REVIEW ARTICLE

New Directions for Rabbit Antithymocyte Globulin (Thymoglobulin®) in Solid Organ Transplants, Stem Cell Transplants and Autoimmunity

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Abstract In the 30 years since the rabbit antithymocyte globulin (rATG) Thymoglobulin® was first licensed, its use in solid organ transplantation and hematology has expanded progressively. Although the evidence base is incomplete, specific roles for rATG in organ transplant recipients using contemporary dosing strategies are now relatively well-identified. The addition of rATG induction to a standard triple or dual regimen reduces acute cellular rejection, and possibly humoral rejection. It is an appropriate first choice in patients with moderate or high immunological risk, and may be used in low-risk patients receiving a calcineurin inhibitor (CNI)-sparing regimen from time of transplant, or if early steroid withdrawal is planned. Kidney transplant patients at risk of delayed graft function may also benefit from the use of rATG to facilitate delayed CNI introduction. In hematopoietic stem cell transplantation, rATG has become an important component of conventional myeloablative conditioning regimens, following demonstration of reduced acute and chronic graft-versus-host disease. More recently, a role for rATG has also been established in reduced-intensity conditioning regimens. In autoimmunity, rATG contributes to the treatment of severe aplastic anemia, and has been incorporated in autograft projects for the management of conditions such as multiple sclerosis, Crohn's disease, and systemic sclerosis. Finally, research is underway for the induction of tolerance exploiting the ability of rATG to induce immunosuppresive cells such as regulatory T-cells. Despite its long history, rATG remains a key component of the immunosuppressive armamentarium, and its complex immunological properties indicate that its use will expand to a wider range of disease conditions in the future.

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Key Points

In the 30 years since the rabbit antithymocyte globulin (rATG) Thymoglobulin® was first licensed, there have been profound advances in its use, including a widening of its role in optimizing immunosuppression for solid organ transplant recipients and in hematology indications.

rATG dosing has decreased over time, refining the risk:benefit ratio and reducing early safety concerns.

A growing understanding of the complex immunological properties has prompted new research into other therapeutic fields.

1 Introduction

It has been 30 years since the rabbit antithymocyte globulin (rATG) Thymoglobulin® was first licensed for clinical use in April 1984. Of the three polyclonal agents currently available—Thymoglobulin®, the rabbit preparation manufactured by Fresenius (ATG-Fresenius), and, in certain markets, the equine antithymocyte globulin (eATG, ATGAM®)—rATG is the most widely used. Over time, its role in the management of solid organ transplant patients and other therapeutic areas has expanded progressively. It is now the most widely prescribed induction agent in the US [1], administered to approximately half of all de novo kidney transplant recipients [2]. From the early evidence focusing on kidney transplantation, rATG administration has widened to all types of solid organ transplantation, including liver, heart, lung, pancreas, and intestinal transplantation, as well as to hematopoietic stem cell transplantation (HSCT) and aplastic anemia [3]. It has also been included in immunosuppressive regimens following pioneering composite tissue transplant procedures (hands, face, etc.), and as part of experimental protocols attempting to achieve operational tolerance. Part of this expansion has arisen from increasing awareness of additional clinical applications for the drug. As well as providing rejection prophylaxis, and treatment for steroid-resistant rejection episodes, it is used to help avoid delayed graft function (DGF) in at-risk individuals and, more recently, to facilitate steroid-sparing and calcineurin inhibitor (CNI)-sparing regimens in the quest for reduced long-term morbidity after organ transplantation.

Over the intervening years there has also been a steady shift towards lower rATG dosing as experience has grown, refining the risk:benefit balance. Moreover, understanding of the immunological impact of rATG has improved, with recent studies confirming a significant depletion of CD3^{+}, CD4^{+}, CD8^{+} and natural killer (NK) cell depletion, followed by preferential reconstitution of central memory CD4^{+} T-cells at the expense of naïve CD4^{+} cells [4–6]. Long-term follow-up data have shown that CD4^{+} T-cell reconstitution remains impaired for up to 21 years in kidney transplant patients treated with rATG compared with controls receiving interleukin (IL)-2 receptor antagonist (IL-2RA) induction [7].

There is now a substantial evidence base relating to the use of rATG in different therapeutic settings from the last three decades [3, 8–10]. At this milestone in its development, it is timely to focus on the most recent clinical data regarding the use of rATG based on contemporary treatment protocols.

2 Methodology

A literature search on the PubMed database was undertaken with no time limits. Single search terms included 'ATG', 'rATG', 'antithymocyte globulin', and 'Thymoglobulin', across all therapy areas. Only articles with an English abstract were reviewed. Abstracts from relevant congresses during 2013 and 2014 were also searched using the same search terms. While all relevant publications were reviewed, emphasis is placed on randomized trials where possible.

3 The Basis for Rabbit Antithymocyte Globulin (rATG) use in Solid Organ Transplantation

rATG exerts its immunomodulatory and immunosuppressive effects via a wide range of immune and non-immune targets, adhesion molecules, and chemokine receptors [11]. rATG administration induces a significant depletion of CD3^{+}, CD4^{+} and CD8^{+} T-cells and NK cells, as well as other T-cell subsets [11], while leaving the B-cell count unaffected [4]. CD3^{+} cell count diminishes rapidly, with most patients having almost no CD3^{+} cells within 24 h after the start of treatment [12]. The proportion of naïve CD4^{+} cells decreases, while central memory CD4^{+} T-cells increase. Using a typical dosing strategy of 1.5 mg/kg on days 0–3 (cumulative dose 6 mg/kg), rATG remains at therapeutic levels for approximately 19 days [4]. The half-life of rATG is about 3 weeks, with complete elimination from the serum within 1 year [12].

Randomized trials and non-randomized trials of rATG during the 1990s and early 2000s established the immunosuppressive potency of rATG for both the treatment and prevention of solid organ graft rejection, but also highlighted safety concerns. The first randomized trials of rATG were comparative studies versus other lymphocyte-depleting agents for the treatment of allograft rejection following kidney transplantation [13, 14]. In one trial, a non-significant trend to improved rates of response and prevention of recurrent rejection was observed versus muromonab-CD3 (OKT3), with a more favorable safety profile [14]. Another early randomized study showed that compared with eATG, rATG achieved a higher rate of rejection reversal and a lower incidence of recurrent rejection, with a similar safety profile [13]. Shortly afterwards, a randomized, double-blind trial of rATG versus eATG for prevention of rejection in de novo kidney transplant patients was published [15]. In this trial, 72 patients received rATG (1.5 mg/kg/day) or eATG (15 mg/

kg/day) for 7 days, with maintenance immunosuppression comprising cyclosporine, azathioprine and steroids in both groups. At 1 year, the incidence of acute rejection was significantly lower in the rATG arm (4 % vs. 25 %; $p = 0.014$) and a composite endpoint of death, graft loss or rejection was less frequent (6 % vs. 27 %; $p = 0.0005$), with a lower incidence of cytomegalovirus (CMV) infection [15]. Mourad et al. [16] also demonstrated the efficacy of rATG in preventing rejection after kidney transplantation in a multicenter study of rATG (1.25 mg/kg/day for 10 days) with tacrolimus initiated on day 9 post-transplant versus immediate tacrolimus with no induction. Biopsy-proven acute rejection (BPAR) was less frequent in the rATG group (15.2 % vs. 30.4 %; $p = 0.001$), but adverse events such as CMV infection, herpes simplex infection, fever, and thrombocytopenia were increased in rATG-treated patients. A large multicenter trial of 555 de novo kidney transplant patients randomized to rATG with tacrolimus, rATG with cyclosporine, or tacrolimus with no induction, all with azathioprine and steroids, showed the lowest rate of acute rejection in the rATG-tacrolimus group ($p = 0.004$ vs. tacrolimus and no induction) [17]. Again, with an rATG dose of 1.25 mg/kg/day for 10 days (adjusted as necessary based on clinical findings), higher rates of adverse events, including hematological disturbances and infections, were observed in patients receiving rATG. In a randomized trial of 50 heart transplant patients published in 2002, rATG and ATG-Fresenius were associated with a similar incidence and number of rejections when combined with a maintenance regimen of cyclosporine, azathioprine, and steroids [18]. However, the study used relatively high doses of both rATG (five doses of 2.5 mg/kg/day) and ATG-Fresenius (five doses of approximately 3.2 mg/kg/day), and the overall rate of infections was high (rATG 58 %, ATG-Fresenius 75 %) [18].

4 Contemporary rATG Dosing Regimens in Solid Organ Transplantation

As experience with rATG grew during the late 1990s and early 2000s, it became apparent that the high doses of rATG (typically 1.25–1.5 mg/kg/day for 7–10 days) administered in early clinical studies [13, 15–18] were not necessary to achieve sustained lymphocyte depletion. Protocol-specified doses have since declined (Fig. 1a–c). In a non-randomized trial, Agha et al. [19] demonstrated that a total dose of 6 mg/kg achieved similar efficacy to a dose of 10.5 mg/kg (1.5 mg/kg/day over 7 days) in a cohort of historical controls. Indeed, with an intraoperative dose of 3 mg/kg and two subsequent doses of 1.5 mg/kg, lymphocyte depletion appeared to be more sustained

than with the high-dose regimen [19]. Even lower doses (<6 mg/kg in total) have been explored [20, 57–61] (Table 1), but T-cell depletion appears to be diminished [21]. Limited retrospective data have suggested that early acute rejection may be more frequent if the total rATG dose is less than 6 mg/kg [66], although good outcomes with lower doses have also been reported [61]. Cumulative doses in the range of 3–6 mg/kg may be adequate in elderly recipients, in whom a retrospective analysis has reported excellent outcomes with an average total rATG dose of 5.4 mg/kg [67], and in lower-risk individuals such as living-donor recipients [68]. However, very low doses of rATG are likely to be inadequate, even in low-risk groups. A retrospective analysis of 100 living-donor kidney transplant patients given a single rATG dose of 1.5 mg/kg found the rate of acute rejection at 1 year to be 17 % and 35 % in recipients of related and unrelated grafts, respectively [62]. In a controlled study of 40 kidney transplants given a total dose of 1.5 mg/kg, 3.0 mg/kg, or 6.0 mg/kg of rATG as induction with tacrolimus, mycophenolate mofetil (MMF) and steroids, the T-cell count returned to normal by month 3 in the 1.5 mg/kg group, and during the first year in the 3.0 mg/kg group, but remained lower than in controls in the patients given a dose of 6.0 mg/kg [69]. Experimental evidence indicates that a total dose of approximately 6.4 mg/kg achieves lymphocyte depletion in peripheral blood and the spleen and lymph nodes [70]. Overall, it appears that a cumulative rATG dose of 6 mg/kg is generally appropriate for induction therapy [4, 69].

A further imperative to reduce rATG dosing came from the realization that early high-dose regimens increased the risk of infectious disease, particularly CMV infection [15]. In one study, a dose of 1.5 mg/kg/day for 9 days (13.5 mg/kg in total) was associated with a significantly higher rate of CMV disease versus no induction in kidney transplant patients [16], while in liver transplantation a very high total dose of 25 mg/kg over 10 days resulted in a higher rate of fatal infections than a 3-day course with a total dose of 7.5 mg/kg [71].

