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Clinical Immunosuppression in Solid Organ and Composite Tissue Allotransplantation

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1. Introduction

Although organ and tissue transplantation has been a fantasy for centuries, the epidemic of discovery in transplantation has taken place primarily during the past 55 years. In 1954, Dr J. Murray was presented with the unique opportunity to transplant a human kidney between identical twins without facing the challenges of acute or chronic allograft rejection as well as side effects of long-term immunosuppression (1, 2). Adding to scientific knowledge through basic research helped us to perform complex vascularized composite allotransplants (VCA) like the hand and face today and vascularized tissues recovered from a different individual will soon be extended to all reconstructive transplant procedures currently requiring autologous tissues (3-5).

The development of novel surgical techniques and the discovery of potent immunosuppressive drugs in the second half of the 20th century propelled the clinical development of organ transplantation(6). The combination of corticosteroids and azathioprine, which was the primary immunosuppressive regimen, used from the late 1960's until 1980 culminated in one-year survival rates of only 40% - 50%. Most notably, the discovery of cyclosporine A and tacrolimus in the 1970's and 1980's represented another major milestone in solid organ transplantation resulting in excellent short-term and acceptable long-term survival rates. With current immunosuppressive regimens mainly consisting of the triple combination of corticosteroids, mycophenolate mofetil, and tacrolimus the overall graft and patient survival has improved substantially and reached one-year graft survival rates of 80%-95% leading to consider organ and tissue transplantation as treatment modality of choice for patients with end–stage organ failure or severe tissue defects due to trauma or burn. Despite significant improvements in acute rejection rates, long-term solid organ allograft survival remained unchanged for the last 15 years (7). The major causes for late graft loss include chronic allograft rejection and death with a functioning graft (8, 9).

Since the immunologic graft-loss-rate seemed to be highest within the first months after transplantation, it became the rule that heightened immunosuppression is required early, with progressive reduction over time, leading to the definition of three distinct periods of immunosuppression after transplantation: The perioperative "induction period", where immunosuppressants are initially given at high doses, the "early maintenance period", which is characterized by progressive taper of the individual drugs, and the "chronic

maintenance period", characterized by the combination of different immunosuppressants used at their lowest effective doses.
At the end of 20th century, vascularized composite allotransplantation (VCA) like the hand and face has been performed in humans with success using the same immunosuppressive medications and therapeutic principles used for solid organ transplantation (10). However, since hand and face transplants must be considered as non life-saving operative procedures, novel immunosuppressive treatment protocols for these types of transplants must be developed not only to minimize graft rejection, but also to avoid complications related to adverse effects. Several challenges seem to impede the pharmaceutical industry in bringing novel immunosuppressive agents to the clinic. However, new powerful immunosuppressants are urgently in demand to enable the transplantation of highly immunogenic tissues like the skin and at the same time reduce the incidence of drug-induced toxicity. This goal can only be achieved by either combining synergistic immunosuppressive medications to maximize efficacy and minimize toxicity or by developing minimization protocols where conventional immunosuppression is tapered or even withdrawn shortly after transplantation.

2. Maintenance immunosuppression regimens

Maintenance immunosuppression remains the mainstay of therapy for successful outcomes after solid organ transplantation. Over the past decades, immunosuppressive regimens tried to target multiple immune pathways aiming to decrease acute and chronic allograft rejection and maintain long–term graft survival. Although current maintenance therapy after solid organ transplantation typically includes calcineurin inhibitors, antimetabolites, and corticosteroids, newer therapeutic options including induction therapy with biological agents, mTOR inhibitors, and cellular based therapies have emerged as alternative immunosuppressive strategies. The following paragraph will discuss immunosuppressants that are currently employed in solid organ transplantation.

2.1 Calcineurin-Inhibitors – Backbone of current immunosuppressive regimens

Cyclosporine A

The discovery of cyclosporine A (CsA) still has to be considered as one of the most important breakthroughs in transplantation medicine. CsA was initially discovered in 1968 as a product of *Tolypocladium inflatum gams* and isolated from the soil of the Norwegian plain of Hardanger Vidda (11, 12). At the same time, it was retrieved from fungi imperfecti native to Wisconsin. Almost a decade later, in 1976, Jean-Francois Borel described the immunosuppressive effects for the first time and hence, the first clinical use in a cadaveric kidney transplantation was reported two years later in 1978. Since then, CsA represents the backbone of a multitude of maintenance immunosuppressive protocols used in solid organ transplantation.
The immunosuppressive effects of CsA are based on the inhibition of proliferating CD4+ T cells by interfering with the IL-2 pathway. In other words, CsA was observed to form a complex with cyclophilin that furthermore engages the calcium/calmodulin dependent protein phosphatase calcineurin, which in a further step activates "the nuclear factor of activated T cells" (NFAT) in cell nucleoli to ultimately upregulate interleukin-2 (IL-2)

expression. Based on this IL-2 inhibiton, CsA halts T cell growth and T cell differentiation and thereby acts immunosuppressive (13).

