

Chapter 1: Induction Therapy

1.1: We recommend starting a combination of immunosuppressive medications before, or at the time of, kidney transplantation. (1A)

1.2: We recommend including induction therapy with a biologic agent as part of the initial immunosuppressive regimen in KTRs. (1A)

1.2.1: We recommend that an IL2-RA be the first-line induction therapy. (1B)

1.2.2: We suggest using a lymphocyte-depleting agent, rather than an IL2-RA, for KTRs at high immunologic risk. (2B)

IL2-RA, interleukin 2 receptor antagonist; KTRs, kidney transplant recipients.

Background

Except perhaps for transplantation between identical twins, all kidney transplant recipients (KTRs) need immunosuppressive medications to prevent rejection. Induction therapy is treatment with a biologic agent, either a lymphocyte-depleting agent or an interleukin 2 receptor antagonist (IL2-RA), begun before, at the time of, or immediately after transplantation. The purpose of induction therapy is to deplete or modulate T-cell responses at the time of antigen presentation. Induction therapy is intended to improve the efficacy of immunosuppression by reducing acute rejection, or by allowing a reduction of other components of the regimen, such as calcineurin inhibitors (CNIs) or corticosteroids. Available lymphocyte-depleting agents include antithymocyte globulin (ATG), antilymphocyte globulin (ALG) and monomurab-CD3. Basiliximab and daclizumab, the two IL2-RAs that are currently available in many parts of the world, bind the CD25 antigen (interleukin-2 [IL2] receptor α -chain) at the surface of activated T-lymphocytes and thereby competitively inhibit IL2-mediated lymphocyte activation, a crucial phase in cellular immune response of allograft rejection.

Rationale

- There is high-quality evidence that the benefits of IL2-RA vs. no IL2-RA (or placebo) outweigh harm in a broad range of KTRs with variable immunological risk and concomitant immunosuppressive medication regimens.
- There is moderate-quality evidence that a lymphocyte-depleting agent vs. no lymphocyte-depleting agent (or

placebo) reduces acute rejection and graft failure in high-immunological-risk patients.

- There is moderate-quality evidence across a broad range of patients with different immunological risk and concomitant immunosuppressive medication regimens, which shows that (compared to IL2-RA) lymphocyte-depleting agents reduce acute rejection, but increase the risk of infections and malignancies.
- Economic evaluations for IL2-RA demonstrate lower cost and improved graft survival compared with placebo.
- Although there are sparse data in KTRs <18 years old, there is no biologically plausible reason why age is an effect modifier of treatment, and the treatment effect of IL2-RA appears to be homogenous across a broad range of patient groups.
- Induction therapy with a lymphocyte-depleting antibody reduces the incidence of acute rejection compared with IL2-RA, but has not been shown to prolong graft survival.
- Induction therapy with a lymphocyte-depleting antibody increases the incidence of serious adverse effects.
- For KTRs \geq 18 years old, who are at high risk for acute rejection, the benefits of induction therapy with a lymphocyte-depleting antibody outweigh the harm.

In a large number of long-term, randomized controlled trials (RCTs) in adults, it has been consistently shown that induction therapy with either lymphocyte-depleting agents or IL2-RA reduces acute rejection in patients treated with 'double therapy' (calcineurin inhibitor [CNI] and prednisone), or 'triple therapy' (CNI, an antiproliferative agent [e.g. mycophenolate or azathioprine], and prednisone). Lymphocyte-depleting antibody induction also reduces the risk of graft failure while, in more recent studies, IL2-RA reduced the risk of death-censored graft failure, but not overall graft loss. Oral maintenance therapy may not produce immediate effects on the immune response when it is most needed, that is at the time of transplantation and antigen presentation. Pharmacokinetic and pharmacodynamic properties of oral maintenance agents may delay their full effect on immune cells.

The efficacy and safety of IL2-RA (compared to placebo or no treatment) have been confirmed in the most recent Cochrane review of 30 RCTs and 4670 patients followed to 3 years (2). In this review, IL2-RA consistently reduced the risk of acute rejection (e.g. for biopsy-proven acute rejection: 14 RCTs, 3861 patients, relative risk [RR] 0.77,

064–0.92) and graft loss (censored for death: 16 RCTs, $n = 2973$ patients, $RR = 0.74$, $0.55–0.99$). IL2-RA did not affect all-cause mortality (24 RCTs, $n = 4468$, $RR 0.73$, $0.50–1.07$), malignancy (14 RCTs, $n = 3363$, $RR 0.70$, $0.38–1.29$) or cytomegalovirus (CMV) infection (17 RCTs, $n = 3767$, $RR 0.90$, $0.76–1.06$), although all point estimates favor IL2-RA (all outcomes are at 1 year). The use of IL2-RA has also been found to be cost-effective compared to placebo (3).

