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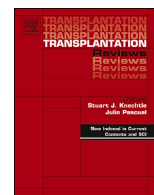

Review article

The use of lymphocyte-depleting antibodies in specific populations of kidney transplant recipients: A systematic review and meta-analysis

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ABSTRACT

Background: Recommendations of the use of antibody induction treatments in kidney transplant recipients (KTR) are based on moderate quality and historical studies. This systematic review aims to reevaluate, based on actual studies, the effects of different antibody preparations when used in specific KTR subgroups.
Methods: We searched MEDLINE and CENTRAL and selected randomized controlled trials (RCT) and observational studies looking at different antibody preparations used as induction in KTR. Comparisons were categorized into different KTR subgroups: standard, high risk of rejection, high risk of delayed graft function (DGF), living donor, and elderly KTR. Two authors independently assessed the risk of bias.
Results: Thirty-seven RCT and 99 observational studies were finally included. Compared to anti-interleukin-2-receptor antibodies (IL2RA), anti-thymocyte globulin (ATG) reduced the risk of acute rejection at two years in standard KTR (RR 0.74, 95%CI 0.61–0.89) and high risk of rejection KTR (RR 0.55, 95%CI 0.43–0.72), but without decreasing the risk of graft loss. We did not find significant differences comparing ATG vs. alemtuzumab or different ATG dosages in any KTR group.
Conclusions: Despite many studies carried out on induction treatment in KTR, their heterogeneity and short follow-up preclude definitive conclusions to determine the optimal induction therapy. Compared with IL2RA, ATG reduced rejection in standard-risk, highly sensitized, and living donor graft recipients, but not in high DGF risk or elderly recipients. More studies are needed to demonstrate beneficial effects in other KTR subgroups and overall patient and graft survival.

Abbreviations: ALG, Antilymphocyte Globulin; ATG, Antithymocyte Globulin; ATG-F, Antithymocyte Globulin Fresenius; BPAR, Biopsy-Proven Acute Rejection; CI, Confidence Interval; CMV, Cytomegalovirus; CNI, Calcineurin Inhibitors; CrCL, Creatinine Clearance; DGF, Delayed Graft Function; DSA, Donor-Specific Antibodies; GFR, Glomerular Filtration Rate; GLCD, graft loss censored for death; hATG, Horse Antithymocyte Globulin; IL2RA, Anti-Interleukin-2 receptor antibodies; KT, Kidney Transplantation; KTR, Kidney Transplant Recipients; mTORi, Mammalian Target of Rapamycin Inhibitors; PRA, Panel Reactive Antibodies; PTDM, Posttransplant Diabetes Mellitus; PTLD, Post-transplant Lymphoproliferative Disorders; rATG, Rabbit Antithymocyte Globulin; RCT, Randomized Clinical Trial; RR, Risk Ratio; SCR, Serum Creatinine; SMD, Standard Mean Difference.

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1. Introduction

The current standard of care for initial immunosuppression after kidney transplantation (KT) includes an induction strategy based on antibody therapies [1]. There are two main groups. Firstly, IgG monoclonal antibodies targeting different T-cell antigens: a) the α-chain (CD25) of the T-cell interleukin-2 receptor on activated T cells (IL2RA, basiliximab/daclizumab) [2]; b) the cell surface glycoprotein CD52 (alemtuzumab or campath) present on the surface on mature lymphocytes; or c) anti-CD3 (muromonab or orthoclone OKT3). Secondly, different preparations of lymphocyte-depleting polyclonal antibodies against human lymphocytes (anti-thymocyte globulin (ATG)) [3], mainly horse ATG (hATG) derived from horse serum after immunization of horses with fresh human thymocytes, from rabbit serum (rATG) after immunization of rabbits with fresh human thymocytes (thymoglobulin), or the so-called Grafalon (ATG—F) that is produced from rabbits after immunization with a T-lymphoblastic cell line (Jurkat cell line). These polyclonal antibody formulations are primarily targeting T-cells but also impact other immune and non-immune cells [4].

The recommendations of the use of different induction treatments are based on moderate quality evidence and guidelines based on historical studies [1,5,6]. ATG is useful in high immunological risk patients despite some well-known adverse effects, primarily related to the strongly induced immunosuppression that could induce more risk of infections, cancer, or diabetes. However, there is less clear its usefulness in standard risk KT recipients (KTR) or in high-risk of delayed graft function (DGF) subgroups.

This systematic review aims to reevaluate the effects of different antibody preparations when used as induction therapy in KTR. We aim to determine how the benefits and adverse events vary for each antibody preparation in specific subgroups of recipients.

2. Methods

Relevant studies were obtained from a systematic literature search. We searched MEDLINE and CENTRAL (Cochrane Central Register of Controlled Trials) until April 2022 (supplemental digital material [=suppl] p.1). We selected randomized controlled trials (RCT) and observational cohort studies looking at different antibody preparations used as induction in KTR. Adults or children KTR not receiving other organs were included. As immunosuppression agents, we included ATG (including hATG, rATG and ATG—F), IL2RA (basiliximab or daclizumab), alemtuzumab, calcineurin inhibitors (CNI, tacrolimus and cyclosporin), mammalian target of rapamycin inhibitors (mTORi) and belatacept. With the described search strategy, we obtained potentially relevant titles and abstracts. They were screened independently by two authors. The full text of the selected studies was assessed by two authors to determine if they satisfied the inclusion criteria.

2.1. Data extraction, outcomes, and quality assessment

Data extraction was carried out independently by all authors, using standard data extraction forms. Comparisons were categorized in five subgroups of KTR: a) standard; b) high risk of rejection; c) high risk of DGF; d) living donor; e) elderly recipients. In each of these types of patients, we compared the following interventions: 1) ATG vs no induction, 2) ATG vs IL2RA; 3) ATG vs alemtuzumab 4) different ATGs; 5) ATG at different doses (total dose) or posologies (different time intervals for the same total dose).

