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Rabbit Antithymocyte Globulin (Thymoglobulin®)

A Review of its Use in the Prevention and Treatment of Acute Renal Allograft Rejection

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Data Selection

Sources: Medical literature published in any language since 1980 on 'antithymocyte globulin', identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: MEDLINE, EMBASE and AdisBase search terms were (['antithymocyte globulin' or 'thymoglobulin' or 'thymoglobuline' or 'ATG'] and ['renal transplant rejection' or 'renal transplant rejection prevention' or 'renal transplant']). Searches were last updated 20th July 2009.

Selection: Studies in patients with allograft rejection who received antithymocyte globulin. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Antithymocyte globulin (rabbit), transplant rejection, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability.

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Summary

Abstract

Rabbit antithymocyte globulin (rATG) [Thymoglobulin®; Thymoglobuline®] is a purified, pasteurized preparation of polyclonal gamma immunoglobulin raised in rabbits against human thymocytes that is indicated for the prevention and/or treatment of renal transplant rejection in several countries worldwide.

rATG induction in combination with immunosuppressive therapy is more effective in preventing episodes of acute renal graft rejection in adult renal transplant recipients than immunosuppressive therapy without induction. The efficacy of rATG induction is generally better than that of equine antithymocyte globulin (eATG) induction and generally no different from that of basiliximab or low-dose daclizumab induction in this patient population. However, in high-risk patients, rATG induction was more effective than daclizumab or basiliximab induction in preventing acute renal graft rejection. In the treatment of renal graft rejection in adult renal transplant recipients, rATG was more effective than eATG in terms of the successful response rate, although the agents generally did not differ with regard to most other endpoints.

Both induction and treatment with rATG are generally well tolerated, although adverse events, such as fever, leukopenia and thrombocytopenia, appear more common with rATG than with other antibody preparations. The overall incidence of infection associated with rATG induction was generally no different from that seen with eATG or basiliximab induction, although was higher with rATG than with basiliximab in high-risk patients. The incidence of cytomegalovirus (CMV) disease generally did not differ between rATG and eATG induction, and there was no significant difference between rATG and daclizumab induction with regard to the incidence of CMV infections or the proportion of patients who received treatment for a CMV episode or infection. Relative to basiliximab, the incidence of CMV infection was generally higher with rATG, except in high-risk patients. In the treatment of acute renal rejection, the nature and incidence of infections were generally similar with rATG and eATG. The incidence of malignancies is generally low with rATG therapy and generally does not differ from that seen with other agents.

Further prospective comparative studies would be beneficial in order to definitively position rATG with respect to other antibody preparations. In the meantime, available clinical data suggest that rATG is an effective and generally well tolerated option for the prevention and treatment of acute renal graft rejection in renal transplant recipients.

Pharmacological Properties

rATG displays specificity towards a wide variety of surface antigens on both immune system and endothelial cells. The precise mechanism(s) of action underlying its immunosuppressive efficacy is unclear, although T-cell depletion is considered to play a key role. Other mechanisms include lymphocyte surface antigen modulation, transcription factor activation, and interference with processes of immune system cells, such as cytokine production, chemotaxis, endocytosis, stimulation and proliferation. rATG may also induce apoptosis, antibody-dependent lysis or complement-mediated lysis of various immune system cells, and negate leukocyte-endothelial cell adhesion. Treatment with rATG sustained T-cell depletion more effectively than eATG in renal transplant recipients experiencing acute renal rejection. Moreover, rATG induction was at least as effective as eATG induction in depleting lymphocytes, and as expected, was associated with lower lymphocyte levels than basiliximab or daclizumab induction in renal transplant recipients.

Serum concentrations of rATG appear to increase during treatment with intravenous rATG, and the serum concentration of total rATG, but not active rATG, is closely related to the cumulative dose. Levels of rATG in serum decline steadily after infusion cessation, with an elimination half-life of 2–3 days after an initial dose of 1.25–1.5 mg/kg, although the decline of active rATG levels appears to be more rapid. Among renal transplant patients who received rATG 1.5 mg/kg/day for up to 14 days, rATG and active rATG were present at measurable levels in 81% and 12% of patients 90 days after initiation of therapy.

Therapeutic Efficacy

Prevention of Acute Renal Transplant Rejection: In two randomized, open-label, multicentre trials in adult renal transplant recipients, rATG induction in combination with tacrolimus-based immunosuppressive therapy was more effective than tacrolimus-based therapy without induction in preventing acute renal graft rejection at 6 or 12 months post-transplantation. In one of these studies, the incidence of biopsy-confirmed acute rejection (BCAR) in recipients of rATG induction with tacrolimus-based therapy did not significantly differ from that seen in recipients of rATG induction with ciclosporin-based therapy. Moreover, the median time to BCAR was >1 week longer with rATG induction therapy than with noninduction therapy, although there were no significant differences between regimens in terms of patient or graft survival.

rATG induction was generally more effective than eATG induction in adult renal transplant recipients receiving immunosuppressive therapy in a double-blind, single-centre trial. rATG recipients had a lower incidence of BCAR episodes and greater event-free survival than eATG recipients up to 10 years post-transplantation, and greater graft survival up to 5 years post-transplantation, although there was no significant between-group difference in terms of patient survival. Moreover, in three randomized, open-label, multicentre studies, the efficacy of rATG induction therapy was generally no different from that of basiliximab or low-dose daclizumab in adult renal transplant recipients receiving triple immunosuppressive therapy. There were generally no differences between rATG and these agents in terms of the incidence of BCAR, or patient or graft survival at 6 months or 1 year post-transplantation, with rATG and basiliximab also not differing with regard to the composite of BCAR, graft loss or death at these timepoints.

Induction with rATG was also effective in combination with corticosteroid-free immunosuppressive therapy in adult and paediatric renal transplant recipients in a prospective noncomparative study. Furthermore, rATG induction in combination with an early corticosteroid withdrawal immunosuppressive regimen provided efficacy not significantly different from that of an immunosuppressive regimen with standard corticosteroid use in adult renal transplant recipients in a randomized, multicentre trial.

rATG induction, in combination with triple immunosuppressive therapy, has also demonstrated efficacy in renal transplant recipients at high risk of acute rejection or delayed graft function. In a large, randomized, multicentre trial, the efficacy of rATG was generally no different to that of basiliximab at 1 year post-transplantation, with no significant between-group difference in the composite endpoint of first BCAR, delayed graft function, graft loss or death, or most of the individual components of the composite; however, the incidence of BCAR was lower with rATG than with basiliximab. In a similarly designed trial comparing rATG with daclizumab, rATG provided better efficacy in terms of the incidence of BCAR 1 year after transplantation and was associated with a longer median time to rejection, although the treatment groups did not significantly differ with regard to rates of patient or graft survival. Longer term, rATG may provide benefits over basiliximab up to 5 years post-transplantation, according to a retrospective analysis of one of these trials. Data from three retrospective studies indicated that rATG induction therapy is effective in African-American renal transplant recipients.

In two retrospective studies in paediatric renal transplant recipients, the efficacy of rATG in combination with immunosuppressive therapy in preventing episodes of acute rejection was not significantly different to that of immunosuppressive therapy alone or in combination with basiliximab at 1 year post-transplantation, whereas rATG was associated with fewer BCAR episodes than eATG up to 3 years post-transplantation in the largest of these studies. There were generally no differences between rATG and these regimens with regard to most other endpoints.

Treatment of Acute Renal Graft Rejection: In a large randomized, double-blind, multicentre, phase III trial conducted in adult renal transplant recipients receiving concomitant immunosuppressive therapy, more rATG than eATG recipients achieved the endpoint of successful response (i.e. a return of serum creatinine levels to baseline by end of treatment or within 14 days of treatment initiation), although the treatment groups generally did not differ in terms of graft survival at 30 days, graft function or the proportion of patients who had an improvement in rejection severity of one Banff grade. However, among those who achieved a successful response, fewer episodes of recurrent rejection occurred in rATG than eATG recipients within 90 days of treatment cessation, although there was no between-group difference in graft or patient survival 1 year after treatment completion.

Tolerability

Both induction and treatment with rATG were generally well tolerated in adult renal transplant recipients in clinical trials. More patients who received rATG induction in combination with immunosuppressive therapy experienced leukopenia, fever, serum sickness and thrombocytopenia than those who received immunosuppressive therapy without induction. In trials comparing rATG with other induction agents, rATG was associated with a lower median incidence of serious treatment-emergent adverse events than eATG, although it generally did not differ from basiliximab in terms of the incidence of any adverse events or serious adverse events, or from daclizumab in terms of the incidence or severity of adverse events. The most common selected adverse events (other than infection) reported in recipients of rATG and other induction agents were fever, gastrointestinal disorder, leukopenia and thrombocytopenia; rATG was associated with a higher incidence of leukopenia than basiliximab or eATG and a higher incidence of fever and thrombocytopenia than basiliximab in some studies. Adverse events considered to be study drug related occurred in more rATG than basiliximab induction recipients, with fever, gastrointestinal disorder, cutaneous rash and serum sickness being attributed to rATG. When used in the treatment of acute renal transplant rejection, the tolerability profile of rATG was generally similar to that of eATG, with fever, chills and leukopenia the most common adverse events reported in both treatment groups. However, compared with eATG, rATG was associated with a greater incidence of leukopenia and malaise, and a lower incidence of dizziness and dysuria.

rATG induction in combination with immunosuppressive therapy was generally less favourable than immunosuppressive therapy without induction with regard to the incidence of infection, particularly CMV. However, the overall incidence of infection associated with rATG induction was no different from that seen with eATG or basiliximab induction, although it was higher than with basiliximab in high-risk patients. In studies that assessed CMV parameters as primary tolerability endpoints, the incidence of CMV disease generally did not differ between rATG and eATG induction, and there was no significant difference between rATG and daclizumab induction with regard to the incidence of asymptomatic or symptomatic CMV infection or the proportion of patients who received treatment for a CMV episode. In other induction trials, rATG did not significantly differ from daclizumab with regard to the incidence of CMV infections that required treatment, whereas, relative to basiliximab, the incidence of CMV infection was higher with rATG in two studies, although it was lower with rATG in a study in high-risk patients. In the treatment of acute renal rejection, the nature and incidence of infections were generally similar with rATG and eATG.

The incidence of malignancies was generally low with rATG therapy, regardless of whether the drug was being administered for the prevention or treatment of renal transplant rejection, and generally did not differ from that seen with eATG, basiliximab or daclizumab. Retrospective analyses of data from three US registry databases have produced mixed findings concerning the risk of post-transplant malignancies associated with rATG and other immunosuppressive agents in renal transplant recipients.

1. Introduction

Renal transplantation is now the preferred treatment option for most patients with end-stage renal disease because it offers a clear survival advantage over dialysis.[1,2] Over 400 000 people worldwide were living with renal transplants in 2004,[3] and the number of people awaiting transplantation has more than doubled in the last 10 years in the US alone.[2] However, after transplantation, immune responses of the recipient towards the donor renal tissue can lead to rejection of the graft, a process mediated most commonly via T lymphocytes (i.e. cellular rejection) as well as via antibodies (i.e. humoral rejection).[4] Historically, acute graft rejection has proven to be a major obstacle to the success of renal transplants, with the half-lives of cadaveric renal grafts performed in the US in 1995 projected to be 8.8 years in patients who had experienced acute rejection versus 17.9 years in those who had not.[5]

Immunosuppressive agents are used to both prevent and treat episodes of acute rejection in renal transplant recipients, and the progressive development of immunosuppressive therapies over the past decade has reduced the incidence of these rejections.[6] Standard immunosuppressive regimens generally consist of calcineurin inhibitors (e.g. tacrolimus or ciclosporin), antiproliferative agents (e.g. mycophenolate mofetil [MMF]) and corticosteroids to prevent rejections and high-dose corticosteroids or polyclonal or monoclonal antibodies to treat rejections.[2,7] However, induction regimens (i.e. short-term use of antibody preparations from transplantation surgery onwards[8]) to prevent early acute rejection have become increasingly common in recent years,[6] particularly in the US.[9]

Several polyclonal and monoclonal antibody preparations are available for use in renal transplant recipients and can be functionally divided based on whether they deplete or do not deplete patient lymphocyte levels.[10] One such agent is rabbit antithymocyte globulin (rATG) [Thymoglobulin®; Thymoglobuline®], a lymphocyte-depleting polyclonal antibody preparation with specificity towards human thymocytes. rATG is indicated for the prevention[11,12] and/or treatment[11-13] of renal transplant rejection in the US,[13] Canada[12] and several European countries, including the UK.[11] This article focuses specifically on clinical efficacy and tolerability data relevant to the use of rATG in these indications and discusses the pharmacological properties of the agent.

