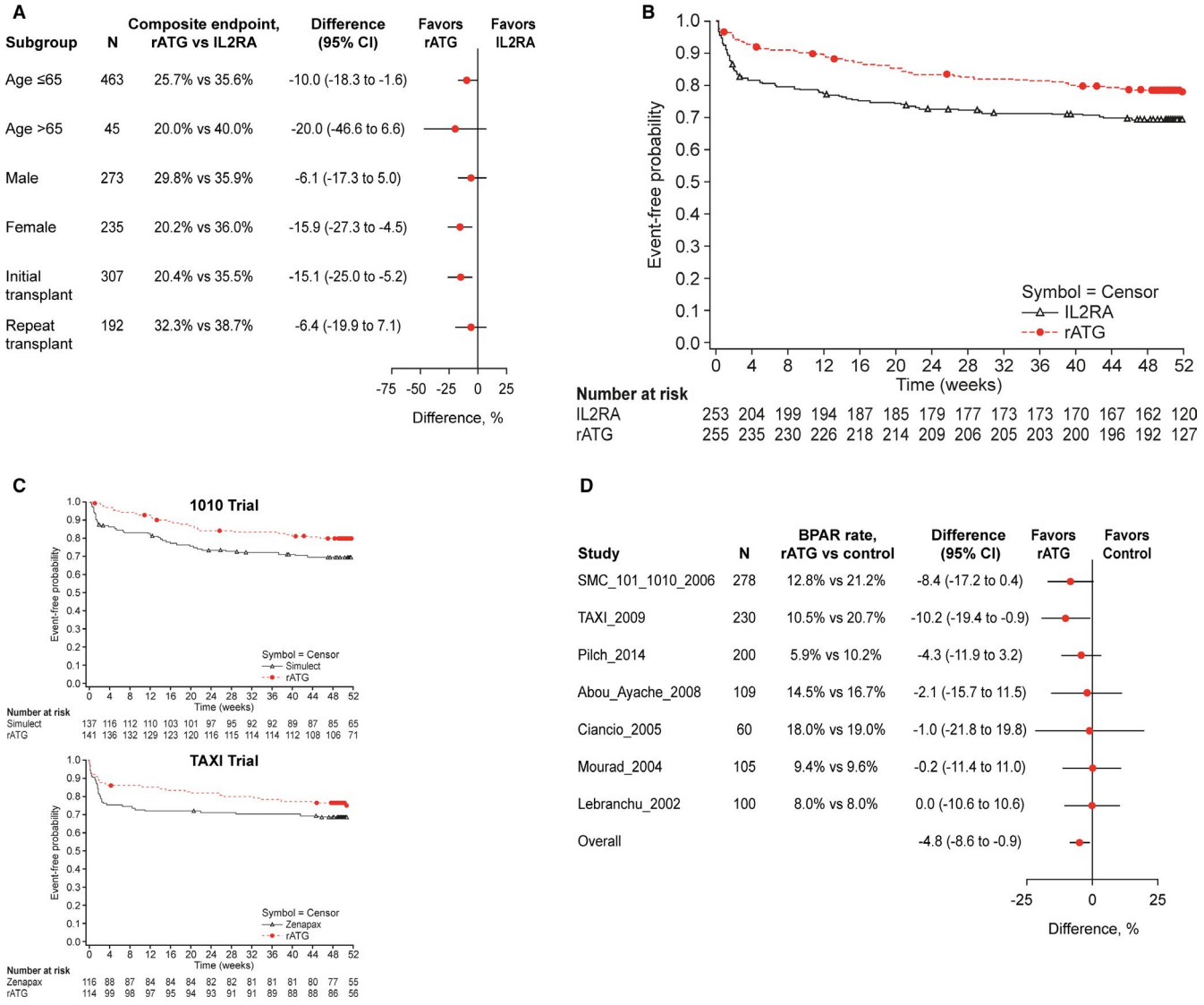

FIGURE 2 Forest plots for the composite endpoint within 12 months posttransplantation by demographic subgroup—trials 1010 and TAXI (ITT populations) (A). Estimates of the event free rates for biopsy proven acute rejection, graft loss, or death within 12 months posttransplantation: pooled analysis of trials 1010 and TAXI (ITT population) (B). Kaplan-Meier analysis of the sensitivity analyses for the event free rate for biopsy proven acute rejection, graft loss or death at 12 months for the 1010 and TAXI trials (ITT population) (C). Meta-analysis for biopsy-proven acute rejection at 12 months by study and overall for trials with interleukin 2-receptor antagonists as the control (D)

severe than or comparable to IL2RA,[9,10,14,16,18-20,28] alemtuzumab,[17] or equine ATG.[15] Rabbit ATG trials have shown statistically significant reductions in the incidence of BPAR compared with IL2RA and alemtuzumab.[17] The majority of trials report BPAR rates at 12 months posttransplant of 6% to 15% with rATG.[10,14,19,20,24] BPAR is lower or comparable among trials reporting long-term follow-up.[25,27]

