Chapter

Induction Therapy in the Current Immunosuppressive Therapy

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Abstract

The current immunosuppressive therapy including calcineurin inhibitors, mycophenolate mofetil, and steroids, has substantially suppress rejections and improved clinical outcomes in heart transplant (HTx) recipients. Nevertheless, the management of drug-related nephrotoxicity, fatal acute cellular rejection (ACR), antibody-mediated rejection and infections remains challenging. Although previous some studies suggested that perioperative induction immunosuppressive therapy may be effective for the suppressing ACR and deterioration of renal function, increased incidence of infection and malignancy was concerned in recipients with induction immunosuppressive therapy. The international society of heart and lung transplantation (ISHLT) guidelines for the care of heart transplant recipients do not recommend routine use of induction immunosuppressive therapy, except for the patients with high risk of acute rejection or renal dysfunction, however, appropriate therapeutic regimen and indication of induction immunosuppressive therapy remains unclear in HTx recipients. We review current evidence of induction immunosuppressive therapy in HTx recipients, and discuss the appropriate therapeutic regimen and indication of induction therapy.

Keywords: induction therapy, interleukin-2 receptor antagonists, polyclonal anti-thymocyte antibodies, acute cellular rejection, renal dysfunction

1. Introduction

Triple immunosuppressive therapy including calcineurin inhibitors (CNI), anti-metabolites, and steroids, has substantially improved clinical outcomes for heart transplant (HTx) recipients. Nevertheless, the management of CNI-related nephrotoxicity, fatal acute cellular rejection (ACR), antibody-mediated rejection (AMR), and infections remains challenging [1]. Immunosuppressive regimens for organ transplantation can be generally characterized as induction, maintenance, or rescue therapies [2]. Recently, desensitization therapy has also been considered for recipients who are highly sensitized to Human leukocyte antigen (HLA) or have donor specific HLA antibodies [3]. Induction immunosuppressive therapy is a powerful and

prophylactic therapy that is used perioperatively to prevent episodes of acute rejection, which is expected to improve the clinical prognosis or make their managements easier in high-risk HTx recipients. Currently, approximate 50% of HTx recipients employ a strategy of induction therapy, however, international clinical guidelines do not recommend the routine use of induction immunosuppressive therapy since the impact of induction therapy on survival in HTx recipients remains unclear [1]. In the more recent clinical situation, tacrolimus, which is recent alternative choice of cyclosporine, significantly reduces the incidence of ACR. And desensitization therapy is also becoming an established medical treatment for sensitized HTx recipients. Appropriate indications and therapeutic regimens for administering induction immunosuppressive therapy to HTx recipients requires further consideration in the recent clinical situations.

This manuscript will provide an overview of the induction immunosuppressive therapy up to now, and future perspective of the induction immunosuppressive therapy in the new era of the current more established immunosuppression.

2. Induction immunosuppressive therapy in HTx

2.1 Immune response system in transplant recipients

Immune response system that influences the rejection in transplant recipients is divided into two categories depending on the immune cells that primarily work, although each response influences the other; T-cell-mediated and antibody-mediated immune response.

2.1.1 T-cell mediated immune response

T-cell mediated immune response system in transplanted recipients is generally explained from three pathway; direct and semi-direct pathway which donor antigen presentation cell (APC) affect, and indirect pathway which recipient APC (**Figure 1**) [2]. Thymic selection in the native thymus occurs without regard for donor-specific allo-antigens. The naïve T cell has a relatively high allo-specific precursor frequency (**Precursor frequency**). This process can be nonspecifically reduced by depletion induction immunosuppressive agents including anti-thymocyte antibodies (ATG), muromonab-CD3 (OKT3), and alemtuzumab (**Figure 1a**). Allo-antigen is presented via donor (direct or semi-direct) or recipient-itself (indirect) APCs in the secondary lymphoid tissues inducing naïve T cell activation (**Antigen presentation**). In transplantation, graft derived APCs likely dominate this process early through reperfusion induced mobilization to the secondary lymphoid tissue and direct pathway. This pathway gives way to recipient derived migratory APCs later through indirect mechanisms and may also be influenced by semi-direct presentation of intact donor HLA by recipient cells. T-cell depleting agents, Interleukin 2 receptor (IL2R) blockage, and methylprednisolone limit this process (**Figure 1b**). T-cell activation occurs as an aggregate effect of many spectral processes (**Activation threshold**). Given that T cells have long been known to be important in rejection, some maintenance immunosuppressive agents including CNI, anti-metabolites and mammalian target of rapamycin (mTOR) inhibitors also alter the threshold of activation of T-cell also affect this process (**Figure 1b** and **c**). T-cells activation in the secondary lymphoid and injured endothelium and ischemic injury (**Figure 1A**) attenuates platelet and

