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Immunosuppression and Tolerance in Adult Liver Transplantation

*A literature review on the immunosuppression-drugs after a liver
transplantation; how to best provide safe treatment and good quality of life.*

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Preface

During my years at medical school it has been one topic that especially interested me; the human body immune system. The immune systems impact in our body, with our environment and our quality in life. It is a very detailed medical and science field, but there is also so much we still don't yet know about it. So, when I got this opportunity to write a whole master thesis about anything, it was an easy choice. I have been working 4 years at the Gastroenterology ward in the University Hospital in the North of Norway, where I have seen many interesting liver transplanted patients. Each one with their own post transplanted challenges.

Purpose for the assignment:

There is interest for collecting knowledge from different research on this field which may facilitate the development of therapeutic strategies to promote indefinite allograft acceptance, while almost eliminating or minimizing the need for immunosuppressive drugs and then prevent the side effects many patients gets from immunosuppressive drugs. (1)

Questions for the assignment:

How much do we know about the side effects in immunosuppressive drugs? How much does it impact patient's lives? Is it possible to completely withdrawn IS after an organ transplantation? Is there a blueprint rule for right medication in liver transplantation? Why is the liver so unique?

I want to thank my supervisor Geir Ivar Nedredal giving me the opportunity to dive in to an area of knowledge I would never have been achieving had it not been for this thesis. His engagement and competence in hepatology and transplantation procedure is unique in our country, and especially in the region Northern Norway.

I also want to express my gratitude to my supportive family.



Tora Elisabeth Almendingen
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Abstract

Background: There is increasing interest in long-term management issues in liver transplantation recipients; quality of life, complications related to extended immunosuppressants, natural development of co-morbidities and recurrent disease. IS agents are used in induction of the liver transplantation, maintenance of the organ, and reversal of organ rejection.(2)

Aim: A systematic literature search with the purpose of summaries the existing clinical research on this specific topic; immunosuppressive medications post-liver transplantation.

Material and methods: Search method in PubMed; Medical Subject Headings, with the terms: ("Liver Transplantation"[Mesh]) AND "Immunosuppression" [Mesh]. The selected studies were assessed for scientific quality and relevance for the thesis.

Results: Steroid-based IS are responsible for a substantial post-LTx morbidity and mortality, hence, minimization of its use is of utmost importance to improve patient's quality of life. Because of systemic steroids impact on all organs in the human body and all its side effects that increases risk factors of morbidity.(3) It is important to comprehend the hepatic disease and the patient, as well as understanding the efficacies and side effects/interactions of IS medication. This way the doctor and the patient can strike a balance between suppression of rejection and minimization of side effects. The patient group are very complex, and this have been shown to be a challenge when it comes to comparing the result on the effect of different studies with different immunosuppression's as the reason for liver failure have a lot to say for graft rejection and patient survival, especially for complication accruing with lifelong IS.

Conclusion: LTx recipients are an inherently complex population, with diverse and serious underlying medical concerns that have the potential to adversely affect posttransplant outcomes, thus would a general IS therapy lead to a greater rejection rate. There is a need for more clinical studies, random control trails, that can help us finding the best immunosuppressive treatment for liver transplanted patients.

Abbreviations

ACR: Acute Cellular Rejection

AILD: Autoimmune Liver Diseases

APC: Antigen-Presenting Cell

AZA: Azathioprin

CKD: Chronic Kidney Disease

CNIs: Calcineurin Inhibitors

CVD: Cardiovascular Disease

CYA: Cyclosporin

DC: Dendritic Cell

EBV: Epstein-Barr Virus

eGFR: Estimated Glomerular Filtration Rate

EVR: Everolimus

GVHD: Graft-Versus-Host Disease

HCC: Hepatocellular Carcinoma

HR: Hazard Ratio

HRQOL: Health-Related Quality of Life

HVG: Host Versus Graft

IS: Immunosuppression

ITT: Intent-To-Treat

LDLT: Living Donor Liver Transplantation

LFA-1: Leukocyte Function-Associated Antigen-1

LTx/LT/OLT: Liver Transplantation/Orthotopic Liver Transplantation

MHC: Major Histocompatibility Complex

MMF: Mycophenolate Mofetil

MS: Metabolic Syndrome

PSC: Primary Sclerosing Cholangitis

PTLD: Post-Transplant Lymphoproliferative Disease

PTMS: Post Transplant Metabolic Syndrome

RCT: Randomized Controlled Trial

STWD: Steroid withdrawal

TAC: Tacrolimus

1 Briefly Summary of Liver Transplantation History

Improvements in medical care, operative techniques and immunosuppressive therapies have led to the fact that more and more patients with decompensated liver disease are treated with liver transplantation. Medical care and operative techniques have been improved, but also many new immunosuppressive therapies have result in to greater outcome for posttransplant patient and graft survival rates. (2)

Like Laika, the first animal launched into earth orbit, she paved the way for human spaceflight, dogs were the first creature liver transplantation was attempted on by C. Stuart Welch in Albany Medical College in the year of 1955, and by Jack Connon in California in 1956. The first human liver transplantation was performed by T.E. Starzl in 1963. It was a 3 year old child with biliary atresia, who received the liver from another child who died from a brain tumour. Sadly, the child had such a massive haemorrhage and died on the operation table. Despite improvements in surgical techniques, liver transplantation remained experimental until 1970, when 1 year patient survival rate was expected around 25%. (4)

From the first era of liver transplantation rejection was a rapid complication. None of the first patients recovered their health, and the longest survival was 34 days. Early immunosuppressive therapy consisted of prednisolone and azathioprine. Despite poor results in survival, the surgeons still had faith in liver transplantation therapy, and during the next decades trials all over the world tried to improve the selection of donors and recipients, the procedure, the post-transplantation medication, and the knowledge about our immune system.

From the beginning of liver transplantation history, it has been recognized that the liver has unique tolerogenic properties. Compared with other solid organs, the liver has lower incidence of rejection and it has also the ability to protect other organs form the same donor against rejection. (1)

Theoretically, it will be possible to apply immunosuppression/immunostimulation in the perfect balanced way to either achieve immunological indifference or to obtain stable antigen-dependent T-cell exhaustion and chimerism.(5)

2 A short Overview on Liver Transplantation

It is a surgical procedure that removes a damaged liver and replace it with another healthy liver. The liver that are removed does not longer function properly (liver failure), and the liver that are transplanted in are a healthy liver from a deceased or living donor.

The liver performs several critical functions like processing hormones, nutrients and medications, and removing bacteria and toxins from the blood. Producing bile and blood clot proteins. Preventing infection and regulate immune responses.

Liver transplantation is a treatment option for people with liver failure, end-stage chronic liver disease, often as one of the last treatment options as their condition can't be controlled with other treatments, like primary liver cancer. Liver failure may happen quickly or over long period of time. Acute liver failure (fulminant hepatic failure) or chronic liver failure that may be caused by many different conditions. The most common is scarring of the liver, *cirrhosis*, and this is also the most frequently cited reasons for liver transplant. The major causes of cirrhosis leading to liver failure and liver transplantation is: Hepatitis B and C, Alcoholic liver disease, non-alcoholic fatty liver disease, genetic diseases affecting the liver or diseases that affects the bile ducts.

Risk and complications of the procedure: bleeding or blood clots, bile duct complications (leaks or shrinking), infections, failure of donated liver, rejection of donated liver, mental confusion or seizures. Recurrence of liver disease is also included in long-term complications.

The number of people with a critical liver disease, waiting for a transplant surgery, has greatly exceed the number of available deceased-donor livers. The unique trait about the human liver is that it regenerates and returns to its normal size shortly after surgical removal of part of the organ, so it is possible for a living-donor liver transplant to be an alternative. Patients receiving liver from a living donor have better short-term survival rates than those who have received a liver form a deceased-donor.

The process ahead to liver transplantation is long and highly evaluated. Briefly summarized the recipient need to be healthy enough to have the surgery and tolerate the lifelong follow-up and post-transplant medications with its side effects. Anti-rejection medications can cause many different side effects and the most common are high blood pressure, high cholesterol, impaired glucose tolerance and diabetes, bone thinning, headaches, diarrhea and increased risk of infections because of the suppression on the immune system.(6) (7)

2.1 Liver transplantation in Norway

There is only one centre in Norway where liver transplantation (LTx) is done, and it is in Oslo University hospital Rikshospitalet. In the period 1984 to 2009; 651 LTx were done in Norway, and during the last years there have been a great increased in the number of surgeries. In the year of 2008; 98 LTx were completed. The median time on the waiting list is 26 days. The most frequent reason for LTx in Norway is severe liver failure caused by primary sclerosing cholangitis (PSC). (8)

Standard induction therapy after liver transplantation is triple treatment with Solumedrol/ Prednisolone, Prograf bid and CellCept. There are some patient groups where the immunological risk is higher, as PSC, PBS or autoimmune hepatitis, and these will be treated with IL-2 antagonist (*Simulect*) and high dose Solumedrol in the induction phase. (9)

3 Introduction to the immune system and immunosuppression in Liver Transplantation

There is increasing interest in long-term management issues in liver transplantation recipients; quality of life, complications related to extended immunosuppressants, natural development of co-morbidities and recurrent disease. The central issue to most organ transplantation is suppression of allograft rejection, and we are using immunosuppressive agents in induction, maintenance, and for reversal of graft rejection.(2)

We do now have very powerful immunosuppressive drugs and it is important to learn how to best use them. If a state of proper tolerance can be given in the majority of patient receiving a donated liver, it will be a quest for true immunological tolerance in the clinic. Understanding the model of alloimmune response will help to understand the medications act.

The alloimmune responses involve both naive and memory lymphocytes. Dendritic cells (DC) of donor and host origin become activated in the graft and the surrounding tissue and goes to T-cell areas of secondary lymphoid organs. Here the dendritic cell which bears the antigen engage alloantigen-reactive native T-cells and memory T-cells. Antigen-experienced cells may also be activated by other cell types than dendritic cells, such as graft endothelium.

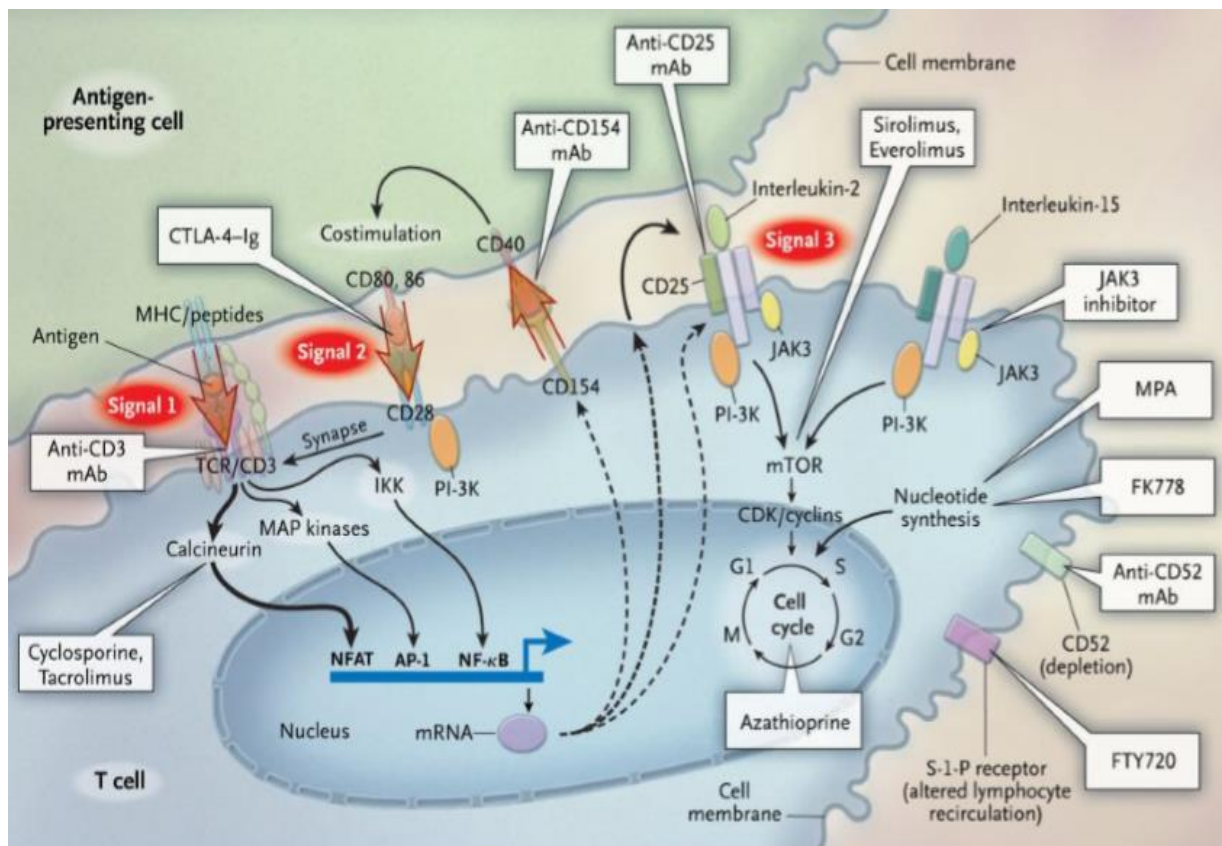
- **Signal 1 – Alloantigen recognition:** An antigen on the surface of DC that triggers T cells with cognate T-cell receptors. It requires presentation of a foreign alloantigen along with a host MHC molecule, presented by the APC. This signal pathway can be aborted by antilymphocyte antibodies.
- **Signal 2 – Costimulation:** CD80 and CD86 on the surface of the DC engage CD28 on T cells. Lymphocyte activation requires stimulation; the T-cell receptor complex is internalized and binds to immunophilin which stimulates calcineurin and then activates nuclear factor for T-cell activation by removing pyrophosphate. Cyclophilin and FK-binding protein, are targets of cyclosporine and tacrolimus. Both agents block calcineurin and are known collectively as calcineurin inhibitors(CINs).
- **Signal 3 – Clonal expansion:** synthesized IL-2 is secreted by T-cells and binds to IL-2 receptors. This receptor is located on the cell surface in an autocrine fashion and stimulate a burst of cell proliferation. The two immunosuppression drugs Dacilumab and Basiliximab both blocks this signal. The drug Sirolimus binds to the mechanistic target of rapamycin. Azathioprine(AZA) and mycophenolate mofetil(MMF) stop the proliferation burst by inhibiting the level of DNA synthesis.

These signals activate three signal transduction pathways, as is shown in *figure 1*, (a) the calcium-calcineurin pathway, (b) the RAS-mitogen-Activated protein (MAP) kinase pathway, and (c) the nuclear factor-kB pathway. Pathway (a), (b) and (c) activate transcription factors that trigger the expression of many new molecules, including IL2, CD154, and CD25. These triggers Signal 3 which is the start of cell proliferation. Cell proliferation also need nucleotide synthesis.

Proliferation and differentiation lead to large numbers of effector T-cells. Together with activated B-cells, producing alloantibody against donor HLA antigens, it will only take a few days for the immune response to generate the agents of allograft rejection.

T-cell proliferation is associated with secretion of cytokines, cell-mediated cytotoxicity, chemokines and adhesion molecules. All which recruit additional inflammatory cells to the graft together with toxic and vasoactive mediators. For decades doctors have controlled this step by using glucocorticoids and antilymphocyte antibodies.

Figure 1. Three-signal model: individual immunosuppressive drugs and sites of action. The signals shown in red, and the immunosuppressive drugs shown in white boxes. (2)



Effector T-cells infiltrate graft and orchestrate an inflammatory response. Effector T-cells, B-cells, plasma cells, activated macrophages, and increased chemokine expression gives an altered capillary permeability, extracellular matrix and deterioration of parenchymal function.

The antibody-mediated rejection is diagnosed by criteria in clinical, immunologic, and histologic characters. Suppression of allograft rejection is the central issue in any organ transplantation. (10) In liver transplantation 25-80% of patients present with acute cellular rejection and 5-10% develop chronic rejection. (4) In liver transplantation the immunosuppression is classified into three phases: induction (initial) phase, maintenance phase, treatment of rejection. These phases will be presented below.

3.1 Induction phase

During this phase high level of immunosuppression is maintained, and the goal is to induce a state where the patient is in acute immunoparalysis. This prevent early cell-mediated reaction. The combination of high dose glucocorticoids and calcineurin inhibitors is good prevention

for the allograft from acute cellular rejection(ACR). The antilymphocyte therapy also has some adverse effects that is necessary to be aware of, like opportunistic infections, post-transplant lymphoproliferative disease. This therapy could also be used as treatment for steroid-resistant rejection episodes. This will be discussed in the later sections. (4)

3.2 Maintenance phase

Gradually we go from induction phase to maintenance immunosuppression therapy, and calcineurin inhibitors are usually the basis. In this phase it is very important to adjust the needs for the patient. To take in consider history of rejection or underlying liver disease. So, if the patient has history of frequent ACR we need to boost the blood levels of immunosuppression for a longer period. But this is very individually, and some patients are doing well with lower levels. It is highly desired that the immunosuppression therapy gradually reduces to avoid side effects caused by immunosuppression, but in the same time also avoid episodes of rejection. (4)

3.3 Treatment of Rejection

There are three types of rejection in liver transplantation:

- Hyperacute rejection, antibody mediated rejection, that can lead to high mortality rate.
- Acute cellular rejection (ACR), treated with high-dose glucocorticoids in high dose bolus or pulse therapy followed by drug tapering.
- Chronic rejection, the treatment is very limited.