Tacrolimus

Since the early 1990's, tacrolimus (FK 506), a macrolide antibiotic, which has been isolated from *Streptomyces tsukubaensis*, represents a mainstay in immunosuppression. Similar to CsA, tacrolimus blocks T cell activation and proliferation by interfering with the IL-2 pathway. FK 506 has been shown to bind the FK-binding protein 12 (FKBP12), which ultimately results in the inhibition of the calcineurin pathway leading to decreased IL-2 mediated T cell proliferation. The binding potency of FK 506 is 10 to 100 times stronger when compared to CsA, which results in decreased dosage demand by nonetheless retaining it's immunosuppressive capacity (14, 15).
Tacrolimus and cyclosporine A have both similar interactions with other medications, because of their common metabolism occurring in the liver by the cytochrome P–450 family. In addition, they also have a similar side effect profile such as acute and chronic renal insufficiency, dyslipidemia, hypertension, electrolyte disturbances, and post transplant diabetes. Furthermore, tacrolimus is more strongly associated with neurological complications including, seizures, headaches, and tremors.

2.2 Mycophenolate mofetil – A powerful substitute for azathioprine in antiproliferative immunosuppressive therapy

Mycophenolate Mofetil (MMF) is an antimetabolite immunosuppressant whose active component, mycophenolic acid (MPA), inhibits the key enzyme in the purine synthesis pathway, inosine monophosphate dehydrogenase (16). The discovery of this antiproliferative agent dates back to 1896, when it was first isolated from cultures of *Penicillium brevicompactum.* Initial analyses and studies to proof the immunosuppressive competence of MMF were conducted in the early 1980's. MMF has been shown to inhibit B and T cells proliferation, and induce apoptosis of activated T cells. It furthermore limits the expression of adhesion molecules on lymphocytes, which results in a decrease of nitric oxide production and hence, decreases the recruitment of inflammatory cells (17). Nevertheless, it took 15 more years until the Food and Drug Administration (FDA) approved this drug for the prevention of renal allograft rejection in 1995 (18).
Several clinical trials in the recent past pointed out that the combination of MMF with calcineurin inhibitors results in enhanced patient and graft survival and reduces events of acute and chronic rejection (19). MMF furthermore might be an alternative drug for patients developing drug-induced nephrotoxicity due to other immunosuppressive treatment (20). Besides bone marrow suppression and subsequent leucopenia, diarrhea, and GI distress are the most notable side effects of this immunosuppressant. However, recently a new " enteric coated" formulation of MMF has been developed, which has been shown to improve the mycophenolate exposure and hence, decreases GI side effects. In addition, MMF replaced azathioprine after 5 decades of its successful utilization as an antiproliferative immunosuppressive agent in the area of solid organ transplantation.

2.3 Azathioprine

Azathioprine has a long history of use in the field of solid organ transplantation (21). As an antimetabolite, azathioprine exerts its immunosuppressive properties by halting DNA replication of T and B cells, as well as by interfering with costimulatory signals, which

ultimately results in lymphocyte depletion (22). Before the discovery of CsA, the combination of azathioprine and steroids represented the standard treatment of choice in solid organ transplantation, however, like most immunosuppressive agents, azathioprine has multiple drug interactions and side effects. If co-administered with allopurinol for the treatment of gout or hyperuricemia due to a decrease in drug metabolism of both agents, azathioprine should only be dosed at 20% to 30% of normal dosage (23). The main toxicity associated with azathioprine is a dose dependent myelosuppression resulting in leucopenia, thrombocytopenia, and macrocytic anemia. Additionally, hepatotoxcicity and an increased incidence in malignancies have been reported. Today, azathioprine has widely been replaced by mycophenolate mofetil.