Following a gradual decline over time, the typical dose of rATG now used in kidney transplant patients receiving a standard triple-dose maintenance regimen is 6.0–7.5 mg/kg (Fig. 1a). Trial results indicate that this dose level achieves high efficacy with a good safety profile in kidney transplant patients, even in high-risk individuals [4, 24, 26, 72]. In recent trials of liver transplantation, total doses have generally been similar to those in kidney transplantation (6–7.5 mg/kg) [73]. Data are more limited in heart transplantation [74–77]. There is evidence suggesting that 1.5 mg/kg/day for 5 days may offer less effective rejection prophylaxis than a 7-day course following heart transplantation [78].

Fig. 1 rATG
(Thymoglobulin®) dose in
clinical studies according to
year of publication with
(**a**) standard triple maintenance
regimen [4, 15, 19–34];
(**b**) steroid-sparing regimen
[35–46] and (**c**) CNI-sparing
regimen [16, 17, 47–56]. Doses
shown are protocol specified or,
if unavailable, mean dose
administered. *CNI* calcineurin
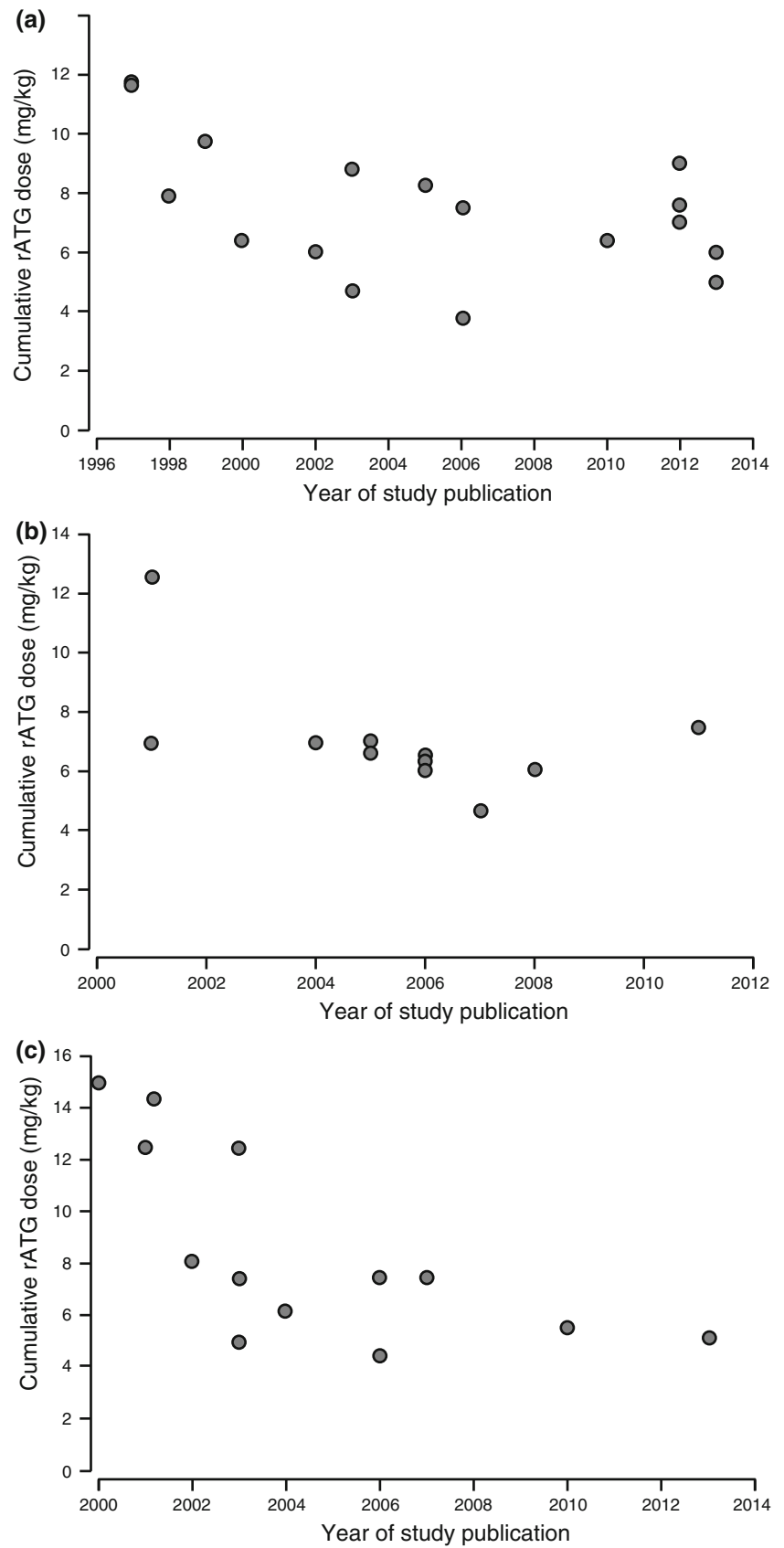inhibitor, *rATG* rabbit
antithymocyte globulin

Table 1 Alternative dosing strategies for rATG (Thymoglobulin®) induction therapy in solid organ transplant patients

Study (year)	Organ	N	Study design	rATG regimen	Comparator group/s	Maintenance immunosuppression	Follow-up	Treatment group	Acute rejection (%)	Other outcomes
Low-dose and/or short-course regimen										
Grafals et al. (2013) [59]	Kidney	68	Prospective Randomized Single-center	Total dose 2.25 mg/kg (0.75 mg/kg days 0–2)	Total dose 3.75 mg/kg (1.25 mg/kg days 0–2)	Not stated	Mean 9.9 and 11.8 months	2.25 mg/kg 3.75 mg/kg	10.0 9.5	DGF more frequent in 2.25 mg/kg group (40 % vs. 14.3 %; $p = 0.041$)
Popat et al. (2013) [60]	Kidney	45	Prospective Non-randomized Single-center	Total dose 3.75 mg/kg (2.5 mg/kg on day 0, 1.25 mg/kg on day 4)	IL-2RA induction	CNI MMF ± Steroids	3 years	rATG IL-2RA	0 13 ($p = 0.001$)	Significantly lower rates of DGF and hospitalization for infection in the rATG group
Laftavi et al. (2011) [57]	Kidney	90	Retrospective Single-arm Single-center	Mean (SD) total dose 3.0 (1.3) mg/kg in older patients (>65 years) or 3.2 (2.1) mg/kg in younger patients (<65 years)	Mean (SD) total dose 3.0 (1.3) mg/kg in older patients	CNI MMF Low-dose steroids	6 months	Older patients Younger patients	0 2.5	4.4 % and 6.7 % viral infections in the older and younger patients, respectively
Wong et al. (2006) [21]	Kidney	16	Prospective Single-arm Single-center	Total dose 3.0 mg/kg (first dose intraoperative, days 0–2)	4.5 mg/kg (first dose intraoperative, days 0–2)	Tacrolimus MMF Steroids	2 years	3 mg/kg	5	T-cell count lower at month 6 with 4.5 mg/kg total dose ($p = 0.016$)
Goggins et al. (2003) [20]	Kidney	58	Prospective Randomized Single-center	Total 3–6 mg/kg in week 1 (no intraoperative)	3–6 mg/kg in week 1 (no intraoperative)	CNI MMF Steroids	Mean 15.1 months	Intraoperative Postoperative	3.6 16.0 (NS)	Less DGF ($p < 0.05$) and lower mean serum creatinine ($p < 0.005$) with intraoperative first dose
Agha et al. (2002) [19]	Kidney	88	Prospective Historical controls Single-center	Total 6 mg/kg (days 0–2)	Total 10.5 mg/kg (1.5 mg days 0–6)	Not stated	1 year	6 mg/kg	5	Lower lymphocyte count at month 1 with 6 mg/kg regimen ($p < 0.05$) Similar safety profile
Eason et al. (2003) [58]	Liver	119	Prospective Randomized Single-center	Total 3.0 mg/kg (days 0–1)	Steroids to month 3 (no steroids in rATG group)	Tacrolimus MMF (withdrawn after month 3)	2 years	rATG (steroid-free) Steroids	25 31 (NS)	Similar patient survival at 1 and 2 years. Greater requirement for steroid treatment of rejection in the steroid group ($p = 0.03$)
Single-dose regimen										
Schenker et al. (2011) [62]	Kidney	100	Retrospective Single-arm Single-center	Total dose 1.5 mg/kg	–	Tacrolimus MMF Low-dose steroids	Mean 52.6 months	Living related Living unrelated	17 35	Low rates of infection
Stevens et al. (2008) [22]	Kidney	142	Prospective Randomized Single-center	Total dose 6 mg/kg (single dose over 24 hours)	Total dose 6 mg/kg (1.5 mg/kg × 4 doses)	CNI to month 6 MMF or sirolimus	6 months	Single dose 4 doses	8 12 (NS)	Change in eGFR to month 6 was better in the single-dose group ($p = 0.02$)

Table 1 continued

Study (year)	Organ	N	Study design	rATG regimen	Comparator group/s	Maintenance immunosuppression	Follow-up	Treatment group	Acute rejection (%)	Other outcomes
De Ruvo et al. (2005) [63]	Liver	52	Retrospective Historical controls Multicenter	Total dose 5 mg/kg (single dose over 4 h)	No rATG	Tacrolimus Steroids to month 3 in non-rATG group	1 year	rATG single dose	36.4	Lower tacrolimus dose in rATG group ($p < 0.05$)
								No rATG	40 (NS)	
Dosing based on immune monitoring										
Peddi et al. (2002) [64]	Kidney	41	Prospective Single-arm Single-center	1.5 mg/kg daily until CD3 + $\leq$30 cells/mm^3 (mean total dose 4.1 mg/kg)	–	CNI MMF Steroids	Mean 340 days	T-cell adapted rATG	12.2	Low rate of rejection in a high-risk population CNI delayed for mean of 6 days post-transplant
Djamali et al. (2000) [23]	Kidney	39	Prospective Non-randomized Single-center	50 mg/day × 3 days then only if CD3$^+$ T-cells were >10 cells/mm^3 Mean (SD) total dose 6.6 (2.9) mg/kg (mean 7.3 doses)	50 mg/day daily Mean (SD) total dose 9.1 (2.2) mg/kg (mean 11.5 doses)	CsA AZA Steroids	1 year	T-cell adapted rATG	19 episodes	Similar depletion of T-cells and peripheral blood lymphocytes Infections and hematological complications were similar
								Standard rATG	13 episodes (NS)	
Koch et al. (2005) [65]	Heart	62	Retrospective Single-center Historical controls	1.5 mg/kg daily until total lymphocytes <100 cells/mm^3, CD4$^+$ T-cells <50 cells/mm^3 and CD8$^+$ <50 cells/mm^3	Total dose 12 mg/kg (1.5 mg/kg × 8 days) (equine ATG Merieux)	CsA AZA Steroids	1 year	T-cell adapted rATG	Mean 0.4 (0.7) episodes	Significantly lower ATG dose ($p < 0.05$) with T-cell adapted dosing Similar patient survival CMV seroconversion 23 % vs. 13 % with standard dosing Deep sternal infection 1.6 % vs. 3.2 % with standard dosing
								Standard equine ATG	Mean 1.1 (1.7) episodes	

