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Review Article

AN OVERVIEW ON COMPLICATIONS OF IMMUNOSUPPRESSANT DRUGS

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Abstract

Immunosuppressant's are essential for cancer chemotherapy, treatment of many autoimmune disorders and successful organ transplantation. They suppress rejection and dampen the autoimmune process.The mechanisms of action of immunosuppressant drugs fall into three main categories: inhibition of the cell cycle (azathioprine, cyclophosphamide, methotrexate and mycophenolate mofetil), immunosuppression of T cells (steroids, ciclosporin and tacrolimus) and B-cell depletion (rituximab). But they also lead to the undesired consequences of immunodeficiency. Some of these drugs have a narrow therapeutic range, so monitoring is required. These drugs increase the risks of infection, malignancy, cardiovascular disease, bone marrow suppression, renal dysfunction, hypertension, and diabetes. Standard immunosuppressant drug must be tailored according to the clinical situation and resources of immunosuppressive drugs.

Key words: Autoimmune disorders, Immunosuppressant, Infections, Malignancy.

Introduction

Immunosuppressants are medications that suppress or prevent the immune response, used to prevent rejection of a transplanted organ and to treat autoimmune diseases such as scleroderma psoriasis, rheumatoid arthritis, and Crohn's disease. They are also referred to as immunodepressants. Some immunosuppressants are chemotherapy drugs;

however, when used to treat autoimmune diseases, the dose is lower than when used in chemotherapy to treat cancer or organ transplant patients. Many of the currently available immunosuppressant's are developed for use in oncology or transplantation. As this treatment is potentially life-saving desperate measures can be justified. However, there are now over 80 autoimmune diseases and several common allergic conditions in which immunosuppressant's could play a role although they may be life-saving [1].

In the early days of immunosuppression therapy in transplatation was rather broad and nonspecific, mainly using high-dose corticosteroids and azathioprine. There after we progressively narrowed the target of immunosuppressive strategy starting with polyclonal antibodies. The introduction of cyclosporine, and tacrolimus further narrowed the target on the T-cell pathways. Later mycophenolate mofetil progressively took the place of azathioprine with its higher lymphocyte specificity and sirolimus and interleukin-2 receptor antibodies were introduced. In this field in constant movement the aim is to find a drug or a regimen that provides optimal immunosuppression therapy with minimal side effects, in other words to find the right balance between over immunosuppression and under immunosuppression therapy [2] .

Advances in transplantation and the treatment of immune disorders have paralleled the development of immunosuppressant drugs. While the newer drugs are associated with superior efficacy, this may come at the cost of a greater incidence of opportunistic infections and malignancy, and adverse effects such as chronic allograft nephropathy,

hyperglycaemia and hyperlipidaemia. Accurate concentration monitoring of cyclosporin, tacrolimus, sirolimus, everolimus and probably mycophenolate is necessary to improve outcomes and minimise toxicity[3].

Complications of immunosuppresants:

In Long term immunosuppressive therapy, the significant risk factor are infections, malignancy, Cardiovascular risks, bone marrow suppression, renal dysfunction, hypertension, diabetes mellitus, hyperlipidemia, Obesity, osetoporosis. As more immunosuppresents come in to use in various combination regimens are being used to reduce the toxicity.

Malignancy

Basically all drugs that affect the immune system carry a possible risk of tumours of various kinds. Firstly many immunosuppressive agents are mutagenic and some have been shown to be frankly carcinogenic. Second, it has been shown experimentally viral oncogenesis that may be potentiated by various immunosuppressive agents. Thirdly, immunosuppressants would be expected to facilitate the growth of those tumours that possess tumour-specific antigens[3].It has been clearly demonstrated that the risk of cancer in transplant recipients is higher than in the general population[4,5] .Although the common types of cancer in the general population, such as carcinomas of the lung, prostate, and breast are not increased in transplant patients, certain cancers that are uncommon in the general population such as lymphomas, skin cancers, and Kaposi sarcoma occur more often in transplant recipients[6] .