Outcomes were evaluated at 0,5–1–2-3-5-8 years and extracted using percentages or number of events or the measurement units for continuous variables. Primary outcomes were death (all-cause), graft loss censored for death (GLCD), and incidence of biopsy-proven acute rejection (BPAR). Secondary outcomes were: kidney allograft function by glomerular filtration rate (GFR), serum creatinine (SCr), creatinine clearance (CrCl), the incidence of DGF and duration of it (days); incidence of bacterial, fungal and viral infectious complications specifically including cytomegalovirus (CMV) and polyoma virus; incidence of posttransplant diabetes mellitus (PTDM), any malignancy, post-transplant lymphoproliferative disorders (PTLD) and lymphoma and appearance of de-novo donor-specific antibodies (DSA).

The risk of bias was independently assessed by two authors using the Cochrane risk of bias for RCT [7] and the Newcastle Otawa Scale for cohort studies [8]. We performed subgroup analysis to explore possible sources of heterogeneity: baseline maintenance immunosuppression, antibody formulation, duration, and dose of antibody treatment.

2.2. Data synthesis and analysis

Data were pooled using the random-effects model, but the fixed-effect model was also analysed to ensure the robustness of the model chosen and susceptibility to outliers. Multiple intervention groups studies were analysed with different methods: 1) using only the groups with the intervention of interest to create a single pair-wise comparison (if there were 3 groups including different induction therapies, only one induction therapy was included) and 2) including each pair-wise comparison separately, but with shared intervention groups divided out approximately evenly among the comparisons. In this last case, for dichotomous outcomes, both the number of events and the total number of patients were divided up and for continuous outcomes, only the total number of participants have been divided up and the means and standard deviations were left unchanged.

Results of the binary outcomes (death, GLCD, BPAR, DGF, bacterial, fungal, and viral infectious complications, PTDM, any malignancy, PTLD and de-novo DSA) were expressed as risk ratios (RR) with 95% confidence intervals (CI). For continuous outcomes (GFR, SCr, and duration of DGF), results were expressed as standard mean difference (SMD) with 95% CI.

Heterogeneity was analysed using a Chi [2] test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test [9]. I^2 values of 25%, 50%, and 75% correspond to low, medium, and high levels of heterogeneity.

Statistical analyses were performed using Review Manager Version 5.4.

3. Results

We followed PRISMA Guidelines [10]. We identified 1266 reports. After removing duplicates and screening titles and abstracts, 212 full-text reports were assessed. Seventy-nine reports were excluded (duplicated 13, no/few data 38; reviews 2; wrong intervention 26). We finally included 136 studies: 37 RCT and 99 observational cohort studies (Fig. 1). Risk of bias was low to moderate in RCT (suppl.p.3–4) and moderate in observational studies (suppl.p.5). The meta-analyses for each comparison and outcome are depicted in subsequent figures, and when a figure is not shown, it is available in the suppl.pp.6–56.

3.1. Standard KT

3.1.1. ATG vs no induction [11–17]

In the three trials comparing ATG vs no induction, BPAR was less frequent with ATG (RR 0.40, 95%CI 0.21–0.79, $p = 0.008$), and GLCD during the first year was also less frequent (RR 0.55, 95%CI 0.41–0.75, $p < 0.001$). No differences were observed in the DGF rate. More CMV infections were detected with ATG (RR 1.23, 95%CI 1.02–1.50, $p = 0.03$).

3.1.2. ATG vs IL2RA [18–55]

In the 37 studies which compared ATG vs IL2RA in standard KT, ATG reduced BPAR at 2 years (RR 0.74, 95%CI 0.61–0.89, $p = 0.002$) with uncertain effects on BPAR at 3 to 8 years. Significance was limited by a high heterogenicity between the included studies (I^2 index 67% and

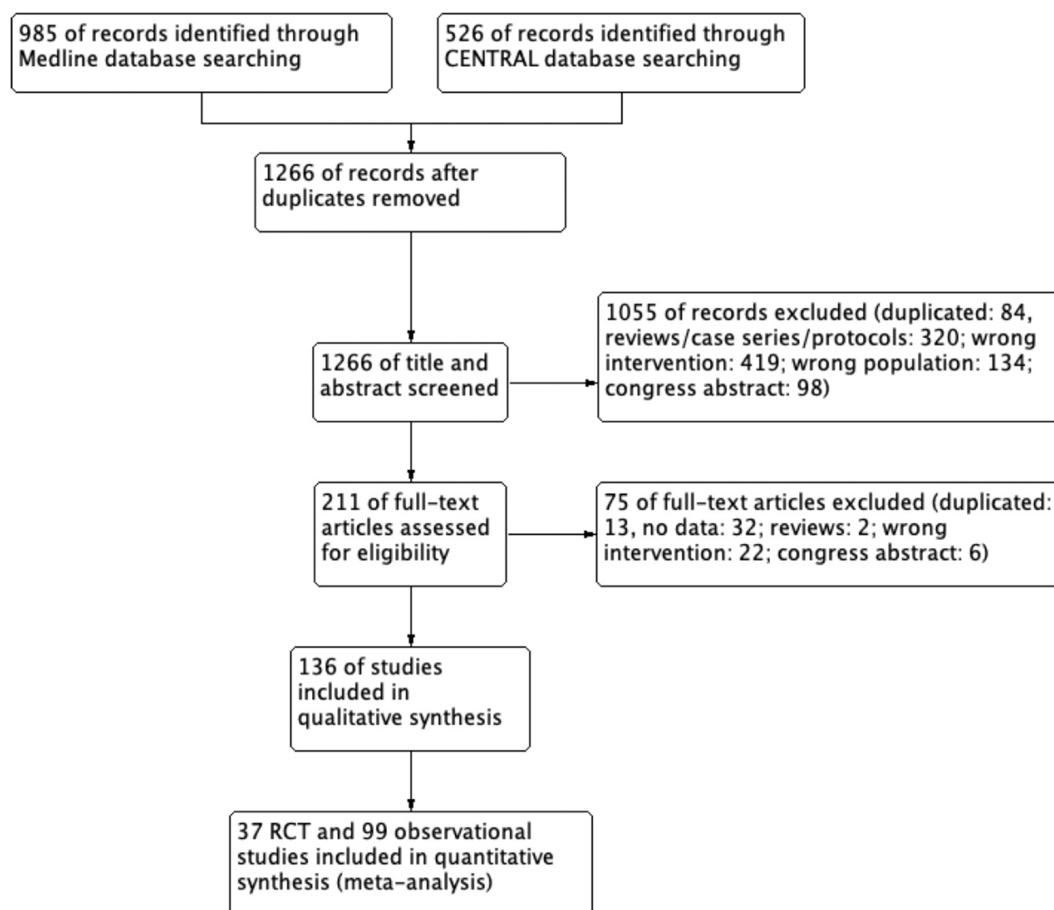


Fig. 1. Study selection flow diagram.

