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Induction Therapy in Living Donor Kidney Transplantation (LDKT): A Literature Comprehensive Review

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1. Abstract

Induction therapy plays a A very important role in kidney transplantation, particularly in Living Donor Kidney Transplant (LDKT) recipients, who typically have a more favorable immunological profile. This review assesses the impact of various induction therapies, focusing on their efficacy, safety, and role in optimizing outcomes. While lymphocyte-depleting agents like Anti- Thymocyte Globulin (rATG) and alemtuzumab offer potent immunosuppression, their routine use in low-risk LDKT recipients may not be warranted. Non-depleting agents, such as basiliximab, continue to be widely used in these patients. This review explores the current evidence and strategies for personalizing induction therapy based on risk stratification and emerging biomarkers.

2. Introduction

Kidney transplantation is the best treatment for End-Stage Renal Disease (ESRD), and Living Donor Kidney Transplantation (LDKT) offers the advantage of better graft survival and reduced wait times compared to deceased donor kidney transplants [1][2]. Induction therapy is a key component of post-transplant immunosuppressive protocols aimed at reducing the incidence of acute rejection and establishing long-term graft survival [3]. In LDKT, the immunological risk is generally lower than in deceased donor transplantation, yet induction therapy remains essential in preventing early rejection episodes. However, the need for and type of induction therapy in low-risk LDKT recipients remain controversial, with studies suggesting that non-depleting agents may be sufficient in most cases [4][5].

3. Methodology

This review includes data from Randomized Controlled Trials (RCTs), cohort studies, and meta-analyses published between 2005 and 2024. PubMed, Scopus, and Embase databases were searched using terms such as "induction therapy," "living donor kidney transplantation, "basiliximab rATG" alemtuzumab," and "immunologic risk." Only studies with a focus on LDKT recipients were included. A total of 45 references were reviewed to summarize current practices and compare the outcomes associated with different induction regimens.

4. Results

Types of Induction Therapies

4.1. Interleukin-2 Receptor Antagonists (IL2-RAs)

IL2-RAs, such as basiliximab and daclizumab, are non-depleting agents that block interleukin-2 receptors on T-cells, thereby preventing T-cell activation and proliferation. These agents are commonly used in low-risk patients due to their favorable safety profile, with minimal adverse effects compared to lymphocyte-depleting agents [6,7].

- Efficacy: IL2-RAs reduce the incidence of acute rejection in the first-year post-transplantation. Basiliximab has been shown to decrease the risk of acute rejection episodes and improve graft function at 1- and 5-years post-transplant [8].
- Safety: IL2-RAs are associated with fewer infections, malignancies, and hematologic disturbances compared to lymphocyte-depleting agents [9].

4.2. Lymphocyte-Depleting Agents

Lymphocyte-depleting agents, such as rabbit antithymocyte globulin (r-ATG) and alemtuzumab, are used in high-risk patients, including those with a higher likelihood of rejection or delayed graft function [10,11].

A. Rabbit Antithymocyte Globulin (r-ATG)

- Efficacy: r-ATG is effective in reducing acute rejection rates and is often preferred in high-risk patients. It has been shown to reduce the incidence of biopsy-proven acute rejection and steroid-resistant rejection [12].
- Safety: r-ATG is associated with a higher risk of infections, cytomegalovirus (CMV) reactivation, leukopenia, and thrombocytopenia compared to IL2-RAs [13].

B. Alemtuzumab

- Efficacy: Alemtuzumab, a humanized monoclonal antibody targeting CD52, provides profound lymphocyte depletion and has been shown to reduce the risk of acute rejection more effectively than IL2-RAs. It is particularly effective in combination with minimal immunosuppression [14].
- Safety: Alemtuzumab is associated with a higher risk of leukopenia and BK polyomavirus infection but does not significantly increase the risk of graft loss or death [15].

4.3. Other Agents

Other agents, such as Mesenchymal Stromal Cells (MSCs), are being investigated for their immunomodulatory effects. MSCs have been shown to reduce infection rates and may offer a promising alternative to traditional induction therapies [16].

Table 1: Comparison of Outcomes with Induction Agents in LDKT Recipients.

Induction Agent	Rejection Rate	Infection Risk	Graft Survival	Cost
Basilixim ab	Low	Low	High	Low
rATG	Moderate	High	Moderate	High
Alemtuzu mab	High	Very High	Low	Very High

Benefits of Induction Therapy in LDKT

4.3.1.Reduction in Acute Rejection

Induction therapy significantly reduces the incidence of acute rejection, which is a major predictor of long-term graft survival. Studies have shown that both IL2-RAs and lymphocyte-depleting agents are effective in this regard, with lymphocyte-depleting agents being more effective in high-risk patients [17,18].