We can achieve immunosuppression by depleting lymphocytes, diverting lymphocyte traffic, or blocking lymphocyte response pathways. And as we use immunosuppressiv drugs there are three categories of effect:

- 1) **Therapeutic effect**; supressing rejection.
- 2) **Undesired consequences of immunodeficiency**, infection or cancer. Such as post lymphoproliferative disease, which are related more to the intensity of immunosuppression than to specific drug agent used.
- 3) **Non-immune toxicity towards other tissues**. This is agent-specific and is often related to the drug mechanism. Each class of immunosuppressiv drugs targets molecules with physiologic roles in non-immune tissues.

4 Classification of Drugs

Immunosuppression can be achieved in different ways. By depleting lymphocytes, diverting lymphocyte traffic or blocking lymphocyte response pathways. And this could also evolve for side effects like characteristic infections and cancer. Fortunately, the newer immunosuppressive agents have shown results in lower incidence of both cancer and opportunistic infections. (10)

Immunosuppressive drugs include small-molecule drugs, depleting and nondepleting protein drugs, fusion proteins, intravenous immune globulin and glucocorticoids.

Table 1. An overview of the most used immunosuppressive drugs in organ transplantation, their mechanism on the immune system and adverse effects:

Medication class	Agent	Mechanism	Adverse effects
Corticosteroid	Prednisolone	↓prostaglandin and leukotriene release. Stabilizes lysosomal membranes. ↑AP-CC cells. ↓CD4-T cells. Inhibits lymphocyte activation.	Hypertension(HT), dyslipidemi, glucose intolerance, psychiatric disturbance, peptic ulcer, obesity, cushingoid features, avascular necrosis, poor wound healing, osteoporosis, cataracts, and adrenal suppression.
Calcineurin inhibitor (CIN)	Cyclosporine	↓phosphatase activity of calcineurin → ↓transcription of IL-2	Acute/chronic renal failure, neurotoxic effects. HT, obesity, hirsutism, gingival hyperplasia.
	Tacrolimus	→ inhibition of T-cell activation	Acute/chronic renal failure, neurotoxic effects, insulin resistance, diarrhea, electrolyte disturbances, alopecia, thrombotic microangiopathy.
Cell cycle inhibitor, mTOR inhibitor	Sirolimus	Inhibits mammalian target of rapamycin → diminished intracellular signalling distal to IL-2 receptor → arrested T-cell replication.	Leukopenia, thrombocytopenia, oral ulcers, proteinuria, peripheral edema, hyperlipidemia, acne, interstitial pneumonitis.
	Everolimus		

Antiproliferative, antimetabolites.	Mycophenolate mofetil (MMF)	Inhibits DNA synthesis by targeting inosine monophosphate dehydrogenase to block synthesis of fuanosine nucleotides	Bone marrow toxicity, abdominal pain, diarrhea, nausea, vomiting.
Antiproliferative purine analogue	Azathioprine	Inhibits DNA and RNA synthesis in T- and B-cells. Inhibits CD28 co-stimulation	Bone marrow toxicity, pancreatitis, hepatotoxicity.
Antibody-based, IL-2 receptor block	Basiliximab	Antagonizes IL-2 receptor with resultant inhibition of IL-2- mediated T-cell activation.	Infection, GI-upset, pulmonary edema, bronchospasm.
	Dacilizumab		

4.1 Corticosteroids, Prednisolone

Glucocorticoids are agonists of glucocorticoid receptors, and the effects are mainly transcriptional through DNA-binding and protein-protein interactions of the steroid receptor complex. Activator protein 1 and nuclear factor- κ B are targeting transcription factors.

- Decrease the cytotoxic T-cell proliferation and cytotoxicity
- Inhibit the production and expression of cytokines like IL-1, IL-2, IL6, TNF
- Block the ability of macrophages to respond to lymphocyte derived signals
- Depress delayed hypersensitivity
- To some extent inhibits antibody-dependent cytotoxicity
- Inhibit production of γ -interferon
- Decreases local inflammation by decreasing migration of neutrophils and inhibiting lysosomal enzyme released by neutrophils.
- At higher doses they have a receptor-independent effect.

Adverse effects of corticosteroids: hyperglycemia, increased appetite and weight gain, insomnia, osteoporosis, cataract, myopathy, neurological impairment – psychosis, insomnia, skin changes, adrenal insufficiency. (4)

4.2 Calcineurin Inhibitors (CNIs)

Early cell cycle inhibitors. Cyclosporin and tacrolimus both act in a similar fashion; inhibition of T-cell activation by binding specific intracellular proteins to form a complex of drug-protein. This drug-protein complex reduces the phosphatase activity of calcineurin. This results in decreased transcription of IL-2. In 2004, 97% of all liver transplanted patients were discharged home with an immunosuppressive regime where a calcineurin inhibitor were incorporated. But the calcineurin inhibitors have several major side effects.

4.2.1 Cyclosporine (CYA)

For two decades cyclosporine has been a cornerstone of immunosuppression in transplantation. The mechanism of a prodrug that engages cyclophilin, an intracellular protein of the immunophilin family, and then forming a complex that then engages calcineurin.

Adverse effect: nephrotoxicity, hypertension, hyperlipidaemia, gingival hyperplasia, hirsutism, haemolytic-uremic syndrome and post-transplantation diabetes mellitus. (10)

4.2.2 Tacrolimus

Tacrolimus also inhibits calcineurin, but with greater molar potency than cyclosporine, because of the creation of a complex by FK506-binding protein 12 (FKBP12).

The use of this drug has increased steadily, and tacrolimus is now the dominant calcineurin inhibitor, but most transplantation programs are exploiting the strength of both CNIs. But the therapy also depending on the risk factors in individual patients.

Adverse effects: hypertension, hyperlipidaemia, risk of rejection which are lower for tacrolimus than cyclosporine, but the risk of diabetes and obesity are greater than for cyclosporine.

4.3 Cell Cycle inhibitors

The immunosuppressive effects of cell cycle inhibitors are by inhibiting the mammalian target of rapamycin, also called mTOR. The drug engages FKBP12 to create complexes that engage and inhibit the target of rapamycin. Preventing cytokine receptors from activating the cell cycle, and arresting cell replication, diminishing intracellular signaling distal to the IL-2 receptor. This prevent the replication of T-cells.

Sirolimus and Everolimus were developed for the use with the immunosuppressiv drug cyclosporine, but the combination increased nephrotoxicity, hypertension and hemolytic-uremic syndrome. Sirolimus and tacrolimus can be combined to avoid toxicity. (10)

Adverse effects: leukopenia, hyperlipidemia, thrombocytopenia, oral ulcers, acne, proteinuria, peripheral edema, interstitial pneumonitis. Poor healing of wound infections and hepatic artery thrombosis are shown with high-dose use of sirolimus. (2)

4.3.1 Sirolimus

Sirolimus (Rapamune, is a macrolide antibiotic and a potent immunosuppressive agent, for the first time used for kidney transplantation in 1999. It is structurally similar to tacrolimus; binds with a higher affinity, the same target FK-binding protein, but it does not inhibit calcineurin. Sirolimus blocks the transductional signal form IL-2 receptor. It then has the power of inhibiting T- and B-cell proliferation. The important different from tacrolimus is its freedom from neuro- and nephrotoxicity. Sirolimus in triple therapy combination with prednisolone and cyclosporine has a very low rejection rate among LTx.

Sirolimus have been proposed as a good choice for patients with HCC because of its antiproliferative activity. But the benefits have not yet been proven in bigger trails. A systematic review that included 11 studies shown that Sirolimus use was associated with a higher risk for rash, ulcers, infection and a higher rate of discontinuation of therapy, but it was not associated with an increased risk of graft failure. (11)

4.3.2 Everolimus

Everolimus (12) is the hydroxyethyl derivative of Sirolimus, and its mechanism of action is via inhibition of mammalian target of rapamycin, also called mTOR. The same mechanism as Sirolimus, but compared it has a higher oral availability and lower plasma binding.

The side effects seem to be related to the dose, but mostly similar to the side effects caused by Sirolimus. Most common; anemia, peripheral edema, nausea, diarrhea, elevated s-creatinine, urinary tract infections and hyperlipidaemia. (11)

4.4 Antimetabolites

Antimetabolites, also called antiproliferative immunosuppressive agents, reduce immune-mediated graft injury. The mechanism is by reducing the expansion of activated B and T cells. The majority of transplant centers are using MMF in conjunction with corticosteroids and CNIs for maintenance therapy, in posttransplant first 6 months.

Use of antiproliferative immunosuppressive agents (AZA and MMF) can be limited by bone marrow toxicity. AZA can cause pancreatitis and hepatotoxicity. The side effects of MMF is associated with the gastrointestinal tract as vomiting, diarrhea, nausea and abdominal pain.

4.4.1 Azathioprine (AZA)

In 1988 Gertrude Elion and George Hitchings received the Nobel Prize for developing Azathioprine. It was the first immunosuppressive agent to achieve widespread use in organ transplantation. (10) It acts by releasing 6-mercaptopurin, which interferes with DNA synthesis.

AZA is a purine analogue that inhibits DNA and RNA synthesis, specific in rapidly proliferating B and T cells. AZA also inhibits CD28 co-stimulation of T lymphocytes.

4.4.2 Mycophenolate mofetil (MMF)

MMF came into use for liver transplantation in the 1990s. The difference between MMF and AZA is that MMF is more selective. It is converted in the liver to mycophenolic acid and targets inosine mono-phosphate dehydrogenase. And this ultimately inhibits DNA synthesis by blocking the synthesis of guanosine nucleotides.

Particularly MMF has been used to minimize CNIs drug use in patients with CNI-induced renal insufficiency. It has been shown that replacement of CNIs with MMF result in renal improvement, as well as improvement in hypertension.

4.5 Antibody-based Drugs

Interleukin-2 receptor blockers were developed in the 1990s. They are monoclonal antibodies that antagonize the IL-2 receptor. This results in inhibition of IL-2 mediated T-cell activation. The drugs have minimal side effects due to their selective action and are generally well tolerated. This has led to their increasing usage in steroid-sparing and CNI-minimizing therapy regimes. (10)

Adverse effect: infection, gastrointestinal related upset, and not so common pulmonary edema and bronchospasm.

4.5.1 Basiliximab

Basiliximab is a chimeric monoclonal antibody against CD25 (IL-2 receptor α chain). The mechanism of the drug is that it binds to and blocks the IL-2 receptor α chain on activated T cells, depleting them and inhibiting interleukin-2-induced T-cell activation, so it prevents T-cell proliferation. The chimeric structure makes the half-lives longer and it is better tolerated. Basiliximab has an elimination half-life of 4 ± 2 days.

Antibodies can help to reduce the use of CNi in patients with renal diseases pre-LTx. Or it can minimize steroid use. As shown in one report; Basiliximab controlled and prevent steroid-resistant rejection after LTx in 4 out of 7 children. (11)

4.5.2 Daclizumab

Daclizumab is a humanized monoclonal antibody against CD25 (IL-2 receptor α chain). The action is similar to Basiliximab. A nonrandomized study of Daclizumab before engraftment with a dose given on day 5 post-LTx shown a much lower rejection rate the first 6 months (18% vs. 40 %). It also showed a marked improvement in renal function, no CMV incidence increase and less infectious complications than compared with the control group who were given standard immunosuppression.

Daclizumab was removed from the drug-marked in 2009, because of commercial reasons. There were no clinical issues identified. (13, 14)

4.6 Newer Immunosuppression Drugs

Immunosuppressive agents that are still under experimental trails.

Alemtuzumab: this drug is a humanized monoclonal, complement-fixing anti-CD52 antibody. B and T lymphocytes express the CD52 on the surface, together with macrophages, monocytes and eosinophils. The activation through complement leads to profound lymphocyte depletion. It has been approved in treatment of chronic B-cell lymphocytic leukaemia, and tried out for solid organ transplantation, and it has been proposed as a method to decrease steroid and CNi drug use.

Belatacept: this drug is a high affinity fusion protein that binds CD80/86 on APC. CD80/86 gets prevented from binding to the T-cell, and this blocks the costimulatory pathway. It can permit immunosuppression without nephrotoxicity and are given as a monthly infusion. Studies have reported an effectiveness in renal transplantation, but it has been related to an increased rate of post-transplant lymphoproliferative disorder. This new immunosuppressive drug is not yet used in liver transplantation.

Efalizumab: a humanized monoclonal antibody, against leukocyte function-associated antigen-1, LFA-1 which plays multiple roles in cell migration, cell adhesion, organ rejection and stabilization of the APC T-cell complex, making it very effective. The role of this potent drug in liver transplantation is still uncertain. (11)

5 Liver Tolerance

Human liver allograft compared to other organs have a lower susceptibility, but in addition, some liver transplant recipients have all their immunosuppressive drugs completely withdrawn. These patients are considered as operationally tolerant. Clinical experience indicates that elective immunosuppressive (IS) drug weaning is feasible in almost 20% of selected liver transplant recipients. (15)

A few patients in Pittsburg have demonstrated operational tolerance after varying periods of treatment with continuous IS after LTx. One woman had no immunosuppressive drugs for 15 years, making her the longest survivor in the world without IS. She didn't use the drugs because she disliked the side effects of the drugs. It is not usual for recipients of other organ transplantation to be able to not take any immunosuppression without acute or chronic rejection of the transplanted organ. We know that the liver is a large MHC antigen source and has an incredible reparative capability even after severe damage. The scientist Pollard had shown that in humans 50% of the circulating Class I MHC antigen in the blood is produced by the liver. Soluble forms of these molecules are also synthesized in the liver grafts. (16)

With markedly improved short-term result of LTx and persistently high numbers of long-term complications, we focus more and more on minimizing IS therapy as much as possible. Post-LT morbidity and mortality are often caused of steroid-based IS, and therefore the minimization of the use is important for improving patient's life. We see that the tendency in clinical

practice is moved more and more towards a steroid minimized treatment or total steroid withdrawal (STWD). Since the very beginning of LTx, steroids have been used as IS drugs, because they are easy to handle and allow control of most rejections at a low cost. But the side effects make great impact on the recipient's life and the active process of graft tolerance. Many studies show that STWD is safe in terms of patient and graft survival and that chronic rejection incidence is much less concern in LTx than in renal transplantation, but long-term follow-up is mandatory to confirm these findings of these patients. STWD have a beneficial metabolic effect. But still, STWD remains controversial due to the lack of evidence-based selection criteria, of well-conducted large clinical trials and of long-term follow-up studies looking at chronic allograft rejection and graft survival. (3, 17, 18)

Some recipients of LTx may develop immunologic tolerance, but the factors predicative of tolerance are not clearly understood. Immunological tolerance is the phenomenon by which some patients maintain normal allograft function as well as normal immunological response in the absence of IS. 20 to 40% of LTx patients show this potential. (17)

In an intention-to-treat analysis, 24 members of the total population with more than 3 years of follow-up after LTx attempted weaning from IS (17.4%). Fifteen (10.9%) were tolerant. Most importantly, there were identified 2 easily obtained variables predictive of tolerance: a longer period since transplantation and lower stimulation lymphocyte reactivity (expressed as the SI). This may be helpful in selecting patients with a potentially high rate of success with IS withdrawal. (17)

6 Material and Methods

This Master Assignment is a systematic review, with summarized result of available healthcare studies, with the purpose of summaries the existing clinical research on this specific topic; immunosuppressive medications post-liver transplantation.

6.1 Search strategy and selection criteria for the literature

Pertinent literature used in this thesis was assembled and identified through MEDLINE database with the help form the search engine PubMed. The period of searching was done in March and April 2019. The search were done by using the method of Medical Subject Headings(3), and the terms used were: ("Liver Transplantation"[Mesh]) AND "Immunosuppression"[Mesh]

The goal was to get a good overview and identify the different post liver transplantation immunosuppressive treatments, which immunosuppressive drugs were used and what were the outcome. The filters used in the search were:

- An adult patient group (age over 19-year-old).
- The period, twenty years, covering the search, from January 1999 to April 2019.
- Only articles written in the English language
- Evaluating human subjects.

With the search method described above, a total of 942 studies were found to be relevant. After constricting the articles for covering publish date in the period of the last twenty years the numbers of articles were narrowed down to 503 articles. Then the filter for text availability were used and narrowed the search down to only free full texts. Resulting in 204 articles.

The 204 remaining articles were then collected and screened for relevancy by reading the abstract. The articles with only one author were excluded. After retrieving the full text of the chosen articles, 77 articles were chosen as eligible and of high relevancy to be used in this thesis. These 77 articles were then included in the final review.

