A Call for Transplant Stewardship: The Need for Expanded Evidenced-Based Evaluation of Induction and Biologic Based Cost Savings Strategies in Kidney Transplantation and Beyond

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ABSTRACT

Rising expenditures threaten healthcare sustainability. While transplant programs are typically considered profitable, transplant medications are expensive and frequently targeted for cost-savings. This review aims to summarize available literature supporting cost-containment strategies used in solid-organ-transplant. Despite widespread use of these tactics, we found the available evidence to be fairly low quality. Strategies mainly focus on induction, particularly rabbit-antithymocyte-globulin (rATG), given its significant cost and the lack of consensus surrounding dosing. While there is higher quality evidence for high-single-dose rATG, and dose-rounding protocols to reduce waste are likely low risk, more aggressive strategies, such as dosing rATG by CD3+ target-attainment or on ideal-body-weight have less robust support, and did not always attain similar efficacy outcomes. Extrapolation of induction dosing strategies to rejection treatment is not supported by any currently available literature. Cost-savings strategies for supportive therapies, such as IVIG and rituximab also have minimal literature support.

Deferral of high-cost agents to the outpatient arena is associated with minimal risk and increases reimbursement, although may increase complexity and cost-burden for patients and infusion centers. The available evidence highlights the need for evaluation of unique patient-specific clinical scenarios and optimization of therapies, rather than simple blanket application of cost-savings initiatives in the transplant population.

INTRODUCTION

Solid organ transplant is associated with improved survival and quality of life.[1] Transplant has been associated with health care cost reductions, particularly kidney transplant.[2] A transplant program is typically considered a profitable venture for healthcare systems. Despite this revenue generation, transplant medications are expensive and frequently targeted for cost savings. There are a number of available strategies to contain costs that have variable degrees of literature support. A blanket application of these strategies to all patients and clinical scenarios may not always be appropriate, however is often employed by transplant centers. The following will review and evaluate available literature supporting the most common cost-savings initiatives with an emphasis on stewardship of solid organ transplant resources rather than basic cost-saving measures, in an attempt to promote safe and appropriate use of drugs and maximize potential for optimal outcomes for each individual patient. A summary of the following information can be found in Table 1.

METHODS

Cost savings strategies were identified through expert consensus via query of the Immunology/Transplantation Practice and Research Network of the American College of Clinical Pharmacy with a focus on high cost-per-unit agents. A review of English language articles using PubMed, the Cochrane Controlled Trials Register (1960-2020), and EMBASE (1991-2020) for studies evaluating cost saving strategies of interest in adult (age >18 years) solid organ transplant recipients was conducted in August 2020. Additional studies were identified by searching bibliographies and abstracts presented at the American Transplant Congress (1990-2020). There were no restrictions on study design. Search terms included basiliximab, interleukin 2 receptor antagonists, rabbit antithymocyte globulin, alemtuzumab, lymphocyte depleting induction, rituximab, eculizumab, bortezomib, antibody mediated rejection, desensitization, cytomegalovirus hyper-immune globulin, immune globulin/IVIG, cost effectiveness/savings/containment and transplant/ation. Given the focus on high cost-per-unit tactics, strategies including maintenance immunosuppression, antimicrobial agents and other commonly used medications in transplant were not included. Eligibility assessment was performed independently in a standardized and unblinded manner by two reviewers. All dollar amounts noted throughout the manuscript are in US dollars unless otherwise specified.

Induction Immunosuppressive Strategies

Induction immunosuppressive agents are medications given at the time of transplant to prevent acute rejection during the inflammatory period of initial immune activation. The choice of induction agent is often determined based on donor and recipient risk factors. Current induction therapies supported in the literature include the non-depleting antibody basiliximab and lymphocyte-depleting antibodies rabbit anti-thymocyte globulin (rATG) and alemtuzumab. Due to associated costs[3] induction immunosuppression is a common target, despite literature that supports its long-term cost-effectiveness.[4] In this section, we will examine potential cost-saving strategies for induction immunosuppression, including dose modification, individualization and timing.

Non-Depleting Strategies

The IL-2 receptor antagonists (IL2RAs) are non-depleting induction agents that block CD-25, the T-cell IL-2 receptor, to prevent proliferation of T-cells.[5] Currently, the only available IL2RA is basiliximab. Basiliximab is a chimerized monoclonal antibody approved for prophylaxis of acute rejection in patients receiving kidney transplantation when used as part of an immunosuppressive regimen including cyclosporine and corticosteroids.[6] Average wholesale price (AWP) for a single 20 mg vial is $3,000. Basiliximab has been studied in four, double-blind, randomized, placebo-controlled clinical studies with the first dose administered within 2 hours prior to transplant surgery (Day 0) and the second dose administered on Day 4 post-operatively. Maintenance immunosuppression consisted of cyclosporine and prednisone with the optional addition of azathioprine or mycophenolate. Basiliximab administered in this way showed an economic advantage over dual therapy alone (difference $3,373), which was presumed to be mediated by reduction in acute rejection in the first post-operative year (38% vs 58%, $p<0.01$).[7]

Given the current climate of cost-conscious care and improved efficacy of maintenance immunosuppression since its initial approval[8] alternative basiliximab dosing strategies have been explored, focusing on dose reduction and modification in the timing or omission of the second dose.

