Primary care of the liver transplant recipient

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A case:

Mr. F. O. is a 53 year old male who presents to a family physician's office for a physical exam and to establish primary care service with a physician. He had a history of hepatitis C and alcohol related liver cirrhosis and had undergone a liver transplantation 16 months before the visit. The patient had no specific complaints at the time of visit. He had a marked increase in liver enzymes 6 months before this visit and a liver biopsy showed changes of alcoholic and hepatitis C liver disease. He adamantly denied alcohol recidivism and liver enzymes normalized spontaneously. He takes a multivitamin and states that he feels more energy with multivitamins.

Review of systems was within normal limits.

PMH includes Hypertension, Obesity, left arm fracture

Medications: includes tacrolimus (Prograf) 2 mg in am and 1 mg in pm,

mycophenolate mofetil (CellCept) 1 gram twice a day

metoprolol 100 mg twice a day, amlodipine 10 mg daily

urosodiol 600 mg in am and 300 mg in pm

Social history: smokes tobacco 1 pack per day

Alcohol in the past and s/p cirrhosis and has not relapsed since the

transplantation

PE: Alert and oriented times three, well nourished, BP 136/88, BMI 35. Pulse 76,

Respiration Rate 18.Tem 98.4, Eyes: not icteric sclera, PERRLA, EOMI, Neck:

no thyroidmegaly, Lungs: clear on auscultation and percussion, Heart: regular

without murmur, PMI not replaced. Abdomen: soft, well healed subcostal

transverse scars. Legs: no pedal edema:

The patient was given instruction to continue his medications and to follow up in

3 months. The patient was also educated regarding smoking cessation.

He was seen by the psychiatry service a few months later. He was referred

because of depression. He mentioned to the psychiatrist that he had onset of

drinking alcohol at age 10. He stated that he had suffered physical abuse as a

boy. He also had history of cocaine, IV heroine and marijuana abuse. He

mentioned that the last time he used alcohol or drugs was 6 years before the

transplantation surgery. He still smokes. He was diagnosed with major depression and started on sertraline.

INTRODUCTION

Liver transplantation outcomes have evolved significantly since the development of the surgical procedure in the 1960s. Survival after liver transplantation has improved significantly with 1 year survival rate over 85%, and liver transplantation has become the treatment of choice for chronic liver failure, acute liver failure and selected patients with early stage, unresectable hepatocellular carcinoma (1). This improved survival was due to the introduction of potent immunosuppression (IS) for the treatment and prevention of cellular rejection. However, potent immunosuppression has led to increased incidence and prevalence of IS associated complications. Immunosuppression is a double edged sword with a need to carefully consider the risk benefit ratio in titrating the doses for the optimal benefit of the liver transplant recipients. With an increasing number of long-term survivors, primary care physicians are expected to see larger numbers of these patients. The purpose of this article is to provide a basic guideline for the care of liver transplant recipients in the office of primary care physicians. It is also important to have close communication and collaboration with the patient's transplantation center for optimal care.

ORGAN REJECTION

<u>Late onset organ rejection</u>

Late onset organ rejection of the liver transplant graft by the host immune system can be divided into acute and chronic rejection. Advances in immunosuppressive medications have allowed liver transplantation to move from a theory to a viable life-saving procedure by decreasing the risk of rejection. However, despite improvements in immunosuppression, patients still remain at risk of developing acute cellular rejection within three months of liver transplantation in up to 20 to 40% of cases (2). These cases are eminently treatable with corticosteroid therapy and long term graft survival is not significantly impaired by these early cases of acute cellular rejection (3).

By the time patients present for follow up to the primary care physician, they are usually at least 6 to 12 months out from liver transplantation. The primary care physician needs to be able to recognize late onset organ rejection and collaborate with the patient's transplant center to effectively manage these cases. Two major types of late onset rejection exist: late acute cellular rejection and chronic rejection.

I. Late acute cellular rejection

Acute cellular rejection is a process characterized by inflammation of the liver graft due to immunological injury occurring as a consequence to immunologic disparities between the donor and recipient immune system. Late acute rejection occurs in up to 10 to 20% of cases, and is a risk factor for the subsequent development of chronic rejection which has an impact of long term survival (4).