From these publications, prospective randomized trials were selected and were further filtered for those with at least 30 patients (single center or multicenter) and where induction therapy had been assigned by randomization, with 1 rATG treatment arm and at least 1 comparator arm (without major differences in maintenance immunosuppressive regimens between arms), and where BPAR at 12 months' follow-up was reported (Figure 1). Of these randomized trials, 7 compared rATG with an approved IL2RA (including the 2 core trials),[9,10,14,16,18-20] compared with alemtuzumab,[17] compared with equine ATG,[15] and 4 trials compared rATG with no antibody induction.[21-24]

In the randomized controlled trials in which rATG was compared with IL2RAs, the incidence of BPAR at ≥6 months posttransplant ranged from 5.9% to 18.0% in the rATG groups compared with 8.0% to 21.2% in patients randomized to IL2RA (Figure 2D).[9,10,14,16,18-20] In a meta-analysis of the 7 trials comparing rATG with an IL2RA, the overall difference (95% CI) in the proportion of patients with BPAR at 12 months was −4.8% (−8.6% to −0.9%) in favor of the rATG group compared with the IL2RA group (Figure 2D).

TABLE 2 Biopsy-proven acute rejection rates over the 12 months posttransplant and stratified Banff grade (ITT population)

	1010		TAXI		Pooled	
	Rabbit ATG n = 141	Basiliximab n = 137	Rabbit ATG n = 114	Daclizumab n = 116	Rabbit ATG n = 255	IL2RA n = 253
BPAR 12 months posttransplant	18 (12.8%)	29 (21.2%)	12 (10.5%)	24 (20.7%)	30 (11.8%)	53 (20.9%)
Patients who experienced graft loss	11 (7.8%)	13 (9.5%)	17 (14.9%)	13 (11.2%)	28 (11.0%)	26 (10.3%)
Banff grade (worst grade in 12 months)						
I	11 (7.8%)	18 (13.1%)	7 (6.1%)	4 (3.4%)	18 (7.1%)	22 (8.7%)
IIA	5 (3.5%)	4 (2.9%)	2 (1.8%)	13 (11.2%)	7 (2.7%)	17 (6.7%)
IIB	0	5 (3.6%)	1 (0.9%)	5 (4.3%)	1 (0.4%)	10 (4.0%)
III	2 (1.4%)	2 (1.5%)	2 (1.8%)	2 (1.7%)	4 (1.6%)	4 (1.6%)

ATG, anti-thymocyte globulin; BPAR, biopsy-proven acute rejection; IL2RA, IL-2 receptor antagonist.

3.4 | Safety analysis

Safety data were collected in full in the 1010 trial. Nearly all patients reported TEAEs in the rATG (99.3%) and basiliximab (98.5%) groups. Infections were generally more frequent in patients treated with rATG compared with those who received the control group. In the 1010 trial, urinary tract infections were the most frequent infections (rATG 41.8% versus basiliximab 28.5%). Fungal infections occurred in 14.9% of rATG patients versus 14.6% of basiliximab patients, respectively. Cytomegalovirus (CMV) infections were lower in the rATG group than in the basiliximab group in the 1010 trial (5.7% versus 17.5%). However, in the TAXI trial, CMV infections occurred in 18.6% of patients in the rATG group compared with 11.2% of patients in the daclizumab group. The lower incidence of CMV infections observed in the rATG group in the 1010 trial may have been due to the prophylactic use of ganciclovir for up to 90 days in recipient CMV-positive or donor CMV-positive transplants in this study,[9] whereas either acyclovir or ganciclovir may have been used for prophylaxis in the TAXI trial.[10] Alternatively, the use of cyclosporine A in the 1010 trial may have led to less MMF exposure and less risk of CMV reactivation.

Serious TEAEs occurred in 73.0% of rATG patients and 72.3% of IL2RA patients in the 1010 trial and 76.1% and 72.4% in the TAXI trial, respectively. Malignancies were reported in 4.3% versus 0.7% in the 1010 trial and 0.9% versus 0% in the TAXI trial in the rATG versus the IL2RA groups, respectively.