Single Dose Basiliximab

The two-dose regimen was chosen to provide 30-45 days of IL-2RA saturation. However,results from phase 1 and 2 studies and a multicenter, prospective, dose-finding study suggest that a single 20 mg dose may sufficiently suppress T-cells and prevent acute rejection in kidney transplant by achieving a concentration of 0.7-1.0 µg/mL and adequately suppressing CD-25A.[9-10] The duration of CD-25A suppression appeared to be dose dependent, as a single dose of 20 mg of basiliximab provided adequate CD-25 suppression for 20±7 days while three doses of 20 mg extended suppression to 53 ± 17 days. In patients receiving basiliximab administration with cyclosporine, corticosteroids and mycophenolate mofetil, the duration of IL-2RA suppression was extended 59 ± 1.7 days.[11]

The second dose of basiliximab was initially advised in the setting of historical maintenance immunosuppression with cyclosporine, azathioprine and prednisone. With the broad utilization of the more potent triple drug regimen including tacrolimus and mycophenolate[8] the necessity of the second dose has been questioned. In a retrospective review of low immunologic risk kidney transplant recipients, a single 20 mg dose of basiliximab was found to be as effective as two 20 mg doses in preventing rejection.[12] Incidence of acute cellular (ACR) and antibody-mediated rejection (AMR) were similar between the single and double dose groups (ACR 4% vs 7%, p=0.2; AMR 19% vs 19%, p=0.9). A second study also found no difference in rejection or graft loss with a second 20 mg dose compared to a single 20 mg dose of basiliximab dose.[13] In this study, patients received either one or two doses based on financial reasons. Information pertaining to immunologic risk factors was not provided.

These findings call into question the benefit of basiliximab over no induction in low-risk patients in the modern era. This is currently under active investigation (ClinicalTrials.gov Identifier: NCT04404127). Based on the current available evidence, a single 20 mg dose of basiliximab for induction in low immunological risk patients could be employed as a safe and effective cost-savings strategy with an estimated savings of approximately $3,000 and minimal risk. In patients with delayed target tacrolimus trough attainment, administration of the second dose to provide ongoing IL-2 inhibition could be considered[14] although this has not been specifically studied.

Low-Dose Basiliximab

Utilization of a split total 20 mg dose of basiliximab has also been investigated. In a study evaluating the efficacy and safety of two 10 mg doses of basiliximab on post-op day 0 and day 4 in 17 de novo heart transplant recipients, 1-year all-cause mortality and ISHLT grade $\geq$2R ACR rate were 6% and 12% lower than those reported in previous trials.[15] Average time to achieve target CNI levels was 14±5 days post-transplant. The incidence of treated infections was also lower than reported in previous studies. At 1-year post-transplant, 25% of patients had been treated for an infection and 35% of patients had asymptomatic cytomegalovirus (CMV) infection. This study was limited by its small size, lack of comparator and single allograft subtype. Utilizing this dosing strategy could result in a cost savings of approximately $3000.

Second Dose Basiliximab Timing

The median length of stay following a kidney transplant was 5 days (IQR 4-6) in 2014, and it is common to prepare patients for discharge as early as post-op day 2-3.[16] In clinical dose-finding studies, basiliximab was administered to adult kidney transplant recipients in single doses up to 60 mg and divided doses over 3-5 days up to 120 mg without serious adverse effect, suggesting potential tolerance of alternate regimens.[6] The second dose of basiliximab has been administered early to decrease costs related to length of stay, and has also be shifted to the outpatient setting to decrease inpatient drug costs and increase reimbursement.

In summary, modification of current FDA-recommended dosing schemes of basiliximab for induction may provide cost-savings without compromising outcomes. Administration of one dose of basiliximab in low risk patients is an attractive option for centers, as it eliminates the cost of the second dose completely. Alternatively, adjusting the timing of the second dose could provide cost savings by decreasing length of stay and overall hospital costs or by improving reimbursement.

Depleting Strategies

Lymphocyte-depleting induction, rATG and alemtuzumab, have been used in solid organ transplantation to reduce the risk of acute rejection in immunologically high-risk patients and facilitate maintenance regimens that employ steroid withdrawal. Evidence exists supporting the cost effectiveness of depleting induction over no induction or IL2RA induction strategies in the setting of deceased donor kidney transplant in all degrees of immunologic risk and most age groups.[17] Despite this, depleting induction, particularly rATG, is a frequent target for cost-containment strategies. The following section describes strategies to decrease costs associated with rATG and the evidence to support these, including substitution with alemtuzumab.

Rabbit anti-thymocyte Globulin Strategies (rATG)

rATG is a lymphocyte-depleting agent that binds T-cell surface antigens to induce cell lysis and reduce circulating T-lymphocytes in a dose-dependent manner. The-FDA-approved dosing for rATG induction in kidney transplant is 1.5 mg/kg for 4-7 days[18] however, the optimal rATG dosing for induction remains debated and increased cumulative dose is associated with increased risk of infection and malignancy.[19]

AWP for a single 25 mg vial of rATG is $797.35, making an average dose for a 70 kg patient $3,189.40[3] and costs continue to rise in the setting of recent FDA approval.[18] rATG is typically given in 4-6 doses, making a total course cost between $12,757.60 - $19,136.40. Numerous cost saving strategies have been examined, including those which reduce the cumulative total dose administered and those that reduce hospital length of stay.

Cumulative rATG Dose Reduction

Given the lack of consensus regarding the optimal regimen in varying populations, as well as the risks associated with rATG, the cumulative rATG dose is an important stewardship target. Potential approaches include stratifying rATG doses based on immunologic risk status, intermittent dosing guided by CD3+ T lymphocyte count and dosing rATG based on ideal body weight (IBW) versus total body weight (TBW).

rATG Dosing Based on Immunologic Risk

The rATG dosing regimen and duration is derived from a pooled analysis of two international clinical trials conducted in high immunologic risk recipients.[18] Exclusion of the low immunologic risk population in this study has

left the optimal dosing and duration in this population ill-defined. Based on this, strategies tailoring the dose of rATG to patients' immunologic risk as a mechanism for reducing cost and adverse effects while optimizing outcomes have been explored.

