

Liver Transplantation and immunosuppressants in Current Scenario : A Short Review

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ABSTRACT

Liver transplantation (LT) is Standard therapy for patients who are suffering from end-stage liver disease and their complications. After the transplantation the graft can't live without immunosuppressants, Medication becomes part of their life thus it increases the survival rate of patients by preventing or reducing the rejection episodes . Although the therapy is mandatory on the same way it is associated with several adverse events like long-term adverse effects of prolonged use of immunosuppressive agents such as malignancies, opportunistic infections, metabolic disorders, and other organ toxicities have now become a major concern, still calcineurine inhibitors stay as the backbone of the graft patients because of their better efficacy . Apart from the age category of people belong, if the patient is indeed for surgery can withstand the therapy, LT is recommended. Another unspoken area of therapy is the financial side, the surgery is very costly which is already known, Also the treatment after transplant also affects the patient financially.

Keywords:

Liver Transplantation, Immunosuppressants , Graft Survival , Cost of therapy

Introduction

Liver transplantation (LT) is the ultimate choice of treatment for people who are suffering from end-stage liver disease, liver failure, and its complication and also for those with selected liver malignancies like hepatocellular carcinoma, etc^[1] Liver transplantation is the replacement of diseased liver or part of the liver affected with the healthy liver from another person. A recipient of liver transplant has an improved survival rate as compared with that of living with diseased liver though they have to take lifelong immunosuppressant drugs. The Surgery of the liver is established because one cannot live without the liver. After all, the liver is a vital organ in the human body that takes part in many essential functions includes

metabolism and excretion of drugs as well as toxins^[2]. Apart from the age category of people they belong to, any patient who can withstand therapy, LT is recommended.

Immunosuppressants are an unavoidable category of medicine in post-liver transplant patients because the grafted part of the liver is new to the body so there are chances of rejection. To prevent rejection and to improve quality of life after transplantation immunosuppressant therapy is recommended. This is beneficial, but on the other hand, it may cause several serious adverse reactions such as the increased risk of infection as it suppresses the body's ability to react to toxins, also cause malignancies in some cases and some other unique adverse events are associated with each agent. Treatment with immunosuppression is tailored according to the patient's need to ensure safety, hence, before starting the treatment one should be done with a benefit-risk ratio. Although the therapy is associated with several adverse events still calcineurin inhibitors stay as the backbone of the graft patients.

Another unspoken area of liver transplantation is its cost and it is known that liver transplantation surgery is very costly including post-transplant maintenance. Since the rejection of the grafted part can happen any time after surgery, immunosuppressants are given. Also, other hidden costs such as laboratory bills, therapeutic drug monitoring of drugs such as Tacrolimus and Everolimus since they are narrow therapeutic drugs and can cause a serious adverse reaction when their level increases than the recommended level. So Therapeutic drug monitoring of such drugs is mandatory and followed up every 6 months^[3].

Immunosuppressants in treating post liver transplant patients:

Immunosuppression remains a major part of maintenance treatment in post-liver transplant patients. In the current scenario, increasing demand for the immunosuppressant had lead to the increased discovery of new drugs.

Table no:1Dose and possible ADR of immunosuppressants.

Drug	Available Dose	Possible ADR
Tacrolimus	0.5 – 3mg	Hyperglycemia Kidney damage, Diarrhea, Stomach Pain
Cyclosporine	25-100mg	Hypertension Chances of infection Female reproductive disorder
Sirolimus	1mg	Increased creatinine level in blood Anemia
Azathioprine	25-50mg	Increased bleeding tendency Decreased WBC count
Mycophenolate Mofetil	250-500mg	Decreased WBC count Abdominal Pain

1.Corticosteroids

Corticosteroids are the backbone of immunosuppression in a transplant after surgery, it is given IV for at least 3 days after transplant via IV with a combination of at least one other immunosuppressant drug. These agents act by preventing the production of cytokines, IL-1, IL-2, IL-6, Tumor necrosis factor, etc. The most commonly used drug among them are methylprednisolone, prednisolone, and prednisone. This category of medication is associated with serious adverse events especially when they are administered in high doses and also when given for a longer duration. Most common adverse event reported is Osteoporosis. Where mild bone resorption will start primarily and later leads to Osteoporosis. This happens when the drug is taken for a longer duration and this is because steroids affect bone metabolism. Osteoporosis sometimes manifested as back pains as a precaution calcium supplement will be given. Sometimes hyperglycemia also occurs as a part of steroid therapy, this happens because the steroids increased hepatic glucose production. Other commonly occurring adverse events are delirium and delayed wound healing these are short-term events and may subside once the treatment is withdrawn^[4].