2. Pharmacodynamic Profile

The pharmacodynamic profile of rATG has been reviewed in detail previously.[14-16] Therefore, this section provides an overview of the key pharmacodynamic properties of rATG relevant to its use in renal transplant recipients. Data are from clinical studies in renal,[17-27] pancreatic[18] or cardiac[27] transplant recipients, and several *in vitro*[18,28-36] and *in vivo* animal[37,38] studies. Further data from some clinical trials are discussed in section 4.[17,19-21] Additional data were obtained from the manufacturer's prescribing information;[11,13] some data are available only as abstracts.[22-26,39]

2.1 General Pharmacodynamic Properties

rATG is a purified, pasteurized preparation of polyclonal gamma immunoglobulin (IgG) raised in rabbits against human thymocytes.[13] rATG binds primarily to peripheral blood lymphocytes, as well as to those from the lymph nodes, spleen and thymus, according to data from an *in vivo* study in monkeys.[38] Being polyclonal, rATG displays specificity towards a wide variety of antigens expressed on the surface of T cells, B cells, dendritic cells, natural killer cells and endothelial cells, including those involved in immune responses, apoptosis, signal transduction, cell adhesion and trafficking.[11,16,18,29,31]

The precise mechanism(s) of action underlying the immunosuppressive efficacy of rATG in renal transplant recipients (discussed in section 4) is unclear at present, although has been primarily attributed to T-cell depletion (section 2.2).[11] However, several other mechanisms may also be responsible. According to data mostly,[18,28,29,31,33-35] but not exclusively,[27] from preclinical studies, rATG modulates the expression of several lymphocyte surface antigens involved in a wide variety of functions ranging from T-cell activation to

endothelial adherence, activates certain transcription factors, and also interferes with numerous immune cell processes, such as cytokine production, chemotaxis, endocytosis, stimulation and proliferation (table I). The effects of rATG have been studied primarily in T and B cells, although more recent data suggest that dendritic and natural killer cells may also be affected by rATG (table I).[18,29,31]

rATG has been shown to induce apoptosis, antibody-dependent lysis or complement-mediated lysis of various immune system cells in *in vitro* and *in vivo* animal studies (table I).[31,34,36,38] The potential clinical implication of the ability of rATG to induce the apoptosis of B cells is of particular interest given that B cells are increasingly being considered pivotal in both the T and B cell-mediated allograft rejection that occurs in transplantation patients.[15] However, limited data from four renal transplant recipients previously sensitized to HLA antigens suggest that memory B cell activation or alloreactive plasma cells may not be inhibited by rATG (table I).[24]

Data from preclinical[30,32] and clinical[26] studies suggest that rATG therapy may induce the expansion and enrichment of certain regulatory T-cell subsets, such as $CD4^+CD25^+$ forkhead box $P3^+$ ($FoxP3^+$) [table I], which are key to immune response modulation and transplant tolerance.[40,41] However, limited data from a comparative trial in renal transplant recipients indicated that alloreactive T-cell expansion was induced both with rATG and basiliximab induction within 3 months post-transplantation.[23] Moreover, the cellular and humoral responses of sensitized renal transplant patients who received rATG induction were generally no different to those who received daclizumab induction, according to limited data from a randomized clinical trial (table I).[22]

Adherence of leukocytes to the endothelium and their subsequent infiltration into the tissue underlie both the ischaemia/reperfusion injury often seen in transplanted organs and the process of organ rejection. rATG may negate leukocyte-endothelial cell adhesion and help to maintain microvascular blood velocity, according to the findings of an *in vivo* monkey reperfusion model (table I).[37] However, in renal transplant patients who received rATG or basiliximab induction therapy in an observational study,[25] coagulopathy occurred only in rATG recipients, although the between-group difference was not significant (table I).

2.2 Lymphocyte Depletion

rATG-induced lymphocyte depletion occurs both peripherally and centrally.[11] Although the exact mechanism(s) by which this process occurs *in vivo* has yet to be determined, data from *in vitro* studies suggest that it may occur via apoptosis, antibody-dependent cytolysis or complement-dependent lysis[11] (section 2.1).

Lymphocyte depletion with rATG therapy has been demonstrated in adult renal transplant patients in several randomized comparative clinical studies ($n = 26$–227 evaluable),[17,19-21,39] and is supported by data from a smaller trial in renal and pancreas transplant recipients ($n = 17$)[18] and an *in vivo* animal study[38] (table I).

T-cell depletion was more effectively sustained with rATG 1.5 mg/kg/day than with equine antithymocyte globulin (eATG) 15 mg/kg/day in renal transplant recipients experiencing acute renal rejection.[20] T-cell counts ($CD2^+$, $CD3^+$, $CD4^+$ and $CD8^+$) were significantly lower with rATG than with eATG both at the end of the 7- to 14-day treatment period and at 30 days ($p < 0.05$ where reported).

Moreover, as an induction therapy, rATG was at least as effective as eATG in depleting T cells in renal transplant recipients.[21] Median counts of both $CD3^+$ and $CD5^+$ T cells were significantly ($p \leq 0.001$) lower with rATG 1.5 mg/kg/day than with ATG 15 mg/kg/day. Furthermore, mean absolute lymphocyte counts were consistently reduced ($p < 0.01$) from baseline with rATG throughout the 1-year study, whereas a significant reduction from baseline occurred only at day 7 with eATG (p-value not reported). Longer term,[42] although there was no significant difference between the groups in terms of $CD3^+$ or $CD8^+$ T-cell counts 2 years post-transplantation, rATG recipients had a significantly ($p < 0.01$) lower $CD4^+$ T-cell count than eATG recipients at this timepoint.

Table I. Overview of the pharmacodynamic properties of rabbit antithymocyte globulin (rATG). Results in renal,[17-27,39] pancreatic[18] or cardiac[27] transplant recipients (n = 4–227, where reported[19-21,23-27,39]) and of *in vitro*[18,28-36] and *in vivo* animal[37,38] studies. Data in transplant recipients generally relate to rATG 1–1.5 mg/kg/day except in some instances (5.6 mg/kg mean dose;[39] 2.5 mg/kg/day usually subsequently reduced to 1.5 mg/kg/day[27]); the dosage was not specified in some studies[22,23,26]

Lymphocyte-depleting effects
Depleted lymphocyte levels in renal transplant recipients (section 2.2)[17,19-21,39] and dose-dependently depleted lymphocytes in the blood, lymph nodes and spleen of monkeys, without producing marked changes in levels of other cell types, in most instances[38]
Reduced NK cell levels for ≤11 d post-transplantation in renal and pancreas transplant recipients[18]
Immune cell-modulating effects
Induced surface expression of CD25,[28,34] CD69,[28,34] CD95 (Fas),[34] CD95 ligand (FasL)[34] and/or CD134 (OX40),[28] and the transient expression of CTLA-4 and FoxP3,[28] by PBL (at some concentrations)[34] or $CD4^+$ T cells[28] *in vitro*
Dose-dependently down-regulated surface expression of several leukocyte adhesion molecules (e.g. CD11a, CCR7) on leukocytes, PBL and/or PHA-activated PBL[33] and CD2, CD3, CD4 and CD8 on monkey PBL[38] *in vitro*
In some instances, down-regulated surface expression of CD2, CD3, CD4 and CD8 on PBL and lymphocytes from the lymph nodes and spleen in monkeys *in vivo*[38]
Induced production of several cytokines (IFNγ,[18,28,29,35] TNFα,[18,35] IL-2,[28] IL-4,[28] IL-10[28] and/or GM-CSF[35]) by $CD3^+$ [35] or $CD4^+$ [28] T cells and NK cells[18,29] *in vitro*, and produced a significant transient increase in levels of TNFα and IL-6, but not IL-1β or IFNγ, 3 h after administration in renal and cardiac transplant recipients (p-value not reported)[27]
Suppressed cytokine-mediated chemotaxis of PBL,[33] PBMC[33] and Jurkat T cells[30] *in vitro*
Impaired the ability of monkey lymph node lymphocytes to proliferate in an *in vitro* mixed lymphocyte reaction test[38]
Inhibited macropinocytosis and receptor-mediated endocytosis of antigens by immature dendritic cells *in vitro*[31]
Activated certain transcription factors involved in the regulation of apoptosis (ERK1/2 and p38) and the maturation and activation (RelA, RelB, p50 and p52) of dendritic cells *in vitro*[31]
Impaired certain cytotoxic activities[18,29] and the degranulation capacity[18] of NK cells *in vitro*
Generally suppressed the stimulation of allogeneic $CD4^+$ and $CD8^+$ T cells and autologous $CD4^+$ T cells by dendritic cells *in vitro*[31] and $CD4^+$ cells pre-treated with rATG attenuated the proliferation of autologous $CD4^+$ T cells in response to allogeneic PMBC *in vitro*[28]
Did not appear to inhibit memory B-cell activation or alloreactive plasma cells in four renal transplant recipients previously sensitized to HLA antigens, as indicated by a significant increase from baseline in levels of donor-specific anti-HLA antibodies at the time of rejection (p-value not reported)[24]
Effects on apoptosis and cell lysis
Induced apoptosis of naive, activated or plasma B cells,[36] PHA-activated PBL,[34] NK cells[18,29] and dendritic cells[31] *in vitro*, and dose-dependently induced apoptosis of lymphocytes in the lymph nodes of monkeys[38]
Induced complement-mediated lysis of resting and PHA-activated PBMC at supramitogenic concentrations, by facilitating the binding of C1q, and induced antibody-dependent lysis of PHA-activated PBMC *in vitro*[34]
Other effects
Induced expansion of regulatory $CD4^+CD25^+$ T cells (with upregulated expression of markers such as $FoxP3^+$,[30,32] cytotoxic T lymphocyte-associated antigen-4[32] and glucocorticoid-induced TNF receptor[32]) from human PBL[32] or PBMC[30] *in vitro*
Induced a shift towards regulatory T cells with a memory phenotype (e.g. $CD4^+$, $FoxP3^+$, $CD45RO^+$) in renal transplant recipients[26]
rATG, like BAS, induced alloreactive T-cell population expansion in renal transplant recipients at 3 mo (8% vs 10% expansion), although the cell population remained noticeably more expanded with rATG than with BAS at 6 mo (11% vs 2%)[23]
rATG and daclizumab induction did not significantly differ with regard to T-cell activation or donor-specific antibody elimination in sensitized renal transplant recipients 6 mo post-transplantation, although 53% and 68% of T cells were $CD4^+$ and 25% and 14% of T cells had a memory phenotype ($CD45^-62L^-$) in the respective treatment groups (both between-group differences $p = 0.05$)[22]
Generally maintained microvascular blood velocity, maintained a higher proportion of free flowing leukocytes, reduced the proportion of leukocytes adhered to endothelial cells and, in some instances, reduced the proportion of rolling leukocytes, relative to no treatment (all $p < 0.05$) in a monkey reperfusion model[37]
rATG induction did not significantly differ from BAS (20-mg dose on d 0 and 4) induction with regard to the incidence of coagulopathy (international normalized ratio >1.5) in renal transplant recipients 2 d post-transplantation (14% vs 0% of patients)[25]

BAS = basiliximab; **FoxP3** = forkhead box P3; **GM-CSF** = granulocyte-macrophage colony-stimulating factor; **HLA** = human leukocyte antigen; **IFNγ** = interferon-γ; **IL** = interleukin; **NK** = natural killer; **PBL** = peripheral blood lymphocytes; **PBMC** = peripheral blood mononuclear cells; **PHA** = phytohaemagglutinin; **TNFα** = tumour necrosis factor-α.