In a single-center retrospective cohort study comparing three different rATG dosing strategies of 3 mg/kg (non-sensitized living donor recipients; n=96), 4.5 mg/kg (non-sensitized deceased donor recipients; n=102), and 6 mg/kg (history of prior transplant, PRA > 20%, or flow cytometry crossmatch positivity; n=26), researchers saw no significant difference in rejection, graft survival, or patient survival between the three groups.[20] The researchers concluded that cumulative doses of 3-4.5 mg/kg of rATG in standard immunologic recipients receiving a living or deceased kidney transplant, demonstrated similar efficacy at one year post-transplant as 6mg/kg given to higher risk patients.

A prospective, single-center study of 16 primary, low PRA kidney recipients evaluated the efficacy of rATG 3 mg/kg versus 4.5 mg/kg.[21] Patients in both arms experienced rapid initial T-cell depletion and lymphocyte depletion within three days post-transplant. Patients receiving rATG 4.5 mg/kg had a more prolonged depletion of CD3+ and CD4+ 30 days and 180 days post-transplant. No acute rejection was reported in either arm.

Reduced cumulative rATG dose has also been investigated in patients with higher immunologic risk. In a retrospective analysis comparing rates of rejection in high-risk kidney transplant recipients, defined as repeat transplant, African American race, or PRA ≥ 20%, rATG at 4.5 mg/kg versus 6 mg/kg resulted in similar rates of acute rejection between both groups at 6 and 12 months post-transplant (6 months: 4.5 mg/kg=10% vs 6 mg/kg=9%; 12 months: 4.5 mg/kg=10% vs 6 mg/kg=11%). Patient and graft survival were also similar.[22]

These studies suggest that in a select group of patients, a reduced cumulative dose of rATG 4.5 mg/kg may achieve similar rates of patient and graft survival with comparable short-term rejection rates to 6 mg/kg and theoretically reduced risk of toxicity. Compared to a 6 mg/kg cumulative dose, administration of 4.5 mg/kg would save approximately $3,189.40 for a 70 kg recipient. In addition to small sample size and single center designs, this evidence is limited by lack of immunologic risk assessment utilizing donor specific antibodies (DSA); therefore, it may be prudent to exclude those with pre-transplant DSA from dose-reduction strategies until further information is available.

rATG Dosing Based on CD3+ Target Attainment

Based on the profound and relatively sustained lymphocyte depletion following rATG administration, intermittent rATG dosing based on a pre-determined peripheral CD3+ T lymphocyte threshold of >10 - 50/mm^3 has been described in several small, single-center studies.[23] The proposed benefits of customized over "flat" dosing include reduced cumulative dose, fewer adverse events and resultant drug cost savings.

In a prospective study, high-risk (PRA >30% or repeat transplant) kidney and kidney-pancreas recipients (n=41) received induction with rATG 1.5 mg/kg/dose intermittently based on peripheral blood CD3+ lymphocyte counts >20 cells/mm^3.[24] Maintenance immunosuppression included a CNI, mycophenolate mofetil, and prednisone. The total cumulative dose of rATG per patient was 4.2 mg/kg, which was 69% lower than the historical control. This resulted in a cost savings of 46% based on center-specific pricing of rATG and CD3+ testing. One-year outcomes were 86% freedom from acute rejection, 92.7% kidney allograft survival, 81.8% pancreas allograft survival, and 95% patient survival, which were comparable to concurrent SRTR reported outcomes.[24]

Another prospective, single-center, comparative study investigated a dosing strategy of low-dose rATG (50 mg) given daily versus intermittently in 39 kidney transplant recipients.[25] In the intermittent dosing group, rATG was given daily for three days and subsequent doses administered when CD3+ T lymphocytes were >10/mm^3. Maintenance immunosuppression included cyclosporine, azathioprine and prednisone. All patients received rATG induction until therapeutic cyclosporine concentrations were achieved, which was approximately 11 days for both groups. Compared to the daily dosing group, the intermittent rATG group received significantly lower mean cumulative doses per patient (381.5±121 vs. 564±134.5 mg/patient, respectively; p=0.0001). Based on center-specific pricing and costs in the year 2000, the authors reported a net savings of $760 per patient with intermittent rATG dosing. Extrapolated to today's costs, this dosing regimen would save approximately $5,820. There was no significant difference in renal function, acute rejections episodes, or adverse events between dosing strategies.

In response to positive results in kidney transplantation, Uber and colleagues studied intermittent rATG dosing using CD3+ T lymphocyte monitoring for induction (n=4) and rejection treatment (n=5) in eight cardiac transplant recipients.[26] Induction with rATG 1.5 mg/kg was initiated at time of transplant and subsequent doses were given to maintain daily CD3+ counts < 25/mm^3 until CNI troughs were therapeutic. All patients also received mycophenolate mofetil and prednisone. Patients in the induction therapy group (n=4) experienced no rejection episodes over the follow-up period of 214 ± 162 days. For rejection, rATG 1.5 mg/kg was given per CD3+ thresholds for 7-10 days. All patients treated for rejection (n=4) responded to initial therapy with resolution of the acute rejection episode; however, two patients had recurrence of rejection with one of these patients requiring additional rATG therapy and ultimately passing away due to graft failure. For all patients studied, an average of 3.8 ± 1.5 doses per treatment course were needed to maintain CD3+ suppression for 9±3 days. Compared to standard daily rATG dosing, the intermittent dosing strategy resulted in a 60% reduction in total mg/kg dosing exposure, and a 58% reduction in the cost of drug therapy per patient.

These studies suggest that customized rATG induction dosing based on target attainment could optimize drug cost and minimize toxicity. Unfortunately, due to delays in laboratory reporting of lymphocyte subsets at most centers and associated testing costs, this strategy has not been widely adopted. Additionally, sensitization as measured by DSA was not specifically evaluated, again limiting this approach in this patient subset. Finally, there is very minimal

evidence to support this strategy in the treatment of rejection, suggesting exclusion of this indication from target attainment dosing strategies.

rATG Dosing Based on Body Weight

The FDA labeling of rATG does not specify body weight type for dosing calculation.[27] A pharmacokinetic study published in 1996 demonstrated lack of rATG distribution into adipose tissue, suggesting it may be appropriate to dose rATG based on IBW.[28] Because of this, many centers have transitioned to IBW dosing as both a cost-savings and theoretical dose-optimization strategy.