Acute rejection is mediated by the cellular arm of the immune system, mainly T cells that develop against donor antigens in the liver graft leading to an inflammatory response directed at hepatocytes and biliary epithelium. Risk factors include a history of autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune cholangiopathy in the recipient. Medication and clinical follow up noncompliance is also a well recognized risk factor for developing acute rejection (5).

Most commonly, acute rejection is detected through asymptomatic elevation in liver chemistries including alkaline phosphatase, GGT, transaminases, and total bilirubin. Clinical symptoms are found in more severe cases which manifest later in their course after significant inflammatory injury to the graft has already occurred. Nonspecific complaints include nausea, fever, malaise, pruritus, jaundice, and abdominal discomfort. Thus, a high index of suspicion must be maintained to diagnose late acute rejection because the nonspecific nature of symptoms and findings can lead to a delay in diagnosis. Liver biopsy with histological examination is mandatory to diagnose acute rejection. Histological

findings include lymphocytic infiltration localized to the portal tracts and central vein with progressive damage to the bile ducts over time (6). However, histological changes may be subtle, especially early in acute rejection, and can easily be confused with recurrent hepatitis C infection. The differential diagnoses include cytomegalovirus (CMV) infection, drug hepatotoxicity, hepatitis C or B, and recurrence of underlying liver disease (7).

A delay in recognition and diagnosis can lead to progression of acute rejection leading to a decrease in response to treatment. Treatment is based on pulse corticosteroid therapy along with an increase in baseline maintenance calcineurin inhibitor levels (8). There is no consensus for optimal corticosteroid therapy, although most transplant centers admit patients for intravenous corticosteroids for the first three days to allow close monitoring of response to therapy. In addition, adjuvant agents such as mycophenolate mofetil or rapamycin are often added. Prognosis in late acute rejection remains similar to early acute rejection except that patients may have a lower response to therapy due to a delay in diagnosis.

II. Chronic rejection

Chronic rejection is an insidious process characterized histologically by diffuse bile duct loss, or ductopenia (9). Chronic rejection is observed usually at least

three months after liver transplantation and occurs in up to 3-4% of liver transplant recipients (10).

The pathophysiology of chronic rejection is incompletely understood but postulated to be multifactorial. Risk factors for chronic rejection include a previous history of acute cellular rejection, history of autoimmune hepatitis, primary biliary cirrhosis, and CMV infection (11, 12). The mechanism is attributed to the cellular arm of the immune system directed against antigens in the vascular endothelium and biliary tract. Vascular insufficiency leading to hypoxia is hypothesized to predispose the graft to immunologic mediated injury. Noncompliance to immunosuppression medications may be an important risk factor for developing chronic rejection (5).

Symptoms of chronic rejection are insidious, with an initial lack of symptoms or nonspecific malaise, fatigue and abdominal discomfort. With development of significant cholestasis, patients may develop pruritus and jaundice. Chronic rejection is suspected in the setting of abnormal liver enzymes: notably alkaline phosphate and bilirubin and to a lesser extent AST and ALT. Diagnosis can only be made based on histology. Hallmark histological findings include ductopenia, leading to the term vanishing bile duct syndrome for chronic rejection. Other less common findings include bile duct atrophy, obliterative arteriopathy and venulitis, lymphoid infiltrates, and centrilobular degeneration (13). The differential diagnoses for chronic rejection include acute cellular rejection, CMV hepatitis,

and recurrence of the original liver disease which necessitated the liver transplantation.

Treatment is directed at increasing the baseline immunosuppressive medications and ensuring compliance to prescribed immunosuppression. The use of pulse corticosteroids is not accepted as a treatment option for chronic rejection due to inefficacy and risk of significant adverse events. Patients on cyclosporine based immunosuppression may respond to conversion of cyclosporine to tacrolimus based therapy. Unfortunately, patients with chronic rejection may continue to progress despite these treatment adjustments, requiring re-evaluation for liver transplantation. Chronic rejection remains a well recognized and feared complication of liver transplantation despite improvements in immunosuppression.

Common immunosuppression medications

In 1994, the US multicenter FK506 Liver Study Group published a seminal paper comparing cyclosporine and tacrolimus for immunosuppression after liver transplantation (14). This study is a landmark in the evolution of liver transplantation. With the introduction of newer immunosuppressive medications, acute rejection rates have decreased and many now believe that excess immunosuppression is the greater concern. Over half of the deaths in liver

transplantation are related to complications attributable to immunosuppressive medications including cardiovascular diseases, renal failure, infection and malignancy (15). To prevent acute rejection and manage potential adverse effects, there is a general strategy of using multiple immunosuppressive medications at high doses early after liver transplantation and fewer immunosuppressive medications at lower doses later.

