Managing Side Effects of Immunosuppressants

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INTRODUCTION

Maintaining an allograft after solid organ transplant (SOT) requires maintenance immunosuppression to prevent rejection and preserve organ function. While there have been improvements in the toxicities of maintenance regimens over the decades, transplant patients are still at high risk of developing side effects to their immunosuppression therapies. These can range from cosmetic changes, metabolic abnormalities, and toxicities to different organ systems.[1-3]

Medication adherence remains a significant challenge for SOT recipients. While difficult to capture the exact scope of its prevalence, it has been reported that medication nonadherence ranges from 22–68% in the SOT community. This is significant due to medication nonadherence being identified as an independent risk factor for poor outcomes after SOT.[4] While there can be many reasons why a patient is non-compliant with their medications, the World Health Organization identified side effects as a significant treatment-related factor for nonadherence.[5] SOT recipients may also seek out alternative therapies to self-treat their side effects, which can have an impact on immunosuppression therapy and organ function.[6,7] A combination of a calcineurin inhibitor (CNI), antimetabolite, and a corticosteroid remains a common maintenance regimen for SOT recipients.[8] While efficacious, these medications are associated with many side effects that can impact patients' quality of life.[1-3] While it may not always be clinically appropriate to change a transplant recipient's medication or reduce their dose, it is important to recognize and manage these side effects.

CALCINEURIN INHIBITORS

Cyclosporine was the first CNI used in SOT, which dramatically changed recipient outcomes.[2] Now, tacrolimus has become the CNI of choice due to its lower rejection rates and trends for increased patient survival.[9] Despite their benefits, CNIs are associated with numerous toxicities such as neurotoxicity, nephrotoxicity, development of new onset diabetes after transplant (NODAT), and cosmetic changes.[1,2,10] In recent years there has been an interest in investigating CNI withdrawal and avoidance regimens in order to avoid the toxicities associated with their long-term use.[2]

Tacrolimus is very lipophilic and plasma bound, which increases its ability to cross the blood-brain barrier. The presence of tacrolimus in the central nervous system may lead to the over production of endothelin, which, if introduced to vascular smooth muscle, can cause vasocontraction and vasospasm. The spectrum of tacrolimus neurological-related side effects includes, insomnia, headache, tremor, mood changes, and seizures.[10] To help prevent these side effects, therapeutic drug monitoring is used to make sure serum concentrations stay within therapeutic range. Analgesic medications can be used to relieve headache and sleep aids can be employed to help with insomnia. Conversion to an extended release tacrolimus product may help reduce certain peak-related side effects, such as tremors.[11] In cases of severe side effects like seizure, discontinuation of tacrolimus may be required. Alternative therapies may conclude conversion to cyclosporine, sirolimus, or belatacept.

The nephrotoxicity of CNIs remains a major concern in the transplant community. Afferent arteriolar vasoconstriction, activation of rein-angiotensin-aldosterone-system, and release of endothelin can lead to acute renal injury. Irreversible structural abnormalities in the kidney are seen after long-term use. Close therapeutic drug monitoring is utilized to prevent acute renal injury, by avoiding supratherapeutic serum concentrations. Use of dihydropyridine calcium channel blockers in patients with concomitant hypertension may counteract the vasoconstriction on the renal artery. There is no evidence to suggest that tacrolimus is less nephrotoxic than cyclosporine. CNI withdrawal and avoidance regimens have been studied with alterative immunosuppression therapies such as sirolimus, everolimus, or belatacept. While there may be long-term benefits of limiting CNI use in SOT recipients, these potential benefits must be balanced with the risks of rejection and graft loss.[2]

Tacrolimus can cause alopecia in 3–6% of patients.[12] Vitamin supplementation with biotin may be beneficial in protecting hair strength. If impacting the SOT recipient's quality of life, alternative immunosuppression therapies may be considered for certain patients. Conversion to cyclosporine can be considered, but hirsutism and gingival hyperplasia can occur.[1] Sirolimus or everolimus can be considered, but acne is a potential cosmetic side effect.

ANTIMETABOLITES

Mycophenolate is the most common antimetabolite currently used in SOT.[8] It has two different preparations; mycophenolate mofetil (MMF) and enteric-coated, mycophenolate sodium (EC-MPA). Both preparations are equally efficacious and have similar safety profiles.[13] Among transplant centers, there will be varying practices as to whether they prefer MMF or MPA for their SOT recipients. Azathioprine is an older antimetabolite that has been used for decades in SOT. Azathioprine's place in therapy is now usually reserved for patients who are unable to tolerate the mycophenolate products or trying to conceive.

Gastrointestinal (GI) side effects are common with mycophenolate products. Mycophenolate, after it is converted to mycophenolic acid, disrupts the production of GI epithelial cells through its anti-proliferative properties.[14] Symptoms may include diarrhea, nausea, vomiting, dyspepsia, and abdominal pain. Depending on the severity of the of the GI side effect and other infectious causes of diarrhea have been ruled out, it may be reasonable to monitor the patient before making any interventions. If symptoms persist or become more severe, dose adjustments may be necessary.[14,15] The GI side effects of mycophenolate are dose dependent. Total daily dose reductions may be appropriate for some patients. However, lowering doses of immunosuppressive agents can increase the risk of rejection and additional allograft monitoring should be performed. An alternative strategy to lowering the total daily dose of mycophenolate is to split the total daily dose over three or four doses instead of two.[15] A limitation of increasing the dosing interval is that it does make regimens more complicated for patients.