In a retrospective cohort study of high-risk kidney transplant recipients researchers compared outcomes in patients receiving a cumulative dose of rATG 7.5 mg/kg based on IBW versus TBW.[29] High-risk patients were defined as those with PRA > 40%, second transplant with early graft loss, third or greater transplant, or by physician discretion. No significant difference in biopsy-proven acute rejection (BPAR) at 90 days post-transplant was seen between the IBW and TBW groups (4.2% vs 0%, p=0.5). There was a numerically higher rate of BPAR at one-year post-transplant in the IBW versus TBW group (8.2% vs 0%, p=0.1), but this was not statistically significant. No difference was seen in patient or graft survival at 90 days or one-year post-transplant. There was also no difference in incidence of delayed graft function (DGF) or renal function at last follow up. No significant difference was seen in incidence of BK, CMV, or fungal infections. Finally, the median cost of rATG induction was lower per patient in the IBW arm compared to TBW, though this was not statistically significant ($17,542 vs $19,934, p=0.3). It is important to note that patients in the IBW arm had a higher TBW, and it has been shown that patients with body mass index (BMI) ≥ 35 kg/m^2 have an increased risk of BPAR compared to those with BMI of 20-24.9 kg/m^2 (HR: 2.43, 1.48-3.99).[30]

In a retrospective, longitudinal, cohort study published in abstract form, cumulative rATG induction doses of >7.5 mg/kg or ≤7.5 mg/kg were assessed, comparing the association of dosing based on TBW, IBW and adjusted body weight (AdjBW) for efficacy and safety outcomes.[31] Immunologic risk was not specifically noted. The authors found no association between TBW, IBW, or AdjBW and acute rejection at any dose between 6-10 mg/kg (p>0.7). However, IBW doses of ≤7.5 mg/kg were significantly associated with increased hospital readmission (p=0.046). Cumulative dose based on IBW were an independent risk factor for infection (p=0.018). The authors noted for every 50 patients who received induction dosing based on IBW, there was a potential cost savings of approximately $220,000.

Based on these limited studies, utilizing IBW for rATG induction dosing is a strategy that may provide similar outcomes to TBW dosing and potential cost savings. Again, these studies did not specifically assess immunologic risk by pre-transplant DSA and only evaluated kidney transplant recipients. Though not statistically significant, reduced cumulative rATG doses trended toward increased rejection/readmissions. IBW dosing was not associated

with improved toxicity over TBW. As with other strategies, blanket application of IBW induction dosing may not be appropriate in all scenarios, and IBW dosing has not been evaluated in the setting of rejection.

rATG Dose Rounding and Capping

Another cost-reduction strategy is rATG dose rounding, including rounding to the nearest vial size (25 mg) to reduce waste and implementing maximum individual or cumulative doses. While these are relatively common practices, they have limited supporting evidence. The FDA labeling of rATG does not recommend any dose rounding or maximum dose.[27]

Dose rounding and capping was evaluated in a retrospective study of 242 adult kidney transplant recipients with early steroid withdrawal utilizing four doses of rATG 1.5 mg/kg TBW, rounded to nearest 25 mg and capped at a single maximum dose of 150 mg.[32] Patients were divided into those who received < 6 mg/kg or those who received ≥ 6 mg/kg. Patients in the ≥ 6 mg/kg group had a significantly lower incidence of BPAR (11% vs. 21.2%, $p < 0.042$), but no difference was seen in patient and graft survival between groups. Additionally, no difference in renal function, leukopenia, or thrombocytopenia was found between groups.

A similar study was conducted in 261 adult kidney transplant recipients maintained on tacrolimus, mycophenolate but with steroid continuation.[33] Patients received rATG induction dosed on TBW to a goal of 5 mg/kg but capped at a total of 500 mg. Patients were divided into rATG cumulative doses of <5 mg/kg and ≥ 5 mg/kg TBW. No difference was found in incidence of BPAR between groups (8.9% vs. 8.7%, respectively, $p=0.944$). No differences were found in other clinical endpoints or adverse effects, leading the authors to conclude that, in the setting of triple drug immunosuppression, modest differences in cumulative doses based on dose capping did not result in compromised efficacy. Cost-savings of capping was not specifically assessed.

In addition to these studies, several other studies have been published that note rounding rATG doses to the nearest vial size.[22,29,34] These studies suggest it is common practice to round to the nearest 25 mg increment to reduce waste, and dose capping and rounding may be implemented safely in transplant recipients, though some caution may be necessary in those with higher body weights. There is no evidence to suggest a maximum lifetime cumulative dose of rATG, and dose capping has not been specifically studied when rATG is used for the treatment of rejection, suggesting exclusion of these patients from dose capping protocols.

rATG Strategies to Reduce Length of Stay

Other mechanisms for cost-savings include administering a higher individual rATG dose to expedite discharge and administering doses of rATG in clinic to decrease inpatient drug costs.

Higher Individual rATG Dose Administration

Administration of higher single doses of rATG to achieve the same cumulative goal can optimize use of rATG, resulting in reductions in length of hospital stay.

In a prospective non-randomized study of 40 kidney transplant recipients receiving rATG for induction immunosuppression, a single intraoperative dose of 3 mg/kg followed by 1.5 mg/kg for two subsequent post-operative days to a cumulative dose of 6 mg/kg was compared to a historical control of 1.5 mg/kg daily with a cumulative dose of 10.5 mg/kg.[35] The authors found no difference in rejection rates (p >0.99), graft (p=0.46) or patient survival (p=0.46) at 1 year. After the first month, absolute lymphocyte counts in the 3-day group were lower than the 7-day (P <0.05). Mean hospital length of stay was significantly reduced (6 days for the 3-day regimen vs 8 days for the historical control, p=0.002).