Early after liver transplantation, most centers use a combination of two to four immunosuppressive medications, including a calcineurin inhibitor, an antimetabolite such as mycophenolate mofetil, and/or corticosteroids. Later, most centers taper doses of immunosuppressive medications and eliminate all but the calcineurin inhibitors and antimetabolites. When the primary care physicians see the patients, patients usually are on a calcineurin inhibitor alone or a calcineurin inhibitor with the addition of mycophenolate. It is important though to understand that small difference in dose or levels can lead to adverse effects or inefficacy of immunosuppression. (Please see the tables for mechanism, dosing, trough level goals and side effects of major immunosuppressive medications. [Table1 and 2])

Calcineurin inhibitors: cyclosporine and tacrolimus

All forms of cyclosporine (Sandimumune ,Neoral, Gengraf) and tacrolimus (Prograf) suppress the immune system through the inhibition of calcineurin, a protein that drives production of cytokines, such as IL-2, and is involved in the activation of T cells, the immune cells that attack the liver allograft. Collectively, cyclosporine and tacrolimus are called calcineurin inhibitors. The majority of patients are maintained on one or the other calcineurin inhibitors lifelong after transplantation. Both are oral agents usually taken every 12 hours. The dosage is adjusted based on trough levels of the drugs and is highly individualized. Higher trough levels are sought initially after liver tranplantation when the risk of rejection is high and lower levels are sought later when concerns about adverse effects start to predominate.

The early challenges of successful transplantation included surgical technique, organ preservation, and immunosuppresion. As surgical technique improved, the need for improvements in immunosuppression became more obvious. A report published in 1980 described a one year survival of only 26 % (16). The introduction of cyclosporine the following year signaled a turning point in liver transplantation (17).

In an update on liver transplantation in 1988, the Pittsburgh group reported that phase 1 trials of FK506 (tacroliomus) had recently begun (18). A year later, the same group described use of FK506 as salvage therapy in patients who had failed with cyclosporine (19). Within about five years, tacrolimus would overtake cyclosporine as the mainstay in liver transplantation. By the mid-1990s, most centers agreed that tacrolimus was associated with superior graft and patient survival. In a landmark study (20) authors compared the efficiency of tacrolimus versus microemulsified cyclosporine in 606 patients undergoing first orthotopic liver transplant using a composite primary endpoint of death, retransplantation, or "treatment failure for immunological reasons" Both treatment regimens were effective, but tacrolimus was superior for both the composite end point and for patient and graft survival. In addition, more patients in the tacrolimus group survived without an episode of significant rejection. The results of the study were updated with a two-year extension of the randomized protocol: tacrolimus remained superior.

Multiple subsequent studies have been performed; the superiority of tacrolimus over cyclosporine was confirmed in a meta-analysis of 16 randomized trials (21). Tacrolimus was superior when analyzed for survival, graft loss, acute rejection, and steroid-resistant rejection in the first year. The incidence of lymphoproliferative disease was similar for the two groups, although de novo diabetes mellitus was more common in the tacrolimus group. More patients stopped cyclosporine than tacrolimus. The authors estimated that treating 100

patients with tacrolimus versus cyclosporine would avoid rejection and steroid-resistant rejection in 9 and 7 patients respectively, graft loss and death in 5 and 2 patients respectively, but that 4 additional patients would develop diabetes after liver transplantation.

There are several side effects common to both calcineuin inhibitors including hyperkalemia, hypertension, neurotoxicity (headaches, tremors, neuropathy and seizures) and nephrotoxicity. Renal insufficiency remains a major cause of morbidity and mortality after liver transplantation. Cyclosporine is more commonly associated with dysplidemia and gingival hyperplasia, while tacrolimus is more commonly associated with diabetes.