As expected, induction with rATG 1.0–1.5 mg/kg/day was consistently associated with significantly ($p = 0.001$) lower lymphocyte counts than the non-lymphocyte-depleting antibody basiliximab 20 mg (on days 0 and 4) from 1 week to 6 months post-transplantation in renal transplant recipients.[19] Similarly, renal transplant patients who received induction with rATG 1.25 mg/kg/day had significantly ($p < 0.001$) lower mean lymphocyte counts from 1 week to 1 year post-transplantation than those who received induction with daclizumab 1 mg/kg (on day 0, then every 14 days for an additional four doses).[17]

These findings are generally supported by limited data from a clinical study that evaluated rATG induction in combination with corticosteroid-sparing immunosuppressive therapy versus immunosuppressive therapy with standard corticosteroid use without induction in renal transplant patients.[39] White blood cell counts at 1 year were significantly ($p = 0.001$) lower in the rATG induction group (mean dose 5.6 mg/kg) than in the noninduction group.

3. Pharmacokinetic Profile

This section provides an overview of the pharmacokinetic properties of rATG which have been reviewed previously;[14] the pharmacokinetic properties of active rATG (i.e. the proportion of rabbit IgG that binds to human lymphocytes and induces the desired immunological effect) are also discussed. This section focuses on data relating to clinically relevant dosages of rATG available from a published study in renal transplant patients ($n = 79$)[43] (further discussed in section 4.2[20]) and the manufacturer's prescribing information.[11,13]

When intravenous rATG 1.25–1.5 mg/kg/day was administered for 7–11 days, the average rATG concentrations 4–8 hours after the first and last dose were 21.5 μg/mL (range 10–40 μg/mL) and 87 μg/mL (23–170 μg/mL) [patient population not reported].[13]

The maximum serum concentration (C_{max}) of rATG was 66 and 171 μg/mL after administration of 6 or 14 doses of intravenous rATG 1.5 mg/kg/day in renal transplant patients, with the cumulative dose relating closely to rATG concentration at all timepoints from 0 to 90 days after treatment initiation.[43] In contrast, a relationship between rATG dose and active rATG concentration was not evident until 30 days after treatment initiation (C_{max} values of 0.04, 0.08 and 0.10 μg/mL in recipients of 10, 11 and 14 days of treatment, respectively).

Serum levels of rATG decline steadily after infusion,[11] with an elimination half-life of 2–3 days after an initial rATG dose of 1.25–1.5 mg/kg.[11,13] However, the decline in levels of rATG after cessation of therapy appear to be less rapid than that of active rATG levels.[11] Among renal transplant patients who received rATG 1.5 mg/kg/day for up to 14 days,[43] rATG and active rATG were present at measurable levels in 81% and 12% of patients 90 days after treatment initiation.[43]

Drug interaction data for rATG are not available,[11,13] although interactions with food and drink are considered unlikely.[11]

4. Therapeutic Efficacy

The clinical efficacy of intravenous rATG in preventing and treating renal graft rejection in renal transplant patients has been evaluated in numerous clinical studies. This section focuses on data from moderate to large randomized trials ($n > 70$) that used the recommended rATG infusion rate (1–1.5 mg/kg/day;[11,13] section 6), except where data are limited. Most studies have been conducted in adult patients, with fewer data available specifically in paediatric[44,45] or African-American[46-48] patients. Most of the studies are fully published, with others available as abstracts.[39,49] Longer term data from one of the studies[21] are available in separate publications.[42,50] Data from retrospective subgroup[51] and longer-term[52] analyses of another trial[53] are also available. Some data were obtained from the manufacturer's prescribing information.[13]

In these studies, eligible patients were aged ≥18[17,19,20,54-57] years (with an upper limit of 60,[19,55] 65,[54,57] 70[17] or 75[56] years), apart from in the studies including paediatric patients,[44,45,58] and were recipients of a first kidney

transplant[19,20,39,54-58] or a retransplant[20,54-56,58] from deceased,[17,19,53-58] living[39,58] or HLA-mismatched living[56] donors, where specified.

Exclusion criteria included multiple organ transplantation[17,19,20,54,56,57] (with the exception of combined kidney-pancreas transplants in one trial[20]), previous transplantation with another organ,[17,19,55] malignancy[19,21,53,54,56,57] (other than of the skin[19,21,53,56]) or neoplastic disease[55] within the last 2[21,53] or 5[19,55,56] years, and allergy to or previous treatment with polyclonal anti-T-cell agents.[20,21] Also excluded were patients who had recently been treated with corticosteroids for autoimmune or renal disease,[57] had received another immunosuppressive agent prior to transplantation[53] (within the last 6 months[19]), had systemic infections that required treatment,[54,55] or had evidence of HIV,[20,21,53-56] human T-lymphotropic virus,[20,21] or hepatitis B[20,21,53] or C[53] virus infection or significant liver disease.[54-57] Patients with negative cytomegalovirus (CMV)[57] or Epstein-Barr virus (EBV)[19] serology were also excluded from some studies.

Several studies also excluded patients with immunological risk factors of acute rejection, such as a positive T-cell crossmatch,[19,54-56] cold ischaemia time >36 hours,[19,57] a panel-reactive antibody (PRA) value >20%[56,57] or 25%,[19] previous graft survival of <1 year[56] or blood group incompatibility.[19,54] In contrast, some studies assessed the efficacy of rATG specifically in patients at high risk of acute transplant rejection or delayed graft function (section 4.1.6).[17,46,47,49,53]

4.1 Prevention of Acute Renal Graft Rejection

This section focuses on the efficacy of rATG induction therapy in preventing renal graft rejection, in combination with other immunosuppressive agents, as evaluated in several randomized,[17,19,21,53-57] double-blind[21] or open-label,[17,19,53-57] single-centre[21] or multicentre[17,19,53-57] trials in adult renal transplant recipients (sections 4.1.1 to 4.1.4). In addition, the efficacy of rATG has been evaluated as part of a corticosteroid-free immunosuppressive regimen in a prospective noncomparative trial[58] and in combination with immunosuppressive therapy with early corticosteroid withdrawal in a randomized, multicentre trial[39] conducted in paediatric[58] and/or adult[39,58] renal transplant recipients, with supporting data provided by two large clinical practice observational studies[59,60] (section 4.1.5). The results of large, randomized, open-label, multicentre trials conducted in patients at high risk of acute renal rejection are discussed separately (section 4.1.6),[17,53] together with data from retrospective studies in African-American patients ($n > 70$);[46-48] limited data from a small ($n = 41$) randomized trial in patients with donor-specific anti-HLA antibodies are also briefly discussed.[49] The efficacy of rATG has also been evaluated in paediatric patients in several observational or retrospective studies ($n = 8$–198);[44,45,61-65] results from the two largest retrospective studies ($n > 80$) are discussed (section 4.1.7).[44,45]

Patient characteristics at baseline were generally well balanced between treatment groups.[17,19,21,39,53-57] However, in some trials, the treatment groups differed significantly ($p < 0.05$) with regard to the mean duration of cold ischaemia (20 hours in rATG recipients vs 18 hours in daclizumab recipients)[57] or the proportion of patients who had previously had one or more transplants (6.5% of rATG plus tacrolimus-based therapy recipients and 8.1% of tacrolimus-based therapy [without induction] recipients vs 15.2% of rATG plus ciclosporin-based therapy recipients)[54] or had a PRA value >50% (3.2% and 1.6% vs 6.5%).[54] Results from retrospective studies should be interpreted with caution as the treatment groups, although generally well matched, significantly ($p < 0.05$) differed with regard to several patient characteristics including age,[46,47] PRA value,[46-48] retransplant status,[46-48] living/deceased donor status,[60] ethnicity,[45] duration of end-stage renal disease,[46] background immunosuppressive therapy[44,48] or diabetes mellitus status.[46,47]

Where specified, the primary measures of efficacy were the incidence of acute rejection[45,47,48] or biopsy-confirmed acute rejection (BCAR), as assessed by Banff criteria,[17,21,54,55] the time to BCAR,[54] patient survival,[21,46] graft

Table II. Efficacy of rabbit antithymocyte globulin (rATG) induction regimens vs noninduction regimens in the prevention of renal graft rejection in adult renal transplant patients (pts). Results of two randomized, open-label, multicentre, 6-[54] or 12-month[55] trials in which induction with intravenous rATG for 10 days in combination with delayed tacrolimus (TAC)-based[54,55] or ciclosporin microemulsion (CsA)-based[54] immunosuppression regimens was compared with immediate TAC-based regimens without induction. Modified intent-to-treat analyses are presented

Reference	Treatment (mg/kg/day)[a]	No. of pts	Time of assessment (mo)	BCAR (% of pts)[b]	Median time to BCAR (d)[b,c]	Pt survival (% of pts)	Graft survival (% of pts)
Charpentier et al.[54]	rATG 1.25[d] + TAC 0.3[e,f]PO[g]	186	6	15.1**	19.5	98.4	95.2
	rATG 1.25[d] + CsA 8[e,f]PO[g]	184	6	21.2	29	97.0	90.8
	TAC 0.3[f,h]PO[g]	185	6	25.4	12	97.0	93.2
Mourad et al.[55]	rATG 1.25 + TAC 0.2[e,f]	151	12	15.2*		97.4	92.1
	TAC 0.2[f,h]	158	12	30.4		96.8	91.1

a All pts received azathioprine and corticosteroids as part of the immunosuppressive regimen;[54,55] muromonab-CD3 was permitted in one study.[55]

b Primary endpoint.

c Between-group statistical analyses were not reported.

d Initial dose administered within 12 h of transplantation; subsequent adjustments were based on clinical condition.

e Initiated 9 days after transplantation.

f Initial dose; subsequent adjustments were based on whole-blood trough concentrations.

g Intravenous administration was permitted when clinically indicated (TAC 0.06 mg/kg/day; CsA intravenous dosage not reported).

h Initiated as soon as possible after transplantation,[54] within 24 h where specified.[55]

BCAR = biopsy-confirmed acute rejection; **PO** = oral; * p = 0.002, ** p = 0.004 vs immediate TAC-based regimen.

survival,[21,46-48] graft function (as measured by serum creatinine levels),[46] or were composites of first BCAR, delayed graft function, graft loss or death,[53] or BCAR, graft loss or death.[39] Tolerability assessments, including the incidence of symptomatic and asymptomatic CMV infections,[57] CMV disease,[21] CMV treated episodes[57] or severe adverse events,[21] were primary endpoints in some studies (discussed in section 5).

Other measures of efficacy included the incidence of corticosteroid-resistant or -sensitive BCAR,[17,54,55] delayed graft function (i.e. a need for dialysis post-transplantation[19,54,56] [within the first week, where specified][17,53,55,57] and/or a serum creatinine level >250 μmol/L 5[57] or 10[19] days post-transplantation, a <20% decrease in creatininaemia 2 days post-transplantation[57] or oliguria for 24 hours[57]) and renal function (as assessed by serum creatinine levels, creatinine clearance and/or glomerular filtration rate [GFR]).[17,19,21,39,42,44,45,48,50,54-58]

Where specified, efficacy analyses were based on the intent-to-treat (ITT) population (i.e. all patients)[53] or the modified ITT population (i.e. all patients who received study drug[17,21,56] [at least one dose where specified][19,54,55,57] and underwent transplantation[17,19,56,57]).

4.1.1 Versus No Induction Therapy

rATG induction in combination with delayed tacrolimus-based therapy was more effective in preventing episodes of acute rejection in adult renal transplant recipients than immediate tacrolimus-based therapy without induction, as determined by the incidence of BCAR (coprimary endpoint). The proportion of patients who experienced BCAR episodes within the first 6[54] or 12[55] months post-transplantation was significantly lower with rATG induction than without induction among recipients of tacrolimus-based immunosuppression (table II). Notably, 6 months after transplantation, the incidence of BCAR in recipients of rATG induction with tacrolimus-based therapy did not significantly differ from that seen in recipients of rATG induction with ciclosporin-based therapy (table II).[54] Moreover, the median time to BCAR (coprimary endpoint) was >1 week longer with rATG induction than with noninduction therapy (table II).[54]

Episodes of acute rejection were generally mild or moderate in severity (Banff grade I or II) in both rATG induction and noninduction treatment groups.[54,55] However, among rATG induction recipients, the incidence of moderate or severe rejections (Banff grade II or III) was significantly ($p = 0.023$) lower in those who received tacrolimus-based therapy compared with those who received ciclosporin-based therapy (5.4% vs 13.6% of patients); 10.8% of immediate tacrolimus-based therapy recipients experienced Banff grade II or III BCAR.[54]

The incidence of corticosteroid-resistant BCAR was generally low and did not significantly differ among patients who received tacrolimus-based therapy with (4.8%[54] and 8.6%[55] of patients) or without (7.0%[54] and 8.9%[55]) rATG induction. However, rATG was associated with a significantly ($p = 0.038$) lower incidence of corticosteroid-resistant BCAR when used in combination with tacrolimus- rather than ciclosporin-based therapy (4.8% vs 10.9% of patients).[54] Notably, the proportion of patients who had corticosteroid-sensitive BCAR was significantly ($p = 0.001$) lower with rATG induction than without induction among patients receiving tacrolimus-based immunosuppression in one study (7.9% vs 22.2%).[55]

However, there were no significant differences between rATG induction regimens and noninduction regimens in terms of patient or graft survival 6[54] or 12[55] months post-transplantation (table II).