In a retrospective, single center study of 118 adult kidney transplant recipients receiving rATG for induction, patients received rATG at 1.5 mg/kg for 4 days or 2 mg/kg for 3 days.[36] No difference in serum creatinine (1.6 ± 1.3 [1.5 mg/kg] vs. 1.6 ± 0.9 [2 mg/kg]; p=0.898) or rejection-free survival (95% in both groups; p=0.983) was found at 2 years. At the time of the study, AWP of rATG was $610 per 25mg vial. The study reported an average cost of $11,569 ± $3,239 in the 1.5 mg/kg group and $10,649 ± $3,178 in the 2mg/kg group (p=0.122), and a numerically longer length of stay for the 1.5mg/kg group that was not statistically significant (6.0 ± 3.7 versus 5.1 ± 1.9 days; p=0.104).

A rigorously designed, randomized, double blind, double dummy, multicenter clinical trial evaluating single dose rATG was published by Stevens et al. in 2016 following preliminary findings by this group.[37-39] This study of 95 kidney transplant recipients evaluated safety and tolerability of single dose rATG (6 mg/kg) versus 4 daily doses of 1.5 mg/kg rATG to the same cumulative induction dose.[39] Primary end points included early safety analysis of fever, hypotension, hypoxia, cardiac events, and DGF. This study was terminated due to early achievement of non-inferiority. No difference was found in occurrence of primary end point events (p=0.58), rejection (p=0.78), graft survival (p=0.47), or patient survival (p=0.35) at 12 months. Additionally, no difference in infectious complications or side effects at 12 months were found between groups. Length of stay was not evaluated. Of note, the two previous studies with longer follow up time found 5-year rates of rejection and infection to be lower in patients receiving single dose rATG when compared to standard of care, leading the authors to claim potential superiority of this administration strategy.[37,38]

In another randomized study in 90 kidney transplant recipients (51% deceased donor) published the following year, three rATG induction regimens were evaluated: 4.5 mg/kg in 3 divided doses over 3 days, 4.5 mg/kg as a single infusion and 6 mg/kg in 3 divided doses over 3 days.[40] Maintenance immunosuppression included tacrolimus, mycophenolate and prednisone. All regimens had similar eGFR, Scr and incidence of rejection at 1 year. Rates of investigator-defined “serious infection” were reduced in those who received 4.5 mg/kg over 3 days compared to the other groups (23% vs 33% and 30% respectively, p=0.01). Incidence of CMV infection was also

significantly lower in this group (16% versus 26% and 33% respectively, p=0.003). BK was more common in the 6 mg/kg group (23% vs 7% in both 4.5 mg/kg groups, p=0.001).

These studies suggest similar safety and efficacy outcomes when employing higher single doses of rATG to the same cumulative induction goal. As a result, some centers may consider this approach to facilitate reductions in hospital length of stay, particularly if patients' immunologic risk limits the ability reduce the cumulative dose. Single dose administration has not been studied in the setting of rejection, and the impact of single dose on infectious outcomes may require more dedicated investigation.

Peripheral and Outpatient rATG Administration

Although the manufacturer does not specify type of intravenous access for the administration of rATG, a central line is often utilized according to the phase III clinical trial.[41] Several single-center reports demonstrated that rATG can be infused through a peripheral line or hemodialysis fistula without serious adverse effects.[34,43,44] Compared to central administration, peripheral administration of rATG offers several advantages by avoiding central catheter placement and associated complications and facilitating outpatient administration.[27,45,46]

Peripheral administration of rATG has been shown to be safe and effective when administered in the ambulatory setting without increased rates of readmissions and resulting in significant reduction in hospital length of stay.[43,46] Infusion time is the major limitation to this strategy. While outpatient administration has not been studied in the setting of rejection treatment, the benefits in this population would theoretically be more substantial, given the higher cumulative dose for this indication and lack of need for inpatient surgical recovery.

Alemtuzumab Substitution

Alemtuzumab is a humanized monoclonal antibody that targets CD52, causing profound depletion of T- and B-lymphocytes, monocyte and NK cells. When used for induction in adult kidney and pancreas transplant recipients, alemtuzumab is administered as a single, 30 mg intraoperative dose.[48,49] Studies found that alemtuzumab reduces rejection rates compared to IL2R blockade in low immunologic risk patients and is associated with comparable rejection rates to rATG in high immunologic risk groups.[48] Alemtuzumab is commonly grouped with rATG in studies, and no specific outcome differences have been found when used for induction.

Alemtuzumab was removed from market by the manufacturer in 2012 due to rebranding, and access was restricted to the Campath Distribution Program. Through this program, approved patients receive drug free of charge. As a result, utilization of alemtuzumab over rATG became an attractive cost-savings measure. Administration of alemtuzumab for induction could save a transplant center approximately $12,600 (70 kg person receiving 4.5 mg/kg rATG) per transplant and provide similar safety and efficacy outcomes as rATG. However, the

company recently increased allocation restrictions, the details of which are not available. As a result, utilization of alemtuzumab induction as a cost-savings measure has become limited.

Given its toxicity, lack of standardized dosing across transplant centers and cost, rATG is a common stewardship target. Most evidence is in the setting of kidney transplant and limited to the use of rATG for induction. The most rigorously evaluated strategy is the use of higher single-dose rATG. Dose rounding is a low-risk and effective strategy to reduce waste. Peripheral ambulatory administration is safe and effective. Dose stratification based on immunologic risk appears to be associated with equivalent outcomes; however, risk has not been assessed utilizing pre-transplant DSA. More aggressive strategies including IBW dosing and dosing based on CD3+ target attainment have less rigorous evidence supporting their use and should not be extrapolated to the use of rATG for treatment of rejection. Additionally, the once attractive option of utilizing alemtuzumab through the drug distribution program is now hindered by limited access.