Antimetabolites

Azathioprine (Immuran ,Azasan), mycophenolate mofetil (CellCept) and mycophenolic acid (Myfortic) are antimetabolites. Antimetabolites refer to a group of medications that interfere with purine nucleotide synthesis, which leads to preferential inhibition of T and B cell lymphocytes. The antimetabolites are generally not potent enough to be used alone, but are important as adjunctive agents. Mycophenolate mofetil or mycophenolic acid may be discontinued within a year after transplant. However, there is evidence that if mycophenolate mofetil or mycophenolic acid is continued, lower doses of calcineuin inhibitors can be used with a resulting improvement in renal function (22). Azathioprine was used

early years of liver transplantation, but in recent years, mycophenolate mofetil and mycophenolic acid have replaced azathioprine as it can be associated with development of cholestatic hepatitis. Known side effects of mycophenolate mofetil and mycophenolic acid include bone marrow suppression and gastrointestinal side effects including gastritis, diarrhea and abdominal pain.

Sirolimus/rapamycin

Sirolimus (Rapamune) is a newer immunosuppressive agent that inhibits T cell proliferation through cell cycle inhibition. It is regarded as an agent that is potent enough to be used as a primary immunosuppressive agent but without the nephorotoxicity of calcineurin inhibitors. Sirolimus is therefore considered as an alternative to calcineurin inhibitors or in some instances in combination with lower doses of one of the calcineurin inhibitors. However, sirolimus has been associated with an increased risk for hepatic artery thrombosis and, as a result, had received a 'black box' warning for liver transplant recipients which has led to avoidance of its use in the early months after transplant. Other side effects include rash, dysplipidemia, cytopenia, poor wound healing, and oral ulcerations. There is also an association with an unusual but potentially fatal interstitial pneumonitis. Due to these side effects, 20-30% of those patients who receive the drug are not able to tolerate it.

Corticosteroids

Corticosteroids (prednisone or prednisolone) are generally given in large doses during the first week after liver transplantation and tapered rapidly to lower levels or completely eliminated within weeks or months following liver transplantation. Given the substantial long-term side effects of corticosteroids, most transplant centers are trying to eliminate or minimize corticosteroids use in transplant recipients. However, in patients with autoimmune liver diseases or history of recurrent rejection, steroids are frequently continued indefinitely.

Drug interactions of immunosuppressants

Tacrolimus, cyclosporin and sirolimus have dose-related toxicity and relatively narrow therapeutic windows. The two pathways that are important for calcineurin inhibitor metabolism are cytochrome P-450 3A4 and P-glycoprotein. Certain drugs can induce, inhibit or slow metabolism of calcineurin inhibitors. For example, use of azithromycin for a simple case of bacterial infection may result in significant elevation of calcineurin inhibitors and cause nephrotoxicity. On the other hand, other drugs such as -phenobarbital or phenytoin may lower the calcineurin inhibitor serum levels and cause rejection. Whenever any new medications are started, it is important to check for possible interactions between the new medicine and calcineurin inhibitors, or consult with the transplant center. Tables 3 and 4 provide a list of substances that can increase or decrease levels of immunosuppressants.

The transplant recipients have a high prevalence of insulin resistance syndromes including hypertension, type 2 diabetes, obesity and dyslipidemia. Drugs that are generally well tolerated include amlodipine, nifedipine, clonidine, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers and beta blockers (except carvedilol) for hypertension; oral hypoglycemics, metformin, sulfonylureas, and thiazolidinediones for diabetes. Statin drugs, ezetimibe, niacin and intestinal binders of bile acids have been used for dyslipidemia. Due to interaction between calcineurin inhibitors and statins or ezetimibe, these lipid-lowering drugs should be given at lower dosages and monitored for side effect and serum trough levels of calcineurin inhibitors (23). Intestinal binders of bile acids should be given 2 hours before or after calcineuin inhibitors and should not be used in patients also taking mycophenolate mofetil or mycophenolic acid (24). Narcotics are usually safe outside their addictive potential and antidepressants are usually well tolerated. Up to 2 grams/day of acetaminophen can be given to liver transplant recipients with functioning livers without reservation.

Selected antibiotics including any of penicillins,cephalosporins, quinolones, sulfonamide and topical (not oral) anti-fungal agents are generally well tolerated.

Opportunistic infections

Despite improvements in surgical techniques, immunosuppressants, and antibiotics over the last 20 years, infections continue to pose the greatest mortality risk after liver transplantation (25). The risk of infection is dependent on the patient's epidemiological infectious risk factors as well as the net state of immunosuppression. These epidemiological risk factors include procedures, surgeries, vaccination history, previous infectious exposures, travel history, location, and antimicrobial use history. The net state or level of immunosuppression is dependent on the type, dose, and duration of immunosuppressant use, underlying medical diseases and comorbidities, presence of fluid collections, catheters, or mechanical devices, as well as immune modulating diseases such as HIV or cytomegalovirus (CMV) infection.