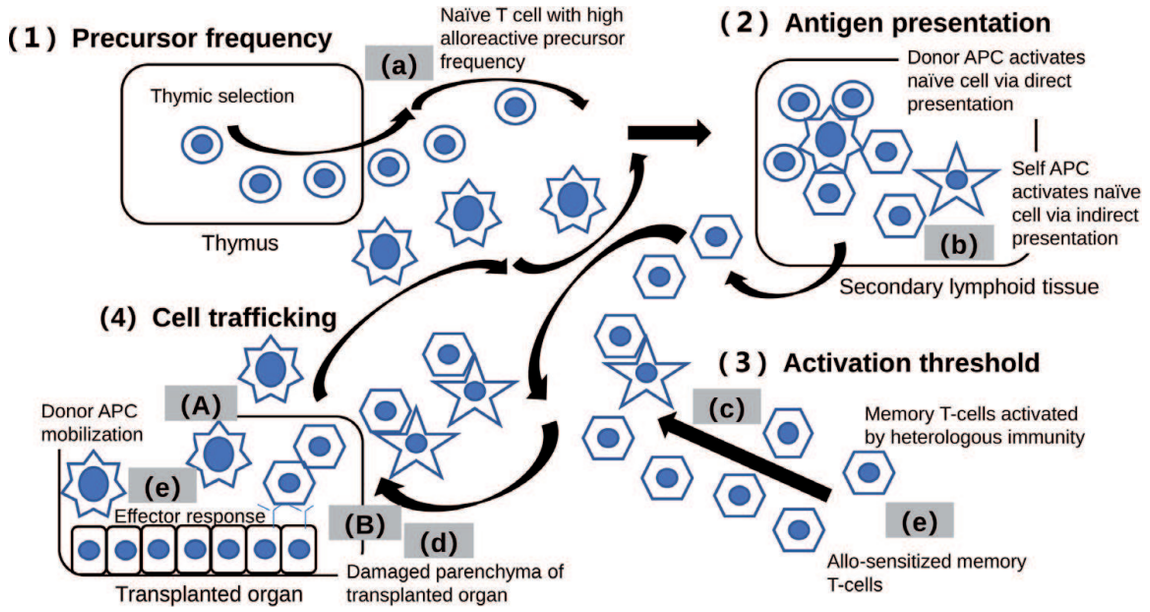

Figure 1.
T-cell mediated immune response.

complement binding and activation thus activating endothelial cells and donor APCs, initiating chemotactic signals, and providing signals to lower the activation threshold of local effector cells (**Figure 1B**). The local cytokine milieu reinforces local cell activation and can be inhibited by IL2R-specific agents, methylprednisolone, CNIs and mTOR inhibitors (**Figure 1d**). Allo-sensitized memory cells and cells activated through heterologous immunity or homeostatic proliferation bypass the need for nodal presentation. Depletion agents can both attenuate and augment this effect (**Figure 1e**). Activated T cells and recipient APCs are attracted to the graft site by chemokines and adhesion molecule expression (**Cell Trafficking**). Reperfusion injury initiates donor derived APCs to mobilize toward the nodes for direct pathway. Depletion agents, polyclonal antibody and methylprednisolone limit chemotaxis and/or adhesion. Cytotoxic T lymphocyte (CTL) encounter the graft in sufficient numbers to cause clinical damage, and are reenforced by a milieu rich in T cell derived cytokines (e.g. IL-2) (**Effector response**). Damage to the organ occurs through contact dependent CTL activity and through the direct effect of cytolytic cytokines (e.g. TNF-α). Depletion agents and selective IL-2 receptor antibodies limits the productiveness of this response and prevents the attainment of milieu that is supportive of CTL activity (**Figure 1e**).