Strategies Targeting Immunomodulatory Therapies

Immunomodulating therapies such as intravenous immunoglobulin (IVIG) and biologics such as rituximab are frequently used following solid organ transplantation to treat and prevent AMR.[50] IVIG preparations are also used to manage common viral infections.[51-53] In this section, we will evaluate optimization strategies for immunomodulatory therapies including IVIG, rituximab and other biologics.

IVIG Strategies

IVIG Dosing Based on Body Weight

IVIG is a commercially available preparation of pooled human IgG antibodies. Depending on indication, doses range from 0.1-0.5 to 1-2 g/kg.[54,55] Package labeling does not specify a recommended dosing weight. The cost of IVIG is not insignificant and varies based on bottle size, manufacturer, and contract pricing. For example, Privigen ® AWP is $17.40/mL, making a single 500 mg/kg dose in a 80 kg patient approximately $7,000. Pharmacokinetic analyses have demonstrated the volume of distribution of IVIG ranges from 0.1 to 0.3 L/kg, indicating minimal distribution into the tissue.[56] This has led centers to pursue IBW dosing as a cost-savings initiative.

Studies in various patient populations have demonstrated significant cost savings associated with IBW dosing. In a prospective review of IVIG use, IBW dosing saved an estimated 6,088 g of IVIG during the two-year study period. This was conservatively associated with an estimated $500,000 USD in cost savings per year. Hypogammaglobulinemia in bone marrow transplantation and hematological malignancy (50.7%) and acute solid organ transplant rejection (11.8%) were common indications for use, suggesting these as targeted patient populations.[57]

In one retrospective study, a multidisciplinary initiative incorporating automated dose rounding, commercial bottle dispensing, and passive indication observation within order entry was evaluated for impact on IVIG stewardship. Prior to implementation the prescribed IVIG dose varied considerably from the expected dosage; 27 months after order set implementation, the prescribed IVIG dose was closer to the expected dose.[58] For non-obese patients, TBW was used in the dose calculation, and in obese patients (> 130% of IBW), AdjBW was used. While this study did not directly assess the clinical implications of this initiative, there was lower dose variability.

A retrospective analysis of IVIG utilization at a comprehensive cancer center assessed three dosing methods by back extrapolation: 1) AdjBW if TBW >120% IBW (Method 1), AdjBW for all doses (Method 2), and IBW for all doses (Method 3).[58] Compared to provider-selected doses of IVIG, Method 1 would be associated with a 21.9% decrease in IVIG (16,658 g/year, $p < 0.001$), Method 2 with a 24.2% decrease (18,371 g/year, $p < 0.001$) and Method 3 with a 35.9% decrease (27,252 g/year, $p < 0.001$). This would also be expected to yield an average cost saving of $2.37 million (Method 1), $2.62 million (Method 2), and $3.89 million (Method 3) and average outpatient infusion time savings of 841 hours (Method 1), 920 hours (Method 2), and 1,366 hours (Method 3) per year. While no studies exist within solid organ transplant that are comparable, other specialties have extrapolated the potential benefits of utilizing IBW or AdjBW dosing, particularly in obese patients.

Despite literature to suggest cost savings with IBW dosing of IVIG for other indications, there are no dedicated studies in the solid organ transplant population. Overall efficacy of IBW vs TBW IVIG dosing is difficult to assess given the variability in dosing at baseline. However, utilization of reduced dosing strategies is a feasible strategy in solid organ transplant given the demonstrated time, cost, and drug savings seen in other populations.

IVIG vs CMV hyperimmune globulin

CMV is a ubiquitous opportunistic virus that causes infection following solid organ transplantation and is associated with negative patient and graft outcomes. CMV hyperimmunoglobulin (CMVIg) is FDA approved for CMV prophylaxis following transplantation. After a shortage disrupted supply, pooled IVIG largely replaced the use of CMVIg, mostly due to the significant cost differential between the two products (approximate AWP for a single 500 mg/kg dose for a 70 kg patient: $5,000 USD IVIG vs $24,000 USD CMVIg).[59] Consensus guidelines endorse the use of IVIG products as adjunctive therapy for both treatment and prophylaxis of CMV; however, they do not guide product selection.[52,53] The majority of available literature supporting the use of IVIG for CMV evaluates CMVIg for prophylaxis in thoracic transplant.[60-61] There are no published clinical studies demonstrating superiority of CMVIg over pooled IVIG. In vitro evidence is conflicting, as these studies utilize IgG subclasses, specifically IgG3, as a surrogate marker of neutralizing titer to determine anti-CMV activity, the accuracy of which has been questioned.[62-65] Overall, measurement of anti-viral antibody activity found in IVIG products is not standardized and is highly variable. Based on available evidence, the substitution of pooled IVIG products for CMVIg as a cost-

containment strategy does not appear to increase risk of treatment failure, but further comparative clinical studies are needed.

Rituximab Strategies

Rituximab is a monoclonal antibody against CD20 on the surface of B lymphocytes. Rituximab in combination with other immunomodulatory therapies have shown benefit in graft survival in the setting of desensitization.[67] Desensitization protocols vary among transplant centers, including flat dosing (500-1000mg) or body surface area (BSA) dosing (375 mg/m^2).[67] Rituximab is also widely utilized for AMR.