82%, respectively) (Fig. 2). The type of induction showed no effect on the DGF rate, neither on its duration. GLCD at ≤1 year was higher with IL2RA (RR 1.24 95% CI 1.16–1.32, $p < 0.001$), but this effect disappeared if the huge retrospective Jindal study [20] was excluded from the analysis (RR 0.73 95% CI 0.45–1.18, $p = 0.20$) (Fig. 3). No effects were observed on GLCD at 3 to 5 years (RR 0.65 95% CI 0.41–1.03, $p = 0.06$), but results favored the use of ATG when the Jindal study was excluded from the analysis (RR 0.55 95%CI 0.36–0.86, $p = 0.008$). Induction type presented uncertain effects on mortality, but the number of studies and participants was scarce. Induction with ATG or IL2RA showed no effect on infections, but the number of studies was limited and the heterogeneity indexes were high. A higher risk of CMV infection at 2 years was observed with ATG (RR 1.45, 95%CI 1.13–1.67) (Fig. 4). There was no difference in graft function. ATG and IL2RA induction showed a similar risk of developing malignancies at 2 years (RR 1.04, 95%CI 0.59–1.85, $p = 0.88$), without a relevant difference if the huge Wang registry [56] was excluded (RR 1.36 95% CI 0.52–3.59 $p = 0.53$). Other outcomes such as the development of de novo DSA or PTDM did not show differences comparing both induction agents.

3.1.3. *ATG vs alemtuzumab [57–67]*

BPAR rate was similar with both agents. GLCD during the first 2 years was less frequent with ATG (RR 0.49, 95%CI 0.31–0.80, $p = 0.004$). The scarce remainder outcomes assessed did not show significant differences, except for PTDM, more frequent with ATG (RR 1.37, 95%CI 1.22–1.54, $p < 0.001$).

3.1.4. *Different ATG preparations [68–71]*

No significant differences were noted when comparing thymoglobulin vs ATG—F. Only the Hardinger study compared thymoglobulin to horse ATG [71], showing higher rates of BPAR and CMV infections with horse ATG.

3.1.5. *ATG at two different doses or posologies [72–81]*

Nine studies compared two different total doses of ATG. Most studies compared a standard high dose of ATG around 6 mg/kg with a lower dose ranging from 1.5 mg/kg to 5 mg/kg [75–80]. The meta-analyses did not show any meaningful difference between higher vs lower dosages.

No significant differences were observed between two posologies (6 mg/kg in one dose or the same total dose but distributed in 4 shots on alternate days) in the unique study assessing this comparison [81].

3.2. *High-risk of rejection*

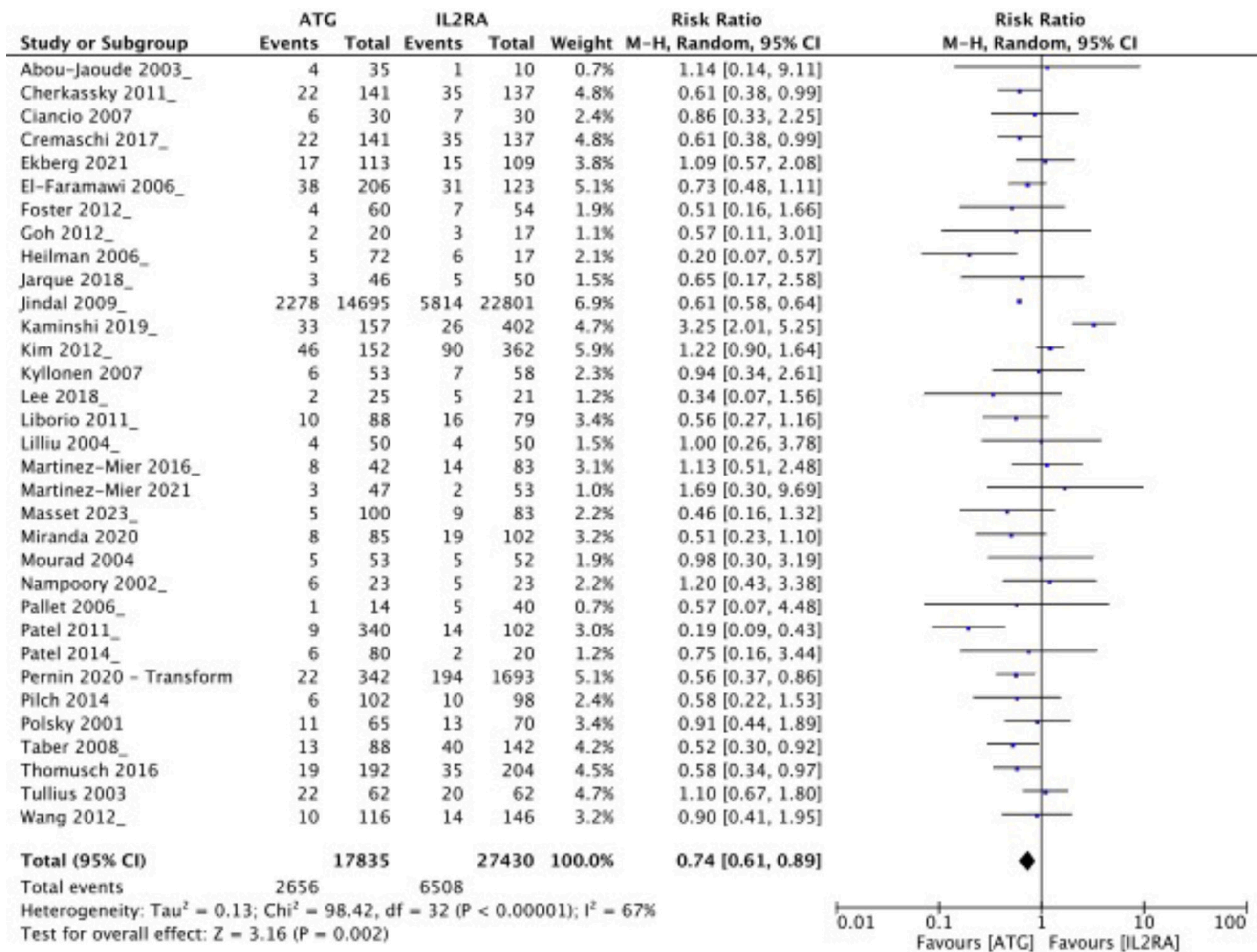
The definition of “high-risk” or “highly sensitized” varied widely among the available studies [84,85,88–94,144].