2.1.2 Antibody-mediated immune response

Anti-body mediated rejection (AMR) is a major limitation to long-term HTx survival and is mainly driven by antibodies directed against the mismatched HLA Class I and Class II antigens (HLA antibodies) expressed on the allograft. Pre-sensitized patients who possess HLA antibodies are disadvantaged by having to wait longer to receive an organ from suitably matched donor. The number of pre-sensitized patients has been increasing, a trend that is likely due to the increased use of mechanical circulatory assist devices [4]. The humoral immune system is responsible for antibody production, which leads to AMR (**Figure 2**) [5]. Naïve B-cells are produced in the bone marrow and become activated in secondary lymphoid tissues when antigen

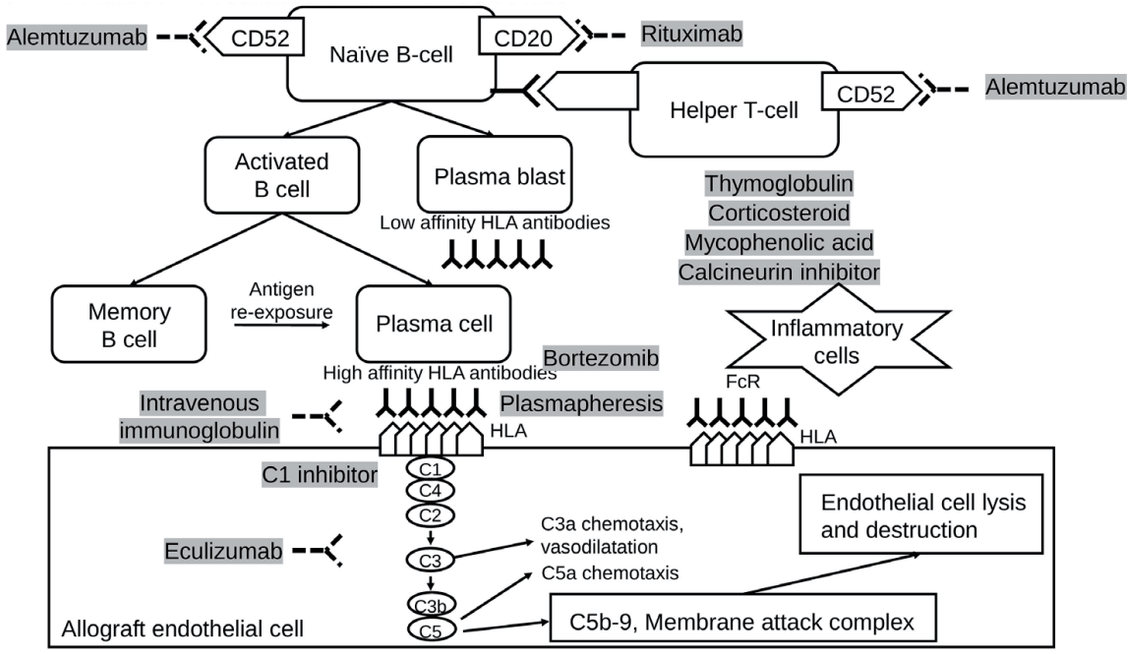

Figure 2.
Antibody-mediated immune response.