Bone marrow suppression is another potential side effect of mycophenolate.[16,17] It has been reported that neutropenia occurs in 5–38% in the kidney transplant population. The evolution of neutropenia for SOT recipients is multifactorial, but medications, infections, and malignancies must all be considered.[17] After neutropenia is identified and infections have been ruled out, all medications should be assessed for their potential to cause bone marrow suppression. For certain patients, it may be preferred to discontinue other bone marrow suppressing medications prior to adjusting their immunosuppression. If neutropenia persists, decreasing or discontinuing the mycophenolate product may be required. Based on the degree of neutropenia, granulocyte colony-stimulating factors may need to be used until the absolute neutrophil count recovers to an acceptable limit.

CORTICOSTEROIDS

Corticosteroids have been utilized in SOT for decades. However, their long-term use has been associated with a significant number of side effects including: osteoporosis, bone fractures, cardiovascular disease, psychiatric disturbances, and dermatological changes.[3,10] The toxicities associated with glucocorticoid steroids are related to the average dose and cumulative duration of use.[3,16] Steroid reduction and withdrawal may be safe for some SOT recipients, but there are certain patient populations that require life-long use. The Scientific Registry of Transplant Recipients (SRTR) annual report from 2018 showed that only 30% of kidney transplant recipients are steroid free.[8] With their use still prevalent, it is important that SOT recipients receive monitoring for corticosteroid-related side effects.

Corticosteroids alter bone metabolism by reducing bone formation and increasing resorption. These changes in bone metabolism lead to an increase risk of bone fractures.[3,16] Bone-protective therapies can be considered for high-risk patients when initiating corticosteroid therapy. High-risk individuals may include patients >65, those with past fractures, or those with a history of osteopenia. Calcium, vitamin D supplementation, and bisphosphonate therapy have all been used as bone protective regimens.[16] Monitoring of bone mineral density is recommended for high-risk populations, prior to steroid corticosteroid therapy and after 1 year of therapy if prednisone doses are expected to be ≥5 mg per day.[3]

Corticosteroids are associated with precipitating or exacerbating cardiovascular risks factors such as hypertension, hyperglycemia, hyperlipidemia, and obesity.[3] Patients on long-term corticosteroids should be monitored for these side effects and counseled on lifestyle modifications with diet and exercise as appropriate. Additional pharmacologic therapies may need to be initiated if these risk factors cannot be controlled despite diet and exercise.[1,3,16]

The neurologic side effects of corticosteroids can range from insomnia, irritability, mood changes, mania, and depression. The onset of these symptoms usually presents within the first couple of days to weeks of therapy. Management usually consists of lowering the dose of the corticosteroid. However, additional management may include sleep aids, antidepressants, or antipsychotics for certain patients.[10]

DIETARY AND HERBAL SUPPLEMENTS

The use of alternative medicine has increased in the United States, with 36% of Americans admitting to using herbs, non-herbal supplements, and vitamins. These products are not subjected to safety and efficacy testing by the FDA and their manufacturing practices are not regulated, which can lead to product inconsistencies.[6] Frequently, dietary and herbal supplements are started without consulting a health care provider. When reconciling medications with SOT recipients, it is important to screen for dietary and herbal supplement use. For SOT recipients, dietary and herbal supplements can be associated with drug interactions, immune stimulating effects, and direct organ toxicity.[6,7]

The drug interactions associated with these products can be clinically significant by affecting serum concentrations

of immunosuppressant medications. St. John's Wort is an inducer of CYP3A4, CYP2C9, and P-glycoprotein (P-gp). The use of St. John's Wort in combination with a CNI would lead to decreased serum concentrations of cyclosporine or tacrolimus. Ginkgo biloba and milk thistle are inhibitors of CYP3A4, CYP2C9, and P-gp. Turmeric is another inhibitor of CYP3A4. The use of these herbs in combination with a CNI would increase the serum concentrations of cyclosporine or tacrolimus.[18]

Some dietary and herbal supplements are marketed as immune stimulants. The concern with these products in the SOT population is that they can precipitate an immune response and interfere with immunosuppression therapy.[7,18] Echinacea, ginseng, astragalus, and vitamin C are examples of herbs and supplements that have immune stimulating effects and generally should be avoided in the SOT population. Vitamin C may also be used to promote wound healing; if its use is required, the risks vs. benefits should be discussed with the patient's transplant provider.

Dietary and herbal supplements can also have a direct effect on renal and hepatic function. Supplements such as chromium, creatine, L-Lysine, and willow bark can be directly nephrotoxic. High-dose vitamin C (>60 g/day), ephedra, and cranberry have been reported to cause nephrolithiasis. Case reports of supplement-induced rhabdomyolysis have been reported with use of wormwood oil, licorice, and creatine.[6] Herbal supplements that are known to be hepatotoxic include: kava kava, comfrey, DHEA, bee pollen, vitamin E, green tea, echinacea, turmeric, and valerian.[6,7,18]

CONCLUSION

In conclusion, SOT recipients are at high risk for developing side effects and toxicities to their maintenance immunosuppressants. It is important to recognize and manage these side effects as they can impact patients' quality of life, affect medication adherence, and cause damage to different organ systems. Patients should be monitored for potential side effects and interventions should be made when clinically appropriate. Patients may require adjunctive therapies to help manage these side effects or modifications to their immunosuppressive regimens may be necessary. SOT recipients should be screened for use of dietary and herbal supplements, due to their potential impact on organ function and drug interactions. If changing a SOT recipient immunosuppression regimen, the risk and benefits must be considered and additional graft monitoring is required.

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