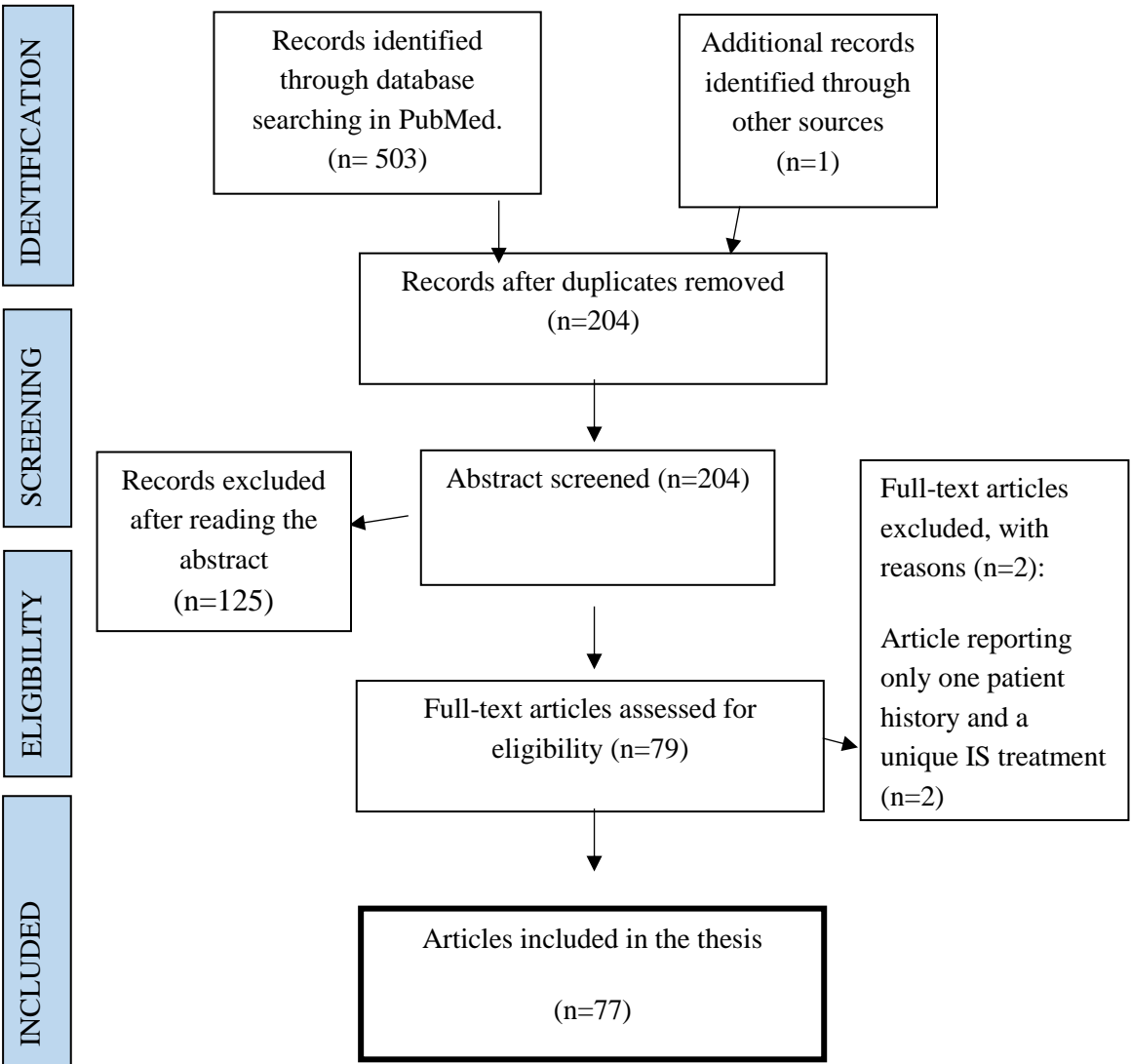
6.2 Data collection

After the search for relevant literature and the selection of articles, I then started to collect data and information from the remaining 77 articles. The list of the final articles were put in the software EndNote X8, a digital library of references.

Figure 2 present the results of the search process. The final list of studies is attached in the end of this thesis (Appendix).

6.3 Selection of articles

Figure 2. A summary of the literature search presented in a PRISMA Flow diagram. Together with the selection of studies.(19)



7 Main results and discussion.

The search process is presented in figure 2 above, and the results are shown as a final table-list of all 77 studies attached to the thesis, *Appendix*.

The study design of the selected articles where 8 RCT, 11 prospective, 24 retrospective, 14 cohort, 11 systematic review, 2 cross section, 2 register studies, 3 single case report studies and 2 postal survey/questionnaire. The number of patients included in the studies varied a lot from just 20 patients to over one thousand, due to what kind of study design and the exposure.

7.1 Rejection rates

The list of factors that have been shown to negatively affect graft survival in LTx patients are long. These factors are usually stratified into donor factors, graft factors and recipient factors. It is not possible to estimate rejection rates only from an immunosuppression point of view.
(2)

Donor factors: many donor factors can negatively affect graft survival in LTx recipients. The most extensive risk factor for graft failure is donor age. Evidence in patients transplanted for HCV show a significant decrease in graft and patient survival rates for those with HCV who receive liver from older donors. But there is evidence that careful choice of recipients and graft from older donors can be used with survival rates comparable with normal population. (20) Donors severity of illness has been demonstrated to predict poorer outcome and higher rejection rates. Prolonged stay at intensive care units is also a negative factor, together with low bicarbonate level and antecedent hypertension and diabetes mellitus. (2)

Graft factors: graft type is important determinant of graft rejection and patient survival prognosis. Donation after cardiac death exposed to ischemia (prolonged cold ischemia time) during cardiopulmonary death, have been shown to have worse outcomes compared with donation of liver after brain death. (20) Graft macrovesicular steatosis increase prevalence of diabetes and obesity in recipient.

Recipient factors: although the number of LTx recipients over the age of 65 have increased 2.5-fold, recipient age has shown to worsen posttransplant prognosis. But it is no consensus on an age limit for LTx. Patients undergoing LTx are evaluated on an individual basis.

Using steroid protocols rarely gives rejection, but it is followed with many deadly side effects. Two meta-analyses evaluating corticosteroid-free IS showed no differences in mortality or graft survival rates, and demonstrated reduced cholesterol levels, de novo DM, CMV-infection and lower rates of HCV recurrence. Rejection rates were increased in individual studies in which steroids were not substituted with other IS; but, when steroids were replaced, rejection rates were not elevated. Because of these data, many transplant centers endeavour to rapidly taper or even completely avoid corticosteroids in LTx therapy. Patients undergoing LTx for immunologic liver diseases, such as autoimmune hepatitis, sclerosing cholangitis, and primary biliary cirrhosis, may have less chance of long-term success with a steroid-sparing strategy. (21, 22)

Type of rejection can be divided into acute rejection, chronic rejection, steroid-resistant rejection, graft lost and death. Lymphoproliferative disease. It got estimated in a meta-analysis where the IS tacrolimus and cyclosporin were compared as primary immunosuppressant post-LTx that if 100 patients got treated with tacrolimus vs. cyclosporine nine would avoid rejection, seven would have avoid steroid-resistant rejection, five would have avoid graft loss and two patients would have avoid death. But additional four patients would have developed diabetes. (23)

7.2 Side effects caused by immunosuppression

The most life-threatening side effects, and those considered most severe, are renal failure. Obesity, glucose intolerance and dyslipidemia are also severe because of the increased risk factors of cardiac arrest and stroke. (24) Presented in table 1, again shown here in table 2, considerably many side effects caused by IS have been assessed.

Table 2. An overview of the most used immunosuppressive drugs used in organ transplantation, and their adverse effects:

Medication class	Agent	Common side effects
Corticosteroid	<i>Prednisolone</i>	Hypertension, dyslipidemia, glucose intolerance, diabetes, psychiatric disturbance, peptic ulcer, obesity, cushingoid features, avascular necrosis, poorer wound healing, osteoporosis, adrenal suppression, cataracts.
Calcineurin inhibitor (CNI)	<i>Cyclosporine</i>	Acute/chronic renal failure, neurotoxic effects. hypertension, obesity, hirsutism, gingival hyperplasia.

	<i>Tacrolimus</i>	Acute/chronic renal failure, neurotoxic effects, insulin resistance, diarrhea, electrolyte disturbances, alopecia, thrombotic microangiopathy.
Cell cycle inhibitor, mTOR inhibitor	<i>Sirolimus</i>	Leukopenia, anemia, thrombocytopenia, oral ulcers, proteinuria, peripheral edema, hyperlipidaemia, acne, interstitial pneumonitis, diarrhea, nausea, UTI.
	<i>Everolimus</i>	
Antiproliferative, antimetabolites	<i>MMF</i>	Bone marrow suppression/toxicity, abdominal pain, ileus, diarrhea, nausea, vomiting, oral ulceration.
Antiproliferative purine analogue	<i>Azathioprine</i>	Bone marrow toxicity, nausea, vomiting, pancreatitis, hepatotoxicity, neoplasia.
Antibody-based, IL-2 receptor block	<i>Basiliximab</i>	Infection, GI-upset, pulmonary edema, bronchospasm
	<i>Dacilizumab</i>	

7.2.1 Corticosteroids and HCV

Cirrhosis caused by HCV infection are the number one indication for people getting LTx in the United States. Patients who are liver transplantated because of cirrhosis secondary to HCV infection are recommended to have only a low-dose steroid indefinitely, and to taper steroids slowly, and if possible total steroid withdrawal. Corticosteroid are in addition to the side effects associated with increased HCV replication. The drug may drive replication directly, or they may permit more effective replication though IS. (13) (21) (25)

7.2.2 De novo malignancy

Immunosuppression increases the risk of malignancy, also in liver transplant recipience. De novo malignancies meaning new arriving malignancy and cancers, are a major cause of late death post LT. Various potentially oncogenic viruses play major roles in causing de novo cancers, and preventing measures include reduction of IS to the level compatible with a good allograft function and prophylactic measures against viral infections. Patients of older age and male sex are associated with a higher risk of malignancy and transplantation of HCC increase the risk of non-melanoma skin cancer. (26, 27)

A retrospective, single-centre analysis with 14,490 person-years of stringent follow-up at outpatient clinic, showed that the cancer incidence rates for the LTx recipients were almost twice as high as those for the age- and sex-matched general population. Also the underlying liver disease can have a role, like alcoholic cirrhosis gave a higher risk than overall standard

incidence ratio for all patients. Esophageal cancer and oral cancer were significant higher. (26) In Dr. Aguiar's study de novo malignancies were diagnosed in 126 patients out of 392 LTx recipients who were followed up for 8,5 years, that's 32%, and out of these there were 64 non-melanoma skin cancer and 81 other malignancies. 18 % of the patients stopped receiving CNI and were maintained on MMF monotherapy. The study showed significant proof that MMF is associated with a lower risk of cancer in LTx recipients compared with maintenance IS with CNI. (28)

Tumour treatment preformed according to accepted guidelines seems adequate. After treatment of de novo malignancies patients had a superior 5-year survival rates for renal cell carcinoma, colorectal cancer, lung cancer and thyroid cancer are compared with the general population. Whereas other tumours were associated with similar or inferior survival rates after the cancer diagnosis. (26)

A retrospective experiment with 609 patients (year 1985-2007) were studying the impact of the two calcineurin inhibitors (CNI); cyclosporine (CYA) vs. tacrolimus (29) and how the IS affects long-term tumour incidence of de novo malignancy following liver transplantation. Multivariate analysis revealed that the significant risk factors were recipient age (HR 1.06), male gender (HR 1.73), and tacrolimus-based IS (HR 2.06). But the mechanisms by which CNI promote the development and growth of cancer remain poorly understood, but a theory is the inhibition of the immune system and then reduction in the human body's ability to react against cancer cells and reaction on their associated antigens. (30) In another study the univariate risk factors for developing de novo cancer were; CYA-treatment, time-period of LTx, and patients age. The study concluded with that only CYA treatment emerged as an independent risk factor, which attributed to more aggressive cancer types. Compared to tacrolimus treatment, CYA treatment with C2 monitoring or in younger patients of less than 50-years-old is associated with a higher incidence of early de novo cancer risk after LTx. (31)

De novo PTLD means; new occurrence of post-transplant lymphoproliferative disorder and EBV-associated PTLD is the most frequently encountered de novo malignancy after LT. It is easily treatable with reduction of IS and by chemotherapy (anti-CD20 monoclonal antibody). Screening programs following LT-recipients can help in early diagnosis of de novo malignancies. (32)

A retrospectively analyse done in England wanted to determine risk factors, clinical characteristics, and outcomes of de novo nonlymphoid malignancies in the post-transplantation period. Of 1140 patients undergoing 1271 LTx, 30 patients (2.6%) developed de novo nonlymphoid malignancy. Skin cancers were the most common(n=13), next oropharyngeal carcinoma(n=2), bladder carcinoma(n=2), acute leukaemia(n=2), breast carcinoma(n=2), and other malignancies(n=9). Although the incidence of de novo nonlymphoid malignancy after LTx is low, patients who underwent LTx for alcoholic cirrhosis appear to have an increased risk for developing post LTx malignancy. (27)

7.2.3 HCC recurrence

Many patients with hepatocellular carcinoma (HCC) are treated with liver transplantation. They are at risk of getting tumour recurrence after LTx, that involves an ominous prognosis and strict selection criteria of transplant candidates on the basis of tumour features, for minimizing the incidence. We also know that the pharmacologic IS required post-LTx can accelerate tumour growth. But the possible influence of the different IS schedules and types of therapy on HCC patients post LTx have been poorly studied. (22, 33-35)

A study on the influence of different schedules of IS and many clinical, histologic and pathologic factors on HCC recurrence were investigated with univariates and multivariate analysis shown that out of 70 consecutive HCC patients who underwent LTx and received cyclosporine-based IS, 26 patients associated with steroids, and steroids and azathioprine in 44 patients did HCC recurred in 10 % of the patients. The study also shown that different IS schedules or the cumulative dosage of steroids and AZA did not influence HCC recurrence that was associated instead with CsA. But high CsA exposure favours tumour recurrence. CsA blood levels are recommended to be kept to the effective minimum in HCC patients. In LTx recipients, presence of pathologic and histologic risk factors, should specific IS protocols be considered. (33)

7.2.4 Cardiovascular risk

Obesity and metabolic syndrome are more common in liver transplant recipients than in the general population, this makes them at increased risk of CVD, as well as a lower rate of patient survival. Cardiovascular diseases are in fact the leading cause of posttransplant morbidity and mortality. As clinical health workers working with this patient group we should have a direct focus on controlling weight gain in LTx recipients, to make impact on

improving long-term outcomes. Smoking history (ever), male or female, hyperlipidaemia and serum ferritin levels are not predictive of CVD.(24)

The effect of IS on CVD after LTx is difficult to interpret. A retrospective study suggested a potential benefit of the IS tacrolimus over other immunosuppressants in lowering the risk of CVD post-LTx, but not versus cyclosporine. Tacrolimus beneficial effect may reflect the reduced incidence and degree of hypertension, hyperlipidaemia, and renal injury compared to other IS. It may be hypothetically plausible that CYA can induce endothelial dysfunction and TAC may have a beneficial effect on endothelial function. (24) In a 2 years RCT study, from 2018, there were found evidence that the risk of major cardiac events increases with deteriorating renal function post LTx. This establish the need for careful CV risk management in patients with renal impairment. IS based on everolimus with TAC withdrawal, or to a lesser amount TAC reduction, improved both renal function and decreased the risk of major CV events compared to standard TAC therapy in LTx recipients. (36) Another RCT study, from 2017, including 719 patients randomized in to three treatment groups; Everolimus + reduced Tacrolimus (n = 245), (2) TAC control group(n=243) and (3) TAC elimination (n = 231). The results shown a mean increase in weight from baseline was higher at month 12 in the TAC control arm (8.15 ± 9.27 kg) than in the EVR + reduced TAC (5.88 ± 12.60 kg, $p=0.056$) and the TAC elimination arms (4.76 ± 9.94 kg, $p=0.007$). Then after 2 years, the TAC control arm displayed a significantly greater weight increase (9.54 ± 10.21 kg) than either the EVR + reduced TAC (6.69 ± 8.37 kg, $P = 0.011$) or the TAC elimination groups (6.01 ± 9.98 kg, $P = 0.024$). Rates of post-transplant metabolic syndrome were similar for the EVR + reduced TAC (71.8%), TAC elimination (70.3%) and TAC control (67.4%). (37)

Gastroenterologist George Therapondos did a prospective randomized trial to investigate the cardiac function of patients on tacrolimus compared with those on cyclosporin IS post-LTx. 40 adult LTx recipients with cirrhosis were randomized either to TAC or CYA + AZA + prednisolone-based immunotherapy. All had detailed clinical, biochemical, electrocardiographic and echocardiographic assessments at regular intervals, followed up within 3 months. Abnormalities in cardiac function were common after LTx and significant deterioration in left ventricular diastolic function was demonstrable up to 3 months in both patient groups. Cardiac function was similar in both groups. Reduced heart rate variability (HRV) and higher mean BNP were identified in the TAC group. The percentage increase in posterior wall thickness was higher in the TAC group. (12) (2)

7.3 Quality of life

As the survival rates following liver transplantation are rising, health-related quality of life is getting increased focus. Numerous studies have shown that health-related quality of life improves significantly after live transplantation and that LTx-recipients report gains mostly in the aspects of health-related quality of life affected by physical health, but not so much improvements in areas affected by psychological functioning. (32, 38, 39)

In a retrospective study done in Germany they found that liver transplant recipients surviving more than 15 years post-LTx scored lower in comparison to the German reference population in all categories; physical functioning, role physical, general health, vitality, social functioning and role emotional. But recipients scored similarly to the reference population in the categories; mental health and bodily pain.