In addition, the astute clinician must be cognizant of the impact of immunosuppression on the liver transplant recipient presenting with infection. Immunosuppression attenuates inflammatory responses and may mute clinical and radiographic signs of infection in the liver transplant recipient, leading to advanced presentations and delays in diagnosis. Due to more advanced presentation of infection and associated delays in diagnosis, the course of

infections may be more aggressive and rapid with a significant risk of morbidity and mortality. Thus, early and accurate diagnosis must be pursued with a low threshold for obtaining imaging studies, removal of foreign bodies and catheters, and tissue diagnosis along with broad empiric treatment while awaiting data to narrow and taper antimicrobial treatment. Clinicians must also be aware of the complexity of antibiotic choices in the setting of drug interactions with immunosuppression as well as the increased risk of underlying and potential antimicrobial resistance.

Infections after liver transplantation can be divided based on time from liver transplantation as well as the type of infection (26, 27). Immediately following liver transplantation and up to 4-6 weeks, the patient remains at the greatest risk for nosocomial or hospital acquired infections associated with surgical procedures, mechanical ventilation, catheter placement, or prolonged antibiotic use. Coupling these risks with the high intensity immunosuppression immediately following liver transplantation, the patient is at increased infectious risk of pseudomonas aeroguinosa, methicillin resistant staphylococcus aureus, (MRSA), vancomycin resistance enterococcus (VRE) , legionella, non-albicans species candida, as well as clostridium difficile. Donor derived infections also pose a rare, but not insignificant risk to the liver transplant recipient.

Up to 6 months after liver transplantation, the patient remains at greatest risk of opportunistic infection due to the high level of immunosuppression. After 6

months, most patients' immunosuppression levels have been titrated to a maintenance level with a lower net level of immunosuppression, attenuating the risk of opportunistic infections. At this point, patients present with community acquired infections such as urinary tract infections, pneumonias, and influenza similar to patients without a history of transplantation.

Atypical infectious organisms causing opportunistic infections include CMV, pneumocystis jiroveci, human herpes virus-6, and aspergillus. Less common viruses include varicella zoster virus (VZV), herpes simplex virus (HSV), Epstein-Barr virus (EBV), adenoviruses, parvovirus B19, and respiratory syncytial virus. Fungal infections such as non-albicans candida can occur as well as Histoplasma capsulatum (Midwest), Coccidioides immitis (Southwest), and Blastomyces dermatitidis (Mississippi and Ohio river) depending on the location of their domicile and travel history (28). Mycobacterium infection, though not as common as the preceding organisms, is a feared opportunistic infection that can be seen in this time period.

CMV is a human herpesvirus, and has a unique impact on liver transplant recipients as it has not only a direct effect on tissues but immune modulating effects. CMV's immune modulating effects lead to an increased risk of bacterial infections, fungal infections, accelerated hepatitis C recurrence and chronic rejection (29). CMV infection (viremia without symptoms) occurs up to 60% of patients after liver transplantation with up to 20% developing CMV disease in the

liver, lungs, GI tract, and retina (30). Evidence of CMV seropositivity is found in 40-60% of healthy adults, leaving them at risk of reactivation of endogenous latent CMV with immunosuppression. However, the greatest risk of CMV infection is in patients without history of CMV exposure who receive a CMV seropositive liver graft. Presentation of CMV disease can be variable with fever, malaise, bone marrow suppression, and arthralgias with less frequent presentation including a tissue specific hepatitis, pneumonitis, gastroenteritis, or retinitis (31).

Universal CMV prophylaxis is recommended for CMV seronegative patients receiving a CMV seropositive donor organ. Patients who are CMV seropositive can receive CMV prophylaxis or be treated with preemptive therapy (monitoring for CMV infection and treatment if patient becomes CMV positive). Treatment regimens vary among transplant centers, though most centers will provide CMV prophylaxis for up to 6 months with ganciclovir or valganciclovir (32). A benefit of universal CMV prophylaxis is that antiviral therapy directed towards CMV has protective activity against other human herpesviruses such as HSV and VZV as well as EBV. Without prophylaxis, patients may have up to 50% recurrence risk of HSV and an increased risk of other viral infections (33, 34). Of note, although valganciclovir is not approved by the FDA for liver transplant patients due to an increased incidence of CMV disease compared to ganciclovir (35), many transplant programs are utilizing valganciclovir due to its greater bioavailability compared to ganciclovir as well as its easier dosing regimen.