AZA azathioprine, *CMV* cytomegalovirus, *CNI* calcineurin inhibitor, *CsA* cyclosporine, *DGF* delayed graft function, *eGFR* estimated glomerular filtration rate, *IL-2RA* interleukin-2 receptor antagonist, *MMF* mycophenolate mofetil, *NS* not significant, *rATG* rabbit antithymocyte globulin, *SD* standard deviation

Various different innovative dosing strategies for rATG have also been explored, notably single-dose regimens or dosing based on immune monitoring (Table 1). In one study, a single infusion of 6 mg/kg instead of four divided doses of 1.5 mg/kg/day was found to offer improved renal function at month 6 after kidney transplantation [22], an intriguing finding that merits further investigation since two infusions of 3 mg/kg instead of four divided doses of 1.5 mg/kg/day induce a similar pattern of T-cell and NK-cell depletion and reconstitution [4]. However, perhaps of more interest is adaptation of dosing based on T-cell count, which has been explored in kidney and heart transplantation (Table 1). Prospective [23, 64] and retrospective [64] studies indicate that the total dose of rATG can be reduced markedly [23, 79] without compromising lymphocyte suppression or immunosuppressive potency. In a prospective, non-randomized trial, Djamali et al. [23] observed that withholding rATG until $CD3^+$ T-cell count exceeded 10 cells/mm^3 led to an approximately 25 % reduction in rATG dose but provided similar T-cell depletion to a standard daily dosing (mean total dose 6.6 mg/kg vs. 9.1 mg/kg). Lymphocyte count has been proposed by some investigators in the field of solid organ transplantation as the preferred tool to adjust rATG dosage, but randomized trials are lacking. This approach is not widely accepted, and overall dosage based on milligrams per kilogram remains the most common mode of administration. Using weight-adjusted dosing, caution should be exercised in patients with body weight below 40 kg or greater than 80 kg, to avoid under- or over-immunosuppression. Pharmacokinetic monitoring techniques are emerging but are not yet routinely used.

Lastly, intraoperative administration of the first dose may help to minimize the risk of DGF in at-risk kidney transplant recipients [20, 80], possibly by ameliorating ischemia-reperfusion injury through suppression of inflammatory cells and mediators as a result of leukocyte and T-lymphocyte depletion [81–83], but this remains unconfirmed.

The duration and dose of rATG therapy, of course, impacts on drug purchase costs. There is also evidence that a shorter course—for example, 3 days at 2 mg/kg/day versus 4 days at 1.5 mg/kg/day—may result in indirect cost savings, largely due to reduced hospital stay [84, 85]. Dosing based on $CD3^+$ monitoring may also lower drug costs versus a fixed-dose regimen [86].

5 rATG in Kidney Transplantation

5.1 Risk Stratification

rATG induction is typically used in high-risk or medium-risk kidney transplant patients, specifically those who are sensitized, or in patients at risk of DGF [87]. The decision to administer rATG or other induction therapy after kidney transplantation is based on demographic characteristics such as age and race, taking into account other clinical factors such as previous transplantation and the type of donor. These variables are coupled with immunological markers of rejection risk: the degree of human leukocyte antigen (HLA) matching, the presence of anti-HLA prior to transplantation [88]. More recently, growing awareness of the predictive role of pre-transplant donor-specific antibodies (DSA) has received intense attention. The presence of pre-transplant DSA (class I or II) [89] and the DSA titer [90] show a close correlation with the risk of acute antibody-mediated rejection after kidney transplantation. However, DSA measurement by the Luminex technique is not always reproducible and suitable cutoff points using other detection techniques, such as complement-dependent cytotoxicity (CDC) cross-match, have not been established. Testing for DSA prior to transplantation is not yet standard. Nevertheless, there is a growing movement towards inclusion of DSA during risk stratification of transplant recipients in order to target rATG induction and other interventions appropriately.

5.2 Rejection Prophylaxis and Graft Survival

The efficacy of rATG in preventing acute rejection in kidney transplant patients is well-established [3, 8, 9]. Randomized trials have shown a lower rate of rejection for rATG versus the antilymphocyte preparation ATGAM [14], or versus IL-2RA induction in patients with moderate to high immunological risk [24, 91] with similar rejection rates to IL-2RA induction in low-risk patients [47, 72, 92, 93] (Table 2). Meta-analyses have confirmed that rATG induction confers a lower rejection risk compared with no induction [95], with similar rates of rejection to alemtuzumab induction [96]. A large-scale analysis of data from the Organ Procurement and Transplant Network (OPTN) showed rejection to be less likely under rATG than IL-2RA induction [87].

In a prospective, randomized study of kidney transplantation comparing rATG versus alemtuzumab induction, in combination with tacrolimus plus MMF and a 5-day course of corticosteroids, alemtuzumab was associated with a lower rate of early BPAR in low-risk individuals but there was no difference in high-risk patients [97]. A meta-analysis of randomized trials in kidney transplantation found no significant difference in the risk of BPAR when rATG induction was compared with alemtuzumab [96].

A recent retrospective case-control series also indicated that in patients undergoing a second kidney transplant, rATG induction achieves similar lymphocyte depletion to that observed after a first course, and is as well tolerated [98]. In pediatric kidney transplant recipients, good outcomes have been reported with rATG at a dose of

Table 2 Randomized trials of rATG (Thymoglobulin®) induction therapy in kidney transplant patients using contemporary dosing regimens (cumulative dose (≤7.5 mg/kg)

Study (year)	N	Immunological risk status	rATG regimen	Comparator group/s	Maintenance immunosuppression	Follow-up	Treatment group	Patient survival (%)	Graft survival (%)	Acute rejection (%)[a]
rATG vs. IL-2RA induction										
Brennan et al. (2006) [24]	278	High	Total dose 7.5 mg/kg/day (days 0–4)	Basiliximab	CsA by day 4, MMF, Steroids	12 months	rATG	95.7	90.8	15.6
							IL-2RA	95.6	89.8	25.5
							p-Value	0.90	0.68	**0.02**[b]
Ciancio et al. (2005) [92]	60	Low	Total dose 7.0 mg/kg/day (days 0–7)	Daclizumab	Tacrolimus, MMF, Steroids	Median 15 months	rATG	92	88	16.6
							IL-2RA	88	88	16.6
							p-Value	NS	NS	0.99
Abou-Ayache et al. (2008) [93]	109	Low	1.0–1.5 mg/kg 4–9 infusions	Daclizumab	Delayed CsA, MMF, Steroids	12 months	rATG	98	95	14.5
							IL-2RA	98	94	16.7
							p-Value	NS	NS	NS
Mourad et al. (2004) [72]	105	Low	1.0 mg/kg Mean 5.4 infusions	Basiliximab	Delayed CsA, MMF, Steroids	12 months	rATG	98.1	96.2	9.4
							IL-2RA	98.1	94.2	9.6
							p-Value	NS	NS	NS
Steroid-sparing vs. standard steroid regimen										
Woodle et al. (2009) [94]	151	Low	Total dose 5–6 mg/kg	Steroid withdrawal by day 8	Tacrolimus, MMF	12 months	Withdrawal	98.9	98.9	13.9
							Standard	100	100	19.4
							p-Value	NS	NS	NS
CNI-free vs. standard CNI regimens										
Glotz et al. (2010) [48]	141	Standard	1.25–1.5 mg/kg 4 doses[c]	CNI free	Sirolimus, MMF, Steroids	12 months	CNI free	95.8	85.9	16.9
				Tacrolimus	MMF, Steroids		CNI	97.1	95.7	12.9
							p-Value	NS	0.044	NS
Büchler et al. (2007) [49]	145	Standard	Total dose 7.5 mg/kg/day (days 0–4)	CNI free	MMF, Steroids (to month 6)	12 months	CNI free	97	90	14.3
				CsA	MMF, Steroids (to month 6)		CNI	97	93	8.6
							p-Value	NS	NS	0.30
Larson et al. (2006) [50]	165	Standard	Total dose 7.5 mg/kg/day (days 0–4)	Sirolimus	Sirolimus, MMF, Steroids	12 months	CNI free	98	94	19
				Tacrolimus	MMF, Steroids		CNI	96	92	14
							p-Value	NS	NS	NS

Table 2 continued

Study (year)	N	Immunological risk status	rATG regimen	Comparator group/s	Maintenance immunosuppression	Follow-up	Treatment group	Patient survival (%)	Graft survival (%)	Acute rejection (%)[a]
Lo et al. (2004) [51]	70	High	Total dose 4.5–10.5 mg/kg	CNI free	Sirolimus MMF Steroids	12 months	CNI free	100	89	7
				Low CNI	Sirolimus Reduced tacrolimus Steroids		Low CNI	98	80	10
							p-Value	NS	NS	NS

Significant p-values are shown in bold

CNI calcineurin inhibitor, CsA cyclosporine, DGF delayed graft function, IL-2RA interleukin-2 receptor antagonist, MMF mycophenolate mofetil, NS not significant, rATG rabbit antithymocyte globulin

[a] Or biopsy-proven acute rejection

[b] Steroid-resistant acute rejection: 1.4 % with Thymoglobulin®, 8.0 % with IL-2RA induction ($p = 0.005$)

[c] Only given to tacrolimus-treated patients in the event of DGF

1.5–2.5 mg/kg/day for 5–10 days [99–103], with promising rates of graft survival in high-risk patients, but dose-finding studies and robust comparisons with other regimens are lacking.

Determining whether an effect on rejection rates translates to higher graft survival rates is more difficult to determine. The number of patients and duration required means that it is impractical for a controlled trial to be adequately powered. The available evidence is largely restricted to retrospective single-center studies or registry analyses, in which patient characteristics are not always fully captured. There are reports in the literature that rATG induction is associated with improved graft survival rates [35, 61, 104–106] compared with no induction or IL-2RA induction therapy, but data from a recent meta-analysis ($n = 892$) [95] and large-scale registry analyses [87, 107] are conflicting. One recent analysis of graft survival rates, based on data from the OPTN for kidney transplants during 2001–2005, reported a lower 6-month incidence of a combined endpoint of rejection, graft failure or death with rATG versus IL-2RA induction or no induction [108]. Moreover, any effect of rATG on graft survival appears to be influenced by the type of patient population; no effect was observed in one analysis of zero-mismatched deceased-donor recipients [109], whereas an analysis of 12,100 deceased-donor recipients with DGF demonstrated a significant improvement in death-censored graft failure ($p = 0.04$) and death with a functioning graft ($p = 0.0005$) versus IL-2RA induction therapy after adjustment for confounding factors [110]. In a large retrospective analysis of 475 kidney transplants undertaken during 2001–2009 at a single center, a low rATG dose (mean 3.2 mg/kg) was associated with higher graft survival than IL-2RA induction, a difference that was more pronounced among obese recipients (90.3 % vs. 63.6 % at an average of 47 months' follow-up; $p < 0.04$) but was still significant in non-obese individuals (88.7 % vs. 68.2 %; $p < 0.01$) [61]. No firm conclusions on an effect of rATG on kidney allograft survival can be drawn, although there are some encouraging indications.

