











# Current Induction Therapy Strategies and Anti-T Lymphocyte Globulin Usage in Kidney Transplantation: Consensus-Based Recommendations by a Turkish Expert Panel

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## ABSTRACT

This advisory committee convened to review national and global kidney transplantation dynamics and provide recommendations on the use of anti-T lymphocyte globulin (ATLG) for prevention and treatment of rejection after allogeneic kidney transplantation. A critical evaluation of 6 relevant articles released up to October 2022 was performed to reveal their importance in clinical practice. Additionally, 27 key questions on the indication, dosage of ATLG, and risk stratification were used for the Delphi technique with 8 members of the Turkish Society of Nephrology including 5 kidney transplantation (KTx) subcommittee members and a surgeon experienced in solid organ transplantation. The committee declared that Türkiye had great potential in KTx; however, increase in transplantation would be possible in the case of raise in the deceased donor transplantation. As a consensus, ATLG was strongly recommended for induction and rejection treatment. Also, committee members recommended the safe dosage range in steroid resistant acute rejection as 2.5-3 mg/kg daily for 5-7 days, and the median of preferred dosage in induction sounded as 2-2.5 mg/kg daily for 3 days in intermediate risk state. Additionally, post-transplant infection and malignancy cases due to immunosuppression were much rarely encountered than they were in the past.

**Keywords:** Anti-T-lymphocyte globulin, induction therapy, renal transplantation

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## INTRODUCTION

Chronic kidney disease is a major public health problem with increasing economic burden from year to year due to aging population with more prevalent comorbidities such diabetes and hypertension.<sup>1</sup> Consequently, kidney

transplantation (KTx) has an increasing trend as treatment option with higher cost-effectivity.<sup>1,2</sup>

Besides the several limiting factors for donor availability, problems in economic sustainability and



standardization of immunosuppressive medication hinders expected increase in KTx.

Herein, the committee aimed to provide recommendation for overcoming existing obstacles in KTx at national level and to state a consensus on dosage specific to ATLG and risk assessment for immunosuppressive medication.

#### METHOD FOR CONSENSUS STATEMENT

Eight members of Turkish Society of Nephrology and a surgeon experienced in solid organ transplantation were appointed for advisory board assembly. Physicians who had organ transplantation experience and actively performed organ transplantation from different regions of Türkiye were selected. All experts in the KTx subcommittee of the Turkish Society of Nephrology were included in the group. The total number of transplants performed by physicians whose expert opinion is consulted reflects approximately 25% of the transplants performed in Türkiye. Before assembly, a questionnaire including 27 relevant questions on the KTx practice were answered by board members as their identities remained confidential to build consensus using Delphi technique. Four chairpersons summarized individual preferences for stating consensus and drafted statements on selected issues were confirmed by board members individually. Assembly was performed in 3 separate sessions on the same day. Current KTx dynamics and practical importance of 6 relevant articles on the comparison of induction therapies in KTx released up to October 2022 were discussed by committee members at first. In following session, risk stratification and trends in KTx practice in Türkiye were discussed. Finally, suggestions to overcome barriers to growth of KTx and on ATLG's strengths and aspects that need improvements were stated individually.

#### KIDNEY TRANSPLANTATION PRACTICE

Organ transplantation is an increasing trend all around the world. Transplantation number increase was 5-fold higher than world population growth in last 5 years (27.8% vs. 5.4%). Fifty-five% of KTx came from deceased donors (DD), slight increase on favor of living donor (LD) transplantation.<sup>3</sup>

The United States has the biggest proportion of KTx worldwide. Türkiye is among top 20 countries regarding KTx rate and has similar KTx rate compared to European. Türkiye is the third and fifth top country in the world regarding for living donor and total KTx numbers.<sup>3</sup> Annual growth in KTx was observed 10.9% for LD and 9.1% for DD in 2022. Living donor transplantations were mostly performed for younger population.<sup>4</sup>

#### Comments and Suggestions

The committee's comments and suggestions on the current state of KTx practice is summarized here.

- Possible reasons for increasing trend in KTx can be increased life expectancy in cases with chronic disease, getting easier

access to health care and improvement in clinical and surgical expertise.