Delayed graft function after transplantation was reported in a proportion of both rATG induction (18–26%[54,55]) and noninduction (24%[55] or 26%[54]) therapy recipients. Mean serum creatinine levels 6 or 12 months after transplantation were 133–134 μmol/L in recipients of rATG induction therapy[54,55] compared with 134[54] or 136[55] μmol/L in recipients of noninduction therapy.[54,55]

4.1.2 Versus Equine Antithymocyte Globulin

At all follow-up assessments up to 10 years post-transplantation, rATG induction was consistently associated with a significantly lower incidence of BCAR episodes and significantly greater event-free survival than eATG induction in adult renal transplant patients receiving triple immunosuppressive therapy (table III).[21,42,50] Graft survival rates were also higher with rATG up to 5 years post-transplantation. Nevertheless, the rATG and eATG groups did not significantly differ in terms of patient survival (table III).[21,42,50]

RATG was associated with less ($p = 0.02$) severe first BCAR episodes than eATG, although renal function, as assessed by serum creatinine levels, did not significantly differ between the treatment groups up to 5 years post-transplantation.[21,42] However, at 10 years, mean levels of serum creatinine were higher in rATG than eATG recipients (150 vs 106 μmol/L; $p = 0.003$), although there was no significant between-group difference in GFR at this timepoint (49 vs 65 mL/min [2.9 vs 3.9 L/h]).[50]

4.1.3 Versus Basiliximab

The efficacy of rATG in combination with MMF-based triple immunosuppression (using delayed ciclosporin microemulsion) was generally no different to that of basiliximab in combination with a similar MMF-based regimen (using immediate or delayed ciclosporin microemulsion) in adult renal transplant recipients (table III).[19,56] The rATG and basiliximab regimens did not significantly differ with regard to the incidence of BCAR at 6 months or 1 year post-transplantation (table III),[19,56] with all episodes classified as mild or moderate in severity (Banff grade I or II). There were also no significant differences between the treatment groups in terms of patient or graft survival or the proportion of patients who experienced the composite of BCAR, graft loss or death (table III).

The incidence of delayed graft function generally did not differ between rATG and basiliximab recipients (22% vs 18%[19] and 30% vs 29%[56] of patients; statistical analyses were not reported in one study[19]). Moreover, serum creatinine levels improved rapidly after transplantation with each of the regimens.[19,56] Mean serum creatinine levels reached nadir (156 vs 163 μmol/L; between-group difference not significant) 11 days post-transplantation in both rATG and basiliximab recipients in one study.[56] In the other trial, there were generally no significant differences between rATG and basiliximab

Table III. Comparative efficacy of rabbit antithymocyte globulin (rATG) in the prevention of renal graft rejection in adult renal transplant patients (pts). Results of randomized,[19,21,56,57] double-blind[21] or open-label,[19,56,57] single-[21] or multicentre[19,56,57] trials comparing rATG with equine antithymocyte globulin (eATG), basiliximab (BAS) or daclizumab (DAC) in combination with triple immunosuppressive therapy.[a] Agents were administered intravenously via infusion unless otherwise noted; modified intent-to-treat analyses are presented

Reference	Treatment (mg/kg/day unless noted otherwise)	No. of pts	Time of assessment (y)	Results (% of pts)				
				BCAR[b]	pt survival[b]	graft survival[b,c]	event-free survival[d]	BCAR, graft loss or death
Versus eATG								
Brennan et al.[21] and Hardinger et al.[42,50]	rATG 1.5[e]	48	0.5	4*	98		94***	
			1	4*	98	98*	94***	
			5	8**	85	77*	73***	
			10	11**	75	48	48*	
	eATG 15[e]	24	0.5	17	96		71	
			1	25	96	83	63	
			5	34	71	54	33	
			10	42	67	50	29	
Versus BAS								
Lebranchu et al.[19][f]	rATG 1–1.5[g]	50	0.5	8	100	100		8
			1	8	100	96		
	BAS 20 mg[h]	50	0.5	8	98	96		14
			1	8	98	96		
Mourad et al.[56]	rATG 1[g]	53	1	9.4	98.1	96.2		15.1
	BAS 20 mg[h]	52	1	9.6	98.1	94.2		15.4
Versus DAC								
Abou-Ayach et al.[57]	rATG 1–1.5[g]	55	1	14.5	98[i]	95[i]		
	DAC 2 mg/kg[j]	54	1	16.7	98[i]	94[i]		

a Generally azathioprine[21,42,50] or mycophenolate mofetil[19,56,57] in combination with corticosteroids and ciclosporin microemulsion. Administration of ciclosporin was generally delayed, although in some studies the drug was administered preoperatively in live donor kidney recipients[21] or within 24 h post-transplantation in recipients of BAS.[19]

b Primary endpoint of 0.5- and 1-y analyses in one study.[21]

c Actual (i.e. uncensored) graft survival, where specified.[21,57]

d Primary endpoint of the 10-y analysis.[50] Includes freedom from death, acute rejection or graft loss.

e Administered intraoperatively and planned to be continued for ≥7 d. However, only one rATG and one eATG recipient received 8 d of therapy, and the number of full doses ranged from none to eight for rATG and from one to eight for eATG recipients (median of 6 vs 7 full doses; $p = 0.008$).

f The trial was not sufficiently powered to demonstrate superiority of one regimen over the other.

g Initial dose (given on d 0 and 1[56] or after transplantation[57] [within 24 h, where specified[19]]) with subsequent dosage adjustments to maintain $CD2^+$ or $CD3^+$ T-cell counts <20/mm^3. Administration continued for 4–9 d,[57] 6–10 d[19] or until a trough ciclosporin concentration of 100 ng/mL was reached.[56]

h Administered via intravenous bolus injection on day 0 (2 h prior to transplantation) and again on day 4.

i Between-group statistical analyses were not reported.

j Initial dose given 24 h before transplantation; a single 1-mg/kg dose was then given 14 d after transplantation.[57] The standard dosage is a total of five 1-mg/kg doses given at 14-d intervals.[66]

BCAR = biopsy-confirmed acute rejection; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs eATG.

with regard to mean serum creatinine levels up to 1 year post-transplantation, except at 4 weeks (151.2 vs 133.5 μmol/L; $p < 0.05$), with differences in creatinine clearance also favouring basiliximab at 4 (53.9 vs 63.8 mL/min [3.2 vs 3.8 L/h]; $p < 0.01$) and 8 (56.6 vs 62.6 mL/min [3.4 vs 3.8 L/h]; $p < 0.05$) weeks.[19]

4.1.4 Versus Daclizumab

RATG in combination with MMF-based triple immunosuppressive therapy (using delayed ciclosporin microemulsion) provided efficacy generally no different to that of daclizumab (two-dose regimen) in combination with the same immunosuppressive regimen in adult renal transplant recipients (table III).[57] One year after transplantation, the proportion of patients who had experienced BCAR did not significantly differ between the rATG and daclizumab groups (table III), with most episodes classified as being Banff grade IA, IB or borderline. Moreover, there were no marked between-group differences in terms of patient or graft survival (table III).

Delayed graft function was evident in 36% and 32% of patients in the rATG and daclizumab groups.[57] However, serum creatinine levels <250 μmol/L were achieved within 1 week post-transplantation in a large proportion of both rATG and daclizumab recipients (75% vs 74%), with mean levels not differing between treatment groups throughout the 1-year follow-up (143 μmol/L in both groups at 1 year).

4.1.5 Corticosteroid-Free or Corticosteroid-Sparing Regimens

rATG induction in combination with corticosteroid-free immunosuppressive therapy has demonstrated efficacy in the long-term prevention of acute renal transplant rejection in adult and paediatric renal transplant recipients (n = 100) aged 3–66 years (median age 39 years).[58] At up to 4.5 years post-transplantation, 13% of patients had experienced an episode of acute rejection, 99% of patients were alive and well, 90% of grafts were functioning well and the graft survival rate was high (97%, 96%, 90% and 82% at 1, 2, 3 and 4 years, respectively). Median creatinine levels were 159–242 μmol/L 1–3 years post-transplantation. All patients received rATG 1.25 mg/kg/day for 10 days and immunosuppression with ciclosporin microemulsion and MMF.

Induction therapy with rATG may also be effective as part of a corticosteroid-sparing immunosuppressive regimen.[39] In adult renal transplant recipients 1 year after transplantation, rATG induction in combination with immunosuppressive therapy with early corticosteroid withdrawal (four doses) [n = 103] did not significantly differ from immunosuppressive therapy with standard corticosteroid use without induction (n = 48) in terms of the incidence of the primary composite endpoint of BCAR, death or graft loss (11.7% vs 25.6% of patients), or the incidence of any of the individual components of the composite: BCAR (9.9% vs 19.4%), graft loss (1.9% vs 0%) or death (0% vs 2.8%). Moreover, the early corticosteroid withdrawal and standard corticosteroid groups did not significantly differ in terms of renal function, as assessed by mean serum creatinine levels (115 vs 124 μmol/L) and GFR (61.4 vs 55.7 mL/min/1.73 m^2 [3.7 vs 3.3 L/h/1.73 m^2]). The mean rATG dose was 5.6 mg/kg and concomitant immunosuppressive therapy consisted of tacrolimus and MMF.

These data are generally supported by two large clinical practice observational studies (n > 300).[59,60] For example, at 5-years' follow-up in the largest study (n = 589),[59] rATG in combination with immunosuppressive therapy with early withdrawal of corticosteroids was associated with actuarial patient and graft survival rates of 91% and 84%, a death-censored graft survival rate of 92% and high rates of both acute rejection-free (84% of patients) and chronic rejection-free (87%) graft survival. rATG 1.25–1.5 mg/kg/day was administered for 5 days (initiated on day 0) and corticosteroids were withdrawn within 5 days of transplantation (methylprednisolone 500 mg on day 0, then prednisone 1 mg/kg tapered to 0.25 mg/kg on days 4 and 5). The maintenance immunosuppressive therapy was ciclosporin and MMF or tacrolimus and sirolimus.

rATG induction in combination with corticosteroid-sparing immunosuppressive therapy has also shown efficacy in African-American patients (see section 4.1.6).[47]

4.1.6 Patients at High Risk

Patients at high risk of acute transplant rejection included those who were of African-American descent[46-48] or who met at least one of the following criteria: two or three previous renal transplantations; a second transplantation scheduled in case of graft loss within 2 years; a current PRA value ≥30%; or a peak PRA value of

Table IV. Comparative efficacy of rabbit antithymocyte globulin (rATG) in the prevention of renal transplant rejection in adult renal transplant patients (pts) at high risk of acute rejection or delayed graft function. Results of two randomized, open-label, multicentre trials[17,53] comparing rATG with basiliximab (BAS) or daclizumab (DAC) in combination with triple immunosuppressive therapy.[a] Agents were administered via intravenous infusion, unless otherwise noted; intent-to-treat (ITT)[53] and modified ITT[17] analyses are reported

Reference	Treatment (mg/kg/day unless noted otherwise)	No. of pts	Time of assessment (y)	Results (% of pts)				
				first BCAR, delayed graft function,[b] graft loss or death	BCAR	graft loss [survival]	patient death [survival]	delayed graft function[b]
Brennan et al.[53]	rATG 1.5[c]	141	1	50.4[d]	15.6*	9.2	4.3	40.4
	BAS 20 mg[e]	137	1	56.2[d]	25.5	10.2	4.4	44.5
Noel et al.[17] [f]	rATG 1.25[c]	113	1		15.0* [d]	[82.3]	[95.6]	31.5*
	DAC 1[g]	114	1		27.2[d]	[86.0]	[96.5]	44.6

a Corticosteroids,[17,53] mycophenolate mofetil[17,53] and tacrolimus[17] or ciclosporin.[53]

b Defined as the requirement for dialysis during the first wk post-transplantation.

c rATG was administered on day 0 prior to graft reperfusion[17,53] and continued until day 4[53] or 7.[17]

d Primary endpoint.

e BAS was administered on day 0 (prior to graft reperfusion) and on day 4.

f This study was specified to be a noninferiority trial, although noninferiority analyses were not reported. The trial was not sufficiently powered to demonstrate significant between-group differences in graft survival.

g DAC was administered via injection on day 0 prior to graft reperfusion and then every 14 d for an additional 4 doses.