4.3.2.Improved Graft Survival

While the primary goal of induction therapy is to prevent acute rejection, some studies suggest that certain agents, such as r-ATG, may also improve graft survival by reducing chronic rejection [19].

4.3.3.Steroid Minimization/Avoidance

Induction therapy, particularly with lymphocyte-depleting agents, allows for steroid minimization or avoidance, reducing the long-term complications associated with steroid use, such as cardiovascular disease and diabetes [20].

4.3.4. Expanded Donor Pool

Induction therapy has facilitated the use of kidneys from expanded criteria donors and Donors after Cardiac Death (DCD), improving graft availability [21].

4.4. Risks and Side Effects

4.4.1.Infections

Lymphocyte-depleting agents are associated with a higher risk of infections, particularly CMV reactivation. Prophylactic measures, such as antiviral therapy, are often necessary [22].

4.4.2.Hematologic Complications

Both r-ATG and alemtuzumab can cause leukopenia and thrombocytopenia, which may require dose adjustments or supportive care [23].

4.4.3. Malignancy

There is a potential increased risk of malignancy, particularly Post-Transplant Lymphoproliferative Disease (PTLD), with the use of lymphocyte-depleting agents [24].

4.4.4. Cytokine Release Syndrome

Some agents, such as r-ATG, can cause cytokine release syndrome, characterized by fever, chills, and hypotension. This is more common with the first dose and can be managed with premedication [25].

Special Considerations in LDKT

1.HLA-Identical Recipients

In HLA-identical living donor kidney transplant recipients, a regimen of tacrolimus and mycophenolic acid without induction therapy may be sufficient. However, basiliximab induction is recommended for non-HLA- identical recipients [26].

2. High-Immunological Risk Patients

High-immunological risk patients, such as those with high panel-reactive antibodies or a history of sensitization, may benefit from lymphocyte- depleting agents like r-ATG or alemtuzumab [27].

3.ABO-Incompatible Transplantation

ABO-incompatible transplantation requires additional immunomodulatory measures, such as immunoadsorption and rituximab, in combination with conventional immunosuppression [28].

4.Pediatric Recipients

In pediatric recipients, induction therapy is often used to minimize the use of corticosteroids and other immunosuppressive agents, reducing the risk of growth retardation and other long-term complications [29].

4.5. Outcomes in LDKT Recipients

LDKT recipients typically exhibit a lower incidence of acute rejection and better long-term graft survival compared to recipients of deceased donor kidneys [30]. Studies have demonstrated that basiliximab provides comparable rejection prevention to rATG in LDKT recipients, with fewer complications related to infection and cytopenia [6,7,31].

4.6. Risk-Based Stratification

In recent years, the practice of tailoring induction therapy to individual immunological risk has gained prominence. High-risk factors include high Panel-Reactive Antibodies (PRA), a positive crossmatch, and a history of sensitization [32]. For low-risk LDKT recipients (e.g., first transplant, negative crossmatch, low PRA), basiliximab is often sufficient [33]. However, in high- risk recipients, such as those with a history of rejection or sensitization, lymphocyte-depleting agents like rATG or alemtuzumab are preferred [34].

5. Discussion

Induction therapy is critical in ensuring successful outcomes following kidney transplantation. Lymphocyte-depleting agents, such as rATG, provide potent immunosuppression, but their use comes with increased risks, particularly infections and leukopenia [35,36]. Non-depleting agents like basiliximab, while less potent, offer a safer profile and are equally effective in preventing acute rejection in lower-risk patients [37,38]. The debate between using depleting versus non-depleting agents often hinges on the immunological risk of the recipient. In high-risk cases, rATG or alemtuzumab may be more appropriate, while basiliximab remains the preferred choice for low-risk patients due to its favorable side-effect profile [39,40]. Moreover, the possibility of steroid-free immunosuppression protocols, combined with effective induction therapy, is an area of active investigation, with studies suggesting that such approaches may reduce long- term complications without compromising graft survival [41].

6. Future Directions

Emerging technologies, such as genomic profiling and biomarker-based risk stratification, hold the potential to further refine the selection of induction therapy in kidney transplantation [39,40]. Personalized medicine, leveraging genetic and immunological data, could lead to more targeted and effective induction strategies, minimizing adverse outcomes and improving graft survival [42,43]. Continued prospective trials are necessary to validate these approaches and establish clear guidelines for the use of induction therapy in LDKT [44,45].

7. Conclusions

Induction therapy in living donor kidney transplantation should be tailored to the immunological risk of the recipient, with non-depleting agents like basiliximab being effective for most low-risk patients. In high-risk recipients, lymphocyte-depleting agents, such as rATG or alemtuzumab, may offer superior protection against acute rejection. Future research should focus on personalizing induction therapy to optimize outcomes while minimizing complications..

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