In the pooled analysis of the 2 trials (1010 and TAXI), the overall frequency of serious TEAEs in the rATG and IL2RA groups was similar (74.4% and 72.3%, respectively, Table 3). Among the most frequent serious TEAEs, the incidence of urinary tract infection (7.1% and 2.8%), pyelonephritis (3.9% and 1.2%), sepsis (3.5% and 1.6%), and acute pyelonephritis (3.1% and 1.2%) was higher in the rATG group than in the IL2RA group, respectively; the incidence of serious CMV infection was lower in the rATG group compared with the IL2RA group (5.1% and 8.3%, respectively). Among the most frequent hematologic abnormalities (under the system organ class blood and lymphatic system disorders, Table 3) reported as serious TEAEs, the incidence was higher in the rATG group than in the IL2RA group for anemia (3.9% and 1.2%, respectively), leukopenia (3.5% and 2.4%, respectively), neutropenia (2.4% and 0%, respectively), and thrombocytopenia (2.0% and 0%, respectively).

4 | DISCUSSION

4.1 | Purpose of the analysis

The primary objective of this pooled analysis was to compare rATG versus IL2RA induction therapy for the prophylaxis of acute kidney rejection after transplant. Two randomized, controlled core trials in relatively moderate to high immunologic-risk kidney transplant recipients were deemed to be adequate, well-controlled trials to provide an evidence base for the use of rATG in induction therapy for prophylaxis of acute transplant rejection: Trial 1010 – United States and Europe[9] and TAXI – France and Belgium.[10] All patient-level data for these 2 trials were reanalyzed based on an updated prospective statistical analysis plan. After submission of these findings to the FDA, rATG received approval for the expanded US label in 2017.

4.2 | Primary data analysis was based on the 2 randomized trials of rATG versus active comparators

Efficacy data from the clinical trials demonstrated that rATG was efficacious when evaluated against the stated composite endpoints and active comparators for each study. Individually, each of the 2 core trials showed positive results against their stated statistical design goal. When data were pooled, the composite endpoint showed the superiority of rATG in reducing treatment failure rates compared with IL2RA. The main driver of the treatment difference seen in the individual components of the quadruple composite endpoint (BPAR, graft loss, patient death, and loss to follow-up) was the lower incidence of BPAR at 12 months in the rATG groups. The efficacy of rATG seen in these 2 core trials in kidney transplant recipients at relatively

TABLE 3 Overview of serious treatment-emergent adverse events (TEAEs) from the pooled 1010 and TAXI trials (safety populations)

n (%)	Rabbit ATG N = 254	IL2RA N = 253
Patients with any serious TEAE (SOC[a] >5% of patients) Overall	189 (74.4)	183 (72.3)
Patients with TEAE leading to death	10 (3.9)	10 (4.0)
Patients with any study drug-related serious TEAE	94 (37.0)	71 (28.1)
Infections and infestations	86 (33.9)	69 (27.3)
Hematologic (blood and lymph disorders)	31 (12.2)	13 (5.1)
Immune system disorders	25 (9.8)	40 (15.8)
Kidney transplant rejection	13 (5.1)	20 (7.9)
Transplant rejection	11 (4.3)	21 (8.3)
Metabolism and nutritional disorders	27 (10.6)	20 (7.9)
Cardiac disorders	25 (9.8)	24 (9.5)
Vascular disorders	32 (12.6)	22 (8.7)
Respiratory, thoracic, and mediastinal disorders	17 (6.7)	17 (6.7)
Gastrointestinal disorders	41 (16.1)	33 (13.0)
Renal and urinary tract disorders	67 (26.4)	62 (24.5)
Renal impairment	19 (7.5)	12 (4.7)
General and administration site disorders	23 (9.1)	24 (9.5)
Pyrexia	14 (5.5)	7 (2.8)
Investigations laboratory	27 (10.6)	16 (6.3)
Blood creatinine increase	21 (8.3)	13 (5.1)
Injury, poisoning, and procedural complications	39 (15.4)	26 (10.3)
Complications of transplanted kidney	15 (5.9)	7 (2.8)
Neoplasms benign, malignant, and unspecified[a]	6 (2.4)	4 (1.6)
Nervous system disorders[a]	9 (3.5)	9 (3.6)
Psychiatric disorders[a]	9 (3.5)	2 (0.8)
Surgical and medical procedures[a]	8 (3.1)	10 (4.0)

ATG, anti-thymocyte globulin; BPAR, biopsy-proven acute rejection; IL2RA, IL-2 receptor antagonist.
[a]Did not reach the system organ class (SOC) >5% threshold.

increased risk of rejection was also verified in 2 other randomized clinical trials, which demonstrated the efficacy of rATG for induction in lower-risk populations, including living donor transplants, compared equine anti-thymocyte globulin[15] or no induction therapy.[24]

These trials also showed that rATG induction is effective when used in combination with a variety of contemporary maintenance immunosuppressive regimens, and the literature suggests the effectiveness with a number of possible combinations of maintenance immunosuppression.[5,10,15,18,21,24,25,27,29-32]

4.3 | Rabbit ATG dosing for induction therapy

The intended dose of rATG used as induction immunosuppression varied in the core trials, but when the actual doses administered in the trials were analyzed, the mean cumulative dose given in the modern trials ranged from 5.9 to 6.53 mg/kg administered over 4-7 days.[9,10,24] This information, along with an analysis of rATG doses from the supporting (published) data, established the recommended induction dose of 6.0-10.5 mg/kg administered over 4-7 days.