BCAR = biopsy-confirmed acute rejection; * $p < 0.05$ vs comparator.

≥50%.[17] In one study,[53] eligible patients were required to meet at least one of the following criteria for high risk of acute graft rejection or delayed graft function: PRA >20% before transplantation; multiple transplantations; at least one donor HLA antigen mismatch; Black race; cold ischaemia time >24 hours; or a donor aged >50 years or who had acute tubular necrosis, high inotropic support or was without a heartbeat.

In adult renal transplant patients at high risk of acute rejection or delayed graft function receiving MMF-based triple immunosuppressive therapy, the efficacy of rATG in the prevention of renal transplant rejection was not significantly different to that of basiliximab in terms of the incidence of the composite of first BCAR, delayed graft function, graft loss or death at 1 year post-transplantation (primary endpoint) [table IV].[53] When each of the component parts of the endpoint were analysed, there was no significant difference between the treatment groups in the proportion of patients who experienced delayed graft function, graft loss or death; however, fewer rATG than basiliximab recipients experienced BCAR (table IV). No BCAR episodes were classified as severe in either treatment group, although BCAR episodes requiring antibody treatment occurred in significantly fewer rATG than basiliximab recipients (1.4% vs 8.0%; $p = 0.005$).

When results of this study were retrospectively stratified by donor criteria (i.e. standard [n = 203] or extended [n = 75] criteria, or normotensive [n = 214] or hypertensive [n = 66] donor transplants), rATG appeared to provide more benefits than basiliximab in lower-risk patient subgroups.[51] At 1 year post-transplantation, rATG was associated with a significantly ($p < 0.05$) lower incidence of BCAR than basiliximab in patients who received a standard criteria (11.9% vs 24.5% of patients) or normotensive (14.0% vs 25.2%) donor transplant, with significantly ($p < 0.01$) fewer rATG than basiliximab recipients also experiencing the composite of BCAR, graft loss or death in these patient subgroups (16.8% vs 33.3% and 17.8% vs 33.6%). In contrast, there were no significant differences between rATG and basiliximab in terms of these endpoints in patients who received expanded criteria or hypertensive donor transplants.

Longer-term data from a retrospective analysis[52] of this study[53] in which patients who participated in the US (n = 183) were matched with data obtained from the Organ Procurement and

Transplantation Network database suggested that rATG provided benefits over basiliximab up to 5 years post-transplantation. rATG recipients (n = 91), compared with basiliximab recipients (n = 92), had a significantly ($p < 0.05$) lower incidence of the composite of acute rejection, graft failure or death (37% vs 51% of patients) as well as acute rejection (15% vs 27%) 5 years after transplantation, although the two treatment groups did not significantly differ with regard to the incidence of antibody-treated acute rejection (3% vs 12%) or patient (76% vs 80%) or graft (69% vs 63%) survival.

rATG was more effective than daclizumab in the prevention of renal graft rejection in renal transplant patients at high risk of acute rejection receiving MMF-based immunosuppressive therapy, as determined by the incidence of BCAR (primary endpoint).[17] Significantly fewer rATG than daclizumab recipients experienced BCAR 1 year after transplantation (table IV), with most rejection episodes being of Banff grade I with rATG and Banff grade IIa with daclizumab.

The median time to rejection was significantly ($p = 0.007$) longer with rATG than with daclizumab (35 vs 13 days) and significantly ($p = 0.002$) fewer rATG recipients had experienced corticosteroid-resistant rejection 1 year after transplantation (2.7% vs 14.9% of daclizumab recipients).[17] However, there was no significant difference between the treatment groups with regard to patient or graft survival at this timepoint (table IV).

The incidence of delayed graft function after transplantation was significantly lower with rATG than with daclizumab (table IV), although no significant between-group differences were evident in terms of renal function 1 year after transplantation, as measured by mean serum creatinine levels (150.3 vs 132.6 μmol/L) and GFR (49.3 vs 50.9 mL/min/1.73 m^2 [2.96 vs 3.05 L/h/1.73 m^2]).[17]

These findings are generally supported by limited data from a smaller randomized 6-month study comparing the efficacy of rATG (n = 21) with that of daclizumab (n = 20) in adult renal transplant patients at high risk of rejection owing to donor-specific anti-HLA antibodies (dosages not reported).[49]

African-American Patients

Three retrospective studies (n = 73–175)[46-48] have evaluated the use of rATG induction, in combination with triple immunosuppressive therapy, in the prevention of renal transplant rejection in African-American patients. In two of the studies, the efficacy of rATG (1.5 mg/kg/day for 4–7[46] or 5[48] days) was compared with that of basiliximab (20-mg dose on days 0 and 4),[46,48] daclizumab (1 mg/kg on days 0 and 7)[48] or no induction,[48] whereas the other study[47] compared the efficacy of early corticosteroid withdrawal (intravenous methylprednisolone 250 mg on day 0 then three consecutive daily doses of 200, 150 and 100 mg) with that of standard corticosteroid tapering in patients receiving rATG induction therapy (1.5 mg/kg/day for 4–11 days). Concomitant immunosuppressive therapy in these studies consisted of corticosteroids,[46-48] MMF,[46-48] calcineurin inhibition[48] (with tacrolimus, where reported[46,47]) or sirolimus.[46,47]

In the largest study,[48] the incidence of acute renal graft rejection 1 year post-transplantation (coprimary endpoint) in African-American patients was significantly ($p < 0.05$) lower in recipients of rATG (n = 54) or basiliximab or daclizumab (n = 81) induction than in patients who received no induction therapy (n = 40) [18% and 26% vs 47% of patients]. However, there was no significant difference between the rATG and noninduction groups in terms of graft survival at 3 years post-transplantation (76% vs 68% of patients) [coprimary endpoint], whereas monoclonal antibody induction was significantly ($p = 0.032$) more effective than noninduction therapy in this regard (85% vs 68%). Notably, the rATG and monoclonal antibody induction groups did not significantly differ in terms of these endpoints, and there were no significant differences between rATG induction, monoclonal antibody induction or noninduction therapy with regard to patient survival (83%, 87% and 81%, respectively) or renal function, 3 years after transplantation.

These findings are, in part, supported by data from a smaller study.[46] At a mean follow-up of 19 months, there was no significant difference between African-American rATG (n = 36) and

basiliximab (n = 52) recipients in terms of patient survival (94% vs 88% of recipients), graft survival (overall: 86% vs 81%; censored for death: 91% in both treatment groups), serum creatinine levels (164–172 μmol/L in both treatment groups; values estimated from a graph) [coprimary endpoints] or the incidence (14% vs 29%) or severity of BCAR episodes.

rATG in combination with an early corticosteroid withdrawal regimen (n = 40) provided efficacy not significantly different from that of rATG in combination with a standard corticosteroid tapering regimen (n = 33), in terms of primary efficacy measures, for up to ≈30 months post-transplantation in African-American renal transplant patients receiving triple immunosuppression therapy.[47] At 1 year post-transplantation, acute rejection had occurred in 13% of early corticosteroid withdrawal recipients compared with 15% of standard corticosteroid tapering recipients and the respective graft survival rates were 100% and 97% (coprimary endpoints). The risk of acute rejection, graft loss or worsening graft function associated with these two rATG regimens did not significantly differ after confounding factors, such as PRA value, HLA mismatch, re-transplantation status and delayed graft function, were adjusted for.

4.1.7 Paediatric Patients

The efficacy of rATG induction (n = 71[44] and 12[45]) in combination with immunosuppressive therapy in paediatric renal transplant patients has been compared with that of eATG (n = 127),[44] basiliximab (n = 29)[45] or no induction (n = 47)[45] therapy, in combination with a corresponding immunosuppressive regimen, in two retrospective, single-centre studies (mean patient age 8–14.5 years). Recipients of induction therapy received rATG (1–1.5 mg/kg/day on days 0–2[45] or 1.5 mg/kg/day for 10 days[44]), eATG (15 mg/kg/day for 14 days)[44] or basiliximab (12 mg/m^2 on days 0 and 4; maximum dose 20 mg)[45] intraoperatively[45] and/or postoperatively.[44,45] Concomitant immunosuppressive therapy consisted of corticosteroids, ciclosporin and azathioprine or MMF in one trial[44] and corticosteroids, MMF and tacrolimus or ciclosporin in the other,[45] with tacrolimus or ciclosporin administered at the physician's discretion according to serum creatinine levels.[45]

In the smaller of these studies,[45] the incidence of BCAR at 1 year post-transplantation (primary endpoint) was not significantly different between rATG, basiliximab and noninduction recipients (0%, 20.6% and 10.7% of patients, respectively). Respective graft survival rates were 91.7%, 100% and 97.9%, and patient survival was 100% in all treatment groups (no statistical analyses reported). However, the renal function of rATG recipients (as assessed by mean GFR; 42.4 mL/min [2.5 L/h]) was significantly ($p < 0.05$) lower than that of patients who received either basiliximab (78.3 mL/min [4.7 L/h]) or no induction therapy (66 mL/min [4 L/h]) at this timepoint.

Up to 3 years post-transplantation in the largest study,[44] rATG induction was associated with a significantly ($p = 0.02$) lower overall incidence of BCAR than eATG induction (33% vs 50%), although the median time to BCAR (5.1 vs 1.6 months) and severity of BCAR did not significantly differ between the two regimens. rATG and eATG recipients also did not significantly differ at 1, 2 or 3 years' follow-up in terms of patient survival (96% [at all timepoints] vs 98%, 97% and 97% of patients, respectively), overall graft survival (93%, 88% and 83% vs 96%, 92% and 92%, respectively) or graft survival censored for death, noncompliance, recurrent disease or technical causes (100%, 100% and 95% vs 100%, 98% and 98%, respectively). There was also no significant between-group difference in the overall incidence of delayed graft function (17% of rATG recipients vs 8% of eATG recipients) or mean serum creatinine levels (80–106 vs 71–115 μmol/L).

4.2 Treatment of Acute Renal Graft Rejection

The clinical efficacy of rATG in the treatment of acute renal graft rejection has been compared with that of eATG in a large (n = 162), randomized, double-blind, multicentre, phase III trial in adult renal transplant patients.[20]

In addition, a small (n = 60) randomized study[67] compared the efficacy of rATG with that of monoclonal muromonab-CD3 in the treatment

of acute corticosteroid-resistant rejection. In this trial, rATG 0.75 mg/kg/day (mean dosage) demonstrated efficacy not significantly different from that of muromonab-CD3 0.05 mg/kg/day (mean dosage) in the treatment of acute rejection. However, as the study used dosages of rATG and muromonab-CD3 approximately half of those recommended by the manufacturers, data from the study are not discussed further.

The large phase III trial[20] was conducted in patients with BCAR of Banff grades I–III, with those with mild rejection (i.e. grade I) also having to exhibit corticosteroid resistance, defined as a ≥10% increase in serum creatinine levels despite treatment with intravenous methylprednisolone ≥250 mg/day for ≥3 consecutive days. Patients with a platelet count of $<100 \times 10^9$/L, evidence of chronic rejection (if levels of serum creatinine were >265 μmol/L prior to rejection) or a current rejection episode with resistance to muromonab-CD3 were excluded from the trial.

Patients were randomized to receive rATG 1.5 mg/kg/day or eATG 15 mg/kg/day for 7–14 days. During enrolment, patients were stratified according to rejection severity as assessed by Banff criteria. Concomitant immunosuppressive agents typically included prednisone, ciclosporin and azathioprine,[20] with tacrolimus and MMF also used during the second half of the study;[13] dosage reductions of these agents were permitted during study drug administration.[20]

The primary efficacy variable was successful response, defined as a return of the serum creatinine level to or below that of day 0 on two consecutive measurements taken ≥2 days apart at the end of treatment or 14 days after treatment initiation.[20] Secondary measures of efficacy included graft survival at day 30, levels of serum creatinine (percentage of baseline) at day 30 and improvement in biopsy grade compared with baseline. The incidence of recurrent rejections 90 days after treatment cessation and graft and patient survival 1 year after therapy were also reported. A composite of a return to baseline of serum creatinine levels within 14 days of rejection diagnosis and a functioning graft at 30 days (reported in the manufacturer's prescribing information[13]) is also discussed.