Based on the available data, rATG induction is appropriate in patients with moderate or high immunological risk as rejection prophylaxis, but in low-risk patients is required only if early CNI-sparing or steroid withdrawal is planned. Use of rATG induction in low-risk kidney transplant patients receiving a standard triple-therapy maintenance regimen is unlikely to be cost effective and unnecessarily exposes the patients to risk of over-immunosuppression.

5.3 Ischemia-Reperfusion Injury and Delayed Graft Function

Beyond its traditional use in rejection prophylaxis and treatment, it is possible that rATG may ameliorate ischemia-reperfusion injury by inhibiting expression of adhesion

molecules and cytokines [82]. Coupled with T-cell depletion, such an effect could help to prevent DGF. In a randomized trial in liver transplant patients, rATG resulted in less clinical evidence of ischemia-reperfusion injury [111], but a similar histological study in kidney transplant patients is lacking. Clinical data are not adequate to assume a benefit for rATG in terms of diminishing injury.

In 2003, Goggins et al. [20] reported a lower incidence of DGF using intraoperative rATG compared with postoperative administration (14.8 % vs. 35.5 %; $p < 0.05$). More recently, Harrison and colleagues observed no difference in renal function during the first year post-transplant in patients given the first rATG dose before reperfusion or postoperatively [112]. In two randomized trials in which the first dose of rATG was given before graft reperfusion, the rate of DGF was significantly lower versus IL-2RA induction in one study of 227 immunologically high-risk, HLA-sensitized patients [91], but no difference was observed in the second trial of 278 patients at high risk for acute rejection or DGF [23]. Other studies have not shown a reduction in DGF rates [34, 47, 74] in patients receiving rATG induction, although the risk and/or severity of rejection is generally lower in patients with DGF who receive rATG [15, 34]. The multifactorial etiology of DGF means it is difficult to confirm a contribution of rATG induction conclusively, but it appears that rATG may offer some benefit in decreasing the risk of DGF [113]; further data are awaited. A recently proposed scale to classify patients according to their DGF risk [114] may help identify high-risk individuals.

5.4 Reducing Maintenance Immunosuppression

In recent years, clinical investigation of rATG in kidney transplantation has centered on its ability to support either early steroid withdrawal or CNI-sparing regimens. The most robust data relating to early steroid withdrawal comes from a multicenter trial in which 151 living-donor kidney transplant patients were randomized to rATG (total dose 5–6 mg/kg) with steroids to day 7, or to an induction-free standard-steroids regimen, both with tacrolimus and MMF [94] (Table 2). At 12 months post-transplant, rates of BPAR and all efficacy endpoints were similar between the two groups, but total cholesterol was lower in the steroid-withdrawal group with trends towards a lower triglyceride level and less weight gain, although leukopenia was more frequent in the rATG cohort. A large, randomized trial by Kandaswamy et al. [36], in which standard-risk patients received rATG at a total dose of 5.0–7.5 mg/kg, demonstrated a low rate of rejection when steroids were withdrawn after day 5 with a variety of maintenance regimens. Steroid withdrawal at month 3 from a maintenance regimen of cyclosporine and MMF

also appears feasible based on data from a randomized, double-blind trial reported by Lebranchu et al. [115] in which 104 patients were given rATG induction according to local practice with cyclosporine and MMF maintenance therapy, but rATG dosing information was not provided. Other prospective or retrospective non-comparative trials have also shown a low rate of rejection following early steroid withdrawal supported by rATG induction [37–39]. In low-risk children, non-randomized trials have suggested that rATG induction can support early (<1 week) steroid discontinuation [116] or steroid-free immunosuppression [117] with a maintenance regimen of CNI and MMF, with no increase in rejection risk. One retrospective study has compared rATG induction (6.0 mg/kg) versus IL-2RA induction with basiliximab in 99 kidney transplant patients for whom early steroid discontinuation on day 6 was planned [118]. By 1-year post-transplant, the incidence of BPAR was lower (7 % vs. 26 %), and mean time to first BPAR (151.4 vs. 53.6 days) was longer, with rATG versus IL-2RA induction. As with standard maintenance immunosuppression, the dose of rATG administered in patients receiving a steroid-sparing regimen has declined over time (Fig. 1b).

The use of rATG induction to facilitate delayed introduction of CNI therapy by up to 9 days—often in an attempt to avoid DGF—has been shown to maintain immunosuppressive efficacy following kidney transplantation [16, 24, 47, 93] and is a recognized therapeutic strategy in patients at risk of DGF. More controversial, single-arm studies [119, 120] and randomized, controlled trials [48–51] have administered rATG induction with an entirely CNI-free, sirolimus-based maintenance immunosuppressive regimen (Table 2). In each of the comparative studies, the rate of acute rejection was low and similar to a standard CNI regimen [48–51], although graft survival was lower with the CNI-free group in one study [48]. In all but one randomized trial [50], renal function was superior at 1 year in the CNI-free arm, either overall [48, 51] or among the subpopulation who remained on a CNI-free regimen [49]. Five-year follow-up data from the Spiesser study [49] confirmed that estimated glomerular filtration rate (GFR) remained higher in the CNI-free treatment group, with no difference in acute rejection rates [121]. In a small, prospective study of seven patients receiving a kidney from an HLA-identical living donor, rATG with MMF or sirolimus and no CNI therapy achieved 100 % graft and patient survival over a median of 26 months' follow-up; rATG induction was continued for 10 days at an unspecified dose [122]. In contrast, de novo immunosuppression with sirolimus and no CNI therapy in patients receiving IL-2RA induction is associated with a high rate of acute rejection (>30 % at 1 year) [123, 124]. It appears that adequate immunosuppression in the early period after

kidney transplantation may require rATG induction if CNI avoidance is attempted.

One novel strategy to reduce both CNI and steroid exposure is to use low-dose rATG in combination with IL-2RA induction. This approach has been assessed in a prospective, single-center, non-randomized study which compared rATG at a total dose of 200 mg combined with basiliximab (total dose 40 mg) versus basiliximab alone [125]. In the rATG group, tacrolimus exposure was reduced and steroids were selectively withdrawn at 3–6 months. At 1 year, the incidence of acute rejection was similar in both groups despite lower exposure to both CNI and steroids. Alternatively, rATG induction (up to 6 mg/kg in total) coupled with maintenance therapy using the co-stimulation blocker belatacept and a mammalian target of rapamycin inhibitor or MMF may enable avoidance of both CNIs and steroids with an acceptable rate of rejection [126]; further data are awaited.

5.5 rATG and Donor-Specific Antibodies

Awareness that the presence of de novo DSA nearly doubles the risk for antibody-mediated rejection after kidney transplantation [89] has focused attention on preventative strategies. There are early data to suggest that rATG preferentially inhibits the proliferation of donor antigen-activated T-cells in kidney transplant patients by inducing expression of donor-specific helios$^-$FOXP3$^+$ regulatory T-cells, an effect not seen with IL-2RA induction agents [127]. B-cell expression and phenotype remained unchanged after administration of low-dose rATG [128], or even after high doses (3 mg/kg/day) [4]. Clinically, a retrospective study of rATG induction with intravenous immunoglobulin (IVIG) in kidney transplant patients with preformed DSA receiving tacrolimus-based triple therapy has demonstrated that sensitized patients with positive flow cytometry cross-match can achieve excellent graft survival rates with acceptable levels of antibody-mediated rejection [129]. In liver transplantation, rATG with rituximab induction has also been shown to result in low rates of antibody-mediated rejection [130].

Data regarding a possible effect of rATG induction therapy on the risk of post-transplant de novo DSA are starting to emerge. In a series of 114 moderately sensitized DSA-positive patients, occurrence of de novo DSA (defined as absence of pre-transplant DSA) increasing at least threefold was monitored for a mean of 12.4 months [32]. rATG was given to 85 of the patients (mean total dose 4.98 mg/kg), and the IL-2RA induction agent basiliximab was given to 29 patients. Multivariate analysis showed that rATG induction was associated with a significant reduction in risk of both de novo DSA and acute antibody-mediated humoral rejection [32] (Table 3). Of all factors assessed,

rATG induction was the single most important variable associated with both de novo DSA and humoral rejection. In a single-center, matched-cohort study of 16 kidney transplant patients and 32 controls [128], there was a lower incidence of de novo DSA at 1-year post-transplant in patients treated with rATG or basiliximab versus alemtuzumab ($p = 0.011$). The difference was maintained at 2 years ($p = 0.010$) because alemtuzumab induces B-cell depletion and regeneration. If these data are confirmed, use of rATG in patients at risk of developing de novo DSA would be of considerable clinical interest. However, other single-center, retrospective analyses have observed no difference in DSA production in kidney transplant patients with or without rATG induction [131, 132]. Further prospective trials are required, including examination of the effect of rATG therapy on the capacity of DSA to bind complement fraction C1q, a variable that shows a strong correlation with risk of antibody-mediated rejection in the first year after kidney transplantation [133].

6 rATG in Liver Transplantation

6.1 Rejection Prophylaxis

Induction therapy is used far less frequently in liver transplant patients compared with kidney transplant recipients [1], although recent evidence that induction therapy is associated with improved long-term graft and patient survival following liver transplantation [134, 135] may contribute to greater use in the future. At present, data relating to the use of rATG after liver transplantation are relatively limited [3, 73, 136].

Induction with rATG in liver transplant patients receiving a standard triple or dual regimen has been compared with no induction in two single-center, randomized trials [111, 137] (Table 4). With follow-up to 5 years [137] or 3 months [111], there were no significant differences in

Table 3 Univariate and multivariate analysis of association between rATG induction and risk of dnDSA and acute AMR in 114 moderately sensitized DSA-positive kidney transplant patients receiving rATG (mean total dose 4.98 mg/kg) or IL-2RA induction [32]

	Univariate analysis		Multivariate analysis	
	HR (95 % CI)	*p*-Value	HR (95 % CI)	*p*-Value
dnDSA	0.1 (0.02–0.48)	0.003	0.16 (0.04–0.5)	0.003
Acute AMR	0.01 (0.001–0.15)	0.0007	0.16 (0.05–0.6)	0.006

Reference IL-2RA induction

AMR antibody-mediated rejection, *CI* confidence interval, *dnDSA* de novo donor-specific antibody, *DSA* donor-specific antibody, *HR* hazard ratio, *IL-2RA* interleukin-2 receptor antagonist, *rATG* rabbit antithymocyte globulin

Table 4 Randomized trials of rATG (Thymoglobulin®) induction therapy in liver transplant patients