3.2.1. *ATG vs no induction*

No studies

3.2.2. *ATG vs IL2RA [82–94]*

In the 13 included studies to compare ATG vs IL2RA in high-risk of rejection KTR, the definition of highly sensitized cases was not homogeneous, considering mainly patients with HLA antibodies identified with classical tools (cytotoxic panel reactive antibodies [PRA] >30 or 50%) and/or those receiving retransplants. ATG reduced BPAR at 2 years (RR 0.55, 95%CI 0.43–0.72, $p < 0.001$) (Fig. 5). Two studies prolonged follow-up and confirmed this lower risk at 3 to 8 years compared to IL2RA (RR 0.44, 95%CI 0.27–0.72, $p = 0.001$). The type of



Study or Subgroup	ATG Events	ATG Total	IL2RA Events	IL2RA Total	Weight	Risk Ratio M-H, Random, 95% CI
Abou-Jaoude 2003_	4	35	1	10	0.7%	1.14 [0.14, 9.11]
Cherkassky 2011_	22	141	35	137	4.8%	0.61 [0.38, 0.99]
Ciancio 2007	6	30	7	30	2.4%	0.86 [0.33, 2.25]
Cremaschi 2017_	22	141	35	137	4.8%	0.61 [0.38, 0.99]
Ekberg 2021	17	113	15	109	3.8%	1.09 [0.57, 2.08]
El-Faramawi 2006_	38	206	31	123	5.1%	0.73 [0.48, 1.11]
Foster 2012_	4	60	7	54	1.9%	0.51 [0.16, 1.66]
Goh 2012_	2	20	3	17	1.1%	0.57 [0.11, 3.01]
Heilman 2006_	5	72	6	17	2.1%	0.20 [0.07, 0.57]
Jarque 2018_	3	46	5	50	1.5%	0.65 [0.17, 2.58]
Jindal 2009_	2278	14695	5814	22801	6.9%	0.61 [0.58, 0.64]
Kaminshi 2019_	33	157	26	402	4.7%	3.25 [2.01, 5.25]
Kim 2012_	46	152	90	362	5.9%	1.22 [0.90, 1.64]
Kyllonen 2007	6	53	7	58	2.3%	0.94 [0.34, 2.61]
Lee 2018_	2	25	5	21	1.2%	0.34 [0.07, 1.56]
Liborio 2011_	10	88	16	79	3.4%	0.56 [0.27, 1.16]
Lilliu 2004_	4	50	4	50	1.5%	1.00 [0.26, 3.78]
Martinez-Mier 2016_	8	42	14	83	3.1%	1.13 [0.51, 2.48]
Martinez-Mier 2021	3	47	2	53	1.0%	1.69 [0.30, 9.69]
Masset 2023_	5	100	9	83	2.2%	0.46 [0.16, 1.32]
Miranda 2020	8	85	19	102	3.2%	0.51 [0.23, 1.10]
Mourad 2004	5	53	5	52	1.9%	0.98 [0.30, 3.19]
Nampoory 2002_	6	23	5	23	2.2%	1.20 [0.43, 3.38]
Pallet 2006_	1	14	5	40	0.7%	0.57 [0.07, 4.48]
Patel 2011_	9	340	14	102	3.0%	0.19 [0.09, 0.43]
Patel 2014_	6	80	2	20	1.2%	0.75 [0.16, 3.44]
Pernin 2020 - Transform	22	342	194	1693	5.1%	0.56 [0.37, 0.86]
Pilch 2014	6	102	10	98	2.4%	0.58 [0.22, 1.53]
Polsky 2001	11	65	13	70	3.4%	0.91 [0.44, 1.89]
Taber 2008_	13	88	40	142	4.2%	0.52 [0.30, 0.92]
Thomusch 2016	19	192	35	204	4.5%	0.58 [0.34, 0.97]
Tullius 2003	22	62	20	62	4.7%	1.10 [0.67, 1.80]
Wang 2012_	10	116	14	146	3.2%	0.90 [0.41, 1.95]
Total (95% CI)		**17835**		**27430**	**100.0%**	**0.74 [0.61, 0.89]**
Total events	2656		6508			

Heterogeneity: Tau² = 0.13; Chi² = 98.42, df = 32 (P < 0.00001); I² = 67%
Test for overall effect: Z = 3.16 (P = 0.002)

Fig. 2. Biopsy proven acute rejection (BPAR) for antithymocyte globulin (ATG) compared to anti-IL-2 receptor antibodies (IL2RA) at ≤2 years in studies including standard-risk kidney transplant recipients.

induction showed no effect on the DGF rate (RR 0.93, 95%CI 0.65–1.32, $p = 0.67$). The study by Brennan et al [83] comparing ATG vs IL2RA in "high-risk of rejection and DGF", high-risk rejection was defined as deceased donor, prolonged ischemia time or low HLA compatibility; mean PRA was 6% in included patients. Consequently, this RCT was assessed within the "High-risk DGF" subanalyses. In this trial, the unique one assessing DGF duration [83] showed a shorter duration with ATG. GLCD, mortality, infections, and malignancies were similar with ATG and IL2RA.