The noninferiority of rATG versus eATG was assessed using a noninferior acceptance limit of −20% for key efficacy variables, based on the lower limit of the one-sided 95% confidence interval for the difference between groups.[20] Efficacy assessments were based on the ITT patient population (exclusive of one eATG recipient who was found not to have BCAR). Improvements in biopsy grade were assessed in 20 rATG and 18 eATG recipients who had post-treatment biopsies.

Patient characteristics at baseline did not significantly differ between treatment groups.[20] Patients in the rATG and eATG groups had a mean age of ≈40 years and the majority were recipients of a first renal transplant (95% and 93%) and had rejections of Banff grade II (71% and 73%). The mean duration of treatment was 10 days.

rATG was more effective than eATG in the treatment of renal graft rejection in adult renal transplant recipients according to primary endpoint analysis, with significantly more rATG than eATG recipients achieving a successful response (table V).[20] In addition, rATG was no less effective than eATG in terms of graft survival at day 30 (table V), and there was no significant between-group difference in terms of serum creatinine levels relative to baseline at this timepoint (72% vs 80% of baseline) or the proportion of patients who had an improvement in rejection severity of one Banff grade (65% vs 50%).[20]

However, among patients who achieved a successful response to treatment, significantly ($p < 0.05$) fewer episodes of recurrent rejection occurred with rATG than with eATG within 90 days after treatment cessation, according to several methods of assessment, including investigator diagnosis (12 vs 22 episodes) and histological confirmation (6 vs 12).[20]

Longer term, rATG and eATG recipients did not significantly differ in terms of graft survival (table V)[20] or patient survival (93% vs 96%)[13] 1 year after completion of treatment.

Additional data from this study reported in the manufacturer's prescribing information[13] generally support these findings. rATG was no less effective than eATG in terms of the proportion of patients who had serum creatinine levels return to baseline within 14 days of rejection

Table V. Comparative efficacy of rabbit antithymocyte globulin (rATG) in the treatment of acute renal graft rejection in adult renal transplant patients (pts). Results of a randomized, double-blind, multicentre, phase III trial[20] comparing rATG with equine antithymocyte globulin (eATG) in combination with immunosuppressive therapy (i.e. corticosteroids, ciclosporin or tacrolimus, and azathioprine or mycophenolate mofetil). Study drugs were administered intravenously via central line infusion for 7–14 days; intent-to-treat analyses are reported

Treatment (mg/kg/day)	Rejection grade	No. of pts	Results (% of pts)			
			successful response[b]	graft survival		SCr ≤b/line[a] + a functioning graft at 30 d[c]
				at 30 d	at 1 y	
rATG 1.5	All	82	88*[d]	94[d]	83	78.0[e]
	Banff grade I	10	90	100	90	90.0
	Banff grade II	58	90	95	86	75.5
	Banff grade III	14	79	86	64	71.6
eATG 15	All	80	76	90	75	67.5
	Banff grade I	8	88	100	78	62.5
	Banff grade II	58	76	91	81	70.7
	Banff grade III	14	71	77	50	57.1

a Within 14 d of rejection being diagnosed.

b Primary endpoint. Defined as a serum creatinine level ≤b/line at end of treatment or within 14 d after treatment initiation.

c Composite endpoint reported in the manufacturer's prescribing information.[13]

d The criterion for noninferiority between rATG and eATG (lower one-sided 95% CI greater than –20%) was met for both successful response (11.4% estimated between-group difference; 95% CI lower limit of +1.6%) and graft survival at 30 d (4.1% estimated between-group difference; 95% CI lower limit of –2.9%), with rATG demonstrating superior efficacy ($p = 0.027$) in terms of successful response.

e The criterion for noninferiority (lower one-sided 95% CI greater than –20%) were met (11.1% estimated between-group difference; 95% CI lower limit of +0.07%).

b/line = baseline; **SCr** = serum creatinine; * $p < 0.05$ vs eATG.

diagnosis and a functioning graft at 30 days (composite endpoint; table V).

As expected, results of stratification by Banff grade indicated that patients with more severe episodes of rejection tended to have worse outcomes irrespective of the treatment regimen (table V).[13,20]

5. Tolerability

The tolerability profile of rATG in renal transplant recipients has been previously reviewed.[14] This section reviews tolerability data related to administration of rATG for the prevention or treatment of renal transplant rejection available from clinical trials discussed in section 4, focusing on data from randomized studies in adults (section 5.1);[17,19-21,39,42,50,53-57] data from retrospective studies in paediatric patients are also briefly discussed (section 5.2).[44,45] Primary tolerability endpoints included the incidence of symptomatic CMV infection (i.e. syndromes and diseases),[57] asymptomatic CMV infection,[57] CMV disease,[21] CMV-treated episodes (i.e. infections, syndromes or diseases)[57] and severe adverse events.[21] Additional data were obtained from retrospective analyses of data from three US registry databases[68-70] and from the manufacturer's prescribing information.[12,13]

5.1 Adult Patients

5.1.1 General Tolerability

Given the nature of immunosuppressive therapy, both induction[19,21,42,50,53-57] and treatment[20] with rATG was generally well tolerated in adult renal transplant recipients, with adverse events generally being of mild or moderate severity[19] and manageable or reversible,[13] where reported.

Treatment-emergent adverse events were experienced by most patients who received immunosuppression with (97.8% or 98.9% of patients who received tacrolimus- or ciclosporin-based therapy) or without (96.8%) rATG induction.[54] In trials comparing rATG induction with non-induction regimens, the most commonly reported (i.e. an incidence ≥35% in any treatment group)

adverse event was leukopenia, which occurred in significantly ($p < 0.001$) more recipients of rATG induction in combination with tacrolimus- or ciclosporin-based therapy than with tacrolimus-based therapy without induction (34.8–38.7%[54,55] vs 8.6%[54] and 9.5%[55]). Leukopenia generally occurred within the first week post-transplantation and lasted for ≤1 week.[54] rATG induction therapy was also generally associated with a significantly ($p < 0.01$) higher incidence of fever (17.7–25.2%[54,55] vs 2.2%[54] and 10.1%[55] of noninduction recipients), serum sickness (15.8% and 16.1% vs 0%),[54] thrombocytopenia (7.6–11.8%[54,55] vs 3.2%[54,55]) and certain infections (discussed in section 5.1.2)[54,55] than noninduction therapy.

Consistent with the tolerability profiles of ciclosporin and tacrolimus, rATG induction in combination with ciclosporin-based therapy was associated with a significantly ($p < 0.05$) lower incidence of tremor than tacrolimus-based immunosuppressive therapy with or without rATG induction (2.7% vs 7.5% and 8.1% of patients) and a higher ($p < 0.05$) incidence of hypercholesterolaemia (6.5% vs 2.7% and 1.6%).[54]

In trials comparing rATG with other induction agents, rATG did not significantly differ from basiliximab with regard to the incidence of treatment-emergent adverse events (99.3% vs 98.5%[53] and 94.0% vs 90.2%[19] of patients) or serious (73.0% vs 72.3% of patients[53]) or severe (25 events with each of the agents[19]) treatment-emergent adverse events. rATG was also associated with an incidence and severity of adverse events generally similar to that of daclizumab (quantitative data not reported).[57] However, rATG recipients had a significantly ($p = 0.013$) lower median incidence of serious treatment-emergent adverse events than eATG recipients (none vs one event), although there was no significant between-group difference in the mean incidence of such events (one vs two events per patient) [primary endpoints].[21]

Where reported, adverse events considered to be possibly related to study drug occurred in significantly ($p < 0.001$) more rATG than basiliximab recipients (24 vs 8 patients).[19] Among those attributed to rATG were infusion-associated reactions, such as fever,[19] gastrointestinal disorders,[19] cutaneous rash[19] and serum sickness.[19,56] Selected adverse events, other than infection (see section 5.1.2), that occurred most commonly (i.e. ≥10% of patients or ≥5 events in any treatment group) in recipients of rATG, basiliximab or eATG induction included fever,[19,56] gastrointestinal disorder,[19] leukopenia[19,21,53,56] and thrombocytopenia.[53,56] Of these events, rATG was associated with a significantly ($p < 0.05$) higher incidence of leukopenia than basiliximab (33.3% vs 14.6%[53] and 51.0% vs 19.2%[56] of patients; 5 vs 0 events[19]) or eATG (56% vs 4% of patients),[21] and a significantly ($p < 0.001$) higher incidence of fever (16 vs 1 event)[19] and thrombocytopenia (30.2% vs 0% of patients)[56] than basiliximab in some studies. Notably, leukopenia generally occurred only during the period of induction,[21] with the incidence of the event no longer differing between rATG and basiliximab after 14 days, where reported.[53]

Post-transplant diabetes mellitus (PTDM) is a recognized complication in patients who undergo solid-organ transplantation.[71] PTDM, where reported, occurred in a proportion of renal transplant patients who received immunosuppressive therapy in combination with rATG (1.1–7.3%),[19,54,55,57] basiliximab (2%)[19] or daclizumab (3.7%)[57] induction, or without induction (4.0%[54] and 4.5%[55]). The incidence of PTDM differed significantly ($p = 0.014$) among patients who received rATG induction in combination with tacrolimus-based (7.3%; 13 of 177 patients) or ciclosporin-based (1.1%; 2 of 177 patients) therapy or tacrolimus-based therapy without induction (4.0%; 7 of 173 patients).[54]

In the treatment of renal transplant rejection,[20] rATG had a tolerability profile generally similar to that of eATG with regard to the nature and incidence (14.6 vs 14.3 events per patient) of treatment-emergent adverse events, with fever (63.4% vs 63.0% of patients), chills (57.3% vs 43.2%) and leukopenia (57.3% vs 29.6%) being the most commonly reported (i.e. incidence >50% in either treatment group).[13] However, significantly ($p < 0.05$) more rATG than eATG recipients experienced leukopenia (57.3% vs 29.6%) and malaise (13.4% vs 3.7%), whereas significantly

($p < 0.05$) fewer rATG than eATG recipients reported dizziness (8.5% vs 24.7%) and dysuria (quantitative data not reported).[13,20]

The manufacturer's prescribing information warns that infusion-associated reactions consistent with cytokine release syndrome may occur in patients who receive rATG.[11,13] Serious infusion-associated reactions such as cytokine release syndrome or anaphylaxis have been reported with rATG therapy,[11-13] albeit rarely,[11,12] with the Canadian prescribing information carrying a boxed warning in this regard.[12]

5.1.2 Infection

Infections (bacterial, viral, fungal and protozoal) may occur in patients receiving rATG in combination with other immunosuppressive agents.[12] Indeed, rATG induction in combination with tacrolimus-[54,55] or ciclosporin-based[54] therapy was generally less favourable with regard to infections than tacrolimus-based therapy without induction in two large trials.[54,55] The overall incidence of infection was significantly ($p = 0.003$) greater with rATG induction (67.7% or 75.0% of patients who received tacrolimus- or ciclosporin-based therapy) than without induction (58.4%) in one study.[54] However, the only infections that occurred in significantly ($p < 0.05$) more rATG induction than noninduction recipients in the two trials were CMV (24.2–32.5%[54,55] vs 15.7%[54] and 19.0%[55] of patients) and herpes simplex virus (17.9% vs 5.7%)[55] infection.

In trials comparing rATG with other induction agents, the incidence of infection with rATG did not significantly differ from that seen with eATG (56% vs 75% of recipients)[21] or basiliximab (53.0% vs 42.3%[56] and 86.0% vs 64.7%[19]), although in high-risk patients, significantly more rATG than basiliximab recipients experienced infections (85.8% vs 75.2%), including confirmed bacterial infections (52.5% vs 37.2%), urinary tract infections (39.0% vs 27.0%) and viral infections other than CMV (21.3% vs 11.7%) [$p < 0.05$ for all comparisons].[53] Moreover, rATG and daclizumab did not significantly differ with regard to the overall incidence of bacterial infections (46.9% vs 46.5% of patients), although the mean number of bacterial infections per patient was significantly ($p = 0.014$) higher with rATG (2.5 vs 1.8 with daclizumab).[17] Where specified,[19] most infections were mild or moderate in severity, with the most commonly reported being respiratory tract or urinary tract infections.