The induction dose was established to be lower than the approved dose for the treatment of rejection. Administering rATG immediately before or during the transplant surgery may be more effective than starting therapy postoperatively according to the published literature,[33] and this was the strategy used in the core clinical trials. From the review of the literature, the majority of trials target a total cumulative dose ≥6 mg/kg (77% of patients, 86% of trials), with limited experience in the context of clinical trials reported for a dose <6 mg/kg. However, these data depend on the patient population enrolled, concomitant immunosuppression, and their level of risk for acute rejection.

4.4 | Safety profile of rATG induction therapy

The safety profile was analyzed in the 2 core randomized trials and was consistent with the known AEs seen in another trial evaluating rATG for the treatment of acute rejection.[34]

Safety data was derived from 4 clinical trials supporting the extended labelling of rATG, which included a total of 730 kidney transplant recipients, of whom 405 received rATG; these 4 trials represented a diverse patient acute rejection risk profile and the use of varying maintenance immunosuppressive regimens.[9,10,15,24] The safety profile in this diverse grouping of patients included known and predictable TEAEs: hematologic abnormalities, infections, and acute infusion–associated reactions.

Malignancy within 1 year posttransplant was noted in 2.5% of patients treated with rATG, but it is difficult to assign causality to these malignancies, as all patients were also taking long-term maintenance immunosuppression. The rate of malignancies was increased with rATG compared with other induction therapies, although rates were low. The incidence of malignancy and post-transplant lymphoproliferative disorder is low, which was noted in the longer follow-up (up to 10 years) reports of the 2 core clinical trials.[26,27]

TEAEs noted in the trials were generally mitigated by the use of appropriate premedications, as described in the prescribing information and with the close supervision by physicians experienced in the immunosuppressive therapy in transplantation. The incidence of death within the 12-month follow-up period was similar in the rATG-treated patients compared with the control groups. Importantly, the safety profile of rATG has been established for >30 years since the first approval in 1984; the findings in the randomized clinical trials evaluating the use as induction therapy in kidney transplant were

similar to the extensive experience with the agent and no new safety issues were uncovered.

A detailed evaluation of the postmarketing experience with rATG from 1985 to 2015 was performed, and the data from this analysis were also consistent with the TEAEs seen in the clinical trials. Contraindications of rATG are allergy or anaphylactic reaction to rabbit proteins or any expedient or active or chronic infections that preclude any additional immunosuppression.[7]

4.5 | Meta-analysis

While some of the studies included in the meta-analysis had results published for follow-up periods longer than 12 months, only the publication reporting the 12-month results were included in the analysis. The formal meta-analysis, which evaluated 1293 kidney transplant recipients of which 662 received rATG, demonstrated that, in well-controlled peer-reviewed clinical trials comparing rATG with active controls, the overall incidence of BPAR at 12 months tended to be favorable for rATG in all 9 trials, and BPAR at 12 months was statistically lower with rATG compared with just the IL2RA in 7 trials (Figure 2D).[9,10,14,16,18-20]

4.6 | Study limitations

Limitations included the absence of recent phase 3 trials and the historic age of the trials in the analyses. Differences in the maintenance treatment within and between trials meant that these were not matched in many trials. One limitation of the TAXI trial was that only SAEs were documented in the study.[10] Also, our reanalysis may not have been fully representative of the transplant recipient population, because the TAXI trial only used kidneys from deceased donors and therefore the recipients were at higher risk of delayed graft function. Other limitations include equal weighting was given to the quadruple endpoint, there was variation in rATG dosing within and between trials, and maintenance immunosuppression was not standardized between trials (cyclosporine versus tacrolimus).

5 | CONCLUSIONS

A rigorous reanalysis of patient-level data from existing randomized, controlled trials comparing rATG and approved active comparators, together with analysis of clinical trials in the literature, established the data for the expanded label for rATG, making it the first T cell–depleting therapy approved for the prophylaxis of acute rejection in kidney transplant in the United States.

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DISCLOSURE

The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*. Dr Alloway and Professor Woodle have received grants and personal fees from Sanofi. Dr Segev has received speaker honoraria from Sanofi and Novartis and has attended advisory boards for CSL Behring. Dr Brennan has received personal fees from Sanofi, Novartis, and Alexion and research support from Bristol Myers Squibb. Drs Jeschke, Ilsley, Somerville, and Castan are employees of Sanofi. Dr Abramowicz has no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

Qualified researchers may request access to patient-level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient-level data will be anonymized and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: https://www.clinicalstudydatarequest.com.

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