- Growth of transplantation rates would be only possible in the case of gaining increase in deceased donor (DD) rates.
- Recent legislative developments are promising for growth in paired kidney exchange transplantations but need for a robust-centralized infrastructure remains.
- In dialysis centers, patient should be informed properly and regularly about transplantation. Regulations such as being in the waiting list for accessing to dialysis therapy could be developed.
- Reimbursement and payment system should be rearranged to encourage health-care professionals and institutions for transplantation. For instance, medical staff involved in every step of deceased donor allocation, especially intensive care department, need to be rewarded in the reimbursement system.
- Seeking family approval for deceased donation is a major hurdle to growth of donation rates. Legal and ethical revision of current code is mandatory to make improvement in current situation.

#### ANTI-T LYMPHOCYTE GLOBULIN AS THE IMMUNOSUPPRESSION INDUCTION AGENT IN KIDNEY TRANSPLANTATION

Rabbit anti-thymocyte globulins are polyclonal T-lymphocyte-depleting agents with potent immunosuppressive effects and are widely used to prevent and treat rejections in kidney transplantation.<sup>5</sup> One of the 2 formulations, anti-T-lymphocytes globulin (ATLG) is a highly purified rabbit polyclonal anti-human T-lymphocyte globulin produced by immunizing rabbits with Jurkat T-lymphoblast cell line, and by using human red blood cells for adsorption of cross-reacting anti-human antibodies.<sup>5-7</sup> The other formulation, anti-thymocyte globulin (ATG), is produced by immunizing rabbits with human thymocytes.<sup>7,8</sup> Anti-T-lymphocytes globulin (Grafalon®) differs from ATG (Thymoglobulin®) with substantial features such as selective targeting of activated T cells<sup>9</sup> and displaying lower level of antigen-binding capacity.<sup>8</sup> Even though no evidence was observed in clinical efficacy with ATLG compared to ATG,<sup>10</sup> a significant improvement in safety profile emerges in favor of ATLG especially in decreasing rates in infection and malignancy.<sup>11,12</sup>

#### Comparison of Efficacy and Safety of Immunosuppressive Medications

In 3 studies, single bolus dose (9 mg/kg) of ATLG was assessed for its efficacy on onset of graft function and long-term consequences (Table 1). Kyllönen et al<sup>13</sup> showed that ATLG reduced delayed graft function compared to basiliximab and triple drug therapy (6% vs. 24% and 16%, respectively,  $P < .025$ ). Moreover, Samsel et al<sup>14</sup> and Yang et al<sup>15</sup> found significant reduction in acute rejection rate in ATLG treated patients compared to rates observed in patients treated by triple drug therapy and basiliximab, respectively. Opelz et al<sup>12</sup> studied long-term safety of

**Table 1.** Evidence on Efficacy and Safety of Single High-Dose Anti-T-Lymphocyte Globulin

Study	Design and Objective		Population	Endpoints
Kyllönen et al, 2007	Prospective Single high-dose ATLG vs. Basiliximab induction in Ktx with CsA, TDT	ATLG 9 mg/kg (d0) + low initial CsA (5 mg/kg) Basiliximab 20 mg (d0 + d4) + low initial CsA 5 mg/kg TDT: conventional initial CsA 10 mg/kg Follow-up: 1 year	n = 155 ATLG (n = 53) Basiliximab (n = 58) TDT (n = 44)	Delayed graft function ATLG: 5.7% Basiliximab: 24.1% TDT: 15.9% <i>P</i> < .025 Need for dialysis (days) ATLG: 0.53 Basiliximab: 2.40 TDT: 3.02 <i>P</i> < .05
Samsel et al, 2008	Prospective Randomized Open phase III Assessing the safety and efficacy of single high-dose ATLG	ATLG 9 mg/kg + CsA/MMF/steroids TDT: CsA/MMF/steroids Switch MMF to AZA after month 4 in both groups Follow-up: 5 years	Immunological normal risk patients with DD KTx ATLG (n = 40) TDT (n = 39)	Acute rejection ATLG: 22.5% TDT: 35.9% <i>P</i> ≥ .05 Steroid-resistant rejection ATLG: 10% TDT: 20.5%
Yang et al, 2008	Retrospective Assessing the safety and efficacy of single high-dose ATLG vs basiliximab	ATLG 9 mg/kg preoperatively Basiliximab: 2 × 20 mg (D0, D4) Both plus TDT: Tacrolimus/MMF/steroids Follow-up: 12 months post-tx	Presensitized kidney allograft recipients ATLG (n = 40) Basiliximab (n = 42)	Acute rejection ATLG: 15% Basiliximab: 35.7% <i>P</i> < .032

