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IMMUNOSUPRESSIVE THERAPY IN THE LUNG TRANSPLANT RECIPIENT

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Summary

Lung transplantation has become a life-saving procedure for individuals with variety of end-stage respiratory diseases. Optimal immunosuppression remains the key to long-term graft survivival. The protocols for immunosuppressive therapy following lung transplantation can be divided into three general categories: induction, maintenance, and treatment of rejection. The goal of induction therapy is to provide intense immunosuppression in the early post-transplantation period, when the risk of allograft rejection is the highest. Induction agents primarily target T lymphocytes, which are considered the effector cells in cell-mediated rejection. Current maintenance therapy typically includes a calcineurin inhibitor, nucleotide blocking agent and corticosteroid. Pulse steroids are generally the first treatment of acute cellular rejection. Therapeutic modalities for treatment of refractory cellular rejection include switch from cyclosporine to tacrolimus, use of lymphocyte depleting agents, azithromycine, and extracorporeal photopheresis. Treatment options for humoral rejections include plasmapheresis and immunoglobulines in combination with rituximab.

***Keywords**:* lung transplantation; immunosuppression; induction therapy; maintenance therapy; rejection.

INTRODUCTION

Lung transplantation has become a life-saving procedure for individuals with variety of end-stage respiratory diseases. The success of transplantation has been closely related to descovery of effective imunosuppressive regimens. In the early 1980s, the introduction of ciclosporin as the mainstay of maintenace immunosuppression was followed by a significant improvement in the survival of lung tran-

splant recipients. Immunosuppressive regimes are employed to reduce the rate of acute and chronic rejection. Adverse effects of immunosupressive therapy include drug-specific toxicities, opportunistic infections and malignancy. Risk of those events directly correlates with the degree of overall immunosuppression. Therefore, immunosuppressive protocols try to achieve delicate balance between risk of adverse events and rejection. General principle is that the highest concentrations of immunosuppressants are targeted in the early post-transplant period when the risk of acute rejection is the greatest. Immunosuppression is slowly decreased over time (as the risk of acute rejection decreases) to help lower adverse effects. Protocols are consisted of several drugs. Combination therapy targets several steps in T-cell activation, allowing lower doses of each individual drug which provide higher tolerability.

Immunosuppressive regimes are generally defined as induction, maintenance, and treatment of rejection.

Induction therapy

Despite the advances in immunosuppressive therapy, acute allograf rejection is still a significant problem in lung transplantation. More than a third of lung transplant recipients are treated for acute rejection in the first transplant year [1]. The rationale of induction therapy is to use the strongest immunosuppressive drugs at the time when the risk of rejection is highest, which is in the first few weeks following transplantation. Induction regimes consist of agents which primarily target T lymphocytes, which are considered the effector cells in cell mediated rejections. Most frequently used antilymphocytic agents are polyclonal antilymphocyte antibodies, interleukin-2 receptor antagonists and anti-CD52 antibodies (alemtuzumab). Induction therapy also allows later introduction of nephrotoxic immunosuppressive drugs in patients with compromised renal function.

Polyclonal anti-lymphocyte antibodies (ATG)

Polyclonal antibodies are derived from immunization of horses (ATGAM) or rabbits (Thymoglobulin) with human tymocytes. These preparations contain antibodies directed againts many surface T- and B-cell antigens. Antithymocyte globulin depletes circulating lymphocytes through multiple mechanisms, including complement-mediated lysis and opsonization in the spleen and liver [2]. The major acute side effects include: cytokine release syndrome, serum sickness reaction, while some patients experience true anaphylaxis. The glucocorticoids, antihistamines, antipyretics are used for prophylaxis. Leukopenia and thrombocytopenia may require either a reduction in dose or termination of therapy.

Based on the analysis of International Society of Heart and Lung Transplantation (ISHLT) data, ATG - induction significantly reduced the incidence of acute rejection (AR) during the first post-transplantation year, compared to no induction [3]. Also, after 2 years, a trend toward a lower incidence of the bronchiolitis obliterans syndrome (BOS) was documented in the ATG-group (20%) versus the non-induction arm [4]. ATG induction therapy results in significany lower incidence of acute rejections without an increase in infection complications [5].

Interleukin-2 receptor antagonists (IL2RA)

Interleukin-2 receptor antagonists are monoclonal antibodies that selectively bind to the alpha subunit of the IL-2 receptor (CD25) on activated T cells. By binding this cell surface receptor, these antibodies inhibit T cell proliferation and diferentiation without T cell depletion. In contrast to polyclonal antibody preparations, IL-2 receptor antagonists show fewer side effects and are well tolerated.