is encountered in the presence of APC and T-helper cells. Activated B-cells develop either into plasma blast secreting low-affinity antibody or interact with follicular dendritic and T-helper cells to form germinal centers [6]. Within germinal centers, B-cells undergo proliferation, hypermutation and affinity maturation to become high-affinity antibody-secreting plasma cells or memory B-cells. Plasma cells migrate back to the bone marrow, whereas memory B-cells circulate through secondary lymphoid organs and in the peripheral circulation. Upon re-exposure to antigen, memory B-cells rapidly proliferate and differentiate into plasma cells, producing high-affinity class-switched antibodies. Sensitized patients, who have already donor-specific antibodies pre-transplantation or memory B-cells against donor HLA by previous exposure, have high risk of hyperacute humoral rejection after HTx. In addition, antibody-mediated allograft injury occurs through complement pathway activation. HLA antibody-antigen complexes on allograft endothelial cells activate C1 triggering complement cascade activation and formation of the C5b-9 membrane attack complex to cause endothelial-cell lysis and destruction. Complement products also cause injury through recruitment of inflammatory cells (C3a, C4a, C5a), mast-cell histamine release (C5a), upregulation of endothelial adhesion molecules (C5a), tissue factor synthesis and thrombotic injury (C5a, C5b-9) and Weibel-Palade bodies (WPB) exocytosis [7]. DSA also exert harmful effects independent of complement activation through Fc-receptor recruitment of inflammatory cells and release of inflammatory mediators. The resulting cellular inflammation, thrombosis, hemorrhage and lysis cause allograft injury and dysfunction.

Desensitization therapy is a specific and important option for increasing donor pool and access to transplantation for the sensitized patient, which reduces or eliminates HLA antibody and/or facilitates transplantation in the presence of DSA. Since T-B-cell interaction is also associated with the plsma-cell antibody production, T-cell directed therapy including mycophenolate acid is also considered as a desensitization therapy. ATG, an option for induction therapy, binds to cell surface antigens on T cells to injure and reduce T cells. Since humoral immune responses are suppressed

when helper T cell function is reduced, ATG has the effect of decreasing sensitization by suppressing T-B cell interactions. Other agents specific to desensitization do not necessarily suppress the T dell mediated immune response. Previous consensus report suggests that post-transplant induction therapy as well as standard maintenance immunosuppression is recommended to prevent rejection in patients who have undergone desensitization [8].

2.2 Induction therapy in the current clinical situation

Historically, all organ transplantation employed induction regimens using some immunosuppressive agents [2]. Their strategies include preoperative high dose therapy with maintenance drugs, including glucocorticosteroids, antimetabolites and intravenous CNI, or specialized induction agents such as antibodies or infusion proteins. The concept that more immunosuppression is required early after transplantation is well established regarding induction therapies to prevent rejections. Specialized induction immunosuppressive agents which do not affect worsening renal function are used in the early perioperative management of patients with known or worsening renal insufficiency, as it may enable delayed initiation with calcineurin inhibitors to prevent the development of acute renal failure. Major concerns of induction therapy may be increased risk of infection and malignancy. Specialized induction immunosuppressive agents can largely be divided into two categories: depleting antibodies and non-depleting antibodies [2]. Depleting antibodies include both monoclonal (OKT3 and alemtuzumab) and polyclonal (ATG) antibodies. Depleting antibodies reduce alloreactive T cells at the time of transplantation, in turn suppressing host response to the allograft. As depleting antibodies acts primitive T-cell and also indirectly suppresses the anti-body mediated response via B-cell, resulting in a stronger suppression of immune responses more than non-depleting antibodies. While, as nondepleting antibodies inhibit T-cell activities which acts against a downstream of immune-response cascade (such as IL-2-driven cell proliferation), it may suppress rejections more specifically.