ATLG, anti-T-lymphocyte globulin; AZA, azathioprine; CsA, cyclosporine A; DD, deceased donor; MMF, mycophenolate mofetil; TDT, triple drug therapy; tx, transplantation.

different agents for induction therapy and reported that treatment with interleukin-2 receptor antagonists (IL-2Ras) or ATLG was not associated with increased lymphoma risk.<sup>12</sup>

### Comments and Suggestions

Committee members shared their own clinical experiences about cytomegalovirus (CMV) infection and malignancy incidence. Although having no available data on the incidence of both conditions, an obvious decrease in incidence was reported by all members according to their years long practice. In assembly, this decline observed in conditions was attributed to some of the concomitant reasons besides to role of ATLG using for immunosuppression management.

### CMV INFECTION

- Optimization of ATLG dose in recent years is an important factor for declining CMV infection rates.
- Scientific improvements in CMV management and universal prophylaxis with valganciclovir could result in lower incidence of CMV infection.
- Also, it has been shared as individual opinion that valganciclovir resistance could be not so common in high doses and letermovir use may be required if donor positive/recipient negative CMV infection rate increases in near future.

### MALIGNANCIES

- An apparent decrease in lymphoma incidence among recipients was observed in last 2 decades despite increased ATLG usage. Decrease in both induction dosage and treatment duration may have a role in lesser incidence of lymphoma

in KT patients. But many factors may be contributed to this result.

- Lower induction doses and restricted lymphocyte-depleting treatment duration in delayed graft function and rejection may have a role in this decreased lymphoma incidence. Moreover, improvements in the immunosuppressive maintenance therapy may have more important impact on this decreasing incidence.
- Selective binding affinity of ATLG to CD21+ lymphocytes<sup>11</sup> may be claimed a reason for decreasing incidence of EBV-related lymphoma.
- Relative shorter graft survival compared to than that in the past due to increased rate of human leukocyte antigen (HLA) mismatch transplants may have a contribution to reduction in lymphoma incidence.
- As referred to individual clinical experience, it has been stated by a participant that lower doses of immunosuppressive agents may have greater causal effect on decrease in lymphoma incidence in elderly population especially older than 65 years.

### DOSAGE OF ANTI-T LYMPHOCYTE IMMUNOGLOBULIN

#### Immunosuppression Induction

Immunosuppression induction intended to improve the efficacy of immunosuppressive treatment by depleting or modulating T-cell responses at the moment of antigen presentation. A lymphocyte-depleting agent or an IL2-RA can be used as induction agent and be administered before, at the time of or immediately after transplantation.<sup>16</sup>

Setting IL2-RAs in priority for cases with lower and standard immunological risk by guidelines (e.g., KDIGO 2009) should be revised regarding recent data on preference rate in clinical practice and absolute risk reduction provided by lymphocyte depleting agents<sup>17</sup> and raising evidence on the lack of improvement in acute rejection rates provided by IL2-RA treatment compared to tacrolimus<sup>18</sup> and cyclosporin A-based regimens<sup>19</sup> even in standard risk patients.<sup>18</sup>

Despite the fact that ATGs have been widely used for KTx daily practice successfully,<sup>20</sup> optimal dosage of ATLG remains uncertain despite its widely use in kidney transplantation. The committee emphasized clinical and laboratory conditions should be considered in dosing of ATLG as induction agent (Table 2). Officially recommended posology for preventing acute rejection in solid organ transplantation sounds in range as 2-5 mg/kg daily for 5-14 days depending on the conditions.<sup>21</sup> Turkish Society of Nephrology recommends much lower doses in the range of 1-2 mg/kg daily for 3-4 days in their former published clinical practice guide.<sup>22</sup> Also, lower dosing regimens were reported in recent studies. For instance, Gupta et al<sup>23</sup> observed the efficacy and safety of ATLG delivered within cumulative dose of 5.8 ± 1.95 mg/kg. Similarly, Yilmaz et al<sup>24</sup> reported the cumulative dose range used in living-donor KTx as 5.1 ± 2.7 mg/kg and in deceased-donor KTx as dose range in deceased-donor KTx as 10.6 ± 3.8 mg/kg<sup>25</sup> in their 2 separate studies.