Induction therapy with IL2RA reduces or delays the incidence of acute rejection, bronchiolitis obliterans syndrome (BOS), and may improve graft and patient survival compared to no induction [4,6].

Alemtuzumab

Alemtuzumab is a humanized rat monoclonal antibody that targets the CD52 antigen expressed on both T and B cells. It leads to depletion of T cells through complement - mediated and direct cellular cytotoxicity [7]. The usual dose of alemtuzumab for induction of immunosuppression is 30 mg i.v. Alemtuzumab can precipitate cytokine storm so patient should be pretreated with steroids. Although alemtuzumab has a half life of 12 days, inflammatory cells needs significantly longer time of recovery after alemtuzumab therapy. B cells recover at 12 months, while 50% recovery of T cells is usually reached at 36 months [8]. If alemtuzimab is administered, the maintenance dose of immunosupressive therapy is tailored in a way that tacrolimus is reduced by 40% of standars target values, while steroids are reduced to 30% of standard dose. Mycophenolate mofetil (MMF) is avoided in the first postoperative year for the risk of severe laeukopenia.

Maintenace therapy

Maintenance immunosuppressive therapy is administered to transplant recipients to help prevent acute and chronic allograft rejection. Maintenance therapy generally consists of combined therapy with a calcineurin inhibitor, a nucleotide blocking agent (antimetabolite), and steroids.

Calcineurin-inhibitors (CNI)

Since the induction of cyclosporine in the early 1980s, the calcineurin – inhibitors serve as the backbone of maintenance immunosuppressive therapy in solid organ transplantation.Calcineurin - inhibitors include cyclosporin (CsA) and tacrolimus (TAC).

Cyclosporine (CsA)

Cyclosporine acts by binding to cyclophilin, an intracellular protein. The complex inhibits the activity of calcineurin, which is responsible for the transcription of IL-2 and several other cytokines including TNF-alpha, granulocyte-macrophage colony – stimulating factor and interferon gamma. This prevents activation and proliferation of CD4+ T cells [9].

Drug dosage should be adapted according to the monitoring trough level. Targeted trough levels are 250 – 350 ng/ml in the first post-transplantation year, and should be reduced by 40% in patients who received alemtuzumab induction therapy. Target drug concentrations are typically reduced over time as the risk of acute rejection decreases. The common side effect of cyclosporine, which are related to the concentration of the drug, include nephrotoxicity, hypertension, hyperlipidemia, gingival hyperplasia, hirsutism, and tremor. Nephrotoxicity, the major adverse effect of cyclosporine, results from vasoconstriction of the afferent glomerular arterioles.

Tacrolimus (TAC)

TAC was previously known as FK506. It is a macrolide and is produced by the fungus Streptomyces tsukubaensis. TAC binds to the cytoplasmic immunophilin, FK binding protein12, and inactivates calcineurin. Through this pathway it inhibits interleukin – 2 and interferon – gamma production and subsequently T-cell proliferation and activation.

Toxicity profile of tacrolimus is similar to that of cyclosporin A, but it is less nephrotoxic. Recently, tacrolimus has been found to be superior to cyclosporin A in lung transplantation in terms of decreased incidences of acute rejection and chronic rejection [10]. Therefore, the use of tacrolimus has increased steadily, and the drug is now the dominant calcineurin inhibitor.

TAC may be administered as a continuous infusion, or orally. The drug dose should be adjusted as per blood levels. The target levels in the first three postoperative months are 15-18 ng/ml. Therapy is gradually decreased over time, with tacroli-

mus target levels at 8 to 10 ng/mL in a second postoperative year, and 8 ng/ml three years after transplantation. In patients who had received alemtuzumab induction therapy, tacrolimus target levels should be reduced by 40%.

Nucleotide blocking agents

Azathioprine (AZA) and mycophenolate mofetil (MMF) are commonly used nucleotide blocking agents after lung transplantation. Most transplant centers use mycophenolat mofetil as a part of maintenance immunosuppressive therapy, due to its increased selectivity for T- and B- lymphocytes [11].

Mycophenolate mofetil (MMF)

The mechanism of action of MMF is via selective inhibition of T- and B-cell proliferation. Mycophenolate reversibly inhibits de novo synthesis of purines during the S phase, a step that is required for the lymphocyte cell division. T and B lymphocytes use only de novo pathway in purine biosynthesis, whereas other cell lines that use both de novo and salvage pathways are not inhibited [12]. Mycophenolate's principal toxicities occur in the gastrointestinal tract and principally manifest as nausea and diarrhea. Due to potent myelosuppression, careful monitoring of complete blood counts should be performed on regular basis. MMF may be administered either orally or intravenously. The usual dosing schedule is 1000 mg. orally given twice daily. Drug levels can be monitored, although this is not done routinely.