The incidence of CMV disease (primary endpoint) was significantly ($p = 0.025$) lower with rATG than with eATG induction at 6 months post-transplantation (10.4% [5 of 48 patients] vs 33.3% [8 of 24 patients]),[21] although the between-group difference was not significant at subsequent follow-ups of 1,[21] 5[42] or 10[50] years (13% [6 of 48 patients] vs 33% [8 of 24 patients] at all timepoints).

Moreover, the tolerability profile of rATG induction was generally similar to that of daclizumab with regard to CMV parameters.[17,57] There was no significant difference between rATG and daclizumab recipients in the incidence of asymptomatic (34.5% vs 33.3% of patients) or symptomatic (16.4% [9 of 55 patients] vs 5.6% [3 of 54 patients]) CMV infection,[57] the proportion of patients with a CMV episode who received ganciclovir treatment (43% vs 33%)[57] [all primary endpoints], the incidence of treated CMV infection (18.6% vs 10.5%)[17] or the overall incidence of CMV episodes (51% vs 39%).[57] Nevertheless, CMV infection was detectable significantly ($p = 0.015$) earlier with rATG than with daclizumab (mean of 34 vs 75 days) in one study.[57]

However, rATG induction was associated with a significantly ($p < 0.05$) higher incidence of CMV infection than basiliximab induction (38.0% vs 11.8%[19] and 41.5% vs 21.2%[56] of patients), except in a study in high-risk patients, in which the incidence of CMV infection was significantly ($p = 0.02$) lower with rATG than with basiliximab (7.8% vs 17.5%).[53]

Limited tolerability data suggested that rATG induction in combination with an early corticosteroid withdrawal immunosuppressive regimen was not significantly different from that of a noninduction immunosuppressive regimen with standard corticosteroid use with regard to the incidence of infections (35.9% vs 45.8% of patients) and CMV disease (1.9% vs 4.2%).[39]

Moreover, in a noncomparative trial,[58] although renal transplant patients who received rATG induction in combination with a corticosteroid-free immunosuppressive regimen had 36 CMV infections and 18 reactivated EBV infections, none developed CMV disease or primary EBV infections.

In the treatment of acute renal rejection, the nature and incidence of infections were similar with rATG and eATG,[13] with 50% and 51% of patients experiencing infectious complications.[20] The most common infections were bacterial (29% of rATG vs 37% of eATG recipients) and viral (21% vs 11%) infections; fungal infections occurred in only 9% of patients in each treatment group.[20] Most infections in rATG and eATG recipients affected the whole body (36.6% vs 27.2% of patients), such as CMV infection (13.4% vs 11.1%), or were urogenital (18.3% vs 29.2%).[13]

It should be noted that most studies used antiviral prophylaxis, where reported.[17,21,53,55-58] Prophylactic agents included acyclovir,[17,21,55,58] ganciclovir[17,21,53,55,57,58] and valacyclovir,[56] although some of these agents were only used when the donor[17,21,53,56,57] or recipient[17,21,53] were seropositive for CMV infection or to prevent CMV disease in CMV-positive patients,[58] where specified; CMV prophylaxis was not given in one study.[19] Some studies also used antibacterial[21,53,56] and/or antifungal[17,21,53] prophylaxis.

5.1.3 Malignancy

Where reported, the incidence of malignancies, such as post-transplant lymphoproliferative disease (PTLD), was generally low with rATG therapy irrespective of whether the drug was being administered for the prevention[17,19,21,39,42,50,53,54,56-58] or treatment[20] of renal transplant rejection.

Only two and four malignant events were documented in recipients of rATG induction in combination with tacrolimus- or ciclosporin-based therapy compared with one event in recipients of tacrolimus-based therapy without induction.[54]

New[19,57] or recurrent[19] malignancies or cases of PTLD[19,21,56,57] were generally not reported within 6–12 months post-transplantation in patients who received rATG,[19,21,56,57] basiliximab,[19,56] daclizumab[57] or eATG[21] induction. Longer term, rATG induction was associated with a significantly ($p = 0.01$) lower incidence of malignancy than eATG at 5 years post-transplantation (6% [3 of 48 patients] vs 21% [5 of 24 patients]),[42] although there was no significant difference between the agents at 10 years (8% [4 of 48 patients] vs 21% [5 of 24 patients]).[50]

In high-risk patients, there was no significant difference between rATG and basiliximab induction with regard to the incidence of malignancies (3.5% [5 of 141 patients] vs 0.7% [1 of 137 patients]), including PTLD (2.1% [3 of 141 patients] vs 0%), renal cell carcinoma in the native kidney (0.7% [1 of 141 patients] vs 0.7% [1 of 137 patients]) and squamous-cell carcinoma (0.7% [1 of 141 patients] vs 0%) at 1 year post-transplantation.[53] Moreover, the incidence of malignancy did not significantly differ between rATG and daclizumab 1 year after transplantation (0.9% [1 of 113 patients] vs 0%) and no cases of PTLD were reported in either treatment group.[17]

In patients receiving rATG or eATG for the treatment of acute renal transplant rejection,[20] only three patients in each treatment group developed a malignancy (either lymphoma, leukaemia or skin malignancy) during a 1-year follow-up period; one patient in each group died from lymphoma.

Registry Analyses

Retrospective analyses of data from three US registry databases have produced mixed findings concerning the risk of post-transplant malignancies associated with rATG and other immunosuppressive agents in renal transplant recipients.[68-70] These studies included data from the Scientific Registry of Transplant Recipients (between the years of 1996 and 2002),[68] the United Network of Organ Sharing Registry (between 1987 and 2003)[69] and the United States Renal Data System (between 1996 and 2000),[70] with one study including only patients who received a first cadaveric transplant.[68]

In the largest of these studies ($n = 84\,907$),[69] induction with rATG, unlike eATG and antilymphocyte globulin (ALG), was not associated

with a significantly increased risk of PTLD relative to no induction therapy. However, it should be noted that the median follow-up in the rATG group was significantly ($p < 0.05$) shorter than in the eATG or ALG group (368 vs 1433 or 2055 days). These findings are generally supported by data from the smallest study (n = 25 127),[70] which demonstrated that although use of antithymocyte globulin preparations or muromonab-CD3 was associated with a significant ($p < 0.05$) risk of developing PTLD, no significant risk of this malignancy was associated with the use of rATG when data for the agent were analyzed separately (n = 684). Similarly, PTLD risk was not increased with use of anti-CD25 antibodies, such as basiliximab or daclizumab.[70]

However, data from another retrospective analysis[68] in which patients were followed for an average of ≈4 years post-transplantation, suggested that most induction agents, including rATG, may significantly ($p < 0.05$) increase the risk of developing PTLD (n = 41 686 evaluable) but not *de novo* solid tumours (n = 38 191), relative to immunosuppressive therapy without induction. In this regard, no significant differences were evident between any of the induction agents evaluated (rATG, eATG, basiliximab, daclizumab, muromonab-CD3).

5.2 Paediatric Patients

rATG induction therapy was generally well tolerated in paediatric renal transplant recipients, according to data from retrospective studies.[44,45] There were no significant differences among paediatric patients who received immunosuppressive therapy in combination with rATG or basiliximab induction or without induction with regard to the incidence of CMV syndrome (8% [1 of 12 patients], 0% or 13% [6 of 47 patients], respectively) or PTLD (0%, 0% or 4% [2 of 47 patients]).[45] However, rATG induction was associated with a significantly ($p = 0.002$) higher incidence of EBV infection than eATG induction (8% [6 of 71 patients] vs 3% [4 of 127 patients]), although there was no significant between-group difference in the incidence of other infections or PTLD.[44]

6. Dosage and Administration

rATG is approved in the US[13] and Canada[12] for the treatment of acute renal transplant rejection, and in the UK[11] for the treatment of corticosteroid-resistant renal transplant rejection. The drug is also approved for the prevention of renal graft rejection in both the UK[11] and Canada.[12] However, rATG is indicated for use only in adult renal transplant recipients in Canada.[12]

rATG should be administered in conjunction with other immunosuppressive agents.[11-13] For the treatment of renal graft rejection, the recommended rATG dosage is 1.5 mg/kg/day for 7–14 days after transplantation.[11-13] The recommended dosage of rATG for the prophylaxis of renal transplant rejection is 1–1.5 mg/kg/day for 3–9 days post-transplantation in the UK,[11] and 1.5 mg/kg/day for ≥7 days (initiated intraoperatively) in Canada.[12]

rATG should be administered via intravenous infusion over ≥6 hours[11] for the first infusion[12,13] and ≥4 hours thereafter.[12,13] rATG infusion should be through a high-flow (central) vein, although peripheral vein infusion may be used in the UK[11] and Canada.[12] Anti-infective prophylaxis and pretreatment with paracetamol (acetaminophen), corticosteroids and/or antihistamine prior to rATG infusion are recommended to reduce the likelihood of adverse events.[11-13]

Monitoring of total white blood cell and platelet counts is recommended during rATG therapy.[11-13] The rATG dosage should be reduced in patients with a white blood cell count of 2000–3000 cells/mm^3 or a platelet count of 50 000–75 000 cells/mm^3, with cessation of rATG therapy considered in those with a white blood cell count <2000 cells/mm^3 or a platelet count <50 000 cells/mm^3.

rATG should be used only by physicians who have experience in administering immunosuppressive therapy[11-13] for the management of renal transplant patients;[12,13] this information features in a boxed warning in both the US[13] and Canadian[12] prescribing information. Local prescribing information for rATG should be consulted for comprehensive information regarding

contraindications, special patient populations, warnings and other precautions.

7. Place of Rabbit Antithymocyte Globulin in the Prevention and Treatment of Acute Renal Allograft Rejection

The overall aim of immunosuppressive therapy in renal transplant recipients is to prevent rejection of the graft and extend both graft and patient survival.[1,72] The past decade has seen considerable changes within transplant immunosuppressive therapy that have resulted in improved short-term outcomes for renal transplant recipients.[2,6]

Standard maintenance immunosuppressive regimens consist of calcineurin inhibitors, antiproliferative agents and corticosteroids.[2] The most widely used agents are still calcineurin inhibitors, although tacrolimus has now largely replaced ciclosporin, and among the antiproliferative agents, azathioprine has largely been superseded by MMF.[2] However, many clinically significant adverse effects remain associated with immunosuppressive therapy, most of which are attributed to corticosteroids (e.g. hypertension, hyperlipidaemia, avascular necrosis, osteoporosis) and calcineurin inhibitors (e.g. nephrotoxicity, hypertension and neurological disturbances, such as tremors).[73]

Induction therapy with antibody preparations has become an increasingly popular strategy to help further reduce the likelihood of acute rejection in renal transplant recipients and to limit the exposure of the grafts to the nephrotoxic effects of calcineurin inhibitors early after transplantation.[1] Antibody preparations currently available for use in induction therapy include those that are lymphocyte depleting, such as polyclonal rATG, eATG and ALG, and monoclonal muromonab-CD3 and alemtuzumab, and non-lymphocyte-depleting antibodies, such as the anti-CD25 monoclonal antibodies basiliximab and daclizumab.[1,4,9] It should be noted that, in addition to rATG, another lymphocyte-depleting polyclonal rabbit antithymocyte globulin antibody preparation known as ATG-Fresenius S® is available for induction.[9] ATG-Fresenius S® is an antibody preparation raised against Jurkat cells that was introduced prior to rATG.