**Comments and Suggestions**

The committee members highlighted additional reasons for such an update in guidelines:

- Demand for safety and growing rate of mismatch transplantations should be considered before such an update.
- Change in actual costs of ATLG and IL2-RA, and difficulties in financial sustainability of IL2-RA due to national

reimbursement policy makes the claim of cost-effectiveness as rationale for prioritizing IL2-RA controversial.

Due to lack of exact limitation confirmed by studies and guidelines, the treatment duration varies according to the individual preference of physicians. In this respect, dosage was discussed in assembly and agreed on cumulative dose delivered within 3-5 days as 4.5 mg/kg for low risk, 7.0-7.5 mg/kg for intermediate risk, and 10.0-10.5 mg/kg for high risk. Additionally, dosage preferred in daily practice was reported by participants in questionnaire. Also, committee members emphasized that clinical and laboratory conditions should be considered in determining exact dosage regimen (Table 2).

Turkish Society of Nephrology’s dose recommendation in 2016 for ATLG (1 mg/kg at 0 and 1 days) in low immunological risk transplantation was considered too low by committee members with respect to their common daily practice.

Single bolus dose induction regimen was not recommended as an alternative option to delivery of total doses in divided doses. Additionally, it is noted that a single 9 mg/kg dose may not be harmful but offers no advantage against divided doses.

Monitoring serum leucocyte, platelet, lymphocyte, and CD3 for dosage adjustment after initiating immunosuppressive induction was discussed as another issue, and committee’s point of view was summarized as below.

- Dosage adjustment under CD3 monitorization is not recommended in living donor transplants and lymphocyte count could be sufficient in these cases. Dosage as 3 mg/kg within 4-5 days could be effective in almost all cases.
- CD3 monitorization is necessary in deceased donor transplants and in refractory rejections in living donor transplants.
- It should be considered that the proper monitorization parameter might change in conditions such LD/DD transplant, induction/rejection treatment and early/late rejection.

If serious lymphocyte depletion occurs during longer ATLG treatment alternative options such as skipping an ATLG daily dose or switching to corticosteroids may be considered.

Giving first dose of ATLG before declamping is an absolute necessity. Different timing of ATLG administration such 1 day before transplant operation might be an alternative, on the other hand earlier administrations of ATLG wasn’t recommended.

Induction therapy in the elderly should be carefully considered due to impaired immune response in these patients. Using lower doses of ATLG than recommendations might decrease immunosuppressive-related complications in the elderly patients.

**Table 2.** Committee’s Recommendations on Immunosuppression Induction

Clinical and Laboratory conditions to be considered in dosing induction agent. Immunologic risk state DSA positivity PRA positivity Retransplantation Younger recipient age and/or older donor age Possible adverse/side effect profile Hematologic parameters, e.g., leukocyte and platelet count Deceased donor with cold ischemia time >24 hours Cases for whom induction may be avoided. Transplantation between identical twins HLA match ratio >3/6, ideally full match with both PRA and DSA negativity
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DSA, deceased donor-specific antibody; PRA, panel reactive protein; SRAR, steroid-resistant acute rejection.