Steroids

Corticosteroids are employed during induction, maintenance and anti-rejection therapy in pulmonary transplantation, emphasizing their crucial role in modulating the host immune response. They suppress prostaglandin synthesis, reduce histamine/bradykinin release, decrease vascular permeability and down-regulate key cytokines by influencing gene transcription [13]. Most common side effects include impaired glucose tolerance, hyperlipidemia, hypertension, hirsutism, M. Cushing, osteoporosis. High-dose steroids are generally administered intraoperatively and postoperatively. Due to the long-term side effects, the corticosteroid dose should be gradual tapering over months. The prednisone dose in the first 3 postoperative month is 0.3 mg/kg body weight, while after first post-transplant year the prednisolone dose is 5 mg once a day.

Tretment of acute and chronic rejection

Rejection therapy refers to immunosuppressive therapy given to reverse an episode of rejection. The intensity and type of rejection therapy depend on the severity of the rejection and type of rejection (whether it is cellular mediated or humoral).

Pulse steroids (500 – 1000 mg/d of methylprednisolone for 3-5 d followed by steroid taper over the ensuring 2-3 weeks) are generally the first treatment for cellular allograft rejection. Despite the many therapeutic options described above, refractory acute and chronic rejection alities in lung transplantation. An internationale retrospective study comparing CsA to tacrolimus revealed a decreased incidence in acute rejection and reversal of refractory acute rejection episodes and improvement of lung function after conversion of CsA to tacrolimus [14]. Therefore, for patients on the cyclosporine based regimen with evidence of rejection, most transplant centers reccommend switch maintenance immunosuppressive agent from cyclosporine to tacrolimus.

Azithromycin is a macrolide antibiotic with anti-inflammatory and immunomodulatory properties. Early initiation of azithromycin in lung transplant recipients may prevent the incidence of BOS and prolong BOS free survival. It may improve or stabilize pulmonary function after the onset of BOS, particularly in those with neutrophil and IL-8 predominant BAL [15].

In a case of a refractory cellular rejection, lymphocyte depleting agents (ATG or alemtuzumab) are used. ATG may decrease or stop the decline of lung function in patients presenting with BOS [16].

Other treatment modalities for refractory cellular rejection include extracorporeal photopheresis (ECP). ECP involves leukopheresis followed by incubation of isolated cells with 8-methoxypsoralen and subsequent exposing the cells to ultraviolet light in the presence of 8-methoxypsoralen. The cells are than reinfused to the patient. ECP is thought to induce apoptosis of the mononuclear cells, resulting in immunologic processing of cellular components after re-injection into the circulation that leads to the production of tolerogenic T-lymphocytes [17,18).

Treatment options for humoral rejections include plasmapheresis (5-6 cycles) and immunoglobulines (1-2g/kg over 3-6 days) in combination with rituximab.

Lung transplantation continues to offer patients with end-stage respiratory diseases chance for better quality and lenght of life. A better understanding of the immune response has led to improved monitoring of rejection and the development of better immunosuppressive regimes. In the future, advances inimmunosuppression protocols and the use of more specific immune monitor tools are likely to lead to significant improvements in outcomes.

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Sažetak

Imunosupresivno liječenje nakon transplantacije pluća

Transplantacija pluća je postupak koji spašava život bolesnicima s krajnjim stadijem različitih plućnih bolesti. Optimalna imunosupresija predstavlja ključ dugotrajnog preživljenja presadka. Protokoli imunosupresivnog liječenja nakon transplantacije pluća mogu se podijeliti u tri glavne grupe: indukcijska terapija, terapija održavanja i terapija liječenja reakcija odbacivanja. Cilj indukcijske terapije je osigurati intenzivnu imunosupresiju u ranom posttransplantacijskom periodu, kada je rizik odbacivanja alografta najveći. Indukcijski lijekovi su primarno usmjereni na T limfocite, koji se smatraju glavnim stanicama u staničnо posredovanoj reakciji odbacivanja. Trenutno se terapija održavanja tipično sastoji od inhibitora kalcineurina, antimetabolita i kortikosteroida. Pulsne doze kortikosteroida su prvi izbor liječenja akutnog staničnog odbacivanja. Načini liječenja refraktornog staničnog odbacivanja uključuju zamjenu ciklosporina takrolimusom, primjenu monoklonalnih i poliklonalnih antilimfocitnih protutijela, azitromicina i ekstrakorporalne fotofereze. Mogućnosti liječenja humoralnog odbacivanja uključuju plazmaferezu i imunoglobuline u kombinaciji s rituksimabom.

Ključne riječi: transplantacija pluća; imunosupresija; indukcijska terapija; terapija održavanja; odbacivanje.

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