Pneumocystis jiroveci, formerly known as pneumocystis carinii, is a yeast like fungus that poses unique risk for immunosuppressed patients. Pneumocystis was previously misclassified as a protozoan and historically called pneumocystis carinii, although that name is now designated only for pneumocystis variants occurring in animals (36). PCP continues to be used as the acronym for **P**neumo**C**ystitis **P**nuemonia given its familiarity and extended history of use. Prophylaxis with daily single strength trimethoprim-sulfamethoxazole or three times a week double-strength trimethoprim-sulfamethoxazole is recommended up to 6-12 months after liver transplantation. Patients who cannot tolerate trimethoprim-sulfamethoxazole due to sulfonamide allergy can be treated with atovaquone, inhaled pentamidine, or dapsone. However, these second line agents do not provide the added benefit of trimethoprim-sulfamethoxazole activity against Toxoplasmosis gondii, nocardiosis, and Listeria monocytogenes.

Vaccination is recommended after liver transplantation for hepatitis A and B as well as pneumococcal, and inactivated influenza. However, active, live vaccines are not recommended including measles, mumps, and varicella.

Non infectious complication of liver transplantation

Hypertension

Hypertension is a common complication in liver transplant recipients (37). Corticosteroids and calcineurin inhibitors increase the risk of blood pressure elevation in transplant recipients. Calcineurin inhibitors cause sympathetic stimulation with resultant vasoconstrictions and sodium retention (38). Cyclosporine is associated with a higher incidence of hypertension following liver transplantation compared to tacrolimus (39).

The goal of antihypertensive therapy should be adequate blood pressure control. Treatment of hypertension may include diuretics especially in those patients with peripheral edema. But those must be used with caution because thiazides may cause gout. The calcium channel blockers, particularly the dihydropyridine class are particularly attractive since their vasodilatory effects may overcome the vasoconstriction caused by the calcineurin inhibitors. Representative dihydropyridine calcium channel blockers include amlodipine, felodipine, and nifedipine. Among other calcium channel blockers diltiazem, verapamil and nicardipine should be avoided since they increase serum levels of the calcineurin inhibitors.

Alpha-blockers such as clonidine and doxazosin are frequently used for posttransplantation hypertension. Beta-blockers can be used and do not affect calcineurin inhibitor levels except carvedilol, which can cause elevated levels of calcineurin inhibitors and usually requires reduction in calcineurin inhibitor dosage to maintain therapeutic serum level (40). ACE inhibitors and angiotensin II receptor blockers are not used initially for hypertension because of the increased risk of renal insufficiency and hyperkalemia in early transplant recipients. However, after the immediate post-transplant period is over, these medications may be helpful in preventing diabetic nephropathy.

Diabetes mellitus

Prevalence of diabetes mellitus is higher in liver transplant recipients than in the general population. The prevalence of diabetes is as high as 33% (41). Risk factors of diabetes in liver transplant recipients include use of corticosteroids, high dose calcineurin inhibitors, hepatitis C seropositivity, ethnicity, pretransplantation diabetes and obesity. Although liver transplantation may cure hepatogenous diabetes, many pretransplant type 1 diabetic patients remain on insulin after liver transplantation.

Management of postransplant diabetes is similar to patients without liver diseases with the same treatment goals to prevent complications such as

coronary artery diseases, renal failure, neuropathy and retinopathy. Education for diet and exercise are important in managing diabetes. Insulin therapy may be needed in the early stages after transplantation. Oral hypoglycemic agents can be used with minimal concern of interaction with immunosuppressive medications or damage to the transplanted liver (42). Early withdrawal or dose reduction of corticosteroid may improve glycemic control. As tacrolimus is associated with diabetes, another therapeutic maneuver may be necessary to lower the dosage of tacrolimus.