**ALLOGRAFT REJECTION**

As a consequence of alloimmune activation to non-self-antigens,<sup>16</sup> acute rejection emerges about 10%-20%<sup>26</sup> among kidney transplant patients in first year of transplant. Acute rejection is still a significant cause of graft loss despite of advances in immunosuppression therapy; however, the rate of grafts that fail during this period has declined in time.<sup>26</sup> Two types of rejection, namely, acute antibody- and T cell-mediated rejections, differ in treatment.<sup>22,27</sup>

In cellular rejection, treatment stands on high dose steroid and polyclonal anti-T lymphocyte antibodies. However, humoral rejection should be treated by plasmapheresis, intravenous immunoglobulin, and rituximab and bortezomib.<sup>16,22</sup>

**Comments and Suggestions**

The committee reached consensus on dosage of ATLG in rejection treatment. Committee members recommended to use ATLG in the dosage range of 2.5-3 mg/kg/day for 5-7 days. It is noted that treatment duration may be assigned as 3 or 10 days in appropriate conditions. Also, a committee member pointed out that the failure in rejection treatment within this dosage range indicates presence of a mixt rejection rather than a cellular one.”

Need for a biopsy before rejection treatment was advised by consensus and it is stated that “every rejection should be proven by biopsy in rare exceptions such inevitable hesitancy in histopathologic examination.”

In steroid resistant acute rejection, ATLG was recommended as first choice by all members. Steroid resistance is considered a lack of serum creatinine reversal within 14 days after starting steroid therapy.<sup>28</sup> However, definitions of steroid resistance vary widely<sup>29</sup> and average time delay in serum creatinine normalization before considering a steroid resistance was reported as 5 days. In assembly, Clinical features for considering steroid resistant acute rejection were listed as below.

- Unresponsiveness to pulse steroid treatment at 48th hour.
- Failure in decreasing creatinine clearance (CC) or sustained higher CC levels.
- Failure in clinical and/or laboratory normalization after 3 doses of pulse steroid within 3-5 days

**STEROID AVOIDANCE**

Steroid-sparing strategies to avoid harmful effects caused by long-term steroid use have been attempted in recent decades.<sup>30</sup> Although in last updated Cochrane review, no difference in safety and efficacy was concluded, in SAILOR study antihypertensive medication intensity was observed lower in steroid avoided cases.<sup>31</sup> In 5 years follow-up of Harmony study,<sup>32</sup> increased patient survival rate observed (89.4% in basiliximab with RSWD (rapid steroid withdrawal), 90.4% in ATG with RSWD

vs. 84.7% in cases with standard care,  $P = .064$ ). Also, in 5 years follow-up, incidence of bacterial infections requiring hospitalization reduced in ATG group ( $P = .004$ ).

Based on these data, steroid-free regimens may be efficient and safe in terms of survival, graft survival, and side effects related to steroid exposure.

**Comments and Suggestions**

Although the committee members were aware of these data, they stated some concerns and insights about the steroid-free regimen in terms of their clinical experience. In this context, 2 participants stated their considerations as “at lower doses (e.g., 5 mg/day methylprednisolone), risk of occurrence steroid induced cardiovascular event or diabetes mellitus might be much lower than risk of graft loss” and as “higher doses of calcineurin inhibitor usage was observed in steroid withdrawal studies.”

**IMMUNOLOGICAL RISK ASSESSMENT AND IMMUNOSUPPRESSION MANAGEMENT**

Risk stratification is essential for tailored a precision immunosuppression strategy to avoid long-term complications of immunosuppressive therapy without increasing the risk of rejection.<sup>33</sup> Despite the recent advances in in laboratory tools and understanding of histocompatibility<sup>34</sup> (STAR 2017), the criteria to define immunological risk level vary between centers.

**Comments and Suggestions**

To highlight individual preferences of committee members in such settings, issues predefined before assembly were asked as a questionnaire. Committee members’ estimations for their institutional practice (Tables 3 and 4) and their individual preferences for risk level assignments sounded as below.

- The committee members advised 2 alternatives to risk level classification as “low–intermediate–high (n = 8)” and “standard–high (n = 1)”. Committee members noticed that “population risk average tends to be higher than that being in the past.”

**Table 3.** Reported Statistics for Institutional Kidney Transplantation and Immunosuppressive Therapy Practice

	Low risk	Moderate Risk	High Risk
Kidney transplantation, n (%)	296 (33.11)	335 (37.47)	263 (29.42)
Agent preference within induction			
No induction, n (%)	164 (18.34)		
Basiliximab, n (%)	42 (4.70)	10 (1.12)	
ATLG, n (%)	90 (10.07)	325 (36.35)	263 (29.42)

DD, deceased donor; HLA, human leukocyte antigen; SRAR, steroid-resistant acute rejection.