2.4 mTOR-Inhibitors

Another powerful class of immunosuppressive drugs comprises inhibitors of the mammalian target of rapamycin (mTOR), a key signaling kinase that affects broad aspects of cellular function like cell growth, as well as protein synthesis, and transcription (24, 25). The first mTOR inhibiting substance, sirolimus (Rapamycin), was isolated from soil obtained on Easter Island (Rapa Nui) and was initially identified as a potent antifungal metabolite (26).
However, this macrolide produced by *Streptomyces hygroscopicus* also turned out to inhibit cell proliferation and thereby produced antitumor and immunosuppressive activity. Finally, in 1999 sirolimus got its FDA approval for the prevention of kidney allograft rejection. Initially, the implementation of sirolimus was supposed to potentiate the therapy with CsA, but the combination controversially increased nephrotoxicity, hypertension, as well as the incidence of hemolytic-uremic syndrome. Hence, a controlled trial in kidney transplantation confirmed increased nephrotoxicity and hypertension in the treatment group of sirolimus combined with tacrolimus, which has been compared to the combined use of mycophenolate mofetil and tacrolimus.
The synthetic derivate of sirolimus, everolimus, showed an increased bioavailability, but there were no affects in interaction with CsA compared to sirolimus observed. Severe side effects of both lipophilic macrolides have been reported including hyperlipidemia, thrombocytopenia, aggravation of proteinuria, mouth ulcers, skin lesions, as well as pneumonitis, and impaired wound healing (27). Especially in kidney grafts, delayed recovery from acute tubular necrosis was observed.

2.5 Corticosteroids

From the early beginnings of solid organ transplantation, corticosteroids have played a key role in maintenance immunosuppression as well as treatment of acute rejection episodes. Today, most immunosuppressive protocols contain high doses of methylprednisolone perioperatively with a subsequent tapering to approximately 5 to 7.5mg per day over the ensuing months.
Although it has been shown that corticosteroids have anti-inflammatory and immunosuppressive properties due to their suppression of prostaglandin synthesis, their stabilization of lysosomal membranes, and subsequently their reduction of histamine and bradykinin, the exact mechanism of action remains incompletely understood (18). Experimental data provide evidence that a continuous corticosteroid treatment due to the presence of glucocorticoid receptors on T cells, results in steroid mediated T regulatory FOXP3 expression and thus suppressor activity (28, 29).

In addition to their therapeutic immunosuppressive effects, corticosteroids have several severe side effects, especially when administered for a long time, which limit their applicability in post-transplant therapy (30). These sequels include inter alia: diabetes, hypertension, obesity, cushingoid features, osteoporosis, poor wound heeling, and adrenal suppression (31). However, despite many transplant clinicians search out steroid-sparing or even steroid–free regimens due to their deleterious side effects, especially induction therapy regimens still continue to include steroids in their treatment regimens.

3. Induction therapy

Many transplant centers in the United States and Europe are currently preferring to apply intense therapy at the time of transplantation with the goal to deplete the recipient's immune system in the immediate post-transplant period to decrease early deleterious interactions between the recipient's immune system and the donor allograft to ultimately induce a tolerogenic state (32). It has been widely accepted that early alloreactivity not only leads to an increase in acute rejection episodes, but also promotes chronic rejection which ultimately leads to poor long–term graft survival. While current induction immunosuppression agents have reduced the incidence of acute rejection, the goal of transplant tolerance has not been realized.

3.1 Antibodies

OKT3

Antibody mediated immunosuppressants have been used as induction therapy to suppress the recipient's immune system immediately after transplantation. There are both, polyclonal as well as monoclonal, antibodies available. OKT3 is a murine monoclonal antibody, which targets the T cell receptor CD3 complex resulting in a decrease of T cell activation (33). As a side effect OKT3 treatment commonly causes a "cytokine release syndrom" with fevers, chills, headaches and myalgias. As a consequence, patients are premedicated with steroids, acetaminophen, and diphenhydramine as a prophylaxis against this inflammatory response. Other less frequent side effects include pulmonary edema, seizures, aseptic meningitis, and renal insufficiency (34).

Basiliximab (Simulect)

Basiliximab is another antibody, commonly used as an induction agent, which interferes with the alpha subunit (CD25) of the IL-2 receptor (35). This monoclonal antibody of chimeric human-murine origin formidably decreases T cell proliferation and differentiation without T cell depletion. It is preferentially used in patients with the risk of low to moderate rejection episodes and it's currently approved for dosing 20mg on the first and fourth day after transplant (36). Being humanized, there were only minimal toxic effects reported, although basiliximab has been associated with pulmonary edema and ARDS-like symptoms (37).