Study (year)	N	Immunological risk status	rATG regimen	Comparator group/s	Maintenance immunosuppression	Follow-up	Treatment group	Patient survival (%)	Graft survival (%)	Acute rejection (%)
Boillot et al. (2009) [137]	93	Standard	Mean total dose 8.78 mg/kg	No induction	Tacrolimus MMF Steroids (withdrawn after month 3)	5 years	rATG	77.3	77.3	11.4
							No induction	87.8	87.8	14.3
							p-Value	NS	NS	NS
Bogetti et al. (2005) [111]	22	Standard	Total dose 4.5 mg/kg (days 0–4)	No induction	CNI Steroids	3 months	rATG	100	100	25
							No induction	100	100	30
							p-Value	NS	NS	NS
Eason et al. (2003) [58]	119	Standard	Total dose 3.0 mg/kg (days 0–1)	Steroids to month 3 (no steroids in rATG group)	Tacrolimus MMF (withdrawn after month 3)	2 years	rATG (steroid-free)	85	82	25
							Steroids	85	80	31.0
							p-Value	NS	NS	NS

CNI calcineurin inhibitor, *MMF* mycophenolate mofetil, *NS* not significant, *rATG* rabbit antithymocyte globulin

acute rejection, graft or patient survival in either trial, although one trial noted a longer mean time to rejection [137] and the other reported a shorter hospital stay [111] in the rATG cohorts. Relatively large retrospective studies, in which patients have received a variety of maintenance regimens, have suggested that rATG induction may reduce the risk of acute rejection versus no induction, but poor study design limits the validity of these findings [138, 139]. Interestingly, a recent retrospective review of 112 positive cross-match liver transplant patients receiving combined induction therapy with rATG and rituximab reported low rates of acute cellular rejection (9 %) and chronic rejection (4 %), and graft survival was only slightly lower than in negative cross-match patients (85 % vs. 89 %; p = 0.26) [130]. Such an approach in this very high-risk patient group may merit further investigation. Elsewhere, another retrospective, single-center experience has reported good outcomes in liver transplant patients receiving delayed rATG in combination with a single dose of rituximab in standard-risk recipients [136]. There is also preliminary evidence (published in abstract form only) from a single-center, retrospective analysis of 89 patients that rATG may significantly reduce the rate of ischemic cholangiopathy (12.5 % vs. 35.2 % with IL-2RA induction; p = 0.017) after liver transplantation from a donor after circulatory death [140]. Ischemic cholangiopathy is a major cause of liver graft loss in patients undergoing a liver transplantation from donors after cardiac death and this potentially important finding requires examination in further studies.

Comparative trials versus IL-2RA agents or other induction therapies are lacking in liver transplant patients.

6.2 Reducing Maintenance Immunosuppression

Randomized trials of CNI reduction or avoidance in liver transplant patients using rATG induction are lacking, but retrospective, single-center data from a series of 391 recipients suggest that rATG induction with CNI initiation delayed to day 3 may reduce the risk of rejection versus a standard CNI therapy (14.5 % vs. 31.8 %; p = 0.0008) [71]. Other retrospective analyses have also indicated that rATG induction with reduced tacrolimus exposure and no steroids [63], or delayed tacrolimus [141], effectively maintains immunosuppressive efficacy. Such approaches may be particularly helpful in liver transplant patients with renal impairment at the time of transplantation, to minimize CNI-related nephrotoxicity and avoid acute renal failure to help preserve long-term kidney function [142].

In terms of steroid avoidance, a randomized trial in 119 liver transplant recipients showed that a low-dose rATG regimen (total dose 3 mg/kg) demonstrated a similar rate of acute rejection in patients receiving a steroid-free regimen versus a standard steroids protocol [58]. These promising data await confirmation in other controlled trials.

6.3 Hepatitis C Virus Recurrence

With modern maintenance regimens, and the decrease in rATG dose over time, early concerns that lymphocyte depletion with OKT3 induction could lead to a permissive environment for hepatitis C virus (HCV) replication following liver transplantation [143] have not been borne out by recent results. Registry analyses of patients receiving induction with an ATG preparation or an IL-2RA agent [135, 144], as well as in subpopulation analyses of HCV-

positive patients in randomized trials [135, 145] and retrospective studies [63, 138, 141, 146], have not indicated any increase in HCV recurrence in patients receiving rATG induction.

7 rATG in Heart Transplantation

7.1 Rejection Prophylaxis

There is a scarcity of randomized trials relating to rATG induction, or other forms of induction therapy, in heart transplantation [77]. Comparative trials of rATG versus no induction, either prospective or retrospective, are lacking. Only two randomized trials of rATG have been published which used a contemporary dosing regimen [147, 148] (Table 5).

In a randomized trial of 35 standard-risk patients, the addition of rATG, at a mean total dose of 5.2 mg/kg, to a CNI-based triple regimen has been shown to achieve a lower rate of grade ≥3A acute rejection than induction with basiliximab (17 % vs. 35 %; the non-inferiority criterion for basiliximab versus rATG was not met) [148]. However, earlier high-dose, randomized [74] or retrospective trials [74, 76] and small, retrospective trials using a total rATG dose of ≤7.5 mg/kg [75, 149], have not

reported a lower rejection rate compared with IL-2RA induction. A trial of 721 de novo heart transplant recipients randomized to everolimus at a dose of 1.5 mg/day or 3.0 mg/day with reduced-dose cyclosporine, or to MMF with standard-dose cyclosporine, permitted centers to chose between basiliximab or rATG induction (dosed according to local practice) [150]. A numerically higher rate of mortality was observed in the everolimus 1.5 mg group compared with the MMF cohort at month 12. The difference was largely attributed to a higher incidence of infection-related death during the first 3 months posttransplant in patients receiving everolimus with rATG, particularly if a left ventricular assist device had been used. By month 24, mortality rates were similar in the two groups. The intensity of immunosuppression in the everolimus arm (rATG, everolimus, CNI, and steroids) appears to have over-immunosuppressed patients. A lower level of CNI exposure than in this study is targeted by most centers that use rATG induction in heart transplant patients, and may be a safer approach.

7.2 Reducing Maintenance Immunosuppression

The International Society of Heart and Lung Transplantation (ISHLT) guidelines for the care of heart transplant recipients comment that rATG can allow for CNI delay due

Table 5 Randomized trials of rATG (Thymoglobulin®) induction therapy in heart transplant patients

Study (year)	N	Immunological risk status	rATG regimen	Comparator group	Maintenance immunosuppression	Follow-up	Treatment group	Patient survival (%)	Acute rejection (%)
Yamani et al. (2008) [147]	32	Low	Total dose 6 mg/kg (steroid-free)	Single dose of rATG (1.5 mg/kg)	Tacrolimus MMF Steroids only in induction-free group	12 months	rATG Standard steroids p-Value	93.8 93.8 NS	50[a] 69[a] NS
Carrier et al. (2007) [148]	35	Standard	Total dose 5.2 mg/kg	Basiliximab	CsA MMF Steroids	6 months	rATG Basiliximab p-Value	78 77 0.9955	17[a] 35[a] *
Mattei et al. (2007) [74]	80	Standard	Total dose 7.5–12.5 mg/kg (mean ∼8.6 mg/kg)	Basiliximab	CsA MMF Steroids	6 months	rATG Basiliximab p-Value	78.6 86.8 0.388	45.2[b] 50.0[b] NS
Schnetzler et al. (2002) [18]	50	Standard	Mean total ∼12.5 mg/kg	ATG-Fresenius	CsA AZA Steroids	12 months	rATG ATG-Fresenius p-Value	84.6 87.5 NS	91.7[c] 84.6[c] NS

[a] Grade ≥3

[b] Grade ≥1B

[c] Any rejection

* Non-inferiority for basiliximab was not shown

AZA azathioprine, *CsA* cyclosporine, *MMF* mycophenolate mofetil, *NS* not significant, *rATG* rabbit antithymocyte globulin

to renal insufficiency [151]. Delgado et al. [152] delayed CNI introduction after a mean of 3.2 days in seven patients receiving rATG induction, and found that renal function was preserved to last follow-up at month 6 with a lower rate of acute rejection than in patients given IL-2RA induction and there were no episodes of rejection with hemodynamic compromise. Delaying CNI initiation until serum creatinine was <150 μM with rATG induction (total dose 7.5 mg/kg) in a small series of 15 patients with postoperative renal dysfunction was associated with a similar rate of rejection as control patients, and renal function improved in the delayed-CNI cohort compared with matched controls [153]. One retrospective, single-center analysis, currently published in abstract form only, has suggested that rATG induction (total dose 4.5 mg/kg) with reduced CNI exposure and everolimus therapy in patients with moderate to severe chronic kidney disease achieves effective rejection prophylaxis with a low rate of infection, and preserves renal function [154], a regimen that merits further evaluation.

Evidence relating to a steroid-sparing role for rATG in adult heart transplant recipients is currently limited to a single, randomized trial [138]. Yamani et al. [147] under-took a single-center randomized trial in which 32 patients at low immunological risk were randomized to rATG induction (total dose 6 mg/kg) without steroids, or to a standard triple-therapy regimen with no induction (Table 5). At 1 year, the rate of acute rejection grade $\geq$3A was similar between groups (mean number of episodes 0.81 with rATG vs. 1.07 in the control arm). The steroid-avoidance patients showed significantly greater muscle strength and less bone loss. Preliminary evidence from a series of 70 children (median age 7.1 years) undergoing heart transplantation at a single center who were treated with rATG then a steroid-free tacrolimus-based dual ther-apy regimen indicated that 87 % of patients were free of rejection at 1 year, with 88 % survival, among the 50 patients who survived to the point of hospital discharge [155]. Further data are awaited.

7.3 Cardiac Allograft Vasculopathy

Experimental evidence [81–83] and preliminary evidence from liver transplantation [111] that ATG preparations may reduce ischemia-reperfusion injury, which, by limiting immunologic damage [156], could potentially attenuate cardiac allograft vasculopathy (CAV) [77]. At present, data are limited to three single-center, retrospective analyses [157–159]. In the largest of these (n = 662), 16.9 % of patients showed signs of CAV during a follow-up period of 1–5 years [157]. On multivariate analysis, rATG induction therapy was significantly predictive of freedom from CAV (risk ratio 0.634; $p < 0.001$) or severe CAV (risk ratio

0.277; $p < 0.001$). The dose of rATG was not specified. Two other single-center series have reported 10-year fol-low-up data [158, 159]. In one analysis by Carrier et al. [159], in which 163 patients were given rATG at a mean total dose of approximately 5.2 mg/kg, the 10-year inci-dence of CAV was 50 % compared with 70 % in 48 induction-free controls. In another single-center analysis, 40 patients were given rATG or an IL-2RA induction agent with a triple-therapy maintenance regimen. The rATG cohort had a lower rate of CAV at 10 years post-transplant (20 % vs. 40 %; $p = 0.031$) but the total rATG dose was exceptionally high (20 mg/kg) [158]. Data from patients receiving ATG-Fresenius are consistent with these findings [160, 161]. There are limited data from patients treated with ATG-Fresenius to suggest that an effect on CAV may be dose-dependent [160], but an effect using modern rATG dose levels appears possible [159] and further investigation is merited.

8 rATG in Lung Transplantation

Immunosuppressive protocols following lung transplanta-tion must be modified to take into account certain organ-specific features. Maintaining adequate immunosuppres-sion appears to be particularly important, especially during the immediate post-transplant period, due to various factors such as T-cell activation caused by donor dendritic cell activity and ongoing exposure of the lungs to endogenous antigens [162]. Acute rejection contributes to the risk of bronchiolitis obliterans syndrome (BOS) [163], the prin-cipal factor limiting long-term graft survival after lung transplantation [164]. CMV pneumonitis is also believed to contribute to the development of BOS [163, 165], height-ening the potential impact of over-immunosuppression.