The evidence for safety and efficacy of lymphocyte-depleting antibodies is more limited than that for IL2-RA. A meta-analysis of seven RCTs ($N = 794$) comparing lymphocyte-depleting agents with placebo or no treatment reported a reduction in graft failure ($RR 0.66$, $0.45–0.96$) (4). In an individual patient meta-analysis of five of these same trials ($N = 628$), the reduction in graft loss at 2 years was greater in patients with high panel-reactive antibody (PRA) levels ($RR 0.12$, $0.03–0.44$), compared to the reduction in risk for patients without high PRA ($RR 0.74$, $0.50–1.09$) (5).

Since publication of these meta-analyses, there have been other trials comparing lymphocyte-depleting agents with placebo or no depleting agent. In a single-center RCT, sensitized patients were randomized to induction with ATG or no induction. Patients treated with ATG had a reduction in acute rejection and improvement in graft survival (6). In a three-arm RCT, the incidence of biopsy-proven acute rejection at 6 months was highest in deceased-donor KTRs receiving tacrolimus, azathioprine and prednisone without induction (25.4%, $N = 185$) compared to a group receiving tacrolimus, azathioprine, prednisone and ATG (15.1%, $N = 184$) and a group receiving cyclosporine A (CsA), azathioprine, prednisone and ATG (21.2%, $N = 186$) (7). However, CMV infection occurred in 16%, 24% and 28% of the patients in these groups, respectively ($p = 0.012$). Similarly, leukopenia, thrombocytopenia, fever and serum sickness were all more common in the two groups receiving antithymocyte induction (7). There is high-quality evidence for a net benefit of IL2-RA compared to placebo for some patient outcomes (graft survival) but not all (all-cause mortality); and high-quality evidence of a net benefit to prevent acute rejection (see Evidence Profile and accompanying evidence in Supporting Tables 1–4 at <http://www3.interscience.wiley.com/journal/118499698/toc>).

There have been a number of RCTs comparing IL2-RA with lymphocyte-depleting agents. Most of these trials have been small and of low quality. A meta-analysis of nine RCTs ($N = 778$) found no difference in clinical acute rejection at 6 months (2). There were no differences in graft survival or patient survival (2). Since this meta-analysis, there have been other RCTs. The largest ($N = 278$), and arguably highest-quality, RCT compared ATG with daclizumab in deceased-donor KTRs selected to be high-risk for delayed graft function (DGF) and/or acute rejection (8). This RCT found no difference in the primary composite end-point, but the ATG induction group had fewer biopsy-proven acute rejections and more overall infections com-

pared to the daclizumab group (8). In an updated Cochrane review, the risk of acute rejection was higher with IL2-RA compared with lymphocyte-depleting agents (nine RCTs, $n = 1166$, $RR 1.27$, $1.00–1.61$), but the risk of graft loss (12 RCTs, $n = 1430$, $RR 1.10$, $0.73–1.65$), and mortality was not significantly different (13 RCTs, $n = 1670$, $RR 1.28$, $0.74–2.20$). Compared with lymphocyte-depleting agents, the risk of CMV infection (13 RCTs, $n = 1480$, $RR 0.69$, $0.49–0.97$), and malignancy (six RCTs, $n = 840$, $RR 0.23$, $0.06–0.93$) is lower with IL2-RA. Thus, there is moderate-quality evidence for trade-offs between IL2-RA and depleting antibodies; depleting antibodies are superior to prevent acute rejection, but there is uncertainty whether this corresponds to improved graft outcomes. Depleting antibodies are associated with more infections (see Evidence Profile and accompanying evidence in Supporting Tables 5–7).

There have been few head-to-head comparisons of different lymphocyte-depleting agents. Thus, it is unclear whether any one of these agents is superior to any other. In meta-analyses, there do not appear to be obvious differences in the effects of different lymphocyte-depleting agents on acute rejection or graft survival.