Alemtuzumab (Campath)

Alemtuzumab is a humanized-rat monoclonal antibody directed against CD52, which is present on the surface of mature lymphocytes (38). Originally prescribed in lymphocytic leukemia and lymphoma, alemtuzumab is currently also used as a potent induction agent in

solid organ and vascularized composite allografts. Although the function of CD52 remains incompletely understood, it is present on the cell surface of B and T cells, as well as macrophages, and NK cells which get depleted upon binding of alemtuzumab. Although alemtuzumab has a half-life of about 2 weeks, different cells have different rates of recovery after therapy. Additionally, alemtuzumab has been shown to deplete T cells inhomogenously, with a relative sparing of memory T cells and T regulatory cells. In terms of side effects, alemtuzumab has been associated with neutropenia, anemia, pancytopenia, first-dose reactions, and autoimmunity (37).

Antithymocyte Globulin

Anthithymocyte globulin (ATG) is a polyclonal antibody derived from animals that have been immunized with human lymphocytes. As a result, ATG is nonspecifically directed against human lymphocytes, which upon treatment get depleted through multiple mechanisms including complement-mediated lysis and opsonisation. In addition, ATG might induce alloantigen specific immunological tolerance as ATG binds lymphocyte costimulatory molecules and similar to OKT3 and alemtuzumab expands T regulatory cells *in vitro and in vivo* (39). Polyclonal antithymocyte globulin is preferrably used as an agent in steroid-free regimes due to its positive effects in the treatment of steroid-resistant rejection episodes. However, ATG treatment frequently induces an acute reaction to initial administration consisting of fever, rigors and anaphylaxis with some patients developing leucopenia and thrombocytopenia.

3.2 Fusion proteins

CTLA4-Ig (Abatacept, Belatacept)

Full T cell activation depends on two signals. The first signal is generated upon MHC-antigen - T cell receptor (TCR) interaction. The costimulation pathway, or signal two, is activated when accessory molecules bind to their ligands. Specifically the CD28/B7 pathway (CD80 and CD86) has proven itself to be relevant for sustained naïve T cell activation. Interfering with these pathways has been one of the most intensively investigated areas in immunology, particularly when considering therapeutic interventions.
After 25 years of research, the fusion receptor protein CTLA4-Ig (abatacept), a competitive antagonist for CD80/CD86 binding, was finally approved for the therapy of rheumatoid arthritis. For the specific use in solid organ transplantation, where an even more robust immunosuppression is required, a second-generation fusion protein called belatacept was developed. Belatacept has proven efficient in prolonging renal allograft survival alone or in combination therapies with basiliximab or MMF and prednisone (40).

3.3 Immunosuppression in Vascularized Composite Allotransplantation

Immunosuppression in vascularized composite allotransplantation (VCA) remains a difficult issue, since the treatment with conventional immunosuppression used in solid organ transplantation is associated with life–threatening infectious complications (41) and metabolic side effects, which seem to be intolerable for non life-saving procedures like hand and face transplantation (42, 43). As a consequence, reconstructive surgeons and immunologists more than ever seek to establish stable donor antigen specific immunological tolerance to vascularized composite allografts, a state that impairs the immune system not to mount responses against a specific allograft, but at the same time facilitates natural defenses