For LTx patients, job rehabilitation after LTx gave a positive effect on quality of life. Patient who returned to their job during the first year after the transplantation scored significantly higher in the categories of physical functioning and role physical. Occupational rehabilitation was the only factor that did have significant positively impact for the long-term survivors. Patients marital status didn't have statistically significant effect on quality of life. Rather didn't the immunosuppression neither. (38)

Professor Jan Lerut are saying that Steroid-based IS are responsible for a substantial post-LTx morbidity and mortality, hence, minimization of its use is of utmost importance to improve patient's quality of life. Because of systemic steroids impact on all organs in the human body and all its side effects that increases risk factors of morbidity. (3)

However, it has not been done any good research focusing on LTx-recipients' quality of life post transplantation, or throughout the years after transplantation. Therefore, more systematic knowledge, qualitative interview, and survey would be an interest for the future.

7.4 The perfect immunosuppressive combination?

As discussed earlier in this thesis, the goal of immunosuppressive therapy is to prevent allograft rejection, optimize the function of the donated graft, and maximize patient survival rates as well as patient's quality of life while concomitantly maintaining immunologic control over neoplasia, infections and minimizing the side effects and their sequelae.

IS used in induction therapy (initiated immediately posttransplant and continued for 1-2 weeks) are most often two or three drugs and most commonly a glucocorticoid, a calcineurin inhibitor, and an antimetabolite. IS used after the induction phase, the maintenance therapy, use calcineurin inhibitor, mostly tacrolimus, as the cornerstone. But clearly management of LTx recipients is an important, diverse and ever-evolving effort.

It is important to comprehend the hepatic disease and the patient, as well as understanding the efficacies and side effects/interactions of IS medication. This way the doctor and the patient can strike a balance between suppression of rejection and minimization of side effects.

7.5 A life without immunosuppressive

Some patients after liver transplantation might develop immunologic tolerance and then they might be able to stop taking immunosuppressants. Attempts on stopping IS treatment is not yet recommended because of the risk of graft rejection and that we still don't have a clear list of which patients who would be a good candidate for IS withdrawal. If a liver transplanted patient today stops with IS, without medical supervision, it is most likely to have fatal rejections then immunologic tolerance, including patients who are many years post-OLT. Patients are therefore never recommended to stop all immunosuppression. (40)(3)

An interesting study with 24 patient who had side effects from IS and were at high risk for developing de novo malignancy, without autoimmune disease or active viral hepatitis, underwent gradual reduction of their IS. After 14 months of follow up 15 patients (63%) were considered to be tolerant because their liver function tests were normal. The other 9 patients didn't get completely withdrawn because of abnormal liver function test. 2 patients of these 9 had graft rejection shown on liver biopsy and was treated with glucocorticoids. (17)

7.6 A unique organ

Liver failure is a serious condition and warrants a multimodal approach. For a failing liver from either acute liver failure or decompensated liver failure is the best option; liver transplantation. Acute liver failure may include progression to hepatic coma and then possibility of cerebral herniation. Patients who have poor prognosis have etiologist like drug-induced acute liver failure, hepatitis B and idiopathic cases. (41) These have approximately only 25% spontaneous survival rates. In Norway 25–30 thousand people have HBV infection, mostly immigrants who were infected as children back in their home country. Worldwide

HBV is one of the most common infections, and approximately 40 percent of the world population have been infected by HBV, 350 million people. More than 600 thousand deaths each year are calculated caused by HBV-infection causing fulminant hepatitis, cirrhosis and liver cancer. HCC is one of the then most common types of cancer worldwide, and we expect that 78% of HCC are caused by HBV and HCV. People living in Southeast Asia, South America, The Middle East, Eastern Europe, and the tropical areas of Africa have the highest prevalence of HBV infections. (42) These are also patients who would never be cured with liver transplantation and IS therapy.

Different approaches to liver failure are being evaluated and some promising including cell transplantation and the application of extracorporeal liver support (like dialysis for kidney failure). These approaches are relevant for acute liver failure, because a complete recovery will not impose sequelae such as lifelong IS with LTx. The treatment with extracorporeal support (biologic or nonbiologic systems) aim in the setting of decompensated cirrhosis, returning the patient to a compensated state. But it will not offer the possibility of cure. A failing liver may not regenerate or recover completely but it can buy time to bridge to a lifesaving LTx. As the waiting lists for LTx increases, and an expansion of indications for transplantation, and the mortality rates remains high, interest in liver-assist devices is great. (41) Maybe extracorporeal or hepatocyte transplantation are the future of life saving treatment for patient with liver failure, as today the waiting lists for liver transplantation unfortunately outpaced the number of organs available.

7.7 Limitation of the thesis

The topic for this thesis is wide and during the work with this thesis answering the research question have evolved to be more and more complex. The patient group are very complex, and this have been shown to be a challenge when it comes to comparing the result on the effect of different studies with different immunosuppression's as the reason for liver failure have a lot to say for graft rejection and patient survival. And especially for the complication accruing with lifelong IS-therapy. This made it difficult to systemise the result from the literature. There is lack of good randomized control trails examine the different effects of IS. There are ethical issues preventing RCT because of the high mortality rates in this patient group. Most articles found in the literature search were retrospective studies, and the number of patients included in the studies were mostly under 150.

8 Conclusion

Minimization, as well as comprehensive management, of early and late posttransplant vascular, biliary, immunologic, infectious, metabolic, cardiovascular, and neoplastic complications can sustain patient and graft survival rates and optimize patient's quality of life. LTx recipients are an inherently complex population, with diverse and serious underlying medical concerns that have the potential to adversely affect posttransplant outcomes, thus would a general IS therapy lead to a greater rejection rate. But clinical studies have given us some recommendation.

Tacrolimus remains the mainstay of IS in many centers. But IS based on everolimus with TAC withdrawal, or to a lesser amount TAC reduction, improved both renal function and decreased the risk of major CV events compared to standard TAC therapy in LTx recipients. EVR vs TAC gives an attenuated weight gain over 1- and 2-years post LTx. TAC based IS may increase the risk of de novo malignancy.

For patients with pretransplant renal failure in whom we wish to minimize the use of CNI, generally use antibody preparations in the immediate post-transplant period along with delayed calcineurin inhibitors. Slowly worsening renal disease in the late post-orthotopic liver transplant period can be managed by reducing the CNI dose, with the addition of MMF, or by switching to sirolimus or everolimus.

Mycophenolate may also lead to lower long-term risks for de novo cancers. Patients who underwent LTx for alcoholic cirrhosis appear to have an increased risk for developing post LTx malignancy. The standardized incidence ratio of malignancy in LTx patients compared to the general population was 2.2.

Some patients will develop immunologic tolerance following LTx and may be able to stop taking IS. However, because of the risk of irreversible graft rejection, and because of lack in tools to assess which patients that are good candidates for IS withdrawal, we never recommend complete cessation of immunosuppression.

There is a need for more clinical studies, random control trails, that can help us finding the best immunosuppressive treatment for liver transplanted patients.

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11 Appendix

11.1 Contract with the supervisor (page 1–2)

11.2 Table with summary of original articles (page i-xlii)

11.3 Summary of GRADE and evaluation of key articles (page I-V)

- “Belatacept-Based Immunosuppression in De Novo Liver Transplant Recipients: 1-Year Experience From a Phase II Randomized Study.”
- “Impact of Immunosuppression Without Steroids on Rejection and Hepatitis C Virus Evolution After Liver Transplantation: Results of a Prospective Randomized Study.”
- “Randomized Controlled Trial of Tacrolimus Versus Microemulsified Cyclosporin (TMC) in Liver Transplantation: Poststudy Surveillance to 3 Years”
- “Cardiac Function After Orthotopic Liver Transplantation and the Effects of Immunosuppression: A Prospective Randomized Trial Comparing Cyclosporin (Neoral) and Tacrolimus.”
- “Association Between Renal Dysfunction and Major Adverse Cardiac Events After Liver Transplantation: Evidence from an International Randomized Trial of Everolimus-Based Immunosuppression”

11.1 Contract with the Supervisor



VEILEDNINGSKONTRAKT FOR MASTEROPPGAVE MEDISIN VED DET HELSEVITENSKAPELIGE FAKULTET

Kontrakten leveres Seksjon for utdanningstjenester, Det helsevitenskapelige fakultet.

1 STUDENTENS PERSONALIA

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2 AVTALEPERIODE

Avtalen gjelder fra 15.01.2018 til 01.05.2019

3 VEILEDNING

Angi hovedveileder og biveileder(e). En av veilederne må være fast vitenskapelig ansatt ved Det helsevitenskapelige fakultet. Hvis veileder planlegger å ha forskningstermin i kontraktperioden, skal studenten informeres om dette når prosjektbeskrivelsen utarbeides. Veileder er i samarbeid med enheten ansvarlig for å sikre studenten veiledning i hele kontraktperioden.

Veileders navn og kontoradresse: Geir Ivar Nedredal, Geir.Ivar.Nedredal@unn.no, D1.609, Universitetssykehuset i Nord-Norge, 9038 Tromsø.

Biveileders navn og kontoradresse:

Veileder skal ha forskningstermin i perioden:

Veilederen skal:

- gi råd om formulering og avgrensning av tema og problemstilling
- drøfte og vurdere hypoteser og metoder
- gi hjelp til orientering i faglitteratur og datagrunnlag (bibliotek, arkiv, etc.)

- drøfte opplegg og gjennomføring av fremstillingen (disposisjon, språklig form, dokumentasjon etc.)
- holde seg orientert om progresjonen i masterstudentens arbeid, og vurdere den i forhold til prosjektplanen, drøfte resultater og tolkningen av disse
- gi studenten veiledning i forskningsetiske spørsmål knyttet til forskningsprosjektet

Studenten forplikter seg til å legge fram rapporter eller utkast til deler av oppgaven for veileder, samt i sitt arbeid å etterleve forskningsetiske prinsipper som gjelder for fagområdet.

Begge parter har krav på jevnlig kontakt og orientering under arbeidets gang.

4 MASTEROPPGAVEN

Tittel: «*Immunosuppression and Tolerance in Adult Liver Transplantation*»

5 RESSURSBRUK

Enhet prosjektet skal utføres ved: Avdeling for Gastroenterologisk Kirurgi, UNN
Samarbeidspartnere av teknisk eller vitenskapelig art:

6 ENDRINGER/BRUDD PÅ KONTRAKTEN

Alle endringer i veiledningskontrakten underveis i studiet (endring av prosjekt, veileder, forlengelse av kontraktperiode og lignende) skal informeres om til Seksjon for forskningstjenester ved Det helsevitenskapelige fakultet.

Brudd på kontrakten skal behandles av Konfliktrådet ved det Helsevitenskapelige fakultet.

7 UNDERSKRIFTER

Undertegnede er kjent med ovenstående retningslinjer som legges til grunn for samarbeidet i den faglige veiledning. Det er både veileders og studentens ansvar at planen blir fulgt, både innholds- og framdriftsmessig.

Sted/dato: 18/1-18 Underskrift:

Veileder:

Biveileder:

(Biveileder):

Student: *Tora E. Almendingen*

11.2 Table of articles

Article nr.	(Reference) First author	Name of study; Journal, year	Study design	Purpose	Study population	Results	Conclusion
1	(36)F. Saliba	<i>Association Between Renal Dysfunction and Major Adverse Cardiac Events After Liver Transplantation: Evidence from an International Randomized Trial of Everolimus-Based Immunosuppression;</i> Annals of Transplantation, 2018	Two-year prospective trial of <i>de novo</i> liver transplant recipients randomized at 30 days post-transplant to (i) everolimus [EVR]/reduced tacrolimus [EVR/rTAC] (ii) EVR with tacrolimus discontinued [TAC Elimination] or (iii) standard tacrolimus [TAC Control].	Prospective evidence is lacking regarding the association between renal dysfunction and cardiovascular events after liver transplantation	719 patients were randomized and formed the ITT population (EVR/rTAC 245, TAC Elimination 231, TAC Controls 243)	By month 24 post-transplant, 32/716 patients had major cardiac event (4.5%): 4.1%, 2.2% and 7.0% of patients in the EVR/rTAC, TAC Elimination and TAC Control groups, respectively (p=0.043). The cumulative eGFR was 119 706, 123 082, and 105 946 mL in the EVR/rTAC, TAC Elimination, and TAC Control groups, respectively, corresponding to a mean eGFR AUC of 82.4, 83.0, and 71.9 mL/min/1.73 m ² . Mean eGFR AUC was inversely associated with time to first major cardiac event: (p<0.001)	Immunosuppressive regimen based on everolimus with tacrolimus withdrawal, or to a lesser extent tacrolimus reduction, improves both renal function and the risk of major cardiac events compared to standard treatment with tacrolimus. Selection of an everolimus-based immunosuppressive regimen may be advantageous in avoiding major cardiac events in liver transplant recipients with renal dysfunction.

2	(43)C. Dopazo	<p><i>Low Total Dose of Anti-Human T-Lymphocyte Globulin (ATG) Guarantees a Good Glomerular Filtration Rate after Liver Transplant in Recipients with Pretransplant Renal Dysfunction;</i></p> <p>Canadian Journal of Gastroenterology and Hepatology, 2018</p>	<p>A prospective single-center cohort study of adult LT recipients with a pretransplant renal dysfunction,</p> <p>Therapy with ATG (ATG group, n=20). This group was compared with a similar retrospective cohort treated with basiliximab (BAS group, n=20)</p>	<p>Evaluate the safety and efficacy of low doses of anti-T-lymphocyte globulin (ATG)-based IS in preserving renalfunction and preventing liver rejection in liver transplant (LT) recipients with pretransplant renal dysfunction</p>	<p>Adult patients on the waiting list for LT from brain-dead donors with pre-LT renal dysfunction were included. Twenty patients received ATG as immunosuppression induction therapy. They were compared with 20 matched patients who received basiliximab immunosuppression induction therapy.</p>	<p>ATG compared to BAS-group; no differences were found between groups regarding age, sex, primary liver disease, comorbidities.</p> <p>50% had recovered their renal function at day 7 after LT, continuing with the same percentage 1 month after LT in the ATG group. 40% of patients 55% had recovered their renal function at day 7 and 1 month after LT, respectively, in the BAS group; these differences were not significant between groups.</p>	<p>The greatest benefit of the use of low-dose ATG as induction therapy was the significant financial saving due to the direct cost of the drug compared to Basiliximab.</p> <p>The major limitations of this study were the low number of patients owing to the exploratory nature of the trial and bias in inclusion criteria</p>
3	(44)F. Garaix	<p><i>Tacrolimus Granules for Oral Suspension as Post-Transplant Immunosuppression in Routine Medical Practice in France: The OPTIMOD Study;</i></p> <p>Annals of Transplantation, 2018</p>	<p>6-month prospective, observational multicentre (25) study that aimed to describe patient characteristics and conditions of use of tacrolimus granules.</p>	<p>Currently, there are no data describing the use of tacrolimus granules in transplant recipients in France.</p>	<p>61 patients included, 55.7% were children (mainly kidney graft recipients) and 44.3% were adults (mostly lung graft recipients).</p>	<p>A 6-month follow-up period is a limited timespan for the observation of long-term outcomes regarding effectiveness and safety. Nevertheless, the results observed during this period did not differ meaningfully from those published in clinical trials.</p>	<p>Results suggest that tacrolimus granules are well tolerated and effective in preventing transplant rejection when administered in routine practice in France.</p>