3.2.3. *ATG vs alemtuzumab [95–100]*

No significant differences were noted.

3.2.4. *Different ATG preparations [101]*

No significant differences were noted when comparing thymoglobulin vs ATG-F. The comparison between rATG vs hATG has not been performed in high-risk of rejection patients.

3.2.5. *ATG at two different doses or posologies [86,102–104]*

In the 3 studies comparing two different dosages in high-risk of rejection recipients, no significant differences were noticed in BPAR, GLCD, mortality, or infections. No study compared different posologies in this setting.

3.3. *High-risk of DGF*

The high risk of DGF included different populations depending on the study. The most usual definition was kidney transplants using a donor after brain death with a cold ischemia time ≥ 18 h or donors after circulatory death.

3.3.1. *ATG vs no induction [105,106]*

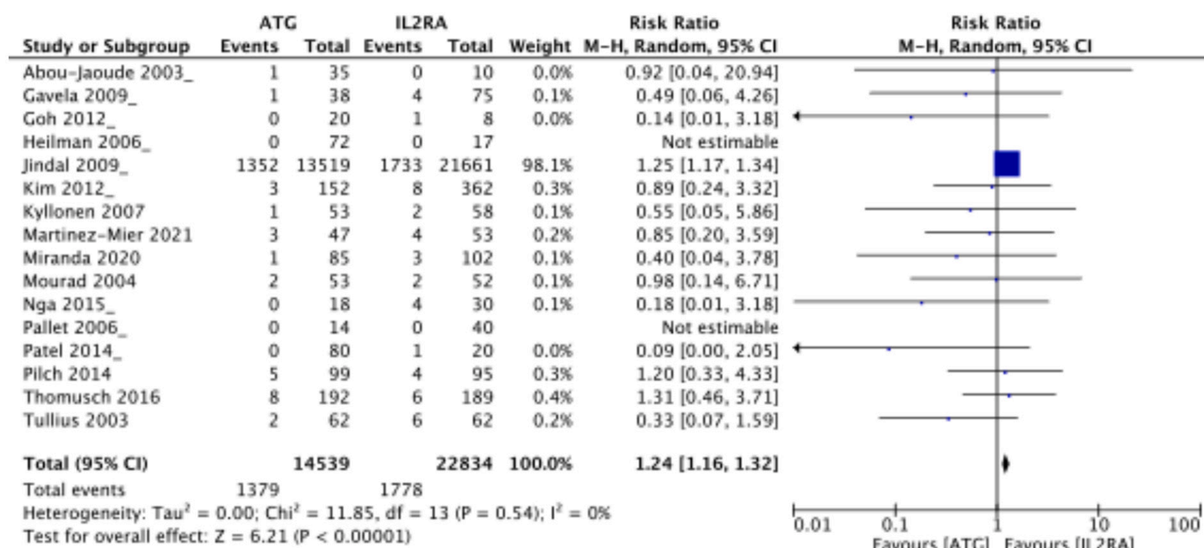
Comparison of induction with lymphocyte-depleting polyclonal antibodies versus no induction included only one small, randomized study with a single dose of ATG-F [105] and a retrospective study with thymoglobulin [106]. No significant differences in DGF rate and duration were observed. More frequent CMV infections were observed with induction (RR 3.00, 95%CI 1.58–5.69, $p < 0.001$), without differences in renal function, GLCD, or mortality.

3.3.2. *ATG vs IL2RA [83,107–113]*

The studies on high-risk DGF KTR are scarce, and the definition of the population in them was heterogeneous. Incidence of DGF was not different between IL2RA vs ATG, with a high heterogeneity (8 studies, RR 0.95, 95%CI 0.69–1.29, $p = 0.74$, I^2:61%). No differences were found in terms of BPAR, GLCD, mortality or graft function. We did not find differences between overall or viral infections, although a trend of higher bacterial infection risk was found with ATG (RR 1.23, 95%CI 1–1.51, $p = 0.05$).

3.3.3. *ATG vs alemtuzumab [114]*

Only one study did this comparison [114], and no significant differences were noted.



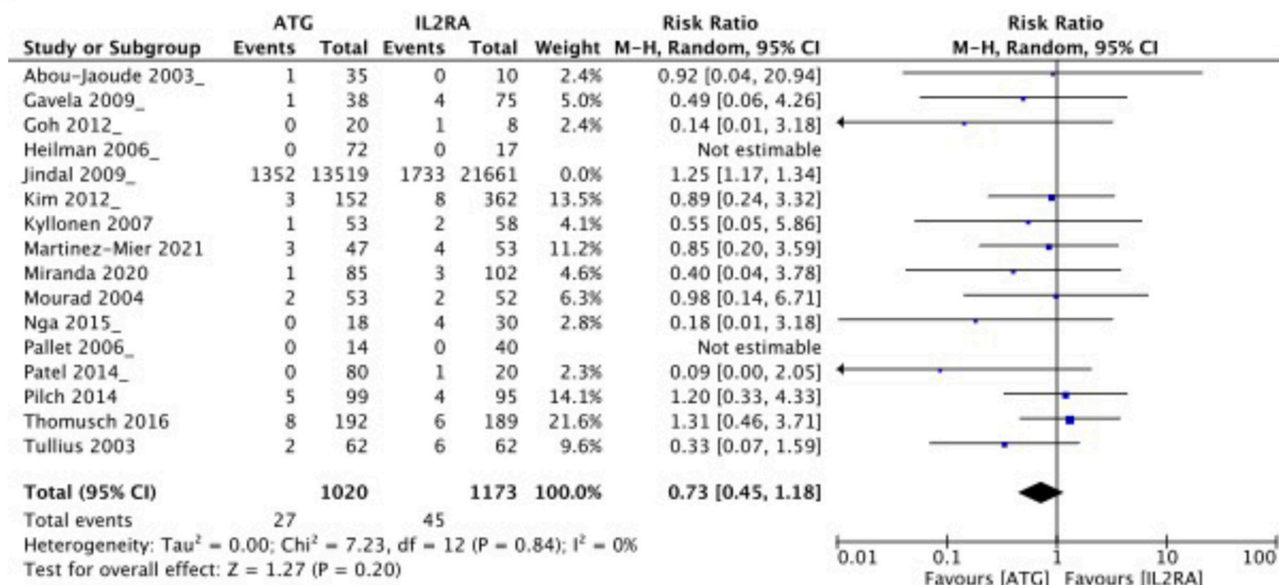


Fig. 3. Death-censored graft loss for antithymocyte globulin (ATG) compared to anti-IL-2 receptor antibodies (IL2RA) at ≤1 year in studies including standard-risk kidney transplant recipients.
a). All
b). Excluding Jindal et al.