A large UK-Austral-asian study showed that, compared to the general population, transplant patients had a relative risk (RR) of 49.4 of developing lymphoma, while a group of non-transplant patients treated with immunosuppressive had a RR of 11.8[7] . The study was later extended to include 643 rheumatoid arthritis (RA) patients receiving immunosuppressive[8]. This group had a RR of 13.0 of developing lymphoma. The risk was the same for azathioprine or cyclophosphamide therapy. There were also reports of RA patients treated with chlorambucil having the risk of developing neoplasm of the immune system (NIM) [9].One of the trial reported that the adult patients, one in the cyclosporine group died of brain lymphoma and four in the same group died of other malignancies, including osteosarcoma, recurrent cardiac rhabdomy sarcoma, lung carcinoma, and testicular embryonal cell carcinoma [10]. Azathioprine(was the first drug to be investigated with regards to enhancing lymphoma risk in RA. An association between azathioprine therapy and Non-hodgkin's lymphoma (NHL) had first been noted in transplant patients. The Canadian registry of azathioprine use reported an 8-fold increased risk of lymph proliferative disorders based on four cases in 530 patients [11].

Immunosuppressive treatments have a clear effect on cutaneous carcinogenesis. The risk of skin cancer is increased in patients treated with immunosuppressive agents. This is well documented in organ transplant patients. The role of

cyclosporine is controversial. Some studies have shown that cyclosporine based immunosuppression increases the risk of squamous cell carcinoma more than combination treatments (azathioprine and prednisone) [12,13].Another trial also suggested the same that the most common skin cancers are squamous cell carcinoma and basal cell carcinoma, which cover over 90 per cent of all skin cancers in this group [14,15]. Danpanich et al. reported 11 colorectal malignancies (12.6%) in 87 renal transplant recipients. The authors identified that the risk of cancer in renal transplant recipients increases significantly by age at transplantation, pretransplant splenectomy, a history of invasive cancer pretransplant, and Cigarette smoking[16].

Diabetes mellitus

Immunosuppressants such as corticosteroid, cyclosporine or tacrolimus may be responsible for raising blood glucose levels. The cause of corticosteroid related post transplanted diabetes mellitus (PTDM) was assumed to be the stimulation of gluconeogenesis and the impairment of glucose uptake by muscle and adipose tissues, which would lead to insulin resistance. Some researchers indicated that the incidence of PTDM Correlated with the dosage of corticosteroids and may reach as high as 46%[17]. The risk of developing PTDM was 5% per 0.01 mg/kg/day of increase in predinisolone[18].During the cyclosporine era, the incidence of PTDM decreased t o 3%-20% [19,20]. The diabetogenic effects of cyclosporine and tacrolimus probably resulted from the drug interaction with corticosteroid. Cyclosporine and tacrolimus both might competitively inhibit the hepatic metabolism of corticosteroids which would increase the side effects of corticosteroids. However, some investigators illustrated that it was possible to increase blood glucose levels by taking cyclosporine alone [21,22].

Several researchers revealed that the mechanism of cyclosporine induce hyperglycemia in probably involved in the reduction of insulin production, inhibition of insulin secretion and decrease of pancreas' ß-cell volume[23,24].Yoshimura et al compared the influence of two different types of immunosuppressive regimens on blood sugar in renal transplant recipients. The results showed that the incidence of PTDM was significantly higher in patients using the regimen of cyclosporine plus prednisolone, rather then patients using the regimen of azathioprine plus prednisolone (17.1% vs. 12.8%; $P < 0.05$). In addition, the incidence of PTDM in patients receiving

cyclosporine correlated with higher cyclosporine trough levels (>350 ng/Ml) [21]. In a study prevalence of new-onset insulin-dependent diabetes mellitus was the same in adults in both the tacrolimus (26%) and Cyclosporine (22%) groups. New-onset insulin-dependent diabetes mellitus developed in one of 50 pediatric patients receiving tacrolimus [10]. The mechanism of hyperglycemia induced by tacrolimus was similar to cyclosporine, which could be contributed to the low insulin secretion and increase in insulin resistance. Maes et al analyzed the incidence of PTDM in 139 renal transplant recipients, and indicated that the incidence of PTDM was 32%. In their study, the tacrolimus trough level (>15 ng/mL) was one of the most important risk Factors[25]. The U.S. Multi center Phase III Trial of tacrolimus therapy in kidney transplantation revealed an increased incidence of PTDM among patients receiving tacrolimus compared with cyclosporine 1 year of follow-up (19.9% vs. 4.0%, respectively,P_0.001) [26].