4	(45)H. Pflugard	<p><i>Longterm Calcineurin Inhibitor Therapy and Brain Function in Patients After Liver Transplantation.</i></p> <p>Liver Transplantation, 2017</p>	<p>A backward multivariate linear regression analysis was applied to identify independent prognostic factors for cognitive function.</p>	<p>Investigated the dose-dependent chronic neurotoxicity of CNI in patients after liver transplantation. Hypothesize that patients on longterm CNI therapy in standard dosage present increased numbers of white matter hyper-intensities and periventricular hyperintensities (PVH), increased ventricular width, and show impaired cognitive function compared with patients receiving a reduced CNI dose, patients with CNI-free IS and controls</p>	<p>85 patients, (65.9%] male) in whom OLT had been performed approximately 10 years ago (median, 10 years; IQR, 8.0-13.5 years) were included.</p>	<p>In the neurological examination, tremor was detected in 5 (6%) of 85 patients. Otherwise, the neurological status was normal in all patients.</p> <p>Considering the median results, the patients with a CNI-free immunosuppression did not differ from controls in any domain of the RBANS.</p>	<p>The regression analysis showed that CNI therapy is a negative independent prognostic factor for cognitive function.</p> <p>The results indicate that longterm CNI therapy after OLT may induce both cognitive dysfunction and structural brain alterations.</p> <p>As long as transplant function is preserved, patients showing CNI toxicity early after OLT might benefit from a change to CNI-free immunosuppression in the long term because cognitive dysfunction might impair patients' everyday life, job-related performance, and health-related quality of life.</p>
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5	(37)M. Charlton	<p><i>Everolimus Is Associated With Less Weight Gain Than Tacrolimus 2 Years After LT: Results of a Randomized Multicenter Study.</i></p> <p>Transplant journal, 2017</p>	Randomized, controlled study.	<p>Weight gain early after transplant is a risk factor for posttransplant metabolic syndrome (PTMS), cardiovascular events, and renal insufficiency.</p> <p>Impact of mammalian target of rapamycin inhibition on posttransplant weight gain and the development of PTMS components were examined.</p>	After a run-in period, patients (N = 719) were randomized at 30 ± 5 days posttransplant in a 1:1:1 ratio to 3 treatment groups: (i) everolimus (12) + reduced tacrolimus (29) (n = 245); (ii) TAC control (n = 243) or (iii) TAC elimination (n = 231).	Mean increase in weight from baseline was higher at month 12 in the TAC control arm (8.15 ± 9.27 kg) than in the EVR + reduced TAC (5.88 ± 12.60 kg) and the TAC elimination arms (4.76 ± 9.94 kg). At month 24, the TAC control arm displayed a significantly greater weight increase (9.54 ± 10.21 kg) than either the EVR + reduced TAC (6.69 ± 8.37 kg) or the TAC elimination groups (6.01 ± 9.98 kg, <i>P</i> = 0.024). Rates of PTMS were similar for the EVR + reduced TAC (71.8%), TAC elimination (70.3%) and TAC control (67.4%).	EVR with reduced-exposure TAC attenuated weight gain at 1 and 2 years posttransplant compared with a standard TAC immunosuppression regimen. Rates of PTMS were comparable between EVR-containing and TAC control regimens.
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6	(46)G. Whitehouse	<p><i>IL-2 therapy restores regulatory T-cell dysfunction induced by calcineurin inhibitors</i></p> <p>Proceedings of the National Academy of Sciences of the United States of America (PNAS), 2017</p>	Case control study.	CNIs are among the most effective agents in controlling effector T-cell responses in humans. However, CNIs also reduce the size of the Treg pool. The functional consequences of this negative effect and the mechanisms responsible remain to be elucidated.	37 liver transplant patients, 24 kidney recipients, 18 patients with chronic liver disease, and 23 age- and sex-matched healthy controls after informed consent and approval.	CNIs compromise the overall Treg immunoregulatory capacity to a greater extent than would be predicted by the reduction in the size of the Treg compartment, given that they selectively promote the apoptosis of the resting and activated Treg subsets that are known to display the most powerful suppressive function.	Current data indicate that CNIs do not interfere with the capacity of IL-2 to expand Tregs. The combination of reduced levels of CNIs and low-dose IL-2 is likely to constitute an optimal immunosuppressive regimen to restrain Tregs while at the same time promoting Treg expansion in clinical transplantation.
7	(47)B. Hamandi	<p><i>Clinical and microbiological epidemiology of early and late infectious complications among solidorgan transplant recipients requiring hospitalization</i></p> <p>Transplant International , 2016</p>	prevalence cohort study evaluated solid-organ transplant recipients requiring hospitalization during 2007–2011. Single center study,	There is limited literature describing the clinical and microbiological characteristics of solid-organ transplant recipients requiring hospitalization for infectious complications. This study reports on the rate and timing of these syndromes and describes the associated microbiological epidemiology.	The study was conducted at the Toronto General Hospital, University Health Network, Toronto, Canada, providing follow-up care to approximately 5000 recipients of heart, lung, liver, kidney, pancreas, and small bowel transplants.	Infectious complications requiring hospitalization 0.43 episodes per 1000 transplant-days, with 85% occurring >6 months post-TLx. The most frequent infectious: respiratory (27%), sepsis /bacteremia (13%), liver or biliary tract (12%), genitourinary (12%), and cytomegalovirus related (9%). 53% presented without fever, 45% had no pathogen isolated, and multidrug-resistant organisms were isolated in 27%.	The increase in the burden of infectious complications may be related to the concurrent use of more potent immunosuppressive agents early post-transplantation along with more aggressive maintenance immunosuppressive strategies to prevent acute graft dysfunction. The most frequent hospitalizations were attributable to respiratory, sepsis or bacteremia, liver and biliary, urinary tract, and CMV infections

8	(28)D. Aguiar	<p><i>Conversion from Calcineurin Inhibitor-Based Immunosuppression to Mycophenolate Mofetil in Monotherapy Reduces Risk of De Novo Malignancies After Liver Transplantation</i></p> <p>Annals of Transplantation, 2017</p>	<p>Retrospective patient cohort study. The incidence and risk factors for de novo malignancies of 392 liver transplant recipients with a survival higher than 3 months and a mean follow-up of 8.5 years were studied</p>	<p>Immunosuppression increases the risk of malignancy in liver transplant recipients. The potential impact of mycophenolate mofetil monotherapy on this risk has not been studied.</p>	<p>392 patients. Recorded data: age, sex, smoking, indication of liver transplantation, and MELD score. Indications of liver transplantation: 1)alcoholic liver disease, 2)post-hepatitis C cirrhosis, 3)and others. The presence/absence of HCC was also recorded</p>	<p>Older age and male sex were also associated with a higher risk of malignancy, and transplantation for hepatocellular carcinoma increased the risk of non-melanoma skin cancer</p>	<p>Mycophenolate mofetil monotherapy is associated with a lower risk of cancer in liver transplant recipients compared with maintenance immunosuppression with calcineurin inhibitors.</p>
9	(48)S.Sood	<p><i>A Novel Immune Function Biomarker Identifies Patients at Risk of Clinical Events Early Following Liver Transplantation</i></p> <p>Liver Transplantation, AASLD, 2016</p>	<p>prospectively monitored in a blinded, observational study. Cohort</p>	<p>We investigate whether a novel immune biomarker based on a laboratory platform with widespread availability that measures interferon c (IFNc) after stimulation with a lyophilized cell containing an adaptive and innate immune stimulant can predict events following transplantation.</p>	<p>75 adult transplant recipients</p>	<p>55/75 (73.3%) patients experienced a total of 89 clinical events. Most events occurred within the first month. Low week 1 results were significantly associated with risk of early infection was associated with the highest risk for infection with minimal rejection risk.</p>	<p>Low IFNc suggesting oversuppression is associated with infections, whereas high IFNc indicating undersuppression is associated with rejection. This assay offers the potential to allow individualization and optimization of immunosuppression that could fundamentally alter the way patients are managed following transplantation.</p>

10	(49)A.Montano-Loza	<p><i>Systematic review: recurrent autoimmune liver diseases after liver transplantation.</i></p> <p>Alimentary Pharmacology and Therapeutic, 2016</p>	A systematic review.	describe the frequency and risk factors associated with recurrent AILD post-LT and provide recommendations to reduce the incidence of recurrence based on levels of evidence.	full-text papers in English-language journals, keywords ‘autoimmune hepatitis (AIH)’, ‘primary biliary cholangitis and/or cirrhosis (PBC)’, ‘primary sclerosing cholangitis (PSC)’, ‘LT’ and ‘recurrent disease’. Management strategies to reduce recurrence after LT were classified according to grade and level of evidence.	Survival rates post-LT are approximately 90% and 70% at 1 and 5 years and recurrent disease occurs in a range of 10–50% of patients with AILD. Recurrent AIH is associated with elevated liver enzymes and IgG before LT, lymphoplasmacytic infiltrates in the explants and lack of steroids after LT (Grade B). Tacrolimus use is associated with increased risk; use of ciclosporin and preventive ursodeoxycholic acid with reduced risk of PBC recurrence (all Grade B).	Recommendations based on grade A level of evidence are lacking. The need for further study and management includes active IS before liver transplantation and steroid use after liver transplantation in autoimmune hepatitis; selective IS with ciclosporin and preventive ursodeoxycholic acid treatment for primary biliary cholangitis.
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11	(50)I.Lenci	<p><i>Complete Hepatitis B Virus Prophylaxis Withdrawal in Hepatitis B Surface Antigen-Positive Liver Transplant Recipients After Longterm Minimal Immunosuppression.</i></p> <p>Liver transplantation AASLD, 2016</p>	Cohort study	We report the results of complete HBV prophylaxis withdrawal after a followup of at least 6 years in LT recipients with undetectable serum HBV DNA and intrahepatic total HBV DNA and covalently closed circular DNA at LT.	We included 30 HBsAg positive, hepatitis B e antigen-negative recipients, 6 with hepatitis C virus and 7 with hepatitis D virus coinfection, who had received HBIG plus NA for at least 5 years after LT	At the end of follow-up, 90% of patients were still prophylaxis-free, 93.3% were HBsAg negative, and 100% were HBV DNA negative; 60% had anti-HBs titers >10 IU/L (median, 143; range, 13-1000).	This small series shows that complete prophylaxis withdrawal is safe in patients transplanted for HBV-related disease at low risk of recurrence and is often followed by spontaneous anti-HBs seroconversion. Further studies are needed to confirm this finding.
12	(35)Q.Wei	<p><i>Efficacy and Safety of a Steroid-Free Immunosuppressive Regimen after Liver Transplantation for Hepatocellular Carcinoma</i></p> <p>Gut and Liver, 2016</p>	Prospective observational study	evaluate the efficacy and safety of an IS regimen without steroids after liver transplantation (LT) for hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC).	66 HCC patient who underwent an immunosuppressive regimen without steroids after LT were enrolled in the steroid-free group. Compared with 132 “steroid group”	In the steroid-free group, the patients who fulfilled the Milan criteria had higher overall and tumor-free survival rates than those in the steroid group (p<0.001). The prevalence of HBV recurrence (3.0% vs 13.6%, p=0.02) was significantly lower in the steroid-free group compared with the steroid group.	After LT, an immunosuppressive regimen without steroids could be a safe and feasible treatment for HBV-related HCC patients, thus resulting in the reduction of HBV recurrence. Based on the observed survival rates, patients who fulfill the Milan criteria may derive benefits from steroid free immunosuppression.

13	(51)E. R. Perito	<p><i>Metabolic syndrome components after pediatric liver transplantation: prevalence and the impact of obesity and immunosuppression</i></p> <p>Am J Transplant, 2017</p>	Cross-sectional study	Metabolic syndrome is associated with long-term morbidity and mortality after adult liver transplant (LT). Whether pediatric LT recipients have a higher prevalence of metabolic syndrome remains controversial	Evaluated 83 pediatric LT recipients aged 8–30 years using National Health and Nutrition Examination Survey (NHANES) protocols. LT recipients were matched by gender, race/ethnicity, and age with 235 controls from NHANES	Among LT recipients, the adjusted odds of IGT doubled for every 7.5 years on calcineurin-inhibitors (CNIs, OR 2.10, 95% CI 1.06–4.17 per 7.5 years on CNIs, p=0.03). Among all subjects with IGT, LT recipients had a lower prevalence of overweight/obesity and less insulin resistance (HOMA-IR) than controls with IGT.	Among normal weight subjects, LT recipients were significantly more likely than controls to have pre-hypertension/hypertension, IGT, low HDL, and metabolic syndrome. Pediatric LT recipients have unique metabolic syndrome profiles and risk factors, and will require tailored screening and management protocols
14	(52)A.Hüsing	<p><i>Long-Term Renal Function in Liver Transplant Recipients After Conversion From Calcineurin Inhibitors to mTOR Inhibitors</i></p> <p>Annals Of Transplantation, 2015</p>	Case report. Retrospectively analysis.	Renal dysfunction often occurs in LT recipients receiving calcineurin inhibitor (CNI)-based immunosuppressive regimens, increasing morbidity and mortality rates. Replacement of CNIs by mTOR inhibitorbased immunosuppressive protocols may prevent renal impairment in LT recipients.	85 patients switched from CNI-based to mTOR inhibitor-based, CNI-free immunosuppression, 78 met the inclusion criteria.	Within the first 6 weeks after switching, the covariable adjusted eGFR increased 5.6 mL/min, but there were no further statistically noticeable changes in eGFR. Concentrations of cholesterol and triglycerides increased statistically, noticeable within the first 12 months after drug conversion. Histologically proven graft rejection was observed in 4 patients (5.1%) after conversion.	Conversion from CNI-based to CNI-free, mTOR inhibitor-based immunosuppression after LT is safe and can result in significant renal recovery. CNI-free, mTOR inhibitor-based immunosuppression is a potential option for patients with contraindications for CNIs and for LT recipients with rapid reduction in kidney function due to CNIs.

15	(53)G.-W. Song	<p><i>ABO-Incompatible Adult Living Donor Liver Transplantation Under the Desensitization Protocol With Rituximab</i></p> <p>American Journal of Transplantation 2016</p>	Retrospective study	The desensitization protocol included a single dose of rituximab and total plasma exchange. In addition, local graft infusion therapy, cyclophosphamide, or splenectomy was used for a certain time period, but these treatments were eventually discontinued due to adverse events.	235 adult patients who underwent ABOi living donor liver transplantation (LDLT) at a single center between November 2008 and December 2013.	3 cases (1.3%) of in-hospital mortality. The cumulative 3-year graft and patient survival rates were 89.2% and 92.3%, respectively, and were comparable to those of the ABO-compatible group (n=1301). Despite promising survival outcomes, 17 patients (7.2%) experienced antibody-mediated rejection that manifested as diffuse intrahepatic biliary stricture; six cases required retrTL, and 3 patients died.	The use of ABOi living liver donors is a very effective and safe method for expanding the donor pool in LDLT. DIHBS, an attenuated form of AMR, remains an unresolved problem despite the fairly effective DSZ protocol.
16	(24)L.Fussner	<p><i>Cardiovascular Disease After Liver Transplantation: When, What, and Who Is at Risk</i></p> <p>Liver Transplantation, 2015</p>	A retrospective review	aim to illustrate the prevalence of obesity and metabolic syndrome (MS), define the cumulative incidence of CVD, and characterize risk factors associated with these comorbidities after LT.	455 consecutive LT recipients from 1999 to 2004 with an 8- to 12-year follow-up was performed.	Tacrolimus use versus noncalcineurin-based immunosuppression (HR, 0.26; 95% CI, 0.14-0.49; P < 0.001) was associated with reduced risk of CVD but not versus cyclosporine (HR, 0.67; 95% CI, 0.30-1.49; P 5 0.322).	CVD is common after LT. Independent of MS, more data are needed to identify nonconventional risk factors and biomarkers like serum TN. Curbing weight gain in the early months after transplant may impact MS and subsequent CVD in the long term.

17	(34)Y.-Y. Liu	<p><i>Comprehensive Comparison of Three Different Immunosuppressive Regimens for Liver Transplant Patients with HCC: Steroid-Free Immunosuppression, Induction Immunosuppression and Standard Immunosuppression</i></p> <p>PLOS, 2015</p>	Retrospective review	This study compared the efficacy and safety of standard IS regimens with the efficacy and safety of steroid-free IS regimen and induction IS regimen in Chinese liver transplantation recipients for HCC.	329 patients who underwent LT from Jan 2008 - Dec12. 1) tacrolimus(29) and MMF (triple-drug regimen group; n=57), 2) basiliximab, steroid, TAC and MMF (BS group; n=241), 3) Steroid-free; basiliximab, TAC and MMF (SF group; n=31)	No significant differences in terms of patient, tumor-free and graft survival rates. The acute rejection rate and rejection time were equivalent in different groups. But compared with BS group, higher incidences of biliary complications (11.52% vs. 30.77%) and graft dysfunction (0.48% vs. 13.64%) were observed in SF group.	Steroid-free IS regimen has no clear advantages in comparison with standard IS regimens for liver transplant recipients with HCC and the postoperative complications should be treated with concentrated attention. Patient, tumor-free and graft survival rates were equivalent among three IS regimens, higher incidences of complications were demonstrated in steroid-free regimen for HCC pts.
18	(54)G. Rompianesi	<p><i>Neurological complications after liver transplantation as a consequence of immunosuppression: univariate and multivariate analysis of risk factors.</i></p> <p>Transplanta International, 2015</p>	Prospective study	Neurological complications (NCs) can frequently and significantly affect morbidity and mortality of LT recipients. We analysed incidence, risk factors, outcome and impact of the immunosuppressive therapy on NC development after LT	We analysed 478 LT in 440 patients, and 93 (19.5%) were followed by NCs	The average LOS was longer in patients experiencing NCs. The 1-, 3- and 5-year graft survival and patient survival were similar in patients with or without a NC. An everolimus-based IS, 7.1% got NCs, vs. the 16.9% receiving a CNI. There was a 1-, 3-, 5-year NC-free survival of 82%, 81% and 77.7% in patients receiving a CNI-based regimen and 95%, 94% and 93% in those not receiving a CNI-based regimen.	In patients undergoing a LT and presenting with nonmodifiable risk factors for developing NCs, an IS regimen based on CNIs is likely to result in a higher rate of NCs compared to mTOR inhibitors. The average LOS was longer in patients experiencing NCs Multivariate analysis: independent risk factors for NC: a MELD score \geq 20 and an IS-regimen based on CNIs.