3.3.4. *Different ATG preparations [107,115]*

Only two observational studies compared the efficacy of thymoglobulin and ATG-F in recipients with high DGF risk. A trend towards a lower incidence of DGF in the thymoglobulin group was found (RR 0.89, 95%CI 0.67–1.19, p = 0.44). Only one observational study [107] reported the duration of DGF, showing a shorter DGF with thymoglobulin (SMD -0.66 days, 95%CI -0.94 - -0.37, p < 0.001). No studies compared rabbit vs horse ATG in this setting.

3.3.5. *ATG at two different doses or posologies [116,117]*

No significant differences were noted when two different doses were compared in high risk DGF patients. No study compared different posologies in this setting.

3.4. *Living donor*

3.4.1. *ATG vs no induction [118]*

Only one study evaluated this comparison [118], and no significant differences were noted.

3.4.2. *ATG vs IL2RA [119–124]*

Of the 8 studies in living donor KT, most compared rATG vs IL2RA, but the outcomes assessed were variable among the studies. BPAR showed a trend to lower rates with ATG (RR 0.61, 95%CI 0.29–1.28, p = 0.19). No significant difference was observed in GLCD at any time point. Data on DGF, KT function, de novo DSA, and BK nephropathy were scarce and did not show differences between groups. ATG increased all-cause infections in a single study (RR 1.63, 95%CI 1.12–2.38, p = 0.01) [124].

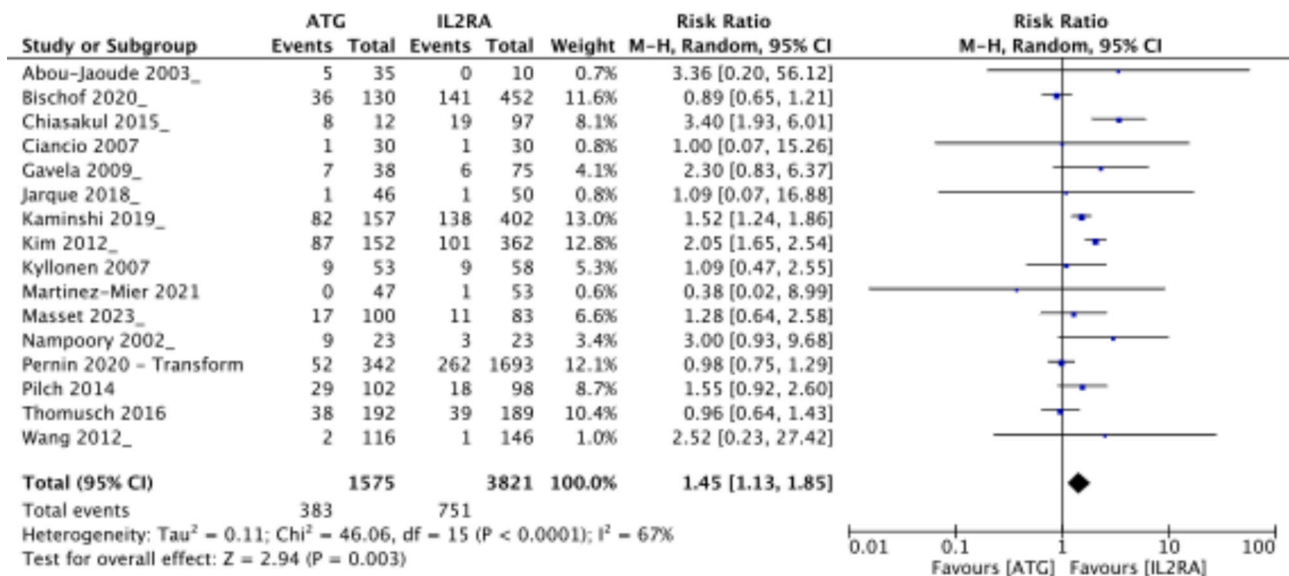
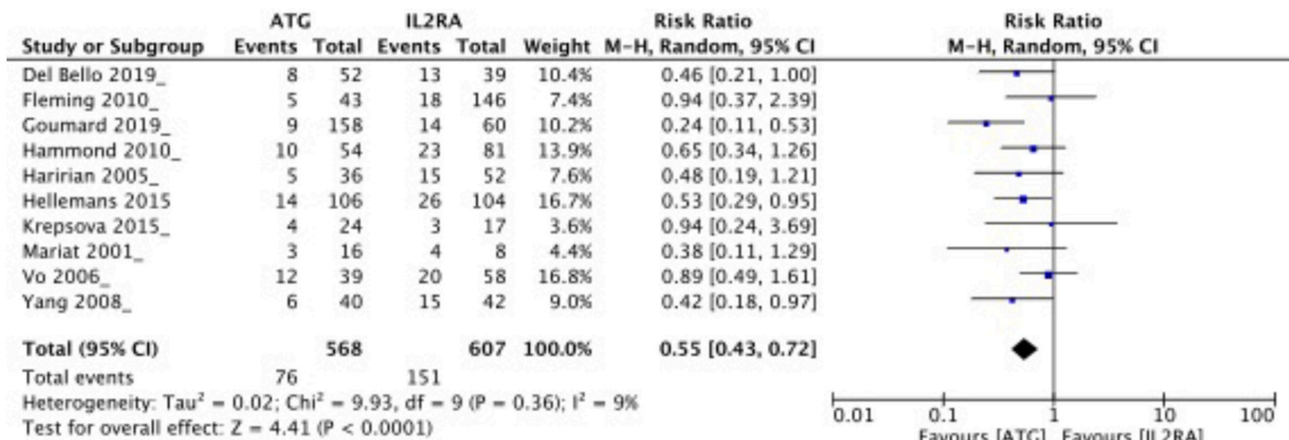


Fig. 4. Citomegalovirus infection for antithymocyte globulin (ATG) compared to anti-IL-2 receptor antibodies (IL2RA) at ≤2 years in studies including standard-risk kidney transplant recipients.