Hypertension

Hypertension (HTN), defined as a systemic BP >140/90, is prevalent in >70% of transplant recipients [27]. HTN is a risk factor for allograft failure, death with a functioning allograft, atherosclerotic cardiovascular disorder, and disorders of cardiac function. The pathogenesis of HTN in transplant recipients is linked to pre-transplantation including pre-transplant HTN, the type of primary kidney disease, and excess renin output from native kidneys.

Some studies proven that HTN was significantly lower before the introduction of CNI[28,29]. CNI cause afferent arteriolar vasoconstriction by sympathetic stimulation and by up regulation of the local renin-angiotensin-aldosterone system [30, 31]. CNI also decrease vasodilator prostaglandins and nitric oxide and increase vasoconstrictor cytokines [32, 33]. Calcineurin inhibitor treatment increased salt and water absorption, and increased sympathetic activity, which contributes to the development of hypertension. Fluid retention due to prednisone therapy may also be of some importance. In a study they suggest that prevalence of new-onset hypertension in adults in the tacrolimus and cyclosporine groups was 47% (39/83) and 84% (80/95). In the pediatric group, 10% of the patients treated with tacrolimus had hypertension [10].

Cyclosporine-induced hypertension may develop from a variety of sources, including vascular dysfunction owing to direct cytotoxic effects on the endothelium, direct contractile effects on vascular smooth muscle cells, impaired

nitric oxide (NO) release. One explanation for the lower rates of hypertension with Tacrolimus use is that, in contrast to Cyclosporin, Tacrolimus does not induce significant endothelin(ET-1) production by the endothelium[34,35]. In a muliti-centered trail that enrolled 85 patients this reports hypertension with TAC 48% and CSA 71% [36].

Hyperlipidemia

Dyslipidemia is present in 50 to 60% of kidney transplant recipients. The KDOQI guidelines recommend that all adult and adolescent transplant recipients be tested for dyslipidemia (complete fasting lipid profile including total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), and triglycerides) [37]. Dyslipidemia is clearly linked to the use of corticosteroids, CNI, and sirolimus. Compared with cyclosporine, tacrolimus has been associated with better lipid profiles, whereas sirolimus has been associated with a greater incidence and severity of dyslipidemia. The major adverse effects of Sirolimus include hyperlipidemia with hypertriglyceridemia and increased LDL cholesterol. Hypercholesterolemia and hypertriglyceridemia are at least partially responsive to dose reduction [38].Sirolimus alters the insulin signaling pathway so as to increase adipose tissue lipase activity and/or decrease lipoprotein lipase activity, resulting in increased hepatic synthesis of triglyceride, increased secretion of very low density lipoprotein (VLDL), and increased hypertriglyceridemia.

Cardiovascular risk

A large cohort study has shown that even after adjustment for known covariates, the relative risk for cardiovascular events in patients receiving high-dose glucocorticoids was 2.56[39].The risks of individual outcomes such as death, heart failure, myocardial infarction, stroke and transient ischaemic attacks are all significantly higher for those prescribed high-dose glucocorticoids. Tight control of cardiovascular risk factors is therefore essential for those taking corticosteroids. A cardiovascular disease event in a transplant recipient may be the result of a pre transplantation disease process, a direct effect of immunosuppressant medications**.** Several investigators have demonstrated that CNI exposure leads to endothelial dysfunction. Clinical studies have shown that Cyclosporin treatment results in endothelial dysfunction in transplantation patients, finding impairment of fore arm blood flow in