Dyslipidemia

As most patients with end stage liver disease have low serum cholesterols due to impaired hepatic synthesis and esterification of cholesterols, they have increased plasma cholesterol after liver transplantation. Risk factors for posttransplant dyslipidemia include cholestatic liver disease, pretransplant cholesterol elevation, diabetes, obesity and use of immunosuppressive agents (43). Cyclosporine, steroids and sirolimus have significant effects on serum lipid levels. Tacrolimus has a minor effect on serum lipids and mycophenolate mofetil and azathiprine have no significant effects on serum lipids. Cyclosporine increases serum total cholesterol, low density lipoprotein (LDL)- cholesterol and triglyceride (44).

Treatment of posttransplant dyslipidemia is similar to the treatment without liver disease. The first step of treatment is lifestyle modification including low fat diet

and exercise. If the life style modification is not successful after approximately 6 months, the next step is switching medications that are associated with dyslipidemia. The transplantation center should be contacted to consider reducing or eliminating steroids and substituting tacrolimus for cyclosporine.

All agents reducing cholesterol have been used in liver transplant recipients successfully but all have potential side effects. Bile acid sequestrants (cholestyramine, colestipol and cholesevelam) can decrease plasma mycophenolate motefil and mycophenolic acid levels by 35% (24). In addition, bile acid sequestrants decrease absorption of calcineurin inhibitors. Thus bile acid sequestrants should not be used in patients taking mycophenolate motefil or mycophenolic acid and should be given greater than 2 hours before or after calcineurin inhibitor dosing. Fibric acid (gemfibrozil fenofibrate and clofibrate) can cause biliary sludge, dyspepsia or myopathy. Statins can cause myopathy or elevation in liver enzymes. If a statin is used, hydrophilic statins (pravastatin or fluvestatin) are preferred since they are not metabolized by the same cytochrome P-450 3A4 metabolic pathway that metabolizes calcineurin inhibitors and sirolimus.

Obesity

The obesity rate in the United States has been rising steadily over the past 3 decades. Unfortunately, 22 % of non-obese liver transplant recipients became obese over a 2 year follow up (45). Liver transplant recipient who were overweight preoperatively tend to gain more weight. Corticosteroids definitely contribute to weight gain, and one study suggests that cyclosporine is associated with more weight gain compared to tacrolimus (46).

Treatment of obesity in liver transplant recipients is not different from patients without liver diseases. Life style modification including portion control, aerobic exercise should be considered first. Also lowering or discontinuing corticosteroids or switching from cyclosporine to tacrolimus should be considered . Orlistat is not recommended for patients who are also receiving cyclosporine, since this combination may decrease cyclosporine absorption. Orlistat has been safely used with tacrolimus based immunosupprssion, but efficacy has not been verified (47).

Psychological aspects of care for liver transplant recipient

Relapse of alcohol use after liver transplantation often affects not only the quality of life, but also adherence to immunosuppressive medications. Problematic and harmful drinking after liver transplantation occurs in up to 20% of liver transplant recipients. Some deaths in this group are related to death due to poor compliance with immunosuppressive agents (48). One study showed potential

predictors of return to harmful drinking: diagnosis of depression, the lack of stable partner, grams per day consumed in the years before assessment for transplant, reliance on 'family and friends' for post-transplant support, tobacco consumption at time of assessment and lack of insight into the alcoholic etiology of liver disease (49). Alcoholic disease is a chronic illness requiring a continuous management, before and after transplantation.

Neuropsychiatric complications, especially depression are frequent in liver transplant recipients. According to a study, the type of immunosuppression did not alter the frequency of complications. Depression, however, is significantly more common in patients transplanted for hepatitis C (50). Underlying depression in patients with hepatitis C should be identified and treated prior to liver transplantation and special attention should be given to patients with hepatitis C who received liver transplantation for post-transplantation depression.

As liver transplant recipients live longer, their quality of life is an important aspect of care by primary care physicians. A meta-analysis of health related quality of life after liver transplantation showed significant improvements in posttransplantation physical health, sexual functioning, general health related quality of health and social functioning, but not psychological health. Authors of the study recommended that transplantation treatment program expand the psychological and social support available to patients both before and after transplantation (51).

The purpose of liver transplantation includes not only the extension of survival and improvement of quality of life, but also the return of the liver transplant recipient as a contributing member of society. Employment is one measure of the ability to return to society. A recent study of 308 adult liver transplant recipients showed that pretransplant variables that were independently associated with posttransplantation employment included the following: lack of disability benefit, the absence of diabetes mellitus, the number of works prior to transplantation, high physical functioning before transplantation, and possession of private medical insurance (52).

Key points.