19	(55)C.Dopazo	<p><i>Analysis of adult 20-year survivors after liver transplantation</i></p> <p>Hepatology International, 2015</p>	<p>A retrospective study was conducted from prospective, longitudinal data collected at a single center of adult LT recipients surviving 20 years.</p>	<p>To evaluate the clinical outcome and allograft function of survivors 20 years post-LT, cause of death during the same period and risk factors of mortality.</p>	<p>Between 1988 and 1994, 132 patients received 151 deceased-donors LT and 28 (21 %) survived more than 20 years.</p>	<p>Renal dysfunction was observed in 40 %, median eGFR among 20-year survivors was 64. 61% of 20-year survivors had arterial hypertension, 43 % dyslipidemia, 25 % de novo tumors and 21 % diabetes mellitus. Infections were the main cause of death during the 1st year post-transplant (32 %) and between the 1st and 5th year post-transplant (25 %). After 5th year from transplant, hepatitis C recurrence (22 %) became the first cause of death.</p>	<p>Factors having an impact on long-term patient survival were HCC (p = 0.049), pretransplant renal dysfunction (p = 0.043) and long warm ischemia (p = 0.016); furthermore, post-transplant factors were DIA (p = 0.001) and liver dysfunction (p = 0.05) at 1 year. The results showed the effect of IS used during decades on long-term outcome in our LT patients in terms of morbidity (arterial hypertension, diabetes mellitus, dyslipidemia and renal dysfunction) and mortality; infections, hepC</p>
20	(56)A. Schmitzbauer	<p><i>Delayed Bottom-Up and Amended Simple Method of Dosing with Once-Daily Tacrolimus Application to Achieve Stable Trough Levels in LT.</i></p> <p>Annals of Transplantation, 2014</p>	<p>Data were extracted retrospectively from electronic patient charts and analyzed accordingly.</p>	<p>Tacrolimus once-daily formulation (TacOD) was introduced as an alternative to twice-daily formulations de novo. Dosing recommendations range between 0.1 to 0.2 mg/kg BW/d.</p>	<p>TacOD was given to 101 patients undergoing primary LT at University Hospitals of Frankfurt, Goethe University Frankfurt/Main who received TacOD as de novo immunosuppressive agent were included in the analysis.</p>	<p>A median of 9 mg/d of TacOD were necessary to establish the trough levels by day 10, which was then 5.4 ng/ml. Incidence of (AE); neurological AEs (n=3), were low. Efficacy failure (acute rejection) was low (4.9%). Renal function was stable and did not deteriorate under CNI treatment.</p>	<p>This is the first report of bottom-up, amended, and simple dosing of TacOD in LT. The algorithm is feasible, safe, and efficient, avoiding trough level peaks and top-down strategies.</p>

21	(57)L. S. Nacif	<p><i>An analysis of tacrolimus-related complications in the first 30 days after liver transplantation.</i></p> <p>Clinics, 2014</p>	Retrospective comparative study	<p>Orthotopic LT has improved survival in patients with end-stage liver disease; however, therapeutic strategies that achieve ideal immunosuppression and avoid early complications are lacking. To correlate the dose and level of Tacrolimus with early complications, e.g., rejection, infection and renal impairment, after LT.</p>	From November 2011 to May 2013, 44 adult liver transplant recipients were included in the study	<p>5 cases ACR (11.37%), 16 cases of infection (36.37%). The blood samples: significant correlation between the Tacrolimus blood level and the deterioration of glomerular filtration rate and serum creatinine. Patients with infections had a higher serum level of Tacrolimu. The dose and presence of rejection were significantly different (p=0.048) and the mean GFR was impaired in patients who underwent rejection compared with patients who did not.</p>	<p>Blood Tacrolimus levels greater than 10 ng/ml were correlated with impaired renal function. Doses greater than 0.15 mg/kg/day were associated with the prevention of acute cellular rejection but predisposed patients to infectious disease.</p>
22	(58)S. Richter	<p><i>Effect of delayed CNI-based immunosuppression with Advagraf on liver function after MELD-based LV (IMUTECT).</i></p> <p>BMC Surgery, 2014</p>	Prospective observational study	<p>Assess the effect of standard low-dose Calcineurin inhibitor-based IS regime with Advagraf on the reate of infectious complications, graft and renal function after LT.</p>	50 patients with de novo low-dose standard Advagraf-based IS consisting of Advagraf, MMF and corticosteroids after LT. 2 group with 25 patients.	<p>Low-dose Advagraf-based IS regime would decrease both the infection rate (CMV-reactivation, wound infection, Urinary tract infections, and pneumonia) and associated negative side effects of a CNI-based IS strategy, especially in patients with renal impairment.</p>	<p>Prolonged-release, low-dose Advagraf is predicted to better protect patients from CNI side effects when compared to standard IS regime, while simultaneously maintaining graft function and not elevating the rate of organ rejection.</p>

23	(59)G. B. Klintmalm	<p><i>Belatacept-Based Immunosuppression in De Novo Liver Transplant Recipients: 1-Year Experience From a Phase II Randomized Study.</i> American Journal of Liver Transplantation, 2014</p>	<p>A randomized, partially blinded, active-controlled, parallel group, multicenter, phase II clinical trial in adult recipients of first LTs.</p>	<p>Evaluate the efficacy and safety of belatacept in adult recipients of first LTs from a deceased donor. To identify an optimal IS regimen in LT recipients, three belatacept regimens were studied and compared with two tacrolimus reg.. In addition, a follow-up long-term extension (26) study was conducted to assess longer-term safety and tolerability.</p>	<p>Patients were randomized (N=260) to one of the following IS regimens: (i) Basiliximab+ belatacept high dose [HD] + MMF, (ii) belatacept HD+MMF, (iii) belatacept low dose [LD]+MMF, (iv) Tacrolimus + MMF, or (v) tacrolimus alone. All received corticosteroids.</p>	<p>The proportion of patients who met the primary end point (composite of acute rejection, graft loss, death by month 6) was higher in the belatacept groups (42–48%) versus tacrolimus groups (15–38%), with the highest number of deaths and grafts losses in the belatacept LD group.</p>	<p>Distinguishing the contribution of belatacept alone or an interaction between belatacept and such factors in the context of this phase II study is not feasible. An additional limitation of the study includes the open-label design (belatacept vs. tacrolimus assignments).</p>
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24	(60)G.Oldani	<p><i>Incidence of anti- HLA donor specific antibodies in liver- transplant patients given mTOR inhibitors without calcineurin inhibitors.</i></p> <p>Journal of Hepatology, 2014</p>	Retrospective study	The incidence of de novo DSAs using the Luminex assay in liver-transplant patients receiving mTOR inhibitor-based IS is unknown.	<p>Between 2008-2013, 394 LT patients were followed-up. The patients had different IS regimes.</p> <p>56 LT patients converted from CNIs to mTOR inhibitors and were included in the study.</p>	After conversion from CNIs to an mTOR inhibitor-based CNI-free IS, three of the 56 patients developed de novo DSAs (6.5%), a biopsy-proven acute-rejection episode occurred in four of the 56 patients (7%), and a biopsyproven or suspected acute-rejection occurred in 6/ 56 patients (10.7%).	In maintenance LT, the incidence of de novo DSAs seems to be relatively infrequent and similar between patients receiving mTOR-based CNI-free IS and CNI based IS, after late conversion to mTOR based treatment, usually as part of a dual-drug cocktail.
25	(61)M. Kikuchi	<p><i>Successful Telaprevir Treatment in Combination of Cyclosporine against Recurrence of Hepatitis C in the Japanese Liver Transplant Patients</i></p> <p>Biol. Pharm. Bull, 2014</p>	Treatment Case report study	Telaprevir (TVR) is a protease inhibitor used in combination with pegylated interferon alfa-2b and ribavirin for hepatitis C, and TVR strongly inhibits CYP3A4 and CYP3A5. We reported successful TVR treatment of liver transplant patients with recurrence of hepatitis C during receiving is therapy.	<p>4 cases.</p> <p>The clinical characteristics of the patients in this study are summarized in Table 1. All patients showed a recurrence of HCV genotype 1b after liver transplantation. The median (range) of duration between liver transplantation and initiation of TVR treatment was 21.</p>	we found the rapid elimination of inhibitory effect of TVR on the disposition of cyclosporine in the all four cases and therefore, rapid increase in the dosage of cyclosporine would be required immediately after the end of TVR administration.	<p>These results suggest that frequent measurement of cyclosporine levels was important for successful TVR triple therapy and prevention of rejection.</p> <p>Treat patients with recurrence of hepatitis C after LT by TVR therapy to avoid liver graft rejection. Controlling the drug interaction between TVR and cyclosporine was the most important aspect to achieving both treatment of hepatitis C and prevention of liver graft rejection.</p>

26	(62)H. Egawa	<p><i>Impact of Rituximab Desensitization on Blood-Type-Incompatible Adult Living Donor Liver Transplantation: A Japanese Multicenter Study</i></p> <p>American Society of Transplant Surgeons, 2013</p>	Retrospective study	evaluated the effects of rituximab prophylaxis on outcomes of ABO-blood-type-incompatible living donor liver transplantation (ABO-I LDLT)	<p>381 adult patients in the Japanese registry of ABO-I LDLT.</p> <p>(calcineurin inhibitor and steroids; n=36) or triple (calcineurin inhibitor, steroids and antimetabolites; n=345) IS.</p>	After adjustment for era effects in the multivariate analysis, only absence of rituximab prophylaxis was a significant risk factor for AMR, and there were no significant risk factors for survival. Rituximab prophylaxis sign. decreased the incidence of AMR, especially hepatic necrosis. In the rituximab group, other B cell desensitization therapies had no add-on effects	Multiple or large rituximab doses significantly increased the incidence of infection, and early administration had no advantage. In conclusion, outcomes in adult ABO-I LDLT have significantly improved in the latest era coincident with the introduction of rituximab
27	(26)H. Schrem	<p><i>Incidence and Long-Term Risk of De Novo Malignancies After Liver Transplantation With Implications for Prevention and Detection</i></p> <p>Liver Transplantation, 2013</p>	A retrospective, single-center analysis	Characterization of long-term cancer risks after liver transplantation (LT) with implications for prevention and detection	14,490 person-years of stringent follow-up (mean follow-up 5.725 years) at our outpatient clinic up to December 31, 2011.	The cancer incidence rates for the LT recipients were almost twice as high as those for the age- and sex-matched general population.	Risk-adapted cancer surveillance is proposed. Tumor treatment performed according to accepted guidelines appears adequate. Mycophenolate may lead to lower long-term risks for de novo cancers.

28	(63)V.G. Agopian	<p><i>The evolution of liver transplantation during 3 decades: Analysis of 5347 consecutive liver transplants at a single center.</i></p> <p>Annals of Surgery, 2013</p>	<p>To analyse a 28-year single-center experience with orthotopic liver transplantation (OLT) for patients with irreversible liver failure. Retrospective study.</p>	<p>The implementation of the model for end-stage liver disease (MELD) in 2002 represented a fundamental shift in liver donor allocation to recipients with the highest acuity, raising concerns about posttransplant outcome and morbidity.</p>	<p>5347 consecutive OLTs performed in 3752 adults and 822 children between 1984-2012; comparisons of recipient and donor characteristics, graft /patient outcomes, postoperative morbidity before (n = 3218) and after (n=2129) MELD allocation system</p>	<p>Overall, 1-, 5-, 10-, and 20-year patient and graft survival estimates were 82%, 70%, 63%, 52%, and 73%, 61%, 54%, 43%, respectively. Of 17 recipient and donor variables, era of transplantation, etiology of liver disease, recipient and donorage, prior LT, MELD score, hospitalization at time of OLT, and cold and warm ischemia time were independent predictors of survival.</p>	<p>We present the world's largest reported single-institution experience with OLT. Despite increasing acuity in post-MELD era recipients, patient and graft survival continues to improve, justifying the "sickest first" allocation approach.</p>
29	(30)C.D. Wimmer	<p><i>Impact of cyclosporine versus tacrolimus on the incidence of de novo malignancy following liver transplantation: a single center experience with 609 patients.</i></p> <p>Transplant international, 2013</p>	<p>Retrospective study.</p>	<p>De novo malignancies are a major cause of late death after liver transplantation. Aim of the present study was to determine whether use of cyclosporine versus tacrolimus affects long-term tumor incidence considering potential confounders.</p>	<p>De novo malignancies in 609 liver transplant recipients at Munich Transplant Centre between 1985 and 2007 were registered.</p>	<p>Multivariate analysis revealed recipient age [hazards ratio (HR) 1.06], male gender (HR 1.73), and tacrolimus-based IS (HR 2.06) as significant risk factors</p>	<p>a tacrolimus-based IS should be discussed especially in older male patients. Whether reducing tacrolimus target levels may reduce the risk for de novo malignancies has yet to be determined in prospective trials.</p>

30	(22)T. Xing	<p><i>Comparison of Steroid-Free Immunosuppression and Standard Immunosuppression for Liver Transplant Patients with Hepatocellular Carcinoma.</i></p> <p>PLOS, 2013</p>	Retrospective study review	Evaluated the efficacy and safety of using basiliximab in place of a corticosteroid for IS following LT for HCC.	178 Chinese patients with HCC who underwent orthotopic liver transplantation from Jan 2003 to Dec 2009. Basiliximab (n=78), steroids (n=100)	The median overall and disease free survival was similar between basiliximab (50.8 months and 19.6 months, respectively) and steroid treated patients (64.2 months and 23.8 months, respectively). The 5-year overall survival and disease free survival rates was also similar between the basiliximab and steroid.	These findings provide further evidence of the negative impact of steroids as a part of immunosuppression therapy following liver transplantation for HCC. Patients w. Milan criteria were basiliximab associated with greater 5-year overall survival rate (88.9% vs. 57.4%).
31	(64)W.N. Schoening	<p><i>Twenty-Year Longitudinal Follow-Up After Orthotopic Liver Transplantation: A Single-Center Experience of 313 Consecutive Cases.</i></p> <p>American Journal of Transplantation, 2013</p>	A detailed analysis of 20-years follow-up concerning overweight (HBMI), hypertension (HTN), diabetes (HGL), hyperlipidemia (HLIP) and moderately or severely impaired renal function. Systematic review.	Impact on long-term outcome was studied and a comparison to life expectancy of matched normal population was performed.	Three hundred thirty-seven LT were performed in 313 patients (09/88–12/92).	Patient and graft survival at 1, 10, 20 years were 88.4%, 72.7%, 52.5% and 83.7%, 64.7% and 46.6%, respectively. Recurrent disease 21.3%, infection 20.6%, de novo malignancy (19.9%) common causes of death. Prevalence of HTN 57.3–85.2%, MIRF 41.8–55.2%, and HBMI 33.2–45% increased true follow up, while prevalence of HLIP (78.0–47.6%, declined.	Recurrent disease (21.3%), infection (20.6%) and de novo malignancy (19.9%) were the most common causes of death. LT has conquered many barriers to achieve these outstanding long-term results. However, much work is needed to combat recurrent disease and side effects of immunosuppression.

32	(65)J. Howell	<p><i>Cyclosporine and Tacrolimus Have Inhibitory Effects on Toll-Like Receptor Signaling After Liver Transplantation</i></p> <p>Liver Transplantation, 2013</p>	A Cross-sectional study, one single adult transplant center.	Toll-like receptors (TLRs) play a key role in transplantation biology. The effect of IS on TLR function after liver transplantation is unknown.	Peripheral blood mononuclear cells (PBMCs) from 113 post-LT patients, 13 healthy controls were stimulated with TLR-specific ligands for 24 hours. PBMCs from 5 healthy controls were also cultured with therapeutic concentrations of cyclosporine A (CYA) and tacrolimus (29).	PBMCs from patients on CNI after LT produced less IL-6 and TNF α in response to TLR2 stimulation, compared with healthy controls. Both CD56bright and CD56dim NK cells from patients on CNIIN also produced less IFN γ with TLR7/8 stimulation compared with healthy controls. Similar findings in healthy PBMCs cultured with CYA.	Patients on calcineurin inhibitors had impaired inflammatory cytokine production in response to TLR2, TLR4, and TLR7/8 stimulation compared comparison with healthy controls. TAC and CYA appear to have different effects on TLR signaling. Impaired TLR function has repercussions for risk of infection, graft rejection, and disease recurrence after LT, and the different IS profiles of CYA and TAC may guide the choice of therapy.
33	(17)R. G. Garza	<p><i>Trial of Complete Weaning From Immunosuppression for Liver Transplant Recipients: Factors Predictive of Tolerance.</i></p> <p>Liver Transplantation, 2013</p>	Prospective study	Recipients of liver transplantation (LT) may develop immunological tolerance. Factors predictive of tolerance are not clearly understood.	Transplant recipients with normal liver function tests and without active viral hepatitis or autoimmune disease who presented with side effects of immunosuppression or a high risk of de novo malignancies were selected. 24 patients fulfilled the criteria	Median tolerance of 14 months. Tolerant patients had a longer median interval between transplantation and inclusion in the study (156 for tolerant patients versus 71 months for nontolerant patients, P50.003) and a lower median SI (7.49 for tolerant patients versus 41.73 for nontolerant patients).	A high proportion of select LT recipients can reach tolerance over the long term. Two simple basal variables—the time from transplantation and the SI—may help to identify these patients.