patients give Cyclosporin compared with controls [40-43]. cardiomyopathy with progression to severe hypertrophic obstructive

cardiomyopathy and congestive heart failure in some patients has also been noted in liver and/or bowel-transplant recipients receiving tacrolimus[44]. Azathioprine and mycophenolate mofetil (MMF) [45-47] have the lowest adverse cardiovascular risk/toxicities of the currently available immunosuppressive agents. This has recently been high lighted for MMF in the results of the latest cardiac trial [48] . Cyclosporin causes contraction of small arteries, probably by damaging the endothelium, with subsequent imbalance in the synthesis/release of vasodilatory and vasoconstrictions substances, sirolimus have a vasodilatory effect: endothelium dependent vasodilation is increased[49].

Nephrotoxicity

Long-term treatment with calcineurin inhibitors causes a reduction in renal function. That is more rapid during the first year post-transplantation and slower during the following years. The reason for this renal impairment is the vasoconstriction of preglomerular afferent arterioles due to increased-sensitivity vasoactive constrictors, such as endothelin and thromboxane. The trial by Grimmand colleagues agrees that there is not much difference, but notes that the incidence of kidney disorders over time is slightly lower with tacrolimus than Cyclosporin [49]. Kobashigawa and colleagues 5-year results comparing tacrolimus to cyclosporin microemulsion found significant decreases in creatinine levels of patients taking tacrolimus compared with those taking cyclosporin, although the authors noted that the number of patients requiring hemodialysis over the 5-year period was similar between groups[51]. The adverse effects of cyclosporine are many owing in part to the ubiquitous tissue distribution of cyclophylins. Nephrotoxicity has been the greatest concern. Its incidence has been reported between 40% and 70% [52]. Acute nephrotoxicity occurs secondary to intrarenal vasoconstriction and is reversible. Chronic nephrotoxicity is likely a long-term secondary sequela of persistent renal vasoconstriction and ischemia and is irreversible with obliterative vasculopathy and interstitial fibrosis on histology. Bryan d. Myers et al conclude that continuous CSA

therapy for more than 12 months causes a chronic injury to renal micro vessels that is rarely reversible and potentially progressive[53].

Hepatotoxicity

A study reports that immunosuppressant like Azathioprine related hepatotoxicity is defined as Alanine aminotransferase (ALT) and/or gamma glutaryl transferase(GGT) levels greater than 5 times the upper normal limit, or Alkaline phosphatase (ALP)levels greater than 3 times the upper normal limit, excluding viral hepatitis. When withdrawing AZA or reducing the dose, the above indexes recover to normal[54]. Hepatotoxicity occurs with methotrexate at a frequency of 1 per 35 patient years. It is usually associated with a cumulative dose of at least 1.5 g. Alcohol is a major risk factor and should be avoided. The general practitioner should enquire regularly about the patient's alcohol intake. Coexisting hepatitis B and C also increases the risk of hepatotoxicity. The current recommendation is for 1–3monthly monitoring of liver function. Liver biopsy is indicated if six of twelve tests are abnormal [55].

Marrow suppression and cytopenia

Bone marrow suppression is a common dose-limiting toxicity for most of the immunosuppressive drugs; Candy et al. reported a dose reduction of azathioprine (AZA) due to a leukocyte count of less than 4 $x10^9$/l in 13 of 33patients. All returned to white cell count levels of above 4 x 10^9/l after dose reduction. No-one had to discontinue the treatment[56]. A severe leukopenia, thrombocytopenia or anaemia or a combination can be the result. Present reported a leukopenia of less then 2.5 x 10^9/l in 2% of the patients treated with 6-Mercapto purine 1.5mg/kg/day[57].Marrow suppression with neutropenia is common after six weeks of Cyclophosphamide treatment. For Sirolimus and everolimus therapeutic drug monitoring is essential because of the risk of toxicity such as anaemia, leucopenia and thrombocytopenia[1]. A study reports therapy with corticosteroids induced dose-dependent lymphocyte depletion. Concomitant application of cytotoxic disease modifying drugs and corticosteroids caused an additive effect on lymphocytopenia, Patients receiving chronic immunosuppressive therapy can develop severe lymphopenia that cause susceptive to infections[58].