**Table 4.** Reported Anti-T-Lymphocyte Globulin Dosage Range Used in Daily Practice from Questionnaire

In Induction	Overall	Low Risk	Moderate Risk	High Risk
Total dose, mg/kg, median (minimum–maximum)	6.75 (0.0-15.0)	3 (0.0-12.5)	7.5 (4.0-12.5)	10.0 (4.5-15.0)
Total dose, mg/kg, weighted mean ± SD	7.74 ± 2.65	4.57 ± 4.21	6.79 ± 1.98	10.00 ± 2.69
In SRAR treatment	Overall			
Total dose, mg/kg, median (minimum–maximum)	14.0 (6-56)			
Total dose, mg/kg, weighted mean ± SD	20.74 ± 13.14			

DD, deceased donor; HLA, human leukocyte antigen; SRAR, steroid-resistant acute rejection.

**Table 5.** Individual Preferences for Patient’s Immune Risk Assessment

Immunologic Risk Assessment								
Pretransplant Donor–Recipient Laboratory Evaluation								
Case	CDC Cross-match	Flow Cross-match	Single Antigen Bead	History of Sensitization	HLA Mismatch	Immunologic Risk Level		
						Low	Intermediate	High
1	DSA positive	DSA positive	DSA positive					+++
2	Negative	DSA positive	DSA positive					+++
3	Negative	Negative	DSA positive					+++
4	Negative	Negative	Negative	Pregnancy or prior transplant with repeat MM			++	+
5	Negative	Negative	Negative	cPRA with unknown repeat MM			++	+
6	Negative	Negative	Negative	Negative	High	+	++	
7	Negative	Negative	Negative	Negative	Low	++	+	
8	Negative	Negative	Negative	Negative	None (HLA identical)	++	+	

<sup>1</sup>Adapted from Sensitization in Transplantation: Assessment of Risk (STAR) 2017 Working Group Meeting Report<sup>34</sup>; + refers to 0–3/9 committee members agree; ++ refers to 4–6/9 committee members agree; +++ refers to 7–9/9 committee members agree. DSA, donor-specific antibody; HLA, human leukocyte antigen; MM, mismatch; PRA, panel reactive protein.

- Individual preferences for immunologic risk level assignment of cases with hypothetic laboratory profiles were summarized as above (Table 5). In this respect, it was noticed that “cases with DSA-negative/PRA-positive serology should be evaluated as being at intermediate risk level” and “even PRA negative cases may not be at low risk level.”
- Need for examining anti-HLA antibody positivity for cases with HLA full match was voted by 8 members. One of the participants stated additionally that “In case of PRA positivity, testing anti-HLA antibody positivity thought to be beneficial.”
- Attitude for using polyclonal or monoclonal antibodies as induction agent was identified as “polyclonal agents for all cases (n = 6)” and “monoclonal agents for cases qualified as having low risk with specific conditions (n = 3).”
- Impact of treatment cost on choosing the induction agent was ranked as “no (n = 3),” “low (n = 3),” “intermediate (n = 3),” “high (n = 0).”

**Limitations**

The main limitation of this study is that data presented in this study were based on participant’s estimations of their individual

practice. Academic cover was restricted to the predefined issues and consensus statement based on the participants’ answers to questionnaire and shared opinions in assembly. Data presented and opinions shared by participant herein do not officially reflect the scope and content of their institutional health care policy.

**CONCLUSION**

As one of the widely used medications for the induction and treatment of rejection in Türkiye, ATLG (Grafalon®) is the backbone of the kidney transplantation practice. It has been widely used for decades, considering its efficacy and safety concerns. Keeping in mind the increasing rate of high mismatch/risk transplantations, policies getting easier for the financial and logistic affordability of ATLG will be vital for increasing the success rate in kidney transplantation practice.