Commonly one oral immunosuppressant like Calcineurin inhibitors (CNI), Mycophenolate mofetil (MMF), or Azathioprine is added with steroids to reduce the dose of administration so that can avoid chances of steroid-induced reactions.

2.Calcineurine Inhibitors

It is a class of drugs that act by inhibiting the activation of T lymphocyte through a series of events like, blocking the action of calcineurin hence the name calcineurin inhibitors, calcineurin is a critical molecule in the production of cytokine which is then responsible for the T lymphocyte activation. Calcineurin inhibitors are a group of three drugs include cyclosporine, Tacrolimus, and pimecrolimus though these act by inhibiting T lymphocyte activation the binding protein of these are different which are cyclophilin, FK-binding protein, and macrophilia 12 respectively. These are the mainstay of patients who require immunosuppression especially in transplant patients, and the important characteristics of these drugs are they are narrow therapeutic, which simply means they have to be used with caution and frequent measurement of therapeutic drug monitoring is important. Cardiovascular disease is the outcome of liver transplant patients who are on treatment with cyclosporine as it causes endothelial dysfunction and hypertension. According to previously reported studies, it is proven that tacrolimus causes fewer cardiovascular events than other immunosuppressants. Hence Tacrolimus has become the main immunosuppressive agent in LT patients since it reduces one-year mortality rate, rate of rejection and also helps for steroid-free treatment.

3. Antimetabolites

Azathioprine and mycophenolate mofetil (MMF) are the two antimetabolites used as immunosuppressants that work by diminishing the proliferative response of B and T lymphocytes. Azathioprine was the major immunosuppressant used in solid organ transplant in past years but later after the introduction of more potent drugs like tacrolimus, it became the adjuvant therapy with calcineurin inhibitor. Evidence suggests that they are less effective as compared to CNI. Hence it is used along with any other immunosuppressant's. The major problem associated with this category is increased adverse reactions like azathioprine is associated with predominant myelotoxicity and hepatotoxicity. And the most important problem

associated with azathioprine is bone marrow suppression this is due to insufficient thiopurinomethyltransferase (TPMT) activity. Though immunosuppressive drugs are very costly and may add financial burden to the patient for survival, azathioprine preferred in such cases since azathioprine is less costly as compared to others.

Mycophenolatemofetil acts by diminishing the activity of T and B cells with anti-proliferative activity, MMF is an inactive compound and in the body, it gets converted into its active form MPA which is responsible for the mechanism. MMF was introduced back then in the 1990s as an immunosuppressant because it is free from nephrotoxicity it was found useful in renal dysfunction patients who are recommended to reduce the dose of CNI. MMF is also useful in combination with other immunosuppressants to obtain adequate suppression patients and also for steroid-free treatment. Compared to other immunosuppressants, MMF doesn't need drug level monitoring it is because the same has high bioavailability still in rare cases it is advised to do so. Hematological and gastrointestinal, bone marrow suppression is also observed and which is dose-dependent and usually will respond to dose reduction. MMF is not commonly using nowadays due to the high reports of Nausea, vomiting, abdominal discomfort, and diarrhea are common complaints in patients taking Mycophenolic acid derivatives. Another reason to convert MMF is the cost of the drug, many patients on MMF treatment face difficulty to manage the cost of therapy lead to the conversion of MMF to other drugs like Azathioprine.

4. Mammalian target of rapamycin inhibitor:

Sirolimus belongs to macrolide antibiotic which is structurally similar to tacrolimus binds to mTOR inhibitor rather than CNI. Sirolimus and Tacrolimus are not competing with each other instead they act synergistically for a better result, Sirolimus got approval for the use of immunosuppression in the year 1999 and it shows that it doesn't cause any renal dysfunction and it is safe to use in LT patients with renal dysfunction. Hence the drug has not proven any increased graft and better results in combination with tacrolimus the same is not using widely. Another mTOR inhibitor is Everolimus which shows a promising effect in combination with tacrolimus in case of both rejection and beneficial effect, However rejection rate was common in everolimus alone groups. Like other medication mTOR category is also associated with several side effects, Among that more common in hyperlipidemia, edema, and oral ulcers.