Infections

All immunosuppressive drugs have an on specific and extremely heterogeneous mechanism of action, but their main consequence and side-effects are infection. Patients may be infected by common community-acquired and opportunistic organisms. The risk of infection increases with the degree of immunosuppression. Infections with pneumocystis irovecii, nocardia, aspergillus, cryptococcus and reactivation of Varicella zoster, herpes simplex, cytomegalovirus, hepatitis Band C as well as tuberculosis are common immunosuppressed

Viral infection

Infections with cytomegalovirus (CMV) and herpes viruses are very common in transplant recipients. CMV infection occurs in a large proportion of transplant patients and is the most common viral cause of clinical disorders in these patients. In one of the large studies, tissue-invasive CMV, not specified for site, was diagnosed in6.8% of CSA and 9.3% of TAC patients[59]. In the US trial, tissue-invasive CMV disease was more common in the MMF groups, with rates of 7% for azathioprine (AZA) group, 11-12% for MMF[60].

Bacterial infection

Viale et al through his study found that bacteria (in particular Enterobacteriaceae, non-fermenting Gram-negative bacilli and Enterococcus spp) and Candida spp are a frequent cause of urinary tract infection in the early post-transplantation phase [61]. A study suggests that the use of newer immunosuppressive agents in recent years is associated with some changes in the epidemiology of post-transplant infections. 127 infections were reported in 65 patients, consisting of urinary tract infection (UTI) (47%), viral infections (17%), pneumonia(8%), and surgical wound infections (7%).UTI was the most common infection in all post-transplant periods. Enterococcus spp. (33%) and Escherichia coli (21%) were the most prevalent uro pathogens[62]. Tuberculosis is a common infection of renal transplant recipients in developing countries. The peak incidence is after the first year of transplantation and mortality is considerable. Renal transplant recipients are more prone to develop this infection, the risk being nearly

50 times higher than in the normal population Tuberculous and atypical mycobacterial infections are rare, comprising less than 2% of pneumonias in the transplant recipient[63,64].

Fungal pathogens and protozoa

Another consequence of immunosuppression is susceptibilty to infection by protozoan or metazoan parasites. Microspo-Idia is obligate intracellular protozoan parasites. Gumbo *et al.* described four cases in which microsporidial infection led to unexplained chronic diarrhea, fatigue, and weight loss in solid organ transplant recipients[65].The incidence of invasive fungal infection in solid organ transplantation is 5–50%. Colonization with Candida species is most common, occurring in the early period post-transplant but rarely causing pneumonia. In contrast, Aspergillus species, with an incidence of 18–22%, represents the classic opportunistic fungal infection[66]. The study of Infections in Renal Transplant Recipients was conducted at MS Ramaiah Hospitals, Bangalore reports that Urinary tract infection (36.11%) was the most common infection seen in the post-transplant period followed by candidiasis (16.62%). Candidiasis was statistically found more in diabetics compared to non-diabetics in the pre-transplant period ($p < 0.01$) [67].

Conclusion

Immunosuppresant are now established as targeted therapies for malignancies, transplant rejection, autoimmune and infectious diseases, as well as a range of new indications. However, administration of immunosuppressants is also associated with significant adverse effects and toxicity. Health professionals involved in the patient's management need to be vigilant and proactive in preventing monitoring and managing adverse effects. This surveillance may need to continue long after the drugs have been stopped. Ultimately, clinicians must decide the best means of optimizing therapy for individual patients based on risk factors such as rejection, delayed graft function, and other adverse events such as diabetes mellitus, hypertension, dyslipidemia and cosmetic changes. By assessing the risks for each individual patient, the physician can choose the most appropriate immunosuppressive initially and adjust the regimen accordingly to provide optimal immunosuppression.

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