2.2.1 Current trend of Induction therapy regimens

Cai and Terasaki reviewed renal transplant recipients in the United Network for Organ Sharing (UNOS) database, [9] there had been three distinct time periods of induction regimens: (1) 1987–1993, the old, low-induction antibody era, when fewer than 30% of all kidney recipients received induction therapy, consisting mostly (80%) of anti-lymphocyte globulin or OKT3; (2) 1994–2002, the transitional, high-induction antibody era, when approximately 80% of kidney transplant recipients received induction therapy, and anti-lymphocyte globulin and OKT3 starting to be replaced by daclizumab (1998), basiliximab (1998), and rATG (1999); and (3) 2003–2010, the modern high-induction antibody era, with induction therapy remaining high, more than 80% of all transplant patients receiving induction therapy, mostly rATG, basiliximab, daclizumab, or alemtuzumab (2003). Regarding to HTx recipients, Whitson et al. evaluated the usefulness of induction therapy using UNOS database from 2001 to 2012 in HTx recipients [10]. Of the 17,857 HTx recipients, 8216 (46%) recipients had induction therapy; 55% were IL-2R antibodies (IL-2RA), 40% some depletion agents including ATG, and 4% alemtuzumab. Nozohoor et al., reviewed 27,369 adult HTx recipients in the International Society for Heart and Lung Transplantation (ISHLT) registry database, showed that 11,681 (43%) recipients had

induction therapy; 59% were ATG and 41% basiliximab [11]. Tzani et al. showed the trend in induction therapy utilization in patients who underwent HTx from 1990 to 2020, using UNOS Registry Standard Analysis and Research database [12]. The utilization of induction therapy gradually increased, reaching almost 50% in 2006, and then maintained similarly until 2016, with a recent gradual decrease to almost 40 % of all HTx in 2020. The use of alemtuzumab and OKT3 decreased significantly while the use of IL-2RA and ATG increased, and since 2003, IL-2RA has been used primarily as induction therapy. The international registry data base has also showed that almost 50% of HTx programs employ a strategy of induction therapy. Although multitude induction agents are available as mentioned above, IL-2RA and polyclonal ATG were commonly used [1].

2.2.2 Current clinical implication of induction therapy

The purpose of induction therapy is primarily to achieve high intensity immunosuppression early in the postoperative period to reduce the incidence of rejection and to delay the initiation of nephrotoxic immunosuppression with CNI in recipients with compromised renal function [9]. In addition, reduced risk of incidence of rejection may result in suppressing the development of cardiac allograft vasculopathy [13]. The potential disadvantage of induction therapy is the increased risk of infection in early phase and malignancy in the long-term post-HTx [13]. A previous meta-analysis showed that acute rejection might be reduced by induction therapy compared with no induction, and did not show other clear survival benefits or harms associated with the use of any kind of T-cell antibody induction agents compared with no induction [14]. Another systematic review showed that patients receiving induction therapy had similar risk of moderate-to-severe rejection, all-cause death, infection, and cancer with patients who did not receive induction therapy [15]. A more recent retrospective analysis using large cohort date of UNOS registry showed that induction therapy was associated with lower mortality and treated rejection episodes than no induction therapy [12].

In the current clinical situation, the improvement and establishment of new maintenance immunosuppression agents such as tacrolimus replaced cyclosporine and mycophenolate mofetil replaced azathioprine have significantly reduced risk of acute T-cell mediated rejection in acute phase post-HTx, which may lead that previously observed benefits of induction therapy tend to decrease overtime. Thus, although the clinical need of induction therapy to suppress T-cell mediated rejection may be decreasing, younger patients, multiparous women, African Americans, patients with longer term ventricular assist device, [16] and patients with long ischemic time [17] may be still good indication for the induction therapy in HTx. On the other hand, long awaiting time for HTx due to the severe donor shortage and increasing in the implantation of left ventricular assist device pre-HTx have increased risk of sensitization and pre-existing renal dysfunction before HTx. Highly sensitized patients, and those with positive cross-match may also have been considered as the candidate for the induction therapy in the past, however, since evidence for desensitization therapy is being established, truly high risk patients for hyperacute antibody-mediated rejection with high intensity of donor-specific should be considered more specific desensitization rather than introduction immunosuppressive therapy. And induction therapy may be generally used in combination with desensitization therapy, not induction therapy alone [3, 5]. Patients with pre-existing renal dysfunction may still be the best indication of induction therapy in the current clinical situation [17–20].