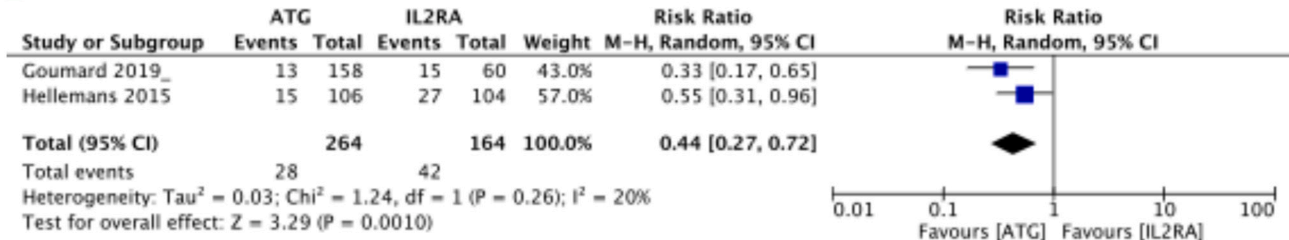


Fig. 5. Biopsy-proven acute rejection comparing antithymocyte globulin and anti-IL-2 receptor antibodies in studies including patients at high risk of acute rejection.
a) BPAR at ≤2 years
b) BPAR at 3–8 years

3.4.3. ATG vs alemtuzumab [125]

Only one study evaluated this comparison [125], and no significant differences were noted.

3.5. Elderly recipients

3.5.1. ATG vs no induction

No studies.

3.5.2. ATG vs IL2RA [126–128]

Few studies compared induction therapies in elderly recipients.

Comparing ATG versus IL2RA no differences were observed regarding BPAR, de novo DSA, DGF, mortality, malignancy, and all-type infections. One study suggested that bacterial and CMV infection may be lower in old patients receiving IL2RA [126]. Another single study described that PTDM was lower using ATG rather than ILRA (RR 1.48, 95%CI 1.07–2.04, $p = 0.02$) [127].

4. Discussion

Multiple studies including several systematic reviews and/or meta-analyses have tried to determine the role of ATG as induction immunosuppression in KT, but its influence on the overall KT results is unknown [2,129–140]. These reviews have analysed diverse transplant outcomes such as BPAR or graft loss by comparing different interventions in standard or specific subgroups of KTR [2,25–36]. Specifically, it is not known which groups of patients would benefit most from ATG induction, what is the optimal regimen, or how to monitor it to optimize the response and limit its toxicity. This lack of knowledge leads to a great discrepancy in the use of ATG in different centers and geographical areas [4,141–143]. We focused our study on specific subgroups of KTR to help clinicians to decide the best induction therapy for a donor-recipient pair. Besides, because of the limited data available for most subgroups and different results in previous meta-analyses [2,25–36], we selected both RCTs and observational cohort studies.

4.1. Standard risk KT

Use of ATG versus no induction for standard-risk KTR reduced BPAR and GLCD during the first year. It did not change mortality, infection, or DGF rate. The number of studies and patients included in the meta-analysis were too low to draw definitive conclusions. Comparing ATG vs IL2RA, mortality, GLCD, DGF rate, renal function, malignancy, 1-year overall infection rate, and polyomavirus infection were not significantly different. By contrast, ATG was related with a higher risk of CMV infection during the first 2 years.

Without differentiating any specific subgroup of patients, Webster [2] reported a reduction in BPAR at 1 year with ATG compared to IL2RA, similar GLCD and mortality rates, and higher malignancy and CMV rates, and did not analyze DGF length or rate [2]. A smaller metanalysis, including six RCT in standard-risk KTR did not find differences in acute rejection, graft survival, patient survival, or malignancy and only a trend to lower CMV with IL2RA [135]. Hence, our results confirm that the use of lymphocyte-depleting antibodies reduces acute rejection but increases the risk of CMV infection in standard-risk KTR. Consequently, more studies are needed to elucidate which agent is more appropriate in this setting. The use of lymphocyte-depleting antibodies in standard-risk patients may be recommended when prescribing special immunosuppressive regimens, such as steroid withdrawal or CNI minimization.

Regarding ATG dose, the lack of significant differences in the main outcomes comparing high vs. low doses suggests that using high ATG doses does not add substantial benefits for this subgroup of KTR. A previous meta-analysis including studies of standard and high immunological risk KTR reported that ATG doses $\leq$4.5 mg/kg were as effective as higher doses concerning primary allograft outcomes while allowing minimizing adverse effects [138]. The results of our study suggest that it is not necessary to reach a dose of 6 mg/kg in standard-risk patients, and that lower doses could be adequate. The study by Masset et al [29] in standard risk KTR is of particular interest, as the use of low-dose ATG (mean total 2 mg/kg) may be associated with some advantages (a trend to decreased BPAR and lower diabetes risk) compared with the use of basiliximab.

4.2. High risk of rejection

The definition of "high-risk" or "highly sensitized" varied widely among the available studies [84,85,88–94,144]. The study by Brennan et al [83] comparing ATG vs IL2RA in "high-risk of rejection and DGF", was assessed within the "High-risk DGF" subanalyses and showed a higher rejection with ATG vs IL2RA, without differences in DGF.