Rituximab is FDA approved for various indications. Dosing is based off of BSA in oncologic indications, while rheumatoid arthritis uses a fixed-dose strategy.[67] A pharmacokinetics study comparing BSA dosing and flat dosing of 2,000 mg in patients with rheumatoid arthritis found that the area under the curve was similar between both dosing schemes.[68] While there are no pharmacokinetic studies available in solid organ transplant patients comparing these dosing schemes, both strategies have been utilized in the literature. A prospective study of a single rituximab dose of 375 mg/m^2 in patients with steroid-resistant AMR showed significant reductions in SCr from admission to discharge.[69] Flat-dose rituximab at 500 mg demonstrated significantly improved SCr with patient and graft survival of 100% at a median of 20 month follow up in a small study of seven patients.[70] In this report, they estimated that patients received an average of 252 mg less rituximab utilizing a flat-dose strategy. At AWP, this could be associated with roughly $28,000 in cost savings per patient.

Rituximab biosimilars are also now readily available. Biosimilars have similar pharmacokinetic and pharmacodynamic profiles as the originator drugs. For instance, rituximab-pvvr (Ruxience®) was compared to the originator drug rituximab (Rituxan®) for rheumatoid arthritis in a phase I study and was found to have a similar pharmacokinetic profile with sustained and significant suppression of B cells up to 25 weeks. Although there is currently no literature on the use of biosimilars in solid organ transplant, usage may be associated with significant cost savings and/or revenue generation depending on contractual costs and associated insurance reimbursement.[72]

Biologics Site of Administration

Site of care is an important consideration for cost savings. Reimbursement for high-cost infusions is different on the inpatient compared to outpatient setting. In the outpatient setting, this is further stratified to hospital outpatient infusion centers, free-standing infusion centers or home infusion. In the inpatient setting, insurances do not reimburse for specific medications given. Rather, they provide a single payment for non-physician services, including drugs. Specifics on reimbursement differences are outside the scope of this paper. However, in the Magellan's 2017 Medical Pharmacy Trend Report, a large difference between high-cost biologics used for

autoimmune disease was noted. For these drugs, the average cost per claim was 1.9 to 2.6 times higher in the hospital outpatient setting than in the physician office.[73] Consideration of site of care for high-cost infusions such as rituximab or eculizumab is an attractive solution to optimize reimbursement and minimize inpatient costs without compromising outcomes.[74,75] However, this remains more of a cost-shifting strategy, and may increase out-of-pocket expenses of the patient, as well as result in increased cost-burden for the infusion center.

Maintenance Immunosuppression Strategies

A review of post-transplant cost savings would not be complete without mention of maintenance immunosuppressive medications. Unfortunately, a full review of this topic is outside of the scope and limits of this piece. However, unlike induction and biologics, there is fairly extensive literature available analyzing risks, benefits and resultant socioeconomic impacts and costs of the maintenance immunosuppression, including tacrolimus and its alternative extended-release formulations, as well as belatacept and mammalian target of rapamycin inhibitors. For an in-depth review of this topic we refer the reader to the following piece.[76] Further in-depth review of costs associated with aspects of maintenance immunosuppression dosing and formulation as well as methods to help balance these is warranted.

CONCLUSION

Our review of the available literature describing common cost-containment strategies suggests fairly low quality of evidence, despite widespread use. Strategies mostly focus on induction, particularly rATG, given its significant cost per dose and the lack of consensus for induction dosing. There is higher quality evidence for high single-dose rATG, and dose-rounding protocols to reduce waste are likely low risk; however, more aggressive strategies, such as dosing by CD3+ target attainment or IBW have less robust support, and did not always attain similar efficacy outcomes. Furthermore, extrapolation of induction dosing strategies to rejection treatment is not supported by any currently available studies. Supporting evidence is mostly derived from the kidney transplant population, so caution should be taken when extrapolating to other allograft subtypes. Cost-savings strategies for supportive therapies, such as IVIG and rituximab also have minimal literature support. Efficacy studies on the use of these agents have similar shortcomings, so impact of cost-savings initiatives are more difficult to assess. Deferral of high-cost agents to the outpatient arena is a strategy associated with minimal risk and is a seemingly straightforward, targeted stewardship intervention to increase reimbursement, however even this is cost-shifting rather than true cost savings in most cases, and could result in higher out-of-pocket expenses for the patient and increased cost-burden to the infusion center. This review highlights the need for stewardship and evaluation of unique patient-specific clinical scenarios and optimization of transplant therapies, rather than simple blanket

application of cost-savings initiatives in the transplant population, although the lack of a precision approach that is relevant to the identification of immunologically high- risk patients remains an issue.

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AUTHOR CONTRIBUTIONS

All authors contributed to concept/design, analysis/interpretation, drafting article and final approval of article. MRJ, JLF, MRL and RRA conducted critical revision of the article.

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PMID: 32400907

Summary Table. Cost-Savings Strategies

Strategy of Interest	Cost (AWP per Lexicomp)	Estimated cost savings of strategy (if applicable)	Literature support	Allograft studied	Benefits v Risks
Basiliximab					
Single dose	$4,719.29 USD per 20 mg dose	$4,719.29 USD per patient	Cunningham KC, et al. Pharmacotherapy 2016;36(7):823-829. Baquero A, et al. Transpl Proc 2006;38(3):909-910.	Kidney	Increased cost savings without increased in ACR or AMR. Primarily applicable to low risk patients.
Low Dose	$3,595.64 USD per 10 mg dose	$2,247.29 USD per patient	Kittipibul V, et al. Clin Transplant. 2017 Dec;31(12)	Heart	Limited data. Note less cost savings then utilizing single dose basiliximab given single dose vial
Second dose modification	$4,719.29 USD per 20 mg dose	N/A	N/A	N/A	This strategy would theoretically improve reimbursement via shifting care to ambulatory setting and reduce costs associated with length of stay.
rATG					
Dosing based on immunologic risk	$1,050 USD per 25 mg vial	$4200-6300 USD per patient	Klem et al. Transpl. 2009; 88: 891-896. Gurk-Turner et al. 2008; 85 (10): 1425-1430.	Kidney	Cost savings not specifically reported in the literature but is estimated based on reduction in total rATG dose by 1.5-2 mg/kg in an 80 kg patient. A reduction in the cumulative dose of rATG based on immunologic risk status provides similar rates of patient and graft survival with the benefit of reducing