2.3 Specific agents for induction therapy

There are many specialized induction agents that are now being used to target the components of immunity heightened during transplantation. Although there is positive evidence in randomized trials and prospective studies comparing with standard maintenance regimens, no-induction or methylprednisolone induction, most trials use the surrogate endpoint of acute rejection, rather than more definitive outcome measures such as patient or graft survival. Several induction regimens have shown to measurably increase the risk of posttransplant lymphoproliferative disease (PTLD) and death from malignancy when combined with conventional maintenance immunosuppression [21]. This manuscript focuses on two specific induction immunosuppressive agents which were commonly used in current clinical situations; ATG and IL-2RA.

2.3.1 Polyclonal antibody

ATG is a polyclonal antibody derived from immunization of mainly rabbits with human thymocytes. The final product includes antibodies against multiple cell surface proteins, and HLA class 1 heavy chains, and is effective in preventing cellular immune responses against a variety of antigenic stimuli, through substantial lymphocyte depletion. Namely, ATGs bind to several antigens on T- and B-cells, causing T- and B-lymphocyte depletion. Given their broad spectrum of specificity, they have frequently been suggested to mediate their anti-rejection properties through means other than depletion, including costimulation blockade, adhesion molecule modulation, and B cell depletion. ATG is the most commonly used induction agent. Around 20% of HTx recipients receive ATG as induction therapy. There are no studies comparing ATG induction therapy with no induction therapy [15], and the efficacy of ATG induction therapy has been investigated in comparison with induction therapy with IL-2RAs which already showed the significant reduction of rejections. A large multicenter study has observed lower rates of rejection and an increased risk of infection with ATG [22].

The xenogeneic (horse or rabbit) origin of ATG may induce a host antibody response leading to acute hypersensitivity response or rarely, serum sickness on subsequent exposure, which is characterized by fevers, chills, tachycardia, hypertension or hypotension, myalgias, and rash, and may occur after the first dose. Rarely, cytokine release syndrome can occur. Furthermore, these ATGs cannot be used repeatedly for rejection to avoid a second or subsequent allergic reaction. ATG mat be left aside for future refractory rejections, not using for introduction.

2.3.2 Interleukin 2 receptor antibody

The high affinity alpha chain IL2 receptor (CD25) was the first molecule to be successfully targeted with a humanized monoclonal antibody in solid organ transplantation. IL-2RA act through the binding of the IL-2 receptor located on activated T-cells, thereby inhibiting the proliferation and differentiation of T-lymphocytes. Basiliximab is a monoclonal antibody that selectively binds to the IL-2 receptor of T-lymphocytes, blocks binding of IL-2 to the receptor complex, and inhibits IL-2 mediated T-lymphocyte proliferation [23]. Daclizumab is a humanized anti-IL-2R (CD25) monoclonal antibody that has the murine antigen-binding sequences molecularly engrafted onto a human antibody [24]; however, daclizumab has since been

discontinued by the manufacturer due to diminishing use. Basiliximab is notable for a significantly lower incidence in drug-related adverse events [25], compared with other specialized agents for induction therapy. Cytokine release syndrome has not been reported after administration of this type of drug.

Three randomized trials have compared with IL-2RA vs. no induction [23, 24, 26]. A systematic review including these randomized trials showed that IL-2RAs significantly reduced the risk of acute rejection. However, because these randomized trials had a high risk of bias despite randomization, this significant superiority of the IL-2 receptor was not clear according to the random effects model. Its survival benefits were also not found [27]. Furthermore, most of the studies to date have been in HTx recipients who received cyclosporine rather than tacrolimus for primary immunosuppression, with limited evidence in the new immunosuppression era. Watanabe et al. in HTx recipients receiving tacrolimus showed that basiliximab-based induction immunosuppressive therapy might suppress mild acute cellular rejection, and improve renal function in recipients with deteriorated renal function, and resulting in the its non-inferior outcome as compared to no-induction group even in recipients with any comorbidity [17].