Alemtuzumab (Campath 1H) is a humanized anti-CD52 monoclonal antibody that depletes lymphocytes. In the United States, it has been approved by the Food and Drug Administration (FDA) for use in patients with B-cell lymphomas. There have been a few small RCTs examining the use of alemtuzumab as an induction agent in KTRs. All of these RCTs lack statistical power to examine the effects of alemtuzumab on patient survival, graft survival or acute rejection. In many of the RCTs, there were differences between the comparator groups other than alemtuzumab, making it difficult to discern the effects of alemtuzumab alone. For example, in a single-center RCT, 65 deceased-donor KTRs received alemtuzumab induction with delayed tacrolimus monotherapy and were compared to 66 KTRs treated with no induction, mycophenolate mofetil (MMF) and corticosteroids. At 12 months, the rate of biopsy-proven acute rejection was 20% vs. 32% in the two groups, respectively ($p = 0.09$) (9). In 21 high-immunological-risk KTRs randomized to alemtuzumab plus tacrolimus vs. four doses of ATG (plus tacrolimus, MMF and steroids), there were two vs. three acute rejections, respectively (10). Among 20 patients randomized to alemtuzumab plus low-dose CsA vs. 10 patients on CsA plus azathioprine and prednisone, there were biopsy-proven acute rejections in 25% vs. 20%, respectively (11). Ninety deceased-donor KTRs were randomly allocated to ATG, alemtuzumab or daclizumab induction, with those receiving alemtuzumab also receiving a lower tacrolimus target, MMF 500 mg twice daily and no maintenance prednisone, while those in the other two groups received MMF 1000 mg twice daily and prednisone. After 2 years of follow-up, acute rejections occurred in 20%, 23% and 23% in the three groups, respectively, but there was borderline worse death-censored graft survival in the alemtuzumab group

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($p = 0.05$), and more chronic allograft nephropathy (CAN) ($p = 0.008$) (12,13). Altogether, these small studies fail to clearly demonstrate that the benefits outweigh the harm of alemtuzumab induction in KTRs.

For KTRs treated with an IL2-RA, the reduction in the incidence of acute rejection and graft loss, without an increase in major adverse effects, makes the balance of benefits vs. harm favorable in most patients. However, it is possible that in some KTRs at low risk for acute rejection and graft loss, the benefits of induction with IL2-RA may be too small to outweigh even minor adverse effects (especially cost in developing countries) and so, in this setting, not administering IL2A is reasonable.

In contrast to IL2-RA, induction therapy with lymphocyte-depleting antibodies increases the incidence of serious adverse effects. For KTRs treated with lymphocyte-depleting antibodies, a reduction in the incidence of acute rejections must be balanced against an increase in major infections. This balance may favor the use of depleting agents in some, but not all, patients. Logic would suggest that the chances of a favorable balance between benefits and harm could be maximized by limiting the use of lymphocyte-depleting agents to patients at increased risk for acute rejection.

In an individual patient, meta-analysis of five RCTs comparing lymphocyte-depleting antibody induction with no induction (or placebo), the reduction in graft failure was greater in patients with a high PRA (5). Unfortunately, there are few, if any, studies comparing the relative effectiveness of lymphocyte-depleting agents vs. IL2-RA in subgroups of patients at increased immunological risk. Nevertheless, observational data can be used to quantify the risk for acute rejection and graft failure, and thereby define patients who are most likely to benefit from lymphocyte-depleting agents compared to an IL2-RA.

Risk factors for acute rejection include (Table 1):

- The number of human leukocyte antigen (HLA) mismatches (A)
- Younger recipient age (B)

- Older donor age (B)
- African-American ethnicity (in the United States) (B)
- PRA $>0\%$ (B)
- Presence of a donor-specific antibody (B)
- Blood group incompatibility (B)
- Delayed onset of graft function (B)
- Cold ischemia time >24 hours (C)

where A is the universal agreement, B is the majority agreement and C is the single study.

Retrospective observational studies have identified a number of risk factors for acute rejection after kidney transplantation (Table 1). Younger recipients are at substantially higher risk than older recipients, although there is no clear age threshold for the risk of acute rejection. Younger recipients may also be better able to tolerate serious adverse effects of additional immunosuppressive medication, making it compelling to treat younger recipients with lymphocyte-depleting antibody than IL2-RA. Kidneys from older donors may impart increased risk for acute rejection to the recipient, but a distinct age threshold has not been clearly defined.

