Understanding immunosuppressive drugs for better management of infectious diseases in transplant recipients

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In the modern medicine era, organ transplantations have been performed more commonly especially in well-established transplant centers. The goal of organ transplantation is to maintain organ function by implementing different modalities of treatment mainly including immunosuppressive agents in order to halt rejection reaction. As an infectious disease (ID) doctor, I did not realize the importance of understanding the rationale, plausible consequences, and so on with immunosuppressive agent use in the beginning of my training since the ID doctors are not the persons prescribing these agents. But when I had to deal with such patients on my transplant infectious disease rotation, new thoughts were inserted into my head that ID physicians should also know some basics about this science as well. Realizing this, understanding the existence of three-signal models of alloimmune responses is suggested and detailed information will be discussed elsewhere.

Effects of immunosuppressants can be classified broadly as depleting lymphocyte effect, diverting lymphocyte traffic, and blocking lymphocyte pathways. With such treatment, therapeutic effect by suppressing rejection is expected. However undesired consequences such as infection or cancer, as well as nonimmune toxicity are not uncommon.1

Categories of agents in organ transplantation

Induction agents

Induction is the use of powerful therapy in the perioperative period to minimize early rejection while avoiding concomitant usage of nephrotoxic agents and to improve graft outcomes.2,3 Available agents are antilymphocyte globulin (ALG), antithymocyte globulin (ATG), alemtuzumab, and interleukin-2 (IL-2) antibodies.

The use of antibody induction therapy has increased significantly over the last 15-20 years. At present, this method is utilized in over 80% of renal transplantations in the US.3 The mechanisms of induction agents remain unclear. Polyclonal agents such as ATG and ALG despite relativity, have nonspecific targets as well as activities against both T and B cells resulting in rapid and profound lymphopenia.4,5 Recovery from immune depletion takes months to years.

Monoclonal antibodies are nondepleting protein drugs such as IL-2 inhibitors; basiliximab and daclizumab which target CD25. Generally these agents do not compromise lymphocyte populations, therefore limited efficacy is anticipated except alemtuzumab that...
binds CD52 as a target and causes profound T-cell depletion through complement-mediated cell lysis. Some studies suggest higher risk of infections.6

**Primary immunosuppressants**

Calcineurin inhibitors (CNIs) are the cornerstone of immunosuppressive therapy. Both cyclosporine and tacrolimus bind to immunophillins, although different subtypes bind to calcineurin and block its action and subsequent T-cell activation. Comparatively, tacrolimus is more potent than cyclosporine in immunosuppressive property.7 Renal toxicity is a well known nonimmune adverse effect of CNIs. Short term toxicity was discovered to be associated with severe vasoconstriction of the afferent arteriole leading to reduction in renal blood flow and glomerular filtration rate (GFR).5,8 On the other hand, patients who have long term toxicity usually present with hypertension which can be explained by findings of interstitial fibrosis and obliterator arteriolar changes due to fibrous intimal thickening evident on histopathology.8 The latter effect is believed to be dose related and irreversible.8

Regarding infectious complication, tacrolimus has been suspected of inducing more BK-related polyomavirus nephropathy than has cyclosporine in kidney transplant patients in particular when used with mycophenolate mofetil (MMF).5

**Adjuvant agents**

Generally one or more medications are prescribed in addition to CNI. Some of the common agents used include corticosteroids, MMF and sirolimus.

Corticosteroids are the least selective agents with a variety of anti-inflammatory and immunomodulatory effects. High lipophilicity and ability to readily cross cell membranes where they bind to cytoplasmic receptors and influence transcription are main characteristics. Their actions have been described as blocking IL-2 production, inhibiting other sites of T-cell and monocyte activation, inducing transplant lymphopenia, blunting antibody production, decreasing extravasation and chemotaxis of neutrophils. The potency seems to be dose specific.9

Infection risks in association with corticosteroid use are fungal, pneumocystis, and mycobacterial infections when macrophage mediated killing qualification has been compromised. Staphylococcal, legionella, aspergillus, and nocardial infections are observed when neutrophilic killing becomes weakened. Interestingly, they have less effect on cytotoxic T-cell mediated killing, therefore reactivation of viruses is not one of the top concerns.10

Azathioprine (AZA) and MMF are currently used, widely. Their active metabolites are incorporated into replicating DNA and halt replication resulting in interference with de novo pathway of purine synthesis and prevent clonal expansion of lymphocytes. Less impact on antibody production is predicted.8

Both agents share quite a few similarities in terms of mechanism of action and associated infections that require cytotoxic T-cell mediated killing, such as viruses. Bone marrow suppression is more prevalent in AZA use. On the contrary, GI symptoms are more prominent with MMF administration described as diarrhea, nausea, vomiting, and abdominal pain.5,8

Another two agents of target of rapamycin inhibitor (TOR) group, sirolimus and everolimus have also gained popularity in solid organ transplantations. Essentially they bind to TOR and prevent usual signaling pathways responsible for cell cycle progression from G1 to S phase.5,11-13 Besides inhibiting TOR, they also inhibit fibroblast growth factors required for tissue repair. This familiar side effect has been praised in cardiology patients undergoing angioplasty in order to prevent intimal proliferation and also in cardiac transplant vasculopathy. However, TORi do not
always provide favorable posttransplant outcomes. They can lead to poor wound healing. Higher incidence of anastomotic dehiscence with sirolimus has been seen in lung transplantation.11-13

Other nonimmune toxicities include a substantial rise in serum cholesterol and triglycerides, elevation of liver enzymes, bone marrow suppression which anemia is most identified, and painful mouth ulcers.5,12 Sirolimus associated interstitial pneumonitis has been reported from time to time. Presenting symptoms are usually difficult to distinguish from some active pulmonary infections. Patients ordinarily come in with fatigue, fever, dyspnea, and non-productive cough. Findings on chest radiograph can be either diffuse interstitial or ground glass infiltrates. The incidence of this phenomena is mostly reported within the first 6 months of transplantation but can be later. To date, this is believed to be closely related. Symptoms by and large improve within three weeks after discontinuation of the drug. Some may require a short course of corticosteroid treatment to enhance the recovery.14

In one organ transplant recipients, this is quite rare to see only one or two immunosuppressants being used peculiarly when they come in with infectious complications. Antimicrobial interactions are not scattered events. Thus, understanding common interactions would benefit ID physicians enormously. Azoles markedly increase blood levels of CNIs and sirolimus through inhibitor of cytochrome P450 metabolism which means initiation of azole therapy requires concomitant dose adjustment and follow-up monitoring of immunosuppressive drug levels. Co-administration of voriconazole and sirolimus is contraindicated as levels of sirolimus can increase 7-11 times and lead to remarkable toxicity.15 Caspofungin levels rise with cyclosporine use and pose higher risk of hepatotoxicity. Tacrolimus levels are lowered in concomitant use of caspofungin by 20% but no obvious reaction is demonstrated with sirolimus co-administration. Micafungin does elevate sirolimus levels by 21%.15-17

In summary, evolving trends in transplant immunosuppression are to minimize use of particular agents to avoid long term adverse effects, steroid withdrawal and CNI-sparing regimens. Potent induction is an ordinary practice in this era on the purpose is to avoid rejection and improve graft outcomes. Multiple immunosuppressants are used routinely to target different points of lymphocyte function. Adverse effects and drug interactions should be anticipated. The risk of infection is prevalent because of the duration and intensity of immunosuppression, rather than specific agents used. “Dialing in” on the correct set point optimizes outcome.

References
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