34	(66)L. Teperman	<p><i>Calcineurin Inhibitor-Free Mycophenolate Mofetil/Sirolimus Maintenance in Liver Transplantation: The Randomized Spare-theNephron Trial</i></p> <p>Liver Transplantation, 2013</p>	prospective, open-label, multicenter study	Mycophenolate mofetil (MMF) and sirolimus (SRL) have been used for calcineurin inhibitor (CNI) minimization to reduce nephrotoxicity following LT.	patients undergoing LT from July 05 - 07 who were maintained on MMF/CNI were randomized 4 to 12 weeks after LT to receive MMF/ SRL (n=148) or continue MMF/ CNI (n=145) and included in the intent-to-treat population	MMF/SRL was associated with a greater renal function improvement from baseline with a mean % change in GFR. The composite endpoint demonstrated the noninferiority of MMF/ SRL vs. MMF/CNI. The incidence of BPAR was significantly greater with MMF/SRL (12.2%) vs. MMF/CNI. Graft loss (including death) occurred in 3.4% of the MMF/SRL-treated patients and in 8.3% of the MMF/CNI-treated.	Malignancy-related deaths were less frequent with MMF/SRL. Adverse events caused withdrawal for 34.2% of the MMF/SRL-treated patients and for 24.1% of the MMF/CNI-treated patients (P50.06). The use of MMF/SRL is an option for liver transplant recipients who can benefit from improved renal function but is associated with an increased risk of rejection (but not graft loss).
35	(29)S. Pungpapong	<p><i>Multicenter Experience Using Telaprevir or Boceprevir With Peginterferon and Ribavirin to Treat Hepatitis C Genotype 1 After Liver Transplantation</i></p> <p>Liver Transplantation, 2013</p>	Retrospective review, at Mayo Clinic in Jacksonville, FL; at Mayo Clinic in Scottsdale, AZ; and at Mayo Clinic in Rochester, MN.	The safety, efficacy, and effect on IS levels of telaprevir (TVR) or boceprevir (67) in combination with peginterferon (PEG-IFN) and ribavirin (RBV) in recipients of with HCV genotype 1 have not been defined	60 pat. started triple antiviral treatment, were followed for 66 weeks 30 of the 35 patients treated with TVR (86%) got undetectable HCV RNA levels after an average of 6 weeks, whereas 12 patients (48%) in the BOC-treated group got undetectable HCV RNA levels after a mean of 11 weeks.	Cytopenias complicated both regimens; all patients required dose reductions of PEG-IFN and/or RBV or the administration of hematological growth factors. One death occurred in each group on triple antiviral treatment	TVR or BOC combined with PEG-IFN/RBV achieved ontreatment virological response rates of approximately 50% to 60% in patients with recurrent HCV after LT, but significant side effects were common.

36	(68)H. Y. Kim	<p><i>The imbalance of T helper 17/ regulatory T cells and memory B cells during the early post-transplantation period in peripheral blood of living donor liver transplantation recipients under calcineurin inhibitor-based immunosuppression</i></p> <p>Brithis Society for Immunology, 2012</p>	Prospective study	Serial changes of T cells and B cells in living donor liver transplantation (LDLT) recipients during the early post-transplantation period were prospectively investigated.	From June 2010 to February 2011, 27 consecutive LDLT recipients were enrolled.	Serial monitoring of immunological profiles showed no significant suppression of Th1, Th2, Th17, mature B or memory B cells, whereas frequencies of Treg cells significantly decreased. Interleukin-17 production by central and effector memory cells was not suppressed during the early post-operative period. The continuous production of interleukin-17 by the memory T cells may contribute to the persistence of Th17cells.	current IS maintained the effector T or memory B cells during the early post-transplantation period but significantly suppressed Treg cells. Serial immune monitoring may suggest clues for optimal or individualized immunosuppression during the early post-operative period in clinical practice.
37	(69)T. Heinboken	<p><i>Impact of immunosenescence on transplant outcome</i></p> <p>Transplant International, 2012</p>	A review article	From a more general perspective, understanding the mechanisms and consequences of IS will have a broad impact on immune therapies in and beyond transplantation	The multifaceted modifications in adaptive and innate alloresponses to immunosenescence may justify both reduced and adapted IS maintenance therapy in old recipients. But, at the same time, may require a potent early IS.	Older organs show impaired repair mechanisms and compromised functional reserves while at the same time, an augmented immunogenicity of older organs has been reported.	Older recipients mount compromised alloimmune responses in experimental and clinical studies. Both, advanced donor and advanced recipient age are thus risk factors for inferior transplant outcome and require adapted organ allocation concepts and modified, clinically validated immunosuppressive protocols.

38	(32) A. Hegab	<p><i>De novo malignancies after liver transplantation: a single-center experience.</i></p> <p>Ann Saudi Med, 2012</p>	Retrospective study of patients referred to LT center between Apr 2001 - Jan 2010. Collected data: type of malignancy and histopathologic features, IS regimen, and patient survival.	The recipients of LT are subjected to lifelong IS with its many drawbacks. De novo and recurrent malignancy in transplant recipients are attributed to attenuation of immunosurveillance. Experience with de novo malignancies encountered after both deceased and living donor LT	248 LT procedures performed in 238 patients (10 retransplants), 8 patients (3.4%) developed de novo post-LT malignancies.	De novo malignancies included PTLD in 5 patients who were all EBV positive, and who were treated successfully with anti-CD20 monoclonal antibody therapy, reduction of IS, and control of EBV activity; urinary bladder cancer in 1 patient, died of bone and lung metastasis within 1 year of diagnosis; endometrial carcinoma in 1 patient, and Kaposi sarcoma in 1 patient survived.	EBV-associated PTLD is the most frequently encountered de novo malignancy after LT and is easily treatable by chemotherapy and reduction of IS.
39	(70)G. J. McKenna	<p><i>Limiting Hepatitis C Virus Progression in Liver Transplant Recipients Using Sirolimus-Based Immunosuppression.</i></p> <p>American Society of Transplantation, 2011</p>	Cohort study.	Hepatitis C virus (HCV) causes progressive liver fibrosis in LT recipients and is the principal cause of long-term allograft failure. The antifibrotic effects of sirolimus are seen in animal models but have not been described in liver transplant recipients.	We reviewed 1274 liver recipients from 2002 to 2010 and identified a cohort of HCV recipients exposed to sirolimus as primary IS (SRL Cohort) and an HCV Control Group (71) of recipients who had never received sirolimus.	Yearly protocol biopsies were done recording fibrosis stage (METAVIR score) with biopsy compliance of >80% at both year 1 and 2. In an intent-to-treat analysis, the SRL Cohort had significantly less advanced fibrosis (stage ≥ 2) compared to the HCV Control Group at year one (15.3% vs. 36.2%) and year two (30.1% vs. 50.5%).	This is the first study among liver transplant recipients with recurrent HCV to describe the positive impact of sirolimus in respect of reduced fibrosis extent and rate of progression

40	(72)A. Balderramo	<p><i>Hepatic encephalopathy and post-transplant hyponatremia predict early calcineurin inhibitor-induced neurotoxicity after liver transplantation</i></p> <p>Transplant International, 2011</p>	Retrospective study	Risk factors and clinical outcome of ECIIN remain largely unknown to Early calcineurin inhibitor-induced neurotoxicity (ECIIN). Estimate the incidence, risk factors, and outcome of ECIIN after LT.	158 patients that underwent LT in a 2-year period and received IS with calcineurin inhibitors (CNI) and prednisone.	ECIIN was considered when moderate/severe neurological events occurred within 4 weeks after LT and improved after modification of CNI. Demographic and clinical variables were analyzed as risk factors. 18% of patients developed ECIIN and the remaining 130 patients were controls. ECIIN group: frequent Acute graft rejection and infections, and longer length of stay.	pre-LT hepatic encephalopathy, surgical time >7 h, and post-LT hyponatremia are risk factors for ECIIN. Clinical complications and a longer hospital stay are associated with ECIIN development.
41	(73)T.Uemura	<p><i>Outcome of induction immunosuppression for liver transplantation comparing anti-thymocyte globulin, daclizumab, and corticosteroid.</i></p> <p>Transplant International, 2011</p>	A registry study based on data from United Network for Organ Sharing,	The effects and long-term outcomes of antibody induction therapy are not well known, especially for hepatitis C (HCV)	16 898 adult primary LT patients who received ATG alone (n = 452), ATG and steroids (ATG + S) (n = 1758), daclizumab alone (n = 683), or steroid alone (n = 14 005), listed as induction IS.	Patients with HCV, ATG + S had sign. inferior graft survival compared with daclizumab + S. The Cox proportional hazards model also showed that ATG + S was a marginal risk factor for graft failure. For patients with all the liver diseases, graft and patient survival were not significantly different between induction regimens.	ATG induction appeared to be preferentially used in patients with renal dysfunction, with improvement in renal function after LT. ATG induction can be used for patients with renal dysfunction in non-HCV diseases. Daclizumab induction achieved satisfactory short-term and long-term outcomes of LT in all the liver diseases including HCV disease.

42	(74)P. Burra	<p><i>Adherence in Liver Transplant Recipients.</i></p> <p>Liver Transplantation, 2011</p>	Literature study. Descriptive study of nonadherent behaviour.	Nonadherence to IS carries a risk of graft rejection and potential graft loss, whereas nonadherence to general medical indications (eg, avoiding alcohol intake, smoking after LT) may be associated with other complications such as de novo tumors and increasing health care costs.	<p>Patients have been split into 2 age groups (adults and children/adolescents) because the scale of the problem and the potential risk factors differ in the 2 groups.</p> <p>At Padua University Hospital in Italy: 103 LT patients got evaluated at a mean of 85.1 6 5.5 months after transplantation.</p>	<p>46% of the patients reported nonadherent behaviour related to the intake of IS drugs. Nonadherence patterns: 26.2% taking their medication late, 18.4% missed a dose, 2.9% changed their dosage without consulting their doctors. 25% smoking, 19.4% alcohol intake, 8.7% smoking+drinking. 11.7% were taking other nonIS not prescribed by their physicians, 3.9% not attending outpatient appointments regularly, 2.9% not turning up for the blood tests.</p>	The alarming picture emerging from the studies analyzed in this review is that poor adherence is an issue for nearly 1/2 LT patients, and this coincides with substantial increases in the rates of LAR, graft loss, and death. Patients and health care providers dealing with LT patients need to be properly trained to address nonadherence and be able to use all available means to improve their patients' adherence. Supported by psychologists.
43	(31)A. S. W. Tjon	<p><i>Increased Incidence of Early De Novo Cancer in Liver Graft Recipients Treated with Cyclosporine: An Association with C2 Monitoring and Recipient Age.</i></p> <p>Liver Transplantation, 2010</p>	Retrospective analyses	The goal of this study was to determine the risk factors for de novo cancer after liver transplantation (LTx)	385 LTx patients who underwent transplantation between 1986-2007. 13.0% of recipients developed de novo malignancy.	Cumulative incidence of de novo cancer at 1, 5, 10, and 15 years: 2.9%, 0.9%, 10.5%, 1.8%, 19.4%, 3.0%, 33.6%, 6.8%. Univariate risk factors for de novo cancer; CsA treatment, time period of LTx, age. Only CsA treatment emerged as an independent risk factor for de novo cancer, which attributed to more aggressive cancer types.	Compared to tacrolimus treatment, CsA treatment with C2 monitoring or in younger patients of <50 years is associated with a higher early de novo cancer risk after LTx. The standardized incidence ratio of malignancy in LTx patients compared to the general population was 2.2

44	(39)E. S. Park	<p><i>Use of an automated clinical management system improves outpatient immunosuppressive care following liver.</i></p> <p>Journal of American Information Association, 2010.</p>	<p>A retrospective cohort study of two patient groups receiving liver transplants at our institution.</p> <p>Only patients who received tacrolimus therapy, with or without mycophenolate mofetil or prednisone, were studied.</p>	<p>IS therapy following LT, if not managed well, can lead to increased drug toxicity or rejection episodes. We investigated whether use of an automated clinical management system in our LT program would improve clinical outcomes in managing LT recipients' IS medications.</p>	<p>A Group of 301 patients transplanted received outpatient IS management using a paper charting system. After instituting an automated clinical management system, the following group of 127 patients transplanted received their outpatient IS management with that system.</p>	<p>Multivariable logistic regression analysis showed the automated system was significantly associated with fewer rejection episodes and fewer tacrolimus toxicity events. Formal cost-effectiveness analysis of the nurses' salaries for 1 year showed the automated system cost US\$197 per patient and the paper system cost US\$1703 per patient. The automated system improved quality of life years.</p>	<p>Use of an automated clinical management system for outpatient IS management for LT patients has resulted in a decrease in both tacrolimus toxicity and rejection episodes and is cost-effective.</p>
45	(75)K. Staufer	<p><i>Sirolimus addition to tacrolimus-based immunosuppression induces complete remission of post-transplant lymphoproliferative disorder in a liver transplant recipient.</i></p> <p>European Society for Organ Transplantation, 2010</p>	<p>A single case study.</p>	<p>Post-transplant lymphoproliferative disorders represent the major cause of malignancy-related mortality after solid OT. Primary or reactivated EBV and CMV infection, treatment with T-cell antibodies, and especially the amount of overall IS are known risk factors.</p>	<p>The first LT recipient with complete remission of a malignant monoclonal B-cell lymphoma after sirolimus add-on to a triple IS regimen without CNI withdrawal: A 20 year old, LT in 1998 for cirrhosis because of primary sclerosing cholangitis.</p>	<p>Complete remission because of sirolimus add-on treatment was achieved within 3 months. Given that sirolimus induced B-cell growth inhibition is reversed by the addition of tacrolimus in vitro, this was an unexpected clinical course.</p>	<p>Complete withdrawal of CNIs is still recommended, but as demonstrated, a slow taper is possible and preferable to avoid rejection episodes. In addition, in patients with limited PTLTD, start of chemotherapy may be delayed under strict surveillance to await response to mTOR inhibitors.</p>

46	(76)A. D. Goralczyk	<p><i>A therapeutic exploratory study to determine the efficacy and safety of calcineurin-inhibitor-free de-novo immunosuppression after liver transplantation: CILT.</i></p> <p>BMC Surgery, 2010</p>	A prospective single-group pilot therapeutic exploratory, non-placebo controlled, two stage monocenter trial	IS with CNI increases the risk of renal dysfunction after OLT. This study protocol was designed to assess the efficacy and safety of calcineurin-inhibitor-free de-novo IS after LT.	29 liver transplant patients was designed to assess the safety and efficacy of de-novo CNI-free IS with basiliximab, mycophenolate sodium, prednisolone and everolimus.	Reducing or delaying CNI is safe and reduces renal impairment. But it is not known if complete abdication of CNI may increase the risk of rejection.	This study represents an intermediate element of the research chain. If the data of the phase II study corroborates safety of de-novo CNI-free IS regimen this should be confirmed in a randomized, prospective, controlled double-blinded clinical trial.
47	(25)P. Manousou	<p><i>Primary Biliary Cirrhosis After Liver Transplantation: Influence of Immunosuppression and Human Leukocyte Antigen Locus Disparity.</i></p> <p>Liver Transplantation, 2010</p>	Retrospective study	Patients with primary biliary cirrhosis (PBC), despite excellent outcomes after LT, may develop recurrent primary biliary cirrhosis (rPBC). The impact of IS and HLA mismatches on rPBC is unclear.	103 consecutive PBC patients who underwent LT (follow-up > 10 months) with serial protocol biopsies. IS was cyclosporine-based in 38 (10 on monotherapy), tacrolimus-based in 62 (19 on monotherapy). Steroids were discontinued in all but 7. Azathioprine was part of the initial IS in 70, 26 discontinued it, and 33 never exposed.	rPBC was associated independently with nonuse/discontinuation of azathioprine. The mean time to rPBC was 74 months with azathioprine, 43 months when AZA was discontinued, and 31 months if no azathioprine was used. Cyclosporine or tacrolimus alone had no impact on rPBC, but cyclosporine with azathioprine was protective for rPBC in comparison with tacrolimus/azathioprine (0/18 versus 7/25)	rPBC was not affected by HLA mismatches. Azathioprine use in PBC patients who underwent LT was associated with less disease recurrence and a longer time to rPBC. Tacrolimus or cyclosporine individually had no effect, but cyclosporine and azathioprine in combination resulted in the least rPBC.