					toxicity and cost
Dosing based on CD3+	$1,050 USD per 25 mg vial	$5,820 USD per patient	Djamali A et al Transplantation. 2000;69(5):799-805. Uber WE, Uber LA, VanBakel AB, et al. Transplant Proc. 2004;36(10):3245-3249.	Kidney, Heart	Cost effective and minimizes rATG associated toxicities, however, obtaining lymphocyte subsets is costly and results are not always available in a timely manner
Ideal body weight dosing	$1,050 USD per 25 mg vial	$2400-4000 USD per patient	Vacha et al. Experimental and Clinical Transplantation 2016; 5: 511-517. Miller R et al. Am J Transpl. 2016; 16 (Suppl 3).	Kidney	Studies evaluating ideal body weight vs total body weight for induction show no difference in outcomes. Though not statistically significant, reduced cumulative rATG doses trended toward increased rejection/readmissions. Ideal body weight dosing was not associated with improved toxicity over total body weight. Has not been studied in rejection
Dose rounding	$1,050 USD per 25 mg vial	Reduces waste; no direct drug cost savings	Pennington et al. (2015). 35(8), 748-754. Trofe-Clark, J. et al. (2012). 94(5), 506-	Kidney	Cost savings may be limited due to rounding to nearest vial size; caution in higher body weights if rounding up

			512.		
Dose capping	$1,050 USD per 25 mg vial	Not specifically studied	Pennington et al. (2015). Pharmacotherapy: The Journal Of Human Pharmacology And Drug Therapy, 35(8), 748-754. doi: 10.1002/phar.1624	Kidney	In the setting of triple drug immunosuppression, modest differences in cumulative doses based on dose capping did not result in compromised efficacy; cost-savings of capping was not specifically assessed
High individual dose	$1,050 USD per 25 mg vial	Decreased length of hospital stay; no direct drug cost savings	Agha IA et al. Transplantation. 2002 Feb 15;73(3):473-5. Hardinger K et al. Journal of Transplantation 2010;2010:1-8. Stevens RB et al. Transplantation 2008; 85: 1391–1399	Kidney	Decreased hospital length of stay with no difference in rejection rates and patient survival; risk of decreased absolute lymphocyte count. High quality data for single 6 mg/kg dose* Effects on infection risk have not been completely elucidated

			Stevens RB et al. Transplantation 2015; 99: 197–209 Stevens RB, et al. Am J Transplant. 2016;16(6):1858-1867.* Nafar M et al. Clin Transplant. 2017;31(e12977):1-8.		
Ambulatory administration	$1,050 USD per 25 mg vial	Decreased length of hospital stay, possibly increased reimbursement	Marvin MR et al. Transplantation 2003;75:488–489. Erickson AL et al. Transpl Int. 2010;23:636-640	Kidney	Safe and effective without increased rates of readmissions and resulting in significant reduction in hospital length of stay. Limitations include prolonged infusion time.
Alemtuzumab substitution	$0 USD per Campath Distribution Program	$12,600 USD (70 kg patient receiving 4.5 mg/kg of rATG)	Hanaway MJ et al. N Engl J Med. 2011 May 19; 364(20):1909-19.	Kidney	Limited availability through the manufacturer distribution program and increased allocation restrictions

IVIG					
IBW dosing	10 g / 100 mL (per mL): $16.63	For a 50 year old 100 kg 5'8" male patient: $5255.08 USD per 1 g/kg dose in cost savings	Rocchio MA et al. Ann Pharmacother. 2017;51(2):135-139.	All SOT/Not Specified	There is a lack of efficacy data comparing actual body weight to ideal body weight in the solid organ transplant patient population. Most data is extrapolated from other disease states.
IVIG substituted for CMVIg	IVIG=10g/100mL (per mL): $16.63 CMVIg=50 mg/mL (per mL): $33.89	~$19,000 USD per 500 mg/kg dose	Miescher SM et al. Vox Sang. 2015;109(1):71-78 Planitzer CB, et al. Transplantation. 2011;92(3):267-270 Shibaguchi H, et al. Yakugaku Zasshi. 2010;130(7):977-982	In vitro	Unclear given lack of standardization of measurement of neutralizing titers and the adjunctive nature of IVIG preparations in the treatment and prophylaxis of CMV
Rituximab					
Flat dose	100 mg/10mL (per mL): $112.74 USD	For a 50 year old 100 kg 5'8" male patient: 500 mg vs. 375 mg/m^2 (821.25 mg) = $3621.77 USD per dose in cost savings	Mulley WR, et al. Transplantation. 2009;87(2):286-9.	Kidney	There is limited data with use of flat dose in antibody mediated rejection for kidney transplant recipients evaluating a small cohort of seven recipients.
Biosimilar Usage	Rituxan(R): 100 mg/10mL (per	For a 50 year old 100 kg 5'8" male patient: 500 mg	Mulcahy AW et al. Rand Health Q.	N/A	There is currently no data for use of rituximab biosimilar in solid organ transplant recipients.

	mL): $112.74 USD Ruxience(R): 100 mg/10 mL (per mL): $86.02 USD	vs. 375 mg/m^2 (821.25 mg) = $2190.08 USD	2018;7(4):3		
Ambulatory administration	100 mg/10mL (per mL): $112.74 USD	Dependent on reimbursement by insurance, hospital specific purchase cost, and site of care (home infusion, hospital OP, or physician's office).	Magellan medical pharmacy trend report / 2018	N/A	Highly dependent on hospital purchase cost, insurance outpatient formularies, and site of care restrictions.