2.3.3 Current evidence of comparison ATG vs. IL-2 RA

Although two randomized controlled trials demonstrated that the IL-2RA, daculizmab, effectively reduced the rate of moderate and severe rejections within first year after HTx [12, 23, 24], such effect could not be observed in trials for ATG. Previous systematic review which evaluated four randomized trials comparing of ATG with IL-2RA [28–31] showed that the use of IL-2RA was associated with significantly higher risk of moderate-to-severe rejection than ATG, but similar risk of death, infections, and malignancy [15]. In the retrospective analyses using large registry or cohort data in HTx, Nozohoor et al. [11] suggested that the recipients receiving ATG showed the better survival as compared with those receiving IL-2RA, however, found more malignancy post-HTx with ATG compared with basiliximab. Tzani et al. [12] showed that ATG has lower risk of treated rejection and mortality as compared with IL-2RA. And Ansari et al. in the retrospective analysis showed similar one-year survival between ATG and IL-2RA, but IL-2RA exhibited decreased long-term survival compared with ATG at 5 years and 10 years post-HTx [32]. On the other hand, Mazimba et al. [33] showed a conflict results when patients were stratified using risk of infection and rejection; IL-2RA was lower incidence of rejection but increased costs for infection in the patients with low risk of rejection and high risk of infection, and had significant lower incidence of rejection in patients with high risk of rejection and low risk infection as compared with ATG. A potential disadvantage of induction therapy is a risk of malignancies induced by its excessive immunosuppression in the long-term post-HTx [34]. ATG depletes cytotoxic T lymphocytes against organisms and virus infected cells as well as transplant organs. Therefore, ATG-based induction therapy may cytotoxic T lymphocytes against Epstein Barr virus (EBV) and EBV infected B lymphocytes which may result in primary-like EBV infection and EBV related B cell type posttransplant lymphoproliferative disorder (PTLD). Most previous studies did not show the difference of the incidence of malignancy between ATG- and IL-2RA-based induction therapies. Nozohoor et al. showed that the use of ATG may be associated with increased malignancy-related mortality, compared with no-induction [11]. Especially in pediatric HTx, ATG-based induction therapy tends to be preferred to IL-2RA-based induction therapy in younger patients, in those with congenital heart diseases, in patients requiring pre-transplant inotropic or mechanical support, and

in more sensitized patients or those with longer ischemic time [35]. Children are at greatly increased risk of PTLD versus adults, and PTLD is the most common form of post-transplant malignancy in children [36]. Although the relative rarity of PTLD makes an accurate assessment of the effect of specific immunosuppressive agents difficult, a recent review concluded no increased risk of PTLD in children given ATG after pediatric HTx [35]. They speculated that it is possible that this reduction in risk may have arisen from the general trend towards less intensive maintenance therapy in recent years. ATG-based induction may also have been used to facilitate CNI-sparing or steroid sparing therapy in pediatric HTx, potentially lowering risk the risk for PTLD.

Regarding maintenance immunosuppression, tacrolimus is more potent than cyclosprone and has proven to reduce rejection rates as well as an effective rescue agent for patients with recurrent or refractory acute allograft rejection. Tacrolimus has replaced cyclosporine in many transplant centers and currently. This raises the question about effectiveness of induction therapy in current tacrolimus-based immunosuppression era. Ali et al. performed meta-analysis to explore the effect of IL-2RA vs ATG on morbidity and mortality in renal transplant patients receiving tacrolimus-based maintenance immunosuppressive therapy, which revealed no significant difference in patient and graft survival when using IL-2RA vs ATG with the tacrolimus-based maintenance immunosuppression. The difference in efficacy between ATG and basiliximab in the era of newer immunosuppressive agents needs to be explored in HTx recipients.

ATG and IL-2RA may not be compared identically as induction therapy because the pharmacological mechanisms of action, response range, and safety of the two immunosuppressive agents are very different. Induction therapy with desensitization in highly sensitized patients or patients with donor specific antibodies may be not sufficient for basiliximab, and ATG should be selected as induction therapy. On the other hand, if induction therapy is administered because of concerns about worsening renal function immediately after transplantation in non-sensitized recipients, ATG may not be appropriate because it may lead to excessive immunosuppression, and the use of safer may be appropriate. Furthermore, since xenogeneic origin of ATG, ATGs cannot be used repeatedly for rejection to avoid a second or subsequent allergic reaction, ATG may require to be left aside for future refractory rejections.