The number of HLA mismatches between the recipient and donor is associated with the risk of acute rejection, but few studies have agreed on the number or type of mismatches (Class 1 [AB] or Class 2 [DR]) that increase the risk for acute rejection. In the United States, African-American ethnicity has been linked to an increased risk of acute rejection. For deceased-donor recipients, the duration of cold ischemia, for example longer than 24 hours, has been associated with acute rejection. DGF has also been associated with acute rejection, although by the time it is apparent that graft function is delayed, it is likely too late to decide whether or not to use a lymphocyte-depleting agent or an IL2-RA. However, induction with a lymphocyte-depleting agent could be used when there is an increased risk for DGF, such as in cases with expanded criteria donation or prolonged cold ischemia time. Finally, the presence of antibodies to a broad panel of potential recipients has been associated with an increased risk of acute rejection.

Table 1: Risk of acute rejection in multivariate analyses

Patient characteristic	Study characteristics							
	United States (14)	Spain (15)	North America (16)	Portugal (17)	Netherlands (18)	Norway (19)	UK (20)	Norway (21)
Country of study								
Number analyzed (N)	27 377	3365	2779 children	866	790	739	518	451
Percent that used living donors (%)	33%	0%	100%	1.4%	0%	100%	0%	33%
Transplant years included	97–99	90, 94, 98	87–97	85–99	83–96	94–04	91–99	94–97
	Acute rejection risk ^a							
Deceased (vs. living donor)	↑	↔		NA		NA	NA	↔
Younger recipient age	↑ per 10 years	↑↑↑ <60 y	↔ <2 years	↑↑↑ <45 years		↑↑↑ <50 years	↔	↔
Older donor age		↔ ≥60 years		↔		↑↑↑ ≥65 years	↑	↑↑ per 10 years
Recipient female (vs. male)	↑	↔				↔	↔	↔
Deceased donor cause of death								
Cerebral vascular death (vs. other cause)				↑↑↑		NA	↔	
Trauma (vs. nontrauma)		↔				NA	↔	
Recipient ethnicity US black (vs. white)	↑↑		↑↑↑					
Recipient Hispanic (vs. non-Hispanic)	↓↓	NA		NA		NA	NA	NA
Recipient diabetes (vs. no diabetes)	↑						↔ ^b	
HLA mismatches								
Any number of ABDR (vs. 0)	↑↑↑							
Any number of AB (vs. 0)								↑↑↑
Any number of DR (vs. 0)			↑↑↑		↑↑↑	↑↑↑	↑↑↑	↑↑↑
Per each ABDR mismatch		↔						
4–6 ABDR (vs. 3–1)				↔				
Panel reactive antibody status				NA			↔	
>0% (vs. 0%)								↑↑↑
>15% (vs. ≤15%)		↑						
>50% (vs. ≤50%)					↑↑↑			
Cold ischemia time								
>24 h (vs. <24 h)	↑↑			↑↑↑		NA		
Per hour		↔				NA	↔	↔
DGF (vs. none)		↑↑↑		↑↑↑	↑↑↑		↑↑↑	
CMV disease (vs. none)								↑↑↑ ^c
CMV infection (vs. none)		↑↑ ^d						↑↑↑ ^e
Recipient size								
BMI ≥35 kg/m ²	↑↑↑							
Body weight				↔				
Prior transplantation		↔				↔	↔	↔

BMI, body mass index; CMV, cytomegalovirus; DGF, delayed graft function; HLA, human leukocyte antigen; NA, not applicable, for example deceased-donor cause of death or cold ischemia time in studies including only living donors.

^aDefined in multivariate analysis by hazards ratios (Cox analysis) or odds ratios (logistic regression):

↔ Indicates not significantly associated with acute rejection ($p < 0.05$); may have been eliminated in univariate analysis.

↑ and ↓ indicate 10–20% more or less risk of acute rejection, respectively.

↑↑ and ↓↓ indicate 20–30% more or less risk of acute rejection, respectively.

↑↑↑ and ↓↓↓ indicate >30% more or less risk of acute rejection, respectively.

^bUnclear if tested in multivariable analysis.

^cInfection and clinical symptoms or signs of disease.

^dNot defined.

^eCMV pp65 antigen in leukocytes.