1. Chronic rejection of liver graft is an insidious process. Primary care physicians should have a high index of suspicion when patients show any sign of malaise, fever or jaundice. Chronic rejection should be suspected in the setting of abnormal liver enzymes: notably alkaline phosphate and bilirubin and to a lesser extent AST and ALT. Diagnosis can be made based on histology.

2. Major immunosuppression medications such as tacrolimus, cyclorsporin and sirolimus have dose-related toxicity and relatively narrow therapeutic windows. Certain drugs can induce or inhibit or slow metabolism of calcineurin inhibitors. Whenever any new medications are started, it is

imperative to check possible interaction between the new medicine and calcineurin inhibitors, or consult with the transplant center.

3. Up to 6 months after liver transplantation, the patient remains at greatest risk of opportunistic infection due to the high level of immunosuppression. After 6 months, most patients' immunosuppression medication levels have been titrated to a maintenance level with a lower net level of immunosuppression, attenuating the risk of opportunistic infections. At this point, patients present with community acquired infections such as urinary tract infections, pneumonias, and influenza similar to patients without a history of transplantation. However, primary care physicians should be vigilant for any unusual opportunistic infection in liver transplant recipients.

4. Long term use of immunosuppression with calcineurin inhibitors may lead to conditions associated with insulin resistance: hypertension, type 2 diabetes mellitus, dyslipidemia and obesity. Lifestyle modification, especially exercise and diet should be encouraged at every visit. When medications are started, they should be used with care paying careful attention to possible interaction with calcineurin inhibitors.

5. As liver transplant recipients live longer, their quality of life is an important aspect of care by primary care physicians. Health related quality of life after liver transplantation showed significant improvement in

posttransplantation physical health, sexual functioning, general health related quality of health and social functioning, but psychological health has only minor improvement. Alcohol relapse and possibility of depression in liver transplant recipients should be a continuous concern for primary care physicians. Depression is common among those who has had hepatitis C.

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Table 1. mmunosupression medications dose and monitoring and adverse event

Agent	Daily Dose	Monitoring	Adverse event
Tacrolimus	1-5 mg BID	5-15 ng/ml	Hypertension
			Hypercholesterolemia
			Neurotoxicity
			Diabetes
			Renal insufficiency
			Osteoporosis
Cyclosporine	100-200 mg BID	50-300 ng/ml	Hypertension
			Hypercholesterolemia
			Neurotoxicity
			Diabetes
			Renal insufficiency
			Osteoporosis
Mycophenolate mofetil	750-1.5 g BID	None	Bone marrow suppression
			GI side effects
Sirolimus	2-5 mg qD	5-15 ng/ml	Hyperlipidemia
			Hypertension
			Bone marrow suppression
			Hepatic artery thrombosis
Azathioprine	1-3 mg/kg qd	None	Bone marrow suppression
			Pancreatitis
Corticosteroids	5-10 mg qd	None	Hypertension
			Hyperlipidemia
			Diabetes
			Osteoporosis
			psychiatric disorders

Table 2. Side effects of major immunosuppression medications.

	Hypertension	Hypercholesterolemia	Diabetes	Neurotoxicity	Renal Insufficiency	Osteoporosis	Bone marrow suppression	GI side effects
Tacrolimus	xxx	x	xx	xx	xx	x	xx	-
Cyclosporine	xxxx	xx	x	-	xxx	xx	xxx	-
Mycophenolate mofetil	-	-	-	-	-	-	-	x
Sirolimus	x	xxx	-	-	-	-	-	-
Azathioprine	-	-	-	-	-	-	-	-
Corticosteroids	xx	x	xxx	xx	x	xxx	xxxx	-

Table 3. Drugs and substances that may increase levels of cyclosporine and tacrolimus and sirolimus(This table is not all inclusive)

Antifungals: fluconazole, ketoconazole, itraconazole, voriconazole, caspofungin

Antibiotics: azithromycin, erythromycin, clarithromycin

Calcium channel blokders: diltiazem, verapamil, nicardipine, nifedipine

Others: danazol
protease inhibitors for HBV or HIV
grapefruit products

Table 4. Drugs and substance that may decrese levels of cyclosporine, tacrolimus and sirolimus (This table is not all inclusive)

Anticonvulsants: carbamazepine, phenobarbital, phenytoin
Antibiotics:rifampin, isoniazid,
Others: St.John'fs wort