48	(77)J. C. Heller	<p><i>Long-Term Management After Liver Transplantation: Primary Care Physician Versus Hepatologist.</i></p> <p>Liver Transplantation, 2009</p>	Postal survey	As long-term survival after LT increases, metabolic complications are becoming increasingly prevalent. Given concerns about which group of providers should be managing liver recipients and how well metabolic complications are managed.	280 transplant hepatologists to determine attitudes, perceptions, and practice patterns in the management of metabolic complications after transplantation. The response rate was 68.2%.	Hepatologists felt that metabolic complications were common, but few strongly agreed that hypertension (33.3%), chronic renal insufficiency (3.8%), diabetes mellitus (8.8%), dyslipidemia (11.1%), bone disease (12.8%) were well controlled. The majority of hepatologists indicated that ideally PCPs should be managing recipients' hypertension, diabetes mellitus, dyslipidemia, and bone disease.	Metabolic complications are perceived to be common but not well controlled post-transplant, and most hepatologists feel that PCPs should take a more active role in the management of these complications.
49	(71)A. M. McGuire	<p><i>Long-term Management of the Liver Transplant Patient: Recommendations for the Primary Care Doctor.</i></p> <p>The American Society of Transplantation and the American Society of Transplant Surgeons, 2009</p>	Guidelines made true literature study / review study.	No official document has been published for primary care physicians regarding the management of liver transplant patients	The data presented are based on formal review and analysis of published literature in the field and the clinical experience of the authors.	These guidelines address drug interactions and side effects of IS agents, allograft dysfunction, renal dysfunction, metabolic disorders, preventive medicine, malignancies, disability and productivity in the workforce, issues specific to pregnancy and sexual function, and pediatric patient concerns.	These guidelines are intended to provide a bridge between transplant centers and primary care physicians in the long-term management of the liver transplant patient.

50	(78)T. Gerhardt	<p><i>Renal Impairment After Liver Transplantation - A Pilot trial of calcineurin inhibitor-free vs. calcineurin inhibitor sparing immunosuppression in patients with mildly impaired renal function after liver transplantation.</i></p> <p>European Journal of Medical Research, 2009</p>	<p>A pilot trial, RCT with only 21 patients.</p>	<p>Chronic kidney disease is frequent in patients after OLT and has impact on survival. Patients receiving CNIs are at increased risk to develop impaired renal function. Early CNI reduction and concomitant use of MMF has been shown to improve renal function.</p>	<p>21 patients were randomized either to exchange CNI for 10 mg prednisone or to receive CNI at 25% of the initial dose each in combination with 1000 mg MMF b.i.d</p>	<p>At month 12 mean SCr and GFR improved in group 2 but remained unchanged in group 1. Main side effects were GI-symptoms (14.3%) and infections (4.8%). Two biopsy proven, steroid-responsive rejections occurred. In group 1 mean diastolic BP increased by 11 ± 22 mmHg.</p>	<p>Reduced dose CNI in combination with MMF but not CNI-free-IS leads to improvement of GFR in patients with moderately elevated SCr levels after OLT. Addition of steroids resulted in increased diastolic blood pressure presumably counterbalancing the benefits of CNI withdrawal on renal function.</p>
51	J. Levitsky	<p><i>Immunoregulatory profiles in liver transplant recipients on different immunosuppressive agents.</i></p> <p>Human Immunology, 2009</p>	<p>Cohort study</p>	<p>Compared peripheral blood immune-phenotyping on differing long-term IS monotherapy with and without peri-transplantation alemtuzumab (AL) induction.</p>	<p>31 adult LT recipients. All patients had been stable on monotherapy with either sirolimus (SRL) (n = 10) or without SRL (tacrolimus (TAC) (n = 10), mycophenolate mofetil (MMF) (n = 11)) for >6 months.</p>	<p>The SRL monotherapy group had significantly higher percentages of CD4 + CD25^{high} + Foxp3⁺ T cells compared with the non-SRL group. The SRL effect was even higher in a subset with prior AL induction and no prior HCV or rejection compared with all other subgroups. TAC patients showed significantly higher “regulatory” DC2:DC1 ratios compared with non-TAC patients.</p>	<p>IS monotherapy provides an opportunity to investigate regulatory roles of individual agents. SRL maintenance and prior AL induction in subsets of patients appeared to show a regulatory T cell immunophenotype. However, TAC patients may have other regulatory characteristics, supporting the need for larger, prospective studies to clarify differences.</p>

52	(3)J. Lerut	<p><i>Minimization of steroids in liver transplantations.</i></p> <p>Transplant International, 2008</p>	A literature review	Because of the markedly improved short-term results of LT and persistently high number of long-term complications, the attention of transplant physicians should be focused on minimizing IS therapy as much as possible.	Liver transplanted patient in different literature and studies.	Steroid-based immunosuppression is responsible for a substantial post-LT morbidity and mortality, hence, minimization of its use is of utmost importance to improve the quality of life of the successfully transplanted liver recipient.	LT can be performed safely with steroid-minimal IS without compromising graft and patient survival. The tendency in clinical practice is to move more and more from steroid withdrawal to steroid avoidance protocols.
53	(21)L. Liadó	<p><i>Impact of Immunosuppression Without Steroids on Rejection and Hepatitis C Virus Evolution After Liver Transplantation: Results of a Prospective Randomized Study.</i></p> <p>Liver Transplantation, 2008</p>	Prospective Randomized Study	The purpose of this study was to evaluate the influence of a steroid-free immunosuppression on hepatitis C virus (HCV) recurrence	198 LT patients were randomized to receive IS with basiliximab and cyclosporine, either with prednisone (St-group) or without prednisone (NoSt-group). The group of 89 HCV-infected patients got biopsies for 2 years after LT. This group of HCV patients are the patients evaluated in the present study.	The rejection rate was 19% (St: 21% vs. NoSt: 17%). Patients in the St group had more bacterial infections (59% vs 38%) 97% of all patients had histological HCV recurrence. The % of accumulated biopsies with gr. 4 portal inflammation at 6 months, 1 year, 2 years were, 23%, 49%, and 49% in the NoSt group, vs. 33%, 55%, and 69% in the St group. For grade 3/4 fibrosis at 6 m, 1 y, 2 y were 0%, 8%, and 22% for the NoSt group, vs. 8%, 19%, and 31% for the St group.	Immunosuppression without steroids in HCV patients is safe, reduces bacterial infections and metabolic complications, and improves histological short-term evolution of HCV recurrence.

54	(38)L. Kousoulas	<p><i>Health-related quality of life in adult transplant recipients more than 15 years after orthotopic liver transplantation.</i></p> <p>Transplant International, 2008</p>	Retrospective study.	With continuously rising survival rates following OLT health-related quality of life (HRQOL) of transplant recipients becomes increasingly important	HRQOL in 104 adult liver transplant recipients surviving more than 15 years after OLT was assessed using the German Version of the 36-Item Health Survey (SF-36).	LT recipients surviving >15 years OLT scored lower in all categories; a poor HRQOL vs. the German ref. pop. A statistical sign. was reached in almost all SF-36 with the exceptions of mental health and bodily pain, where our study pop. = ref.pop. Job rehab. after OLT good effect on HRQOL. Returning to their job during the first year after OLT sign. higher of physical functioning, role phys.	Marital status and the IS used didn't affect HRQOL as there was no statistical significance reached in any of the comparisons performed. > 15 years after OLT, long-term survivors present a poor HRQOL comparable to the reference population. Occupational rehab. was the only factor shown to positively influence long-term HRQOL.
55	(67)A. Galioto	<p><i>Nifedipine Versus Carvedilol in the Treatment of De Novo Arterial Hypertension After Liver Transplantation: Results of a Controlled Clinical Trial.</i></p> <p>Liver Transplantation, 2008</p>	Controlled Clinical Trial, cohort.	The aim of this study was to compare nifedipine and carvedilol in the treatment of de novo arterial hypertension after OLT.	The study included 50 patients who developed arterial hypertension after OLT. 25 patients received nifedipine (group A), and 25 received carvedilol (group B)	All were similar for baseline conditions. At end of study, patients intolerant to monotherapy were 48% of gr. A, 12.5% of gr. B. Full responders were 20% of gr. A and 33% of gr. B. The addition of ramipril normalized BP in 19% of partial responders to m-therapy (75% in partial responders to nifedipine, 30% in partial responders to carvedilol)	In responders to either monotherapy or combined therapy, there was a significant improvement of renal function. In responders to carvedilol, but not in responders to nifedipine, the daily dose of tacrolimus at 1 year should be reduced to 50% compared to the baseline dose to maintain the blood trough level in the therapeutic range.

56	(13)G. B. G. Klintmalm	<p><i>Corticosteroid-Free Immunosuppression With Daclizumab in HCV+ Liver Transplant Recipients: 1-Year Interim Results of the HCV-3 Study.</i></p> <p>Liver Transplantation, 2007</p>	A 1-yr interim analysis of a prospective, randomized, multicenter trial	This study evaluate the effect of corticosteroid-free IS HCV+ LT recipients following LT.	Patients received tacrolimus and corticosteroids (Arm 1; n=80); tacrolimus, corticosteroids, and MMF (Arm 2; n=79); or daclizumab induction, tacrolimus, and MMF (Arm 3; n=153).	At 1 yr, 64.1%, 63.4%, and 69.4% of patients achieved the composite primary endpoint of freedom from rejection, freedom from HCV recurrence, and freedom from treatment failure, respectively. Excellent patient and graft survival did not differ sign. among treatment arms. Freedom from HCV recurrence at 1 yr was 6.2%, 6.1%, and 4.3% in Arms 1, 2, 3. Freedom from rejection was sign. higher in Arm 3 vs. 1.	these results suggest that a corticosteroid-free regimen of tacrolimus and MMF following daclizumab induction is safe and effective in HCV+ liver transplant recipients
57	(79)H. Egawa	<p><i>B-Cell Surface Marker Analysis for Improvement of Rituximab Prophylaxis in ABO-Incompatible Adult Living Donor Liver Transplantation.</i></p> <p>Liver Transplantation, 2007</p>	Cohort study	The effectiveness of rituximab has been reported in ABO blood gr ABO-I LT, but the protocol is not yet established. The impact of timing of rituximab proph. and the humoral immune response of patients undergoing ABO-I LDLT, focus on clinic-pathological findings and the B-cell subset.	30 adult patients were treated with hepatic artery infusion (HAI) protocol without splenectomy for ABO-I LDLT. A total of 17 patients were treated only with HAI (no prophylaxis), and 13 were treated with rituximab prophylaxis.	The mortality of the 30 patients with HAI, without splenectomy, and with/without rituximab prophylaxis was 33% and the main cause of death was sepsis. Early rituximab prophylaxis sign. Depleted B cells and memory B cells in the spleen but not in lymph nodes. BC and memory BC increased and memory BC became dominant during antibody-mediated rejection.	Early prophylaxis with rituximab depletes B cells, including memory B cells, in the spleen and is associated with a trend toward lower humoral rejection rates and lower peak immunoglobulin (Ig)G titers in ABO-I LDLT patients.

58	(80)J. G. O'Grady	<p><i>Randomized Controlled Trial of Tacrolimus Versus Microemulsified Cyclosporin (TMC) in Liver Transplantation: Poststudy Surveillance to 3 Years</i></p> <p>American Journal of Transplantation, 2007</p>	Randomized Controlled Trial	<p>The 1-year results of the tacrolimus vs microemulsified cyclosporin (TMC) study found a benefit with tacrolimus IS after primary LT in adults with respect to freedom from graft loss and immunological failure. This is further 2 years for poststudy surveillance.</p>	<p>The study population comprised adults undergoing their first liver transplant in any of the eight centers in the United Kingdom or Republic of Ireland. 596 patients (298 in each group)</p>	<p>However, freedom from death or reLT no longer achieves statistical sign. A total of 62.1% of patients randomized to tacrolimus were alive at 3 years with their original graft and still on their allocated study medication, as compared with only 41.6% in the cyclosporin limb.</p>	<p>No difference was detected between tacrolimus and cyclosporin in hepatitis-C-positive patients with the available data. The TMC study confirms after 3 years of follow-up the benefits of tacrolimus-based IS over cyclosporin using C0 monitoring.</p>
59	(18)V. Donckier	<p><i>Early Immunosuppression Withdrawal After Living Donor Liver Transplantation and Donor Stem Cell Infusion.</i></p> <p>Liver Transplantation, 2006</p>	A 3 patient study protocol.	<p>Long-term results of LT are still limited by serious side effects of IS drugs. A major issue, therefore, is to elaborate novel therapeutic protocols allowing withdrawal or minimization of IS therapy after LT.</p>	<p>Report on 3 patients prospectively enrolled in an original protocol designed to promote graft acceptance in LDLT, using posttransplant conditioning with high doses of antithymocyte globulin followed by injection of donor-derived stem cells.</p>	<p>In 2 patients, early IS withdrawal was possible, without subsequent graft deterioration. In these 2 cases, in vitro studies showed indices of immunological tolerance as assessed by specific hyporesponsiveness to donor alloantigens in mixed lymphocytes culture. In the third patient, acute rejection rapidly occurred after discontinuation of IS, and minimal IS has to be maintained during long-term followup.</p>	<p>these clinical observations demonstrated that, despite the absence of macrochimerism, donor stem cells infusion combined with recipient conditioning may allow early IS withdrawal or minimization after LT.</p>

60	(14)J. Figueres	<p><i>Daclizumab induction and maintenance steroid-free immunosuppression with mycophenolate mofetil and tacrolimus to prevent acute rejection of hepatic allografts</i></p> <p>Transplantation International, 2005</p>	6-month, open-label, prospective multicenter, pilot study	Steroid-free IS regimens reduce corticosteroid-related side effects in liver transplant recipients although their efficacy is very variable.	102 LT patients treated with daclizumab, mycophenolate mofetil, and tacrolimus.	At 6 months, the acute rejection rate was 9.8%, and patient and graft survival rates were 96% and 95%. Acute rejection rates were for HCV+ patients (8.6%) and HCV- patients (10.4%). Infections in 22% of patients. Post-transplantation HT and DIA developed in 37% and 14% of patients, during the study period, but were markedly less frequent (8% and 6%) at 6 months. Hypercholesterolemia in only 2%.	The steroid-free IS regimen of daclizumab, MMF, and tacrolimus effectively prevents acute rejection after LT without decreasing safety.
61	(81)R. Troisi	<p><i>ABO-Mismatch Adult Living Donor Liver Transplantation Using Antigen-Specific Immunoabsorption and Quadruple Immunosuppression Without Splenectomy</i></p> <p>Liver Transplantation, 2006</p>	Study protocol with 5 patients	A new protocol consisting of daclizumab (DAC) induction, mycophenolate mofetil (MMF)/tacrolimus (29)/steroids without splenectomy	5 recipients (mean age of 47 +/- 14 yr) undergoing ABO-I LDLT were included in this protocol.	Persisting low HA titers were observed over time. No sepsis nor cytomegalovirus infection episodes were recorded. ACR occurred in 1 recipient responding to steroid pulse therapy. Two grafts were lost in 2 patients due to technical failure during the first postoperative month.	ASI using Glycosorb ABO, quadruple IS including DAC and MMF provide high efficiency to lower HA titers over time, avoiding the need for splenectomy. ABO-I LDLT can be performed with this adapted IS protocol.

62	(82)J. Dumortier	<p><i>Conversion From Tacrolimus to Cyclosporine in Liver Transplanted Patients With Diabetes Mellitus.</i></p> <p>Liver Transplantation, 2006</p>	Case control study.	This study characterizes the clinical outcomes of LT patients who experienced DM on tacrolimus-based regimen and were converted to cyclosporine-based therapy.	25 patients were included after a median delay of 54 months after LT, 51 years (range 30-69). There were 11 patients with insulin-treated DM (ITDM), 14 patients with noninsulin-treated DM (NITDM), and the glycemic control was poor 52% of patients.	After a median follow-up of 20 month safter conversion, there were four patients with ITDM, 17 patients with NITDM, and four patients without DM, and the glycemic control was poor in 3/25 patients (12%). Four patients returned to tacrolimus because of arterial hypertension or digestive side-effects.	The results suggest that conversion from tacrolimus to cyclosporine in stable LT patients with DM is well tolerated and beneficial on glycemic control.
63	(83)K. Rifai	<p><i>A New Side Effect of Immunosuppression: High Incidence of Hearing Impairment After Liver Transplantation.</i></p> <p>Liver Transplantation, 2006</p>	A single-centre study. Questionnaire.	Little is known about hearing impairment in patients after LT. Evaluate hearing impairment in patients after OLT	A questionnaire was sent to 695 adult patients after OLT to assess characteristics and course of auditory impairment. Risk factors such as ototoxic drugs were taken into consideration. Clinical follow-up, including immunosuppressive therapy, was analyzed in detail. The questionnaire was completed by 521 patients (75%)	Hearing impairment was reported by 35%. A total of 8% suffered from hearing abnormalities prior to OLT. There maining 141 patients (27%) developed hearing impairment after LT. Main problems were hearing loss (52%), tinnitus (38%), and otalgia (30%). There was no association of post-OLT hearing disorders with age or known risk factors. In 43% of patients, onset of hearing impairment was within 2 yr post-OLT.	subjective hearing impairment is frequent in patients after OLT and contributes to post-OLT morbidity. Calcineurin inhibitor-related neurotoxicity appears as a possible mechanism. Further prospective investigations with objective hearing tests are necessary to confirm these results and to evaluate the role of IS.

64	(84)M. Salizzoni	<p><i>The first one thousand liver transplants in Turin: a single-center experience in Italy.</i></p> <p>Transplant International, 2005</p>	A single-center experience.	Experience of transplantation center in Turin, Italia; highlighting the main changes that have occurred over time	From 1990 to 2002, 1000 consecutive LT were performed in 910 patients, mainly cirrhotics.	Median follow-up of the patients was