Monitoring of immune system

Monitoring of immune system followed by liver transplantation is a very difficult area and the same is very important in improving the life of transplanted patients. Many options are available for monitoring but no single methods satisfy the basic requirements^[5]. Monitoring of the immune system is primarily associated with the treatment of acute and chronic rejection and dysfunction of an allograft. The method involved in monitoring is broadly classified into antigen-specific and non-antigen-specific, This can identify whether it is donor rejected or any other infection that occurred. As a part of the monitoring of immunosuppression therapeutic drug monitoring is carried out, this is done because many of the important drugs like tacrolimus, Everolimus, etc.. this is done to identify the minimum and maximum range to which drug can do their best in the body as well as it has another side of effect that by controlling the dose in this range can avoid the over suppression of immune system which can help in minimizing infections to an extent.

Transplantation in Pregnancy

The first reported pregnancy followed by liver transplantation was reported in 1978, later liver transplantation became successful therapy on major categories of people suffering from liver disease across the world. Severe liver injury and inadequate functioning of the liver lead to an imbalance in the hormonal level thereby there is a chance of occurrence of lack of conception in women. It was reported that around 30% of the women will be back to normal menstruation after 3 months of transplant and strong shreds of evidence are there in declaring improved maternal and fetal survival one year after transplant.

During pregnancy, the drugs prescribed for immunosuppression are the same as that of normal individuals though they are having a bit more adverse events like Calcineurin inhibitors like cyclosporine and tacrolimus are first-line agents suggested for pregnant women these may have chances of causing Maternal diabetes, hypertension, pre-eclampsia, fetal perinatal hyperkalemia and renal dysfunction as in normal individual. Azathioprine combined with CNIs is given for required immunosuppression and the same is associated with adverse events like neonatal infection and sepsis, preterm delivery and low birth weight, Fetal anemia, thrombocytopenia, leucopenia, decreased fetal immunoglobulin levels. Azathioprine is less commonly prescribed in pregnant women as they have FDA rating of D. Mycophenolate (MMF) is avoided during the first trimester of pregnancy because of the chances of pregnancy loss at the particular time. Apart from the other drugs, MMF is having the most severe adverse events and it is also the least prescribed during pregnancy since it has an FDA rank rating of category D.[6]

Life style changes after transplantation

Once the transplantation is done the patient should follow a proper lifestyle modification to make the grafted liver healthy and safe this will also help to promote a better outcome. The first thing one should take care of is the food that they eat, it is recommended to follow eating a balanced healthy diet with adequate nutrition. It is also recommended to avoid the habits like cigarette smoking and alcohol consumptions as they negatively affect the graft. Also, one should follow a correct routine of medicine intake and should do a timely medical follow-up to check the functioning of the liver. Because the transplant surgery requires lifelong immunosuppression, it is better to stay safe and avoid getting an infection as they are more likely to get the same, If the person got infected then one should consult the doctor as soon as possible also it is unsafe to use over the counter medicines without consulting the doctor. Normally a person who can get back to normal activities after 3 months of surgery should consider the doctor's advice before doing the vigorous type of activities[7]. Maintaining proper health by taking proper nutrition, exercise and also by stress reduction

Financial impact after surgery

It is known that transplant surgery is very expensive and the fiscal burden of common people is not known. Immunosuppressant therapy is mandatory in transplant patients to maintain the proper functioning of the graft, which adds to the burden. And the therapy indeed is a costly one for normal people to bear for. Even though the cost for treatment is very high in transplant survival, it is proven in previous studies that comparing to the cost of treatment of transplant survival in India is less as compared to other foreign countries[8]. The cost of therapy is high during the first few months of surgery since the immunosuppression starts as high dose Corticosteroids administered IV and then to the maintenance therapy[9]. Because the drugs are narrow therapeutic it is important to do therapeutic drug monitoring. This will be an additional burden to the patients[10]. A result of a study conducted says that

around 32% of the patients after transplantation feel difficulty paying medication fees, also a total of 29% of people have private insurance in paying such[11]. The program named B40 prime vendor was introduced in the year 1992 for financial relief for the underserved to medical care. So there is an ongoing demand for the identification of newer agents with possible immunosuppression with less financial impact[11]. While the data are limited about this topic and lack of affordability for uninsured therapy, there needs improved support and care^[12].

Conclusion

Liver transplantation and the lifelong immunosuppression benefits people with end-stage liver diseases on one end while the adverse events and scaling up the fiscal burden bring out huge concern. There is no data regarding the cost of treatment after the surgery until a lifetime of the graft. More studies to understand and analyze the financial burden of transplant patients are recommended that help healthcare facilities develop and expand insurance as well as financial policies.

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