Highly sensitized KT recipients are preferentially treated with lymphocyte-depleting agents [1] although controversial results among previous studies preclude reaching a definitive consensus about the best induction therapy in these patients. A previous meta-analysis including only three studies in tacrolimus-treated patients showed a higher risk of rejection in the high-risk group treated with IL2RA compared with ATG [135]. Stratified meta-analysis carried out by Webster et al. in high risk of acute rejection KTR [2] showed no differences in graft loss, death, acute rejection, or malignancy rates comparing ATG versus IL2RA, but a higher risk of CMV disease with ATG. Of interest, we found that the group of hypersensitized patients treated with ATG versus IL2RA developed a significantly lower rate of BPAR at different time-points. Being the mean rejection rate in IL2RA group 25%, a decrease of almost half is relevant to consider that induction with ATG is better than with IL2RA in patients with high rejection risk. This benefit did not lead to long-term improvements in GLCD, but neither in increasing CMV infection, malignancy and PTLD rates, probably due to the low number of included studies. The high number of patients included in these studies to analyze the outcome "BPAR below 2 years" and their low heterogeneity support strongly our recommendation to use ATG instead of IL2RA in this group of patients, despite the uncertainty about a benefit on long term GLCD. On the other hand, the absence of differences in transplant outcomes in hypersensitized patients when comparing ATG versus alemtuzumab precludes making a favorable recommendation for either of them. Similarly, neither individual nor pooled data from three studies comparing high versus low ATG doses in high rejection risk recipients have shown significant differences in BPAR, GLCD, mortality, or infections. Consequently, it is not necessary to reach cumulative ATG induction doses above 7 mg/kg to obtain an adequate benefit-risk balance in high-risk of rejection recipients.

4.3. High risk of DGF

ATG can help to reduce kidney graft damage by inhibiting leukocyte migration and adhesion. In fact, thymoglobulin reduces DGF when used before reperfusion [145]. Besides, ATG allows a delayed introduction of CNI after transplantation while protecting against the risk of acute rejection [146]. Due to the increasing use of cardiac-death and/or old donors, currently the risk for DGF is higher than in the previous decades. Induction can help both to reduce the DGF rate and to protect from acute rejection in high-risk patients. In fact, in a large registry study, ATG or alemtuzumab were better than no antibody induction or IL2-RA to reduce 1-year acute rejection or graft failure [147].

In the landmark trial by Brennan et al [83], BPAR rate was significantly lower with ATG than with IL2RA, however, DGF rate was similar. Our data do not support the use of any specific type of induction to decreased DGF rates in KTR.

4.4. Living donor

Regarding living donor KT, ATG (versus IL2RA) treated patients showed a better non-significant rate of BPAR <2 years. We found no differences in the rest of the transplant outcomes comparing ATG. The finding of a 63% higher global infection rate at 1 year in those who received ATG was based on only one study [124]. The only study analyzing the use of ATG versus IL2RA in ABO incompatible KT reported a lower rate of acute rejection with ATG, but with similar patient and graft survivals, renal function, and complications [89]. Hence, in non-hypersensitized living donor KT recipients, we cannot suggest that any induction type is better than another.

4.5. Elderly recipients

Older transplant recipients are often frail and prone to suffer more infections and mortality and less acute rejection, but with a higher risk of transplant loss after rejection compared with younger patients [56,148–151]. The use of depleting agents as induction in elderly recipients is controversial because they can increase the risk of infection and mortality, but also can help to minimize immunosuppressive drugs, and reduce PTDM risk [126,127]. Our analyses do not show meaningful differences in main outcomes using different induction agents in these population. The lack of association of higher mortality with the use of rATG versus IL2RA has been previously reported in a large registry study [149]. We cannot conclude the best induction type to use in elderly recipients.

4.6. Limitations

Our study has some flaws inherent to all meta-analyses performed in KT that limit its applicability. Publication bias may make more studies with positive results available. Duration and dose of antibody treatment were often not available in included studies. Maintenance immunosuppressive therapy was not probably the same in all the studies, with recipients not receiving CNI or steroids or with different types of CNI. Some outcomes took place at various time points but were pooled between time ranges. Outcomes such as BPAR were robust and usually included in more studies than outcomes that need longer follow-up, mainly GLCD, malignancy, and mortality in which the number of studies was smaller, and the conclusions harder to establish. In addition, there are no consensus definitions for some subgroups such as hypersensitized or DGF risk and these definitions were variable among included studies.

4.7. Strengths

We explored through a meta-analysis for the first time the role of induction in specific groups of patients to draw useful conclusions to prescribe the best induction for each KTR in real life. To increase the number of patients in each subgroup, we included not only RCTs but also observational cohort studies. The review was conducted following Cochrane methodology and the results were consistent with those previously published [2,152]. Most RCTs showed at least a moderate risk of bias.

5. Conclusions

Even though numerous studies have been carried out on induction in KTR, there are no evidence-based conclusions that allow us to recommend the best induction regimen for each group of KTR.

Compared with IL2RA, ATG reduced BPAR in all subgroups. This benefit did not reduce GLCD, but showed a tendency to an increased risk of infections, specifically CMV. No differences were found comparing other induction strategies.

More studies are needed to demonstrate beneficial effects in other KTR subgroups and overall patient and graft survival.

Authors statement

NM and JP participated in research design, performance of research, data analyses and writing the paper.

ER, MC, JMC, AGD, AM and AS, participated in performance of research, data analyses and wrote some parts of the manuscript.

EC, PM, LO, ES and FG participated in data retrieval and analyses.

All authors approved the final version of the article.

Disclosures

NM, ER, MC, JMC, AGD, AM, AS, and JP received honoraria from SANOFI for carrying out the project, and NM, MC, AGD and JP for giving scientific presentations.

ER has received honoraria and speaker fees from Chiesi and Astellas.

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JMC has received honoraria and speaker fees from Chiesi, Vifor, AstraZeneca, Merck Sharp & Dohme and Palex.

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AM has received honoraria and speaker fees from AstraZeneca, Chiesi, GSK and Novartis.

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Declaration of Competing Interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.trre.2023.100795.

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