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**Supplementary Table 1.** Reported Grafalon Dosage Range Used in Daily Practice

	Induction			Acute Rejection
	Low	Intermediate	High	
Panellist 01	1.5 mg/kg/day for 3 days	1.5 mg/kg/day for 3-5 days	1.5 mg/kg/day for 5-10 days	3.0-5.0 mg/kg/day for 10-14 days
Panellist 02	2.0 mg/kg/day for 3 days	2.0 mg/kg/day for 5 days	2.0 mg/kg/day for 5 days	2.0 mg/kg/day for 7 days
Panellist 03	2.0-2.5 mg/kg/day for 3-5 days	2.0-2.5 mg/kg/day for 3-5 days	2.5-3.0 mg/kg/day for 5 days	2.5-3.0 mg/kg/day for 5-7 days
Panellist 04		100 mg/day for 3 days	100 mg/day for 3 days	100 mg/day for 5-7 days
Panellist 05	2.0 mg/kg/day for 3 days	2.5 mg/kg/day for 3 days	3.0 mg/kg/day for 3 days	2.0 mg/kg/day for 7 days
Panellist 06	1.5 mg/kg/day 1 day	1.0-1.5 mg/kg/day for 4 days	1.5-2.0 mg/kg/day for 5-6 days	1.5 mg/kg/day for 4-5 days
Panellist 07		1.5-2.0 mg/kg/day for 5 days	1.5-2.0 mg/kg/day for 5-7 days	2.0-4.0 mg/kg/day for 7-14 days
Panellist 08		2.0 mg/kg/day for 3 days	2.5 mg/kg/day for 3 days	2.0-5.0 mg/kg/day for 5-7 days
Panellist 09	1.0 mg/kg/day for 3 days	2.0-3.0 mg/kg/day for 4 days	3.0 mg/kg/day for 4-5 days	3.0 mg/kg/day for 4-5 days
Total dose, median (min-max)	3 (0.00-12.5) mg/kg	7.5 (4.0-12.5)	10.0 (4.5-15.0)	14.0 (6-56)
Total dose, weighted mean	4.57 mg/kg	6.79	10.0	20.7

**Supplementary Table 2.** Reported Institutional Statistics

	Centre 01	Centre 02	Centre 03	Centre 04	Centre 05	Centre 06	Centre 07	Centre 08	Centre 09	Total
Annual transplantation load, n	105	197	58	18	150	130	11	165	60	894
Low risk, n (%)	20 (19.05)	57 (28.93)	14 (24.14)	16 (88.89)	100 (66.67)	30 (23.08)	0 (0.00)	49 (29.70)	10 (16.67)	296 (33.11)
Intermediate risk, n (%)	60 (57.14)	10 (5.08)	32 (55.17)	2 (11.11)	30 (20.00)	70 (53.85)	8 (72.73)	83 (50.30)	40 (66.67)	335 (37.47)
High risk, n (%)	25 (23.81)	130 (65.99)	12(20.69)	0 (0.00)	20 (13.33)	30 (23.08)	3 (27.27)	33 (20.00)	10 (16.67)	263 (29.42)
Transplantation rate without induction										
Low risk, n (%)	8 (7.62)	57 (28.93)	0 (0.00)	0 (0.00)	50 (33.33)	0 (0.00)	0 (0.00)	49 (29.70)	0 (0.00)	164 (18.34)
Simulect preference rate										
Low risk, n (%)	6 (5.71)	0 (0.00)	0 (0.00)	16 (88.89)	20 (13.33)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	42 (4.70)
Intermediate risk, n (%)	0 (0.00)	10 (5.08)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	10 (1.12)
Grafalon preference rate										
Low risk, n (%)	6 (5.71)	0 (0.00)	14 (24.14)	0 (0.00)	30 (20.00)	30 (23.08)	0 (0.00)	0 (0.00)	10 (16.67)	90 (10.07)
Intermediate risk, n (%)	60 (57.14)	0 (0.00)	32 (55.17)	2 (11.11)	30 (20.00)	70 (53.85)	8 (72.73)	83 (50.30)	40 (66.67)	325 (36.35)
High risk, n (%)	25 (23.81)	130 (65.99)	12 (20.69)	0 (0.00)	20 (13.33)	30 (23.08)	3 (27.27)	33 (20.00)	10 (16.67)	263 (29.42)