Retrospective analyses of data from the ISHLT registry have shown that induction therapy generally is associated with a reduced risk of BOS, presumably due to reduced rejection [162, 166, 167]. One analysis of ISHLT data [158] and one based on OPTN data [124] have indicated higher lung allograft and patient survival with induction versus no induction.

Early published studies of rATG dosing indicate that lower doses were used in lung transplant recipients than in other types of solid organ transplantation [168, 169]. In 2002, Krasinskas et al. [79] demonstrated that by using CD3$^+$ T-cell monitoring in lung transplant patients, the total dose could be reduced by 48 % without affecting the rate of acute rejection. The first robustly designed trial to assess rATG in lung transplantation was a single-center, randomized trial of 44 single or bilateral lung transplant patients given rATG (total dose 4.5 mg/kg) or no induc-tion, both with standard triple therapy comprising

cyclosporine, azathioprine, and steroids [168]. The incidence of acute rejection was significantly reduced in the presence of rATG (23 % vs. 55 %; $p = 0.03$), with a non-significant reduction in the incidence of BOS (20 % with rATG vs. 38 % vs. no induction), findings that were maintained long-term [170]. The rate of post-transplant infections was similar in both arms. In a comparative trial of cyclosporine versus tacrolimus with MMF and steroids, both groups received rATG at a total dose of 7.5 mg/kg, with no marked safety concerns [169].

Few studies have compared induction regimens following lung transplantation. A randomized trial of rATG (total dose 10 mg/kg) versus daclizumab in 50 lung transplant recipients showed similar rates of rejection and BOS in both arms but a significantly higher rate of CMV infection with daclizumab, possibly due to greater CMV serology mismatching [171]. Studies assessing the feasibility of CNI- or steroid-sparing regimens using rATG induction in lung transplant patients are lacking.

9 rATG in Pancreas and Islet Transplantation

Randomized trials of rATG in pancreas or simultaneous pancreas kidney (SPK) transplantation are sparse. A retrospective, single-center analysis of 128 SPK procedures performed during 2001–2008 indicated a lower rate of both acute rejection overall and steroid-resistant rejection, with similar graft and patient survival rates and safety profiles, but rATG dosing and maintenance immunosuppression evolved over the study period and the findings are not necessarily applicable to current regimens [172].

The use of rATG to delay the introduction of CNI therapy was investigated in a randomized trial of 50 patients undergoing SPK transplantation [173]. Patients received either rATG (1.5 mg/kg/day for 10 days, adjusted as necessary) with delayed cyclosporine, or no induction with standard cyclosporine, both in conjunction with azathioprine and steroids. After a mean follow-up of 36 months, the incidence of acute kidney rejection episodes was lower with rATG (36 % vs. 76 %; $p < 0.01$), but at this dose level adverse events were more frequent with rATG (80 % vs. 40 %). No other study has assessed delayed CNI with a more contemporary rATG dose, but a recent randomized trial (published only in abstract form to date) assessed both CNI- and steroid-sparing immunosuppression in a population of 100 SPK transplant patients [174]. Induction comprised a 10-day course of rATG, at an unspecified dose. After an initial regimen of tacrolimus, low-dose steroids, and MMF, tacrolimus was replaced by sirolimus and steroids were withdrawn during days 60–90 post-transplant. At 1-year post-transplant, outcomes (rejection rates, switch of regimen, renal histology, and de novo DSA) favored the control group in whom tacrolimus and steroids were continued.

While CNI withdrawal may be inadvisable after SPK transplantation, steroid reduction in patients receiving rATG induction appears feasible. In an early prospective study of 40 SPK patients given rATG (total dose 8 mg/kg over days 1–14), steroids were withdrawn after day 6 [175]. Maintenance therapy comprised tacrolimus and MMF, or tacrolimus and sirolimus. Compared with historical controls who did not receive rATG and who continued standard steroid therapy, the rejection rate was lower in the rATG/steroid elimination group (2.5 % vs. 19.8 %; $p = 0.034$). Since then, retrospective studies from the mid-2000s using a variety of rATG protocols [176–178], and a more recent retrospective study in which patients received a total rATG dose of 6 mg/kg [179], have also indicated that withdrawal of steroids from a regimen of tacrolimus and MMF with or without sirolimus by the end of the first week after SPK (or pancreas after kidney transplantation) maintains immunosuppressive efficacy. There are also limited data to support rATG induction in an entirely steroid-free protocol [54] but these have not been confirmed.

In the relatively new field of islet transplantation, there is some initial positive experience with an immunosuppression regimen of rATG induction, tacrolimus, and MMF [180], and studies are ongoing [181].

10 rATG in Other Types of Transplantation

10.1 Intestinal Transplantation

No standard immunosuppressive regimen for intestinal or multivisceral transplant recipients has been established, but for the last 15 years rATG has been the most frequently used antibody agent in this setting [182]. The high risk of rejection following such procedures, and the high rate of graft-versus-host disease (GvHD) [183] means that more than one induction agent may be used. In one series of 27 patients undergoing intestinal transplantation at a single center, induction comprised rATG, rituximab, and steroids, with tacrolimus and tapered steroids as maintenance therapy [184]. There were eight episodes of severe infection, and two cases of steroid-responsive skin GvHD with a 1-year graft survival rate of 76 %, outcomes that would be considered good in such an immunogenic setting. An analysis of data from 211 intestinal and multivisceral procedures performed at major centers during 2006–2010 compared acute rejection and infection rates between patients receiving IL-2RA induction (daclizumab) with tacrolimus and steroids, alemtuzumab induction with tacrolimus, or rATG induction with rituximab and tacrolimus [185]. The incidence of moderate acute rejection was 0,

26.3 and 11.7 % in the three groups, respectively, but the infection rates were 62.5, 52.0 and 7.4 %, respectively, with the highest graft and patient survival rates in the rATG/rituximab/tacrolimus group due to the low rate of infection. The authors concluded that the latter regimen was optimal for balancing the risks of rejection and infection [185].

Separately, there is also intriguing preliminary evidence that pre-treatment with a single dose of rATG (5 mg/kg) followed by minimal-dose tacrolimus monotherapy may achieve partial immune tolerance after intestinal transplantation [186, 187].

10.2 Composite Tissues

Transplantation of vascularized composite tissue—for example, face and upper extremities—is still in its infancy but offers a reconstructive approach impossible by other means. More than 150 such procedures have now been performed [188], the majority of which have included rATG in the immunosuppressive protocol [189]. The first ever face allograft recipient was treated with rATG induction, and maintenance immunosuppression comprising tacrolimus, MMF, and steroids [190]. Immunosuppression was well tolerated, and despite two episodes of acute rejection during the first year, after 5 years the patient was doing well and reported normal social interactions [191]. More recent reports of near-total or full-face transplants, including rATG induction therapy, have reported similarly successful outcomes [192, 193]. rATG has also contributed to uneventful postoperative courses following human hand allografting [194], and management of steroid-resistant atypical rejection following hand transplantation [195]. Interestingly, despite high levels of immunosuppression related to the combination of rATG, tacrolimus, and MMF, the incidence of skin rejection in face or hand transplantation is much higher than for internal organ transplants. However, the incidence of chronic rejection has so far been low. The reasons for this discrepancy remain elusive [196].

11 Safety Profile of rATG in Solid Organ Transplantation

Historically, the two key safety concerns related to rATG therapy have been infectious complications and risk of malignancy or post-transplant lymphoproliferative disease (PTLD). Adverse events, notably fevers and chills, and hematological abnormalities such as lymphopenia, neutropenia, and thrombocytopenia, can occur but are usually managed successfully by dose adjustments. As a result of progressive decreases in the cumulative rATG dose and

duration of exposure, the incidence of serum sickness is now estimated to have declined to 0.25 % in patients receiving a cumulative dose of 6 mg/kg over no more than 7 days [171], and can be managed by a combination of plasmapheresis and steroids.

11.1 Malignancy and Post-Transplant Lymphoproliferative Disease

The risk of cancer is estimated to be twice as high in solid organ transplant recipients as in the general population, with the difference most marked for infection-related malignancy diagnosis such as non-Hodgkin lymphoma [197]. Nevertheless, the incidence of PTLD following kidney transplantation is no more than 1 % at 5 years [198, 199], with lower rates for non-Hodgkin lymphoma and other common cancers [197, 200]. Assessment of the risk associated with specific immunosuppressive agents therefore requires the statistical power provided by large-scale transplant registries. Many such analyses have not specifically evaluated rATG induction therapy (and even fewer have specifically assessed Thymoglobulin®) as opposed to lymphocyte-depleting agents as a class. An analysis from 1995 to 2004, which was based on the Collaborative Transplant Study database, observed a marked increase in non-Hodgkin lymphoma with rATG induction versus non-induction [200]. During that period, rATG doses were higher than at present, and this finding is consistent with other registry analyses based solely on data from the 1990s or early 2000s (Table 6). A somewhat more recent analysis of 2,151 adult heart transplant recipients (1995–2008) receiving ATG in the UK (the preparation of ATG was not specified) found no evidence of increased death from lymphoma [201]. An analysis of patients registered with the Australian and New Zealand Dialysis and Transplantation Registry (ANZDATA) registry during 1997 to 2009 indicated that acute rejection treated with lymphocyte-depleting therapy (rATG was not specifically assessed) appears to be associated with an increased risk of cancer [206]. The increase was due to more genitourinary tract cancers but not other site-specific malignancies or PTLD [206]. The authors point out that acute rejection may share a common causal pathway with malignancy, making it difficult to distinguish the contribution of rATG to such an effect, and results of other long-term analyses are awaited [207].