3. Future perspective regarding the induction therapy

3.1 Appropriate indication for induction therapy

The appropriate indications for administering induction therapy have not been established. Previous studies suggested that recipients with an increased risk of rejection, which were younger patients, multiparous women, African Americans, patients with longer term ventricular assist device [16], and patients with long ischemic time [17], are good indication for the induction therapy in HTx, as well as recipients with deteriorated renal function. Watanabe et al. proposed the original indication criteria which included potential difficulty in patient management including donor or recipient older age, impairment of cardiac function or pre-existing coronary atherosclerosis of donor heart in early phase after HTx which may cause intolerance to immunosuppression.

3.2 Appropriate regimens for induction therapy

There is currently no consensus regarding the dose or duration of induction agents in different types of HTx recipients, or the timing and intensity of initial CNI therapy in recipients receiving induction therapy. The immunosuppression protocols for administering induction therapy varies according to the dosage of CNI administered and applies to those recipients who require CNI withdrawal with cytolytic therapy for renal dysfunction or as a modification of the standard triple immunosuppression regimen [23, 24, 27]. And these regimens influence perioperative over- or under immunosuppression particularly, and need to be careful in patients with administered induction therapy. Minimization and optimization of baseline immunosuppressive agents may be useful for improving clinical outcomes. Regarding the optimization of maintenance immunosuppression, some landmark trials in CNI minimization and withdrawal shows the clinical usefulness, however, perioperative optimization in immunosuppression in patients with induction therapy is still controversial [23, 24, 27]. When considering the optimal immunosuppressive regimen with induction therapy, it may be useful to monitor the degree of immunosuppression. Previous review paper suggested that CD3 monitoring, or absolute lymphocyte count is useful to guide ATG dosing [35]. Where this approach is applied, the previous ISHLT guideline advise targeting a CD3 count in the range of 25–50 cells/mm^3, or an absolute total lymphocyte count <100–200 cells/mm^3 [37]. A previous small sample retrospective study showed the patient group managed with CD3 monitoring received a significantly lower total ATG dose, although clinical outcome including survival, rejection and infection did not differ [38]. Regarding IL-2RA based induction therapy, CD25 which expressed on activated T lymphocytes may be useful for assessing the effects of IL-2RA. A previous study monitoring the CD25 count to evaluate the effect of IL2-RA showed that a 2-dose regimen of basiliximab-based induction therapy administered on Day 0 and Day 4 after transplantation still suppressed T-lymphocyte activation for an average 40–50 days after renal transplantation [39]. Watanabe et al. performed an original regimen that CNI dosage was slowly increased to prevent further deterioration of renal dysfunction due to CNI-induced kidney injury for the recipients with renal dysfunction, and to prevent over-immunosuppression for the pretransplant sensitized recipients; trough level of tacrolimus in the induction group was significantly lower than that in the no-induction group until 3 weeks post-HTx. However, recipients receiving induction therapy showed significantly higher incidence of infectious disease. Further investigation is needed for appropriate regimens for induction therapy.

4. Conclusions

This manuscript reviews previous and more current evidence of induction therapy in HTx recipients, and discussed the appropriate therapeutic regimen and indication of induction therapy in the current clinical situation. In previous evidence, conflicting results have been reported with regard to the effect of induction therapy on long-term survival, also the comparison between ATG and IL-2RA. Appropriate patient selection and agent selection may maximize the efficacy of induction therapy. The proper use of induction therapy is still being determined. Recent advances in immunosuppressive agents have changed the clinical course of HTx recipients. Induction therapy should be selected, specifically based on their mechanism of action to specific clinical need and aim.

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Conflict of interest

The authors declare no conflict of interest.

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