As expected, polyclonal antibody preparations, such as rATG (section 2), recognize a wide variety of cell surface antigens involved in numerous immunological processes. The hope that more specific immunosuppression would improve clinical outcomes prompted the introduction of muromonab-CD3, although its unfavourable tolerability profile (e.g. adverse events such as cytokine release syndrome, seizures, aseptic meningitis and PTLD) has severely limited its use.[9] The monoclonal agents basiliximab and daclizumab, which specifically target and block proliferation of activated T cells without affecting resting T cells, were introduced more recently. Unlike antibodies of rabbit, equine or murine origin, these antibodies are chimeric (i.e. murine/human) or humanized, which may potentially minimize their immunogenicity.[74]

Induction therapy is considered optional in current treatment guidelines for renal transplantation produced by the European Renal Association and European Dialysis and Transplant Association.[75] In the most recent treatment guidelines provided by the European Association of Urology,[76] routine use of T cell-depleting induction therapies in recipients of first transplants who are at low risk of rejection is not recommended, with other guidelines[75] suggesting that transplant recipients with low or high PRA to HLA or with delayed graft function may benefit from lymphocyte-depleting induction therapy. Induction therapy with the non-lymphocyte-depleting antibodies basiliximab or daclizumab is considered to be effective in preventing acute renal rejection in current guidelines,[1,75,76] with those produced by the UK National Institute for Clinical Excellence[1] recommending these agents as options in all adult renal transplant recipients irrespective of their immunological risk.

rATG induction in combination with tacrolimus-based immunosuppressive therapy is more effective in preventing episodes of acute renal graft rejection in adult renal transplant recipients than tacrolimus-based therapy without induction, according to primary endpoint data from two randomized, open-label, multicentre trials (section 4.1). Additional results from one of these trials indicate that the efficacy of rATG in this

regard does not differ when used in combination with tacrolimus- or ciclosporin-based therapy. Moreover, the median time to BCAR (coprimary endpoint) was >1 week longer in rATG induction than in noninduction recipients, although there were no significant differences between induction and noninduction regimens in terms of patient or graft survival (section 4.1).

In comparison with other induction agents, data from a double-blind, single-centre trial with up to 10 years' follow-up indicate that rATG induction is generally more effective than eATG induction with regard to the prevention of acute graft rejection, event-free survival and graft survival in adult renal transplant recipients receiving immunosuppressive therapy, although there is no difference between these polyclonal agents in terms of patient survival (section 4.1). Notably, these findings lead to rATG becoming the preferred polyclonal agent for use in induction.[9] Moreover, the efficacy of rATG induction therapy in adult renal transplant recipients receiving triple immunosuppressive therapy is generally no different from that of basiliximab or low-dose daclizumab with regard to the incidence of BCAR, patient or graft survival, or the composite of BCAR, graft loss or death at 6 months or 1 year post-transplantation, according to data from three randomized, open-label, multicentre studies (section 4.1). However, it should be noted that the trials comparing rATG with basiliximab or daclizumab were either not powered to show overall superiority of one regimen over the other,[19] were powered to address safety rather than efficacy parameters,[56,57] or used a limited daclizumab dosage regimen.[57] Therefore, robust trials designed principally to evaluate the efficacy of rATG relative to that of basiliximab and daclizumab in adult renal transplant recipients are warranted in order to definitively position rATG with respect to these monoclonal agents, with longer-term data being of particular interest.

rATG induction, in combination with triple immunosuppressive therapy, has also demonstrated efficacy in adult renal transplant recipients at high risk of acute rejection or delayed graft function. In a large, randomized, multicentre trial, rATG did not significantly differ from basiliximab with regard to most efficacy parameters, including the primary endpoint, 1 year post-transplantation, although rATG was more effective than basiliximab in preventing episodes of BCAR (section 4.1.6). rATG appears to provide more benefit than basiliximab in patients who receive standard or normotensive donor transplants, according to a retrospective subgroup analysis of this study. Moreover, in the longer term, data from another retrospective analysis of this study suggest rATG may provide benefits over basiliximab for up to 5 years after transplantation in terms of the composite of acute rejection, graft failure or death, as well as acute rejection, although patient and graft survival do not differ between the agents. Data from a similarly designed trial indicate that rATG is more effective than daclizumab in preventing BCAR (primary endpoint) 1 year after transplantation and is associated with a longer median time to rejection, although the treatments do not significantly differ with regard to rates of patient or graft survival (section 4.1.6); however, the trial was not sufficiently powered to demonstrate a between-group difference in graft survival. rATG induction therapy is also effective in African-American renal transplant recipients according to data from retrospective studies (section 4.1.6). Additional longer-term comparative studies are needed to assess the efficacy of rATG relative to that of other induction agents in high-risk patients.

rATG induction therapy has shown promise in paediatric renal transplant recipients in retrospective studies (section 4.1.7), although prospective studies are required in order to determine the relative efficacy and tolerability of rATG and other induction regimens in this patient population.

The considerable tolerability concerns associated with long-term corticosteroid therapy have increased interest in immunosuppressive regimens that minimize corticosteroid use in kidney transplant recipients.[77] Limited data in adult and paediatric renal transplant recipients indicate that effective immunosuppression may be achieved with rATG induction in combination with immunosuppressive therapy that is corticosteroid-free or uses early withdrawal of corticosteroids (section 4.1.5). rATG induction in

combination with corticosteroid-sparing immunosuppression therapy may also be effective in African-American renal transplant patients, according to data from a retrospective study (section 4).

Robust prospective trials comparing the efficacy of induction agents in corticosteroid minimization regimens are currently limited. However, a randomized, multicentre trial has compared the efficacy of rATG or basiliximab induction with that of alemtuzumab induction in renal transplant patients receiving maintenance immunosuppression with MMF and tacrolimus with rapid corticosteroid withdrawal (data available as abstracts).[78,79] In this study, no significant difference was evident between rATG (n = 69) and alemtuzumab (n = 70) with regard to the incidence of BCAR (primary endpoint) at 1 (13.0% vs 9.5% of patients)[78] or 2 (12.9% vs 12.7%)[79] years post-transplantation in patients at high risk of rejection. In contrast, in low-risk patients, significantly ($p < 0.05$) more basiliximab (n = 171) than alemtuzumab (n = 164) recipients experienced BCAR at these timepoints (19.6% vs 2.5% at 1 year;[78] 21.7% vs 8.9% at 2 years[79]). The long-term outcomes associated with corticosteroid minimization regimens require further assessment and additional studies investigating the efficacy of such regimens in high-risk patients would also be beneficial.

The progress that has been made in the management of kidney transplantation over recent years is clear, with 51% of renal transplant recipients in the US being treated for acute rejection within 1 year of transplantation in 1996 compared with only 10% in 2005.[80] Current treatment guidelines generally recommend high-dose or bolus corticosteroid therapy for the treatment of acute episodes of renal rejection, with lymphocyte-depleting agents, high-dose corticosteroids or a conversion to tacrolimus being commonly considered for the treatment of recurrent, severe or corticosteroid-resistant acute rejection episodes.[1,75,76] Where specified,[75] polyclonal lymphocyte-depleting antibody preparations are recommended over muromonab-CD3 owing to their more favourable tolerability profiles, with rabbit preparations (e.g. rATG) preferred over those from equine sources (e.g. eATG and ALG).

Data from a double-blind, multicentre, phase III trial indicate that rATG is effective in the treatment of acute renal rejection in adult renal transplant recipients receiving concomitant immunosuppressive therapy (section 4.2). In this study, more rATG than eATG recipients achieved the primary endpoint of successful response (i.e. a return of serum creatinine levels to baseline by end of treatment or within 14 days of treatment initiation), although the treatment groups generally did not differ in terms of graft survival at 30 days, graft function or the proportion of patients who had an improvement in rejection severity of one Banff grade. However, among those who achieved a successful response, fewer episodes of recurrent rejection occurred in rATG than eATG recipients within 90 days of treatment cessation, although there was no between-group difference in graft or patient survival 1 year after treatment completion.

At present, the only monoclonal antibody commercially available for the treatment of acute renal rejection is muromonab-CD3.[81] As yet, there are no robust data to suggest effectiveness of other monoclonal agents, such as basiliximab or daclizumab, in this setting.

Both induction and treatment with rATG were generally well tolerated in adult renal transplant recipients in clinical trials (section 5.1.1). As is typical of lymphocyte-depleting antibodies,[9,74] rATG can be associated with adverse events such as fever, chills, leukopenia, thrombocytopenia and gastrointestinal disorders, as well as serum sickness, a delayed immunological reaction towards proteins within rabbit serum preparations (section 5.1.1). The general tolerability profile of rATG induction appears less favourable than that of some other induction agents, particularly with regard to leukopenia, fever and thrombocytopenia (section 5.1.1). Similarly, in the treatment of acute renal rejection, rATG is more commonly associated with leukopenia and malaise than eATG, although it has the advantage of being associated with a lower incidence of dizziness and dysuria (section 5.1.1). Dosage adjustments are recommended to reverse

the leukopenia and/or thrombocytopenia that may occur during rATG therapy (section 6).[11]

The major concern with immunosuppressive therapy in renal transplantation is the risk of infections.[75] As may be expected, infections, particularly CMV and herpes simplex virus infection, are generally more common in renal transplant recipients given rATG induction in combination with an immunosuppressive regimen than in those given an immunosuppressive regimen without induction (section 5.1.2). However, the overall incidence of infection associated with rATG induction was generally no different from that seen with eATG or basiliximab, although it was higher than with basiliximab in patients at high risk of rejection. In induction studies that assessed CMV parameters as primary tolerability endpoints, rATG generally did not differ from eATG with regard to the incidence of CMV disease and did not differ from daclizumab with regard to the incidence of CMV infections or the proportion of patients who received treatment for a CMV episode. In other induction studies, rATG did not significantly differ from daclizumab with regard to the incidence of CMV infections that required treatment whereas, relative to basiliximab, the incidence of CMV infection was higher with rATG in two studies, although was lower with rATG in a study in high-risk patients. In the treatment of acute renal rejection, the nature and incidence of infections were generally similar with rATG and eATG (section 5.1.2). CMV prophylaxis was administered in several of these clinical studies,[17,21,53,55-57] generally when serological evidence of CMV was present in the donor and/or recipient. Indeed, prophylactic treatment with an appropriate anti-viral agent is advised in patients receiving rATG (section 6).

An increased risk of malignancies is also a concern with immunosuppressive therapy.[75] However, the incidence of malignancies, such as PTLD, is generally low with rATG therapy, regardless of whether the drug is being administered for the prevention or treatment of renal transplant rejection, and generally does not differ from that seen with other agents (section 5.1.3). Nevertheless, retrospective analyses of data from three US registry databases have produced mixed findings concerning the risk of post-transplant malignancies associated with rATG and other immunosuppressive agents in renal transplant recipients (section 5.1.3). Additional studies evaluating the relative tolerability of rATG and other antibody preparations would be beneficial, with longer-term studies to compare the relative risk of malignancies between these agents being of particular interest, given such data are currently limited.

Limited data suggest that rATG induction is generally well tolerated in adults when used in combination with an immunosuppressive regimen that incorporates early corticosteroid withdrawal or that is corticosteroid-free (section 5.1.2) as well as in paediatric patients (section 5.2), although further studies would be useful to confirm these findings.

At present, there are no robust comparative pharmacoeconomic or health-related quality-of-life data available for rATG therapy in renal transplant recipients, although such data would be of interest.

In conclusion, rATG is effective in both the prevention and treatment of acute renal graft rejection in renal transplant recipients. rATG induction in combination with immunosuppressive therapy is more effective in preventing episodes of acute renal graft rejection in adult renal transplant recipients than immunosuppressive therapy without induction. The efficacy of rATG induction is generally better than that of eATG induction and generally no different from that of basiliximab or low-dose daclizumab induction in this patient population. However, in high-risk patients, rATG induction was more effective than daclizumab or basiliximab induction in preventing acute renal graft rejection. In the treatment of renal graft rejection in adult renal transplant recipients, rATG was more effective than eATG in terms of the successful response rate, although the agents generally did not differ with regard to most other endpoints.

Both induction and treatment with rATG are generally well tolerated, although adverse events, such as fever, leukopenia and thrombocytopenia, appear more common with rATG than with other antibody preparations. The overall incidence of infection associated with rATG induction

was generally no different from that seen with eATG or basiliximab induction, although it was higher with rATG than with basiliximab in high-risk patients. The incidence of CMV disease generally did not differ between rATG and eATG induction, and there was no significant difference between rATG and daclizumab induction with regard to the incidence of CMV infections or the proportion of patients who received treatment for a CMV episode or infection. Relative to basiliximab, the incidence of CMV infection was generally higher with rATG, except in high-risk patients. In the treatment of acute renal rejection, the nature and incidence of infections were generally similar with rATG and eATG. The incidence of malignancies is generally low with rATG therapy and generally does not differ from that seen with other agents.

Further prospective comparative studies would be beneficial in order to definitively position rATG with respect to other antibody preparations. In the meantime, available clinical data suggest that rATG is an effective and generally well tolerated option for the prevention and treatment of acute renal graft rejection in renal transplant recipients.

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