A systematic review of trials of rATG (Thymoglobulin®), published during 1999–2009, in kidney and heart transplant recipients (n = 2,246) with at least 3 years' follow-up recently concluded that the cumulative dose showed no association with risk of PTLD [208]. The overall incidence of PTLD was 0.98 % and 1.05 % in kidney and heart transplant patients, respectively. Evidence

Table 6 Safety data reported in registry analyses of transplant patients receiving ATG as induction therapy

Study (year)	Organ	Registry (years of transplant)	Induction	N	Follow-up	Safety outcome
Neoplasms						
Emin et al. (2011) [201]	Heart	UK Cardiothoracic Transplant Audit	ATG (unspecified formulation); No induction	2,086	10 years	Similar rate of death from lymphoid malignancy (1.0 % vs. 1.4 %; p = 0.38) or non-lymphoid malignancy (3.9 % vs. 2.8 %; p = 0.40) with ATG vs. no induction
Gajarski et al. (2011) [202]	Heart (pediatric)	Pediatric Heart Transplant Study	rATG (Thymoglobulin®); No induction	2,374	5 years	No significant association between rATG and risk of lymphoma on multivariate analysis
Kirk et al. (2007) [198]	Kidney	Organ Procurement and Transplant Network (2000–2004)	rATG (Thymoglobulin®)	13,110	≤730 days	Relative risk of PTLD for rATG vs. no induction 1.63 (95 % CI 1.19–2.24; p = 0.003)
Opelz et al. (2006) [107]	Kidney	Collaborative Transplant Study (1995–2004)	rATG (Thymoglobulin®); ATG-Fresenius; ATGAM; OKT3; IL-2RA; No induction	1,875; 856; 440; 1,760; 6,209; 23,066	3 years	Relative risk of non-Hodgkin lymphoma vs. no induction[a]: rATG 21.1; ATG-Fresenius 3.0; ATGAM 22.1; OKT3 31.3; IL-2RA 7.4
Bustami et al. (2004) [203]	Kidney	Scientific Registry of Transplant Recipients (1995–2002)	rATG (unspecified); No induction	Not stated; Not stated	0–4 years	Relative risk of de novo solid tumor 1.53 (93 % CI 0.92–2.56; p = 0.10); Relative risk of PLTD for rATG vs. no induction 3.00 (95 % CI 1.53–5.89; p = 0.001)
Infections						
Emin et al. (2011) [201]	Heart	UK Cardiothoracic Transplant Audit	ATG (unspecified formulation); No induction	2,086; No induction	1 year	Adjusted risk of infection for ATG vs. no induction 1.21 (95 % CI 1.02–1.44; p = 0.027)
Gajarski et al. (2011) [202]	Heart (pediatric)	Pediatric Heart Transplant Study	rATG (Thymoglobulin®); No induction	2,374	5 years	No significant association between rATG and risk of viral, fungal, or bacterial infection
Dharmidharka et al. (2009) [204]	Kidney	Organ Procurement and Transplant Network (2003–2006)	rATG (Thymoglobulin®); No induction	16,746; 13,050	2 years	Adjusted HR for treated BKV infection with rATG vs. no induction 1.42 (95 % CI 1.24–1.63; p < 0.001)
Schold et al. (2009) [205]	Kidney	Scientific Registry of Transplant Recipients (2004–2006)	rATG (Thymoglobulin®); IL-2RA	Not stated; Not stated	1 year	Adjusted OR for treated BKV infection with rATG vs. IL-2RA induction 1.23 (95 % CI 1.03–1.45)
Non-comparative analyses						
Gaber et al. (2012) [68]	Kidney	United Network for Organ Sharing (2003–2008)	rATG (Thymoglobulin®)	2,322	Hospital discharge; 1 year; 5 years	0.005 % serious adverse events possibly or probably related to rATG; Incidence of CMV infection 4.2 %; Incidence of PTLD 0.9 %

ATG antithymocyte globulin, *ATGAM* equine ATG, *BKV* BK polyomavirus, *CI* confidence interval, *CMV* cytomegalovirus, *HR* hazard ratio, *IL-2RA* interleukin-2 receptor antagonist, *OKT3* muromonab-CD3, *OR* odds ratio, *PTLD* post-transplant lymphoproliferative disorder, *rATG* rabbit antithymocyte globulin

[a] Standardized incidence risk compared to a non-transplant control population

from registry studies regarding the risk of PTLD in patients receiving rATG is difficult to interpret since only one has specifically assessed Thymoglobulin®, reporting an increased risk versus no induction for patients transplanted during 2000–2004 [198]. Other registry analyses have described mixed findings, with some showing an increased risk for PTLD with rATG or ATG preparations of any type [199, 203, 209, 210] and others reporting no effect of rATG or polyclonal lymphocyte-depleting agents [211–213]. In one of the most recent large-scale datasets, derived from the TAILOR registry, a non-comparative evaluation of PTLD in 2,322 patients receiving rATG (Thymoglobulin®) after living-donor kidney transplantation during 2003–2008 showed the 5-year incidence of PTLD to be 0.9 % [68]. This is comparable with published incidence rates for the kidney transplant population as a whole [198, 199]. Unlike most registries, TAILOR captures the rATG dose, and in this series the mean cumulative dose was ∼5.3 mg/kg. It appears that the risk of PTLD and malignancy associated with modern rATG induction regimens may be less of a concern than during the high-dose era, but confirmatory data are required. However, close monitoring remains mandatory and includes both short-term evaluation of blood T-cell depletion and longer-term assessment of immune reconstitution [9].

11.2 Infections

Concerns about infectious complications associated with rATG therapy focus on viral infections, most notably CMV infection. Randomized trials of rATG induction versus no induction [16, 17], published in the early 2000s, reported a higher rate of CMV infection in kidney transplant patients receiving rATG [16, 17]. In these studies, the dose of rATG was relatively high by today's standards (12.5 mg/kg), and CMV prophylaxis was not specified. Randomized comparative trials of rATG versus IL-2RA induction have shown mixed results [24, 92, 93, 121]. The differences are largely due to the fact that some trials included systematic CMV prophylaxis while others did not, and because of variations in the incidence of rejection and the consequent requirement for increased immunosuppression. Higher rATG doses appear to increase CMV infection rates compared with IL-2RA induction [47, 91]. In a United Network for Organ Sharing (UNOS) analysis of 2,322 patients undergoing kidney transplantation with rATG induction during 2003–2008, a period when rATG dose was declining, the CMV infection rate was reported to be only 4.2 % [68]. It would appear that with contemporary rATG dosing regimens, and wider use of CMV prophylaxis therapy, the risk of increased CMV infections in rATG-treated kidney transplant patients has diminished but cannot be discounted.

Data in liver transplantation, while limited, do not indicate a higher rate of CMV infections using contemporary rATG regimens [73]. Randomized trials [74, 147] and retrospective analyses [75, 76] in heart transplant recipients have shown no difference in rates of infection overall, or CMV infection specifically, when rATG was compared with IL-2RA induction. A large observational study in pediatric heart transplant recipients found that rATG induction appeared to be associated with a lower rate of infection [202] (Table 6), presumably due to a reduced requirement for rejection treatment or high-dose maintenance therapy. rATG-treated patients should receive prophylactic antiviral therapy, an approach that is typically considered mandatory in donor-positive, recipient-negative transplants.

A more recent potential safety issue to emerge is whether rATG therapy could impact on the risk of BK virus infection after kidney transplantation. Two registry analyses of patients in the US who received a kidney transplant during 2003–2006 [203] or 2004–2006 [205] have suggested that rATG induction is associated with a higher rate of treatment for BK virus infection. These retrospective data are consistent with results from a single-center, prospective study during 2001–2003 in which rATG dose was 7.5 mg/kg, which reported a higher risk of BK virus infection with rATG induction versus IL-2RA induction [214]. A more recent retrospective, single-center analysis, which did not specify rATG dose, found no relationship between rATG administration and risk of BK virus infection on multivariate analysis [215]. Generally, BK virus infection is considered to be associated with any intensive immunosuppressive regimen rather than a specific agent [216], and no direct link to rATG therapy has been established [217].

Monitoring for CMV infection for at least 3 months, with at least 6 months' screening for BK virus infection and 1 year for Epstein-Barr virus (EBV) infection, with risk-adjusted prophylaxis for CMV and pneumocystis infection has been recommended in patients receiving rATG, especially when used to treat steroid-resistant rejection [218].

12 rATG in Hematopoietic Stem Cell Transplantation

Since the early days of HSCT, rATG was thought to be an effective agent for treating and preventing GvHD. Following evidence of improved GvHD prophylaxis with rATG versus other antibody therapies [219], it has since been widely adopted within conditioning regimens before allogeneic HSCT from an unrelated donor. rATG has been included in the conventional myeloablative conditioning regimens, administered prior to HSCT to facilitate

engraftment. In more recent years a role for rATG has also been established in less aggressive non-myeloablative and reduced-intensity conditioning regimens [3].

12.1 rATG in Myeloablative Conditioning Regimens

An early randomized trial in patients with hematological malignancy undergoing unrelated HSCT reported significant protection against extensive chronic GvHD in rATG-treated patients versus controls (Fig. 2) [220, 221]. In particular, the study demonstrated a highly significant reduction in chronic lung dysfunction, a severe and often fatal complication of HSCT, in patients receiving rATG compared with controls (19 % vs. 51 %; $p = 0.005$). However, reduction of acute GvHD appeared to require high rATG dose (15 mg/kg) [220]. Subsequently, further studies confirmed significantly better outcomes with rATG versus controls following unrelated [222–225] or matched-related [224, 226, 227] HSCT, bone marrow or cord blood cell transplantation in terms of chronic GvHD, relapse, and mortality. A retrospective analysis of 110 patients undergoing HSCT for the treatment of β-thalassemia major (all but six of whom received a graft from a related donor) transplanted over the period 1985–2007 at 21 centers in France showed a significant association between rATG as part of the conditioning regimen versus no rATG in terms of thalassemia-free survival (55.1 % vs. 82.5 %; $p = 0.002$) [228]. In a recent prospective study, 47 patients undergoing unrelated HSCT received rATG at a dose of 4.5 mg/kg (1.5 mg/kg/day on days −3, −2 and −1) with tacrolimus and sirolimus for the prevention of acute GvHD [229]. At 2 years, the incidences of acute graft vascular disease (GVD) and chronic GvHD were 23.4 and 33.0 %, respectively, and the regimen was well tolerated. Typically, rATG is now given at a total dose ranging between 4.5 and 7.5 mg/kg within myeloablative conditioning regimens [224, 226, 230].
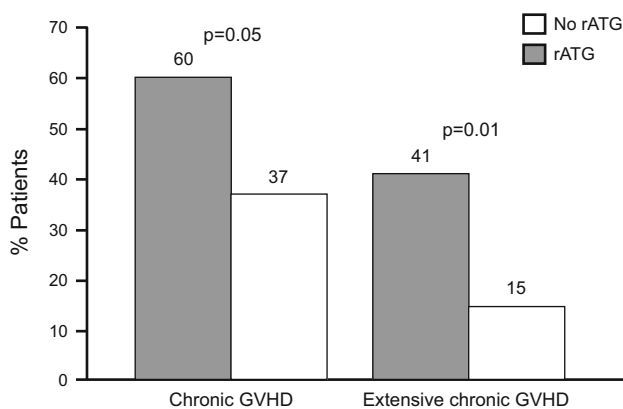
Initial experience in umbilical cord transplantation, an alternative to conventional allogeneic stem cell transplantation, suggests that the use of rATG as part of the pre-transplant conditioning regimen may improve outcomes and ameliorate GvHD [231].