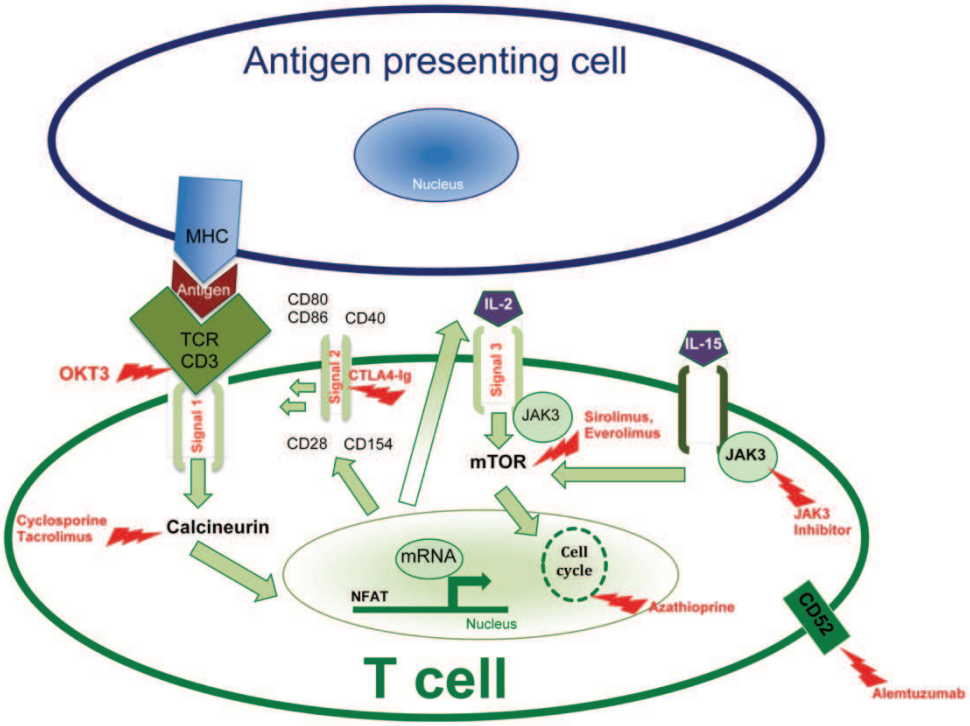

Fig. 1. Immunosuppressive drugs currently used in solid organ transplantation

against viral and bacterial infections. However, in the early days of reconstructive transplantation, immunosuppressive regimens consisted of initial high–dose induction therapy, mainly ATG, or alemtuzumab, which in most cases was followed by a conventional triple combination of corticosteroids, calcineurin inhibitors, and mycophenolate mofetil (44). Exceptions to this conventional immunosuppressive treatment include some recent cases in hand transplantation, where patients received induction therapy with alemtuzumab followed by maintenance immunosuppression with tacrolimus and mycophenolate mofetil (Louisville) or tacrolimus and prednisone (Innsbruck). More recently, the "Pittsburgh Protocol" consisting of an induction therapy with alemtuzumab and a donor specific bonemarrow cell transfusion within 2 weeks after transplantation proofed that maintenance immunosuppression with tacrolimus alone can successfully be achieved in VCA. The idea of donor cell infusion for either the induction of chimerism or the intensification of clonal exhaustion or deletion of alloreactive T cells is appealing, however, the combination of such a concept with high–dose multi drug immunosuppression might be counterproductive, because such phenomena may require the persistence of a certain degree of immune response to be effective. Recent innovative immunosuppressive protocols proofed to be effective in weaning patients off immunosuppression or at least in allowing a reduction of immunosuppression to a minimum level (45, 46). Nevertheless, from the current clinical point of view in reconstructive transplantation, it is difficult to conclude the superiority from one immunosuppressive regimen over another and it seems mandatory to pursue

multicenter prospective trials despite the limited number of patients that are currently eligible to be enrolled in such trials.

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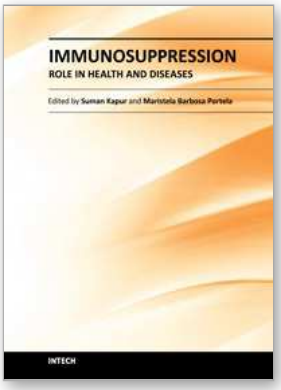

Immunosuppression - Role in Health and Diseases

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A need for a book on immunology which primarily focuses on the needs of medical and clinical research students was recognized. This book, "Immunosuppression - Role in Health and Diseases" is relatively short and contains topics relevant to the understanding of human immune system and its role in health and diseases. Immunosuppression involves an act that reduces the activation or efficacy of the immune system. Therapeutic immunosuppression has applications in clinical medicine, ranging from prevention and treatment of organ/bone marrow transplant rejection, management of autoimmune and inflammatory disorders. It brings important developments both in the field of molecular mechanisms involved and active therapeutic approaches employed for immunosuppression in various human disease conditions. There was a need to bring this information together in a single volume, as much of the recent developments are dispersed throughout biomedical literature, largely in specialized journals. This book will serve well the practicing physicians, surgeons and biomedical scientists as it provides an insight into various approaches to immunosuppression and reviews current developments in each area.

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