12.2 rATG in Reduced-Intensity Conditioning

The optimal dose and administration schedule for rATG within reduced-intensity conditioning to prevent GvHD in patients undergoing HSCT is less well defined. Trials in the early 2000s used a total rATG dose of 7.5–10.0 mg/kg [232, 233] but lower doses later proved to be more relevant. A randomized trial compared two doses of rATG (total dose 4.5 mg/kg and 7.5 mg/kg) within a reduced-intensity regimen in 20 recipients of HSCT from an unrelated donor and found no difference in the incidence of acute or chronic GvHD, or any other efficacy endpoint, at 100 days [234]. The authors concluded that an rATG dose of 4.5 mg/kg was preferable, and a high rATG dose may be unfavorable. A retrospective analysis of reduced-intensity conditioning in 110 consecutive recipients of HSCT from matched unrelated donors found that an rATG total dose of 6 mg/kg was associated with improved results compared with 8 mg/kg; the lower dose predicted improved relapse-free survival on multivariate analysis [235]. Depending on the adjunctive conditioning regimen, relatively low doses have proved effective. A randomized, multicenter study has compared two reduced-intensity conditioning regimens, one with and one without rATG [236]. One hundred and thirty-nine patients with hematological malignancies received HSCT from an HLA-identical sibling. All patients

Fig. 2 Chronic GvHD in patients with hematological malignancy undergoing unrelated HSCT randomized to rATG or no rATG [221]. *GvHD* graft-versus-host disease, *HSCT* hematopoietic stem cell transplantation, *rATG* rabbit antithymocyte globulin
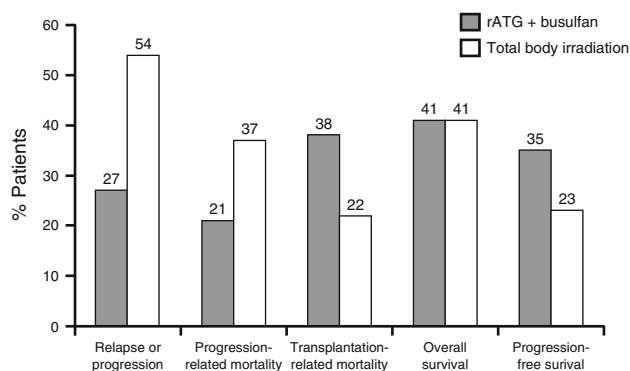
Fig. 3 Five-year outcomes from a randomized trial of patients with hematologic malignancies receiving reduced-intensity conditioning with fludarabine and either rATG (2.5 mg/kg) with busulfan ($n = 69$) or total body irradiation ($n = 70$) prior to HSCT from an HLA-identical sibling [236]. *HLA* human leukocyte antigen, *HSCT* hematopoietic stem cell transplantation, *rATG* rabbit antithymocyte globulin

received conditioning with fludarabine, and were randomized to either receive rATG at a low total dose (2.5 mg/kg) with busulfan, or no rATG with total body irradiation (TBI), with a median follow-up of 54 months. The cohort randomized to rATG and busulfan had a higher rate of acute GvHD (47 % vs. 27 %; $p = 0.01$) and non-relapse mortality (38 % vs. 22 %; $p = 0.027$) but no difference in chronic GvHD and a lower relapse rate (27 % vs. 54 %; $p < 0.01$). At 5 years' follow-up, all outcomes were similar between groups (Fig. 3) [236]. The authors commented that rATG with busulfan offers greater disease control than low-dose TBI, although this did not translate to improved survival. In a small series of 19 children undergoing transplantation for non-malignant indications (12 mismatched unrelated donors, 7 unrelated donors), a regimen of rATG, busulfan, and fludarabine was associated with excellent survival but with a high graft failure rate (21 %) accounted for by the unrelated donor cohort [237].

12.3 rATG as Pre-Emptive Treatment of Acute Graft-versus-Host Disease

Patients at high risk of GvHD and death can be identified on day 7 after HSCT based on laboratory data [238]. In a prospective, randomized trial, all patients grafted from unrelated donors received rATG 7.5 mg/kg pre-transplant [238]. On day $+7$, they were assigned to receive an additional rATG dose of 1.25 mg/kg/day on days 7 and 9 post-transplant, or enter a control arm [239]. One hundred and seventy patients were randomized and were evaluable for non-relapse-related mortality (the primary endpoint) or GvHD (a secondary endpoint). Non-relapse-related mortality was 29 % in the rATG-treated patients versus 35 % in the control arm ($p = 0.3$). GvHD was significantly less frequent under rATG therapy; the incidence of acute GvHD III–IV was 5 % versus 15 % in controls ($p = 0.02$), and the incidence of extensive chronic GvHD was 11 % versus 27 % ($p = 0.03$). Rates of relapse and survival were comparable. These results indicate that rATG can be given to high-risk patients before and after an alternative donor stem cell transplant, and this approach further mitigates acute and chronic GvHD without interfering with the graft versus leukemia (GvL) effect. This strategy can be referred to as pre-emptive therapy of GvHD.

Although the drug is approved in this setting, treatment of established severe acute GvHD has been less satisfactory. This is especially true in steroid-refractory cases, where no agent has been shown to be superior to steroids alone. In a prospective, randomized trial, the combination of rATG and steroids did not prove superior to steroids alone for the therapy of steroid refractory acute GvHD [240]. Nevertheless rATG is commonly used in the management of acute GvHD [241], although an early use (pre-

emptive) has been shown to be more effective than later on in the course of the disease.

12.4 Epstein-Barr Virus Reactivation and Lymphoproliferative Diseases

The risk of EBV reactivation is increased in patients receiving high doses of ATG in the conditioning regimen [242], and may lead to potentially life-threatening lymphoproliferative disorders [242]. Currently, this complication can be prevented through close and regular monitoring of EBV reactivation and use of pre-emptive therapy with rituximab. A low dose of anti-CD20 antibody (rituximab) administered on day $+5$ after HSCT may also prevent this complication [243]. The risk of EBV reactivation after HSCT should be appreciated, and prevented or treated appropriately.

13 rATG in Autoimmunity

13.1 Severe Aplastic Anemia

The role of ATG in conditioning regimens for HSCT in severe aplastic anemia has been the topic of several studies. In a prospective, randomized study performed in the US, patients receiving ATG had comparable survival to controls [244]. In contrast, a recent report from the European Group of Blood and Marrow Transplantation (EBMT) observed that patients with severe aplastic anemia receiving ATG had significantly superior survival compared with controls [245]. In another EBMT study, 100 patients with severe aplastic anemia all received rATG as part of the conditioning regimen, together with fludarabine and cyclophosphamide (FCA), with or without low-dose TBI [246]. Actuarial survival was 73 % for rATG with FCA and 79 % with FCA-TBI. For patients grafted within 2 years of diagnosis, the overall survival rate was 87 %.

While HSCT is the treatment of choice for acquired aplastic anemia, ATG with cyclosporine may be an effective option for patients with severe disease who do not have a matched sibling donor or whose age (>50 years) makes transplantation an unsuitable option [247–249]. The majority of data in this setting relates to eATG, with rATG reserved for second-line therapy in the event of non-response to eATG or relapse [249]. eATG is now available only in some markets. Data for rATG as first-line immunosuppressive therapy remain relatively limited [250–254]. A prospective pilot study comparing rATG with cyclosporine as first-line treatment for 35 patients with aplastic anemia versus 105 matching controls treated with eATG and cyclosporine observed higher 2-year overall survival rates with eATG (86 % vs. 68 %;

$p = 0.009$) and higher transplant-free survival (76 % vs. 52 %; $p = 0.002$). Another smaller, prospective, non-randomized study observed a non-significant difference in response rates that was numerically in favor of eATG [250]. A recent published report from a single-center study in Japan found similar response rates with either rATG (75 %) or eATG (67 %), based on an rATG dose of 12.5 mg/kg. A prospective, randomized trial performed at the National Institute of Health in the US indicated that rATG is inferior in terms of response and survival compared with eATG [255]. The trial enrolled 120 patients (60 in each group) and the response rate at 6 months was 68 % with eATG versus 37 % with rATG ($p < 0.001$), associated with a borderline advantage in survival ($p = 0.04$).

13.2 Other Autoimmune Disorders

The EBMT has developed several trials of autografts in patients with autoimmune disorders, including multiple sclerosis, Crohn's disease, systemic sclerosis, and systemic lupus erythematosus [256]. These trials are based on the hypothesis that high-dose therapy combined with rATG can 'reset' the immune system and induce long-term remission. rATG is typically given at the time autologous stem cells are re-infused, in combination with high-dose cyclophosphamide (200 mg/kg) or high-dose combination chemotherapy (BEAM). This hypothesis has been proven in several phase II trials, and very recently in three prospective, randomized trials which compared this procedure with best available treatment—the ASTIM study in multiple sclerosis [257], ASTIC for Crohn's Disease, and ASTIS for systemic sclerosis. The EBMT registry of autoimmune disorders now has data on 1,700 patients, and the field is moving fast, with increasing numbers of patients being treated following the positive results of these randomized trials.

13.3 Pre-Transplant rATG

Pre-transplant rATG is now considered the standard of care for patients undergoing an unrelated donor–donor transplant. It has been proven to reduce the incidence of acute and especially chronic GvHD, without interfering significantly with the so-called GvL effect. Survival of patients receiving rATG prior to transplant is comparable to patients not given rATG, but with the highly important difference of less chronic GvHD for rATG-treated patients, which has a major impact on quality of life, the duration of immunosuppressive therapy, number of hospital admissions, and cost of treatment. The use of rATG post-transplant in a subgroup of high-risk patients can further reduce the risk of GvHD.

14 Induction of Tolerance

Patients undergoing solid organ transplantation require life-long immunosuppressive therapy, with its associated side effects and complications, including reduced quality of life and chronic graft rejection. rATG induces regulatory NK T-cells (CD161$^+$, CD3$^+$), particularly when combined with total lymphoid irradiation (TLI) [258]. The Stanford group has developed a conditioning regimen of TLI 800 rads in 10 fractions, combined with rATG 7.5 mg/kg (1.5 mg/kg/day for five doses), and followed by allogeneic hematopoietic stem cells with cyclosporine and MMF [233]. This regimen results in a high rate of complete donor chimerism, with little or no GvHD. The same group has since developed a program of combined HSCT and renal transplantation from HLA-identical family donors, the endpoint being discontinuation of immunosuppression. Initial results are encouraging [259]. More patients have been transplanted since 2008 and results remain promising, but work remains in its early stages.

15 Conclusions

Specific roles for rATG in modern immunosuppressive regimens are now relatively well-identified. In solid organ transplantation, the addition of rATG induction to a standard triple or dual regimen is an effective strategy to reduce acute cellular rejection, and possibly humoral rejection. It is an appropriate first choice in patients with moderate or high immunological risk. In patients at low risk, rATG induction may be used if a CNI-sparing regimen is administered from time of transplant, or if early steroid withdrawal is planned. Kidney transplant patients at risk of DGF may also benefit from the use of rATG to facilitate delayed CNI introduction.

rATG also has an established position in HSCT, as an agent which can reduce the risk of both acute and chronic GvHD. In addition to its current applications in solid organ transplantation, there is growing interest in the potential to harness the biological effects of rATG beyond T-cell depletion. The use of rATG combined with stem cell transplantation with the ultimate goal of achieving operational tolerance after allografting shows promise, although clinical data to date is highly preliminary [3, 260–263]. The broad spectrum of rATG activity means a possible role for rATG in new therapeutic areas is being assessed. These include rATG induction with autologous HSCT in patients with type 1 diabetes, which may improve β-cell function and improve glycemic control [264–266], myelodysplastic syndrome in patients with aplastic anemia [267, 268] and B-cell-mediated autoimmune diseases such as lupus erythematosus [269, 270].

Despite the long history of its use, rATG remains a key component of the immunosuppressive armamentarium, and its intriguing properties indicate that its use is to expand to a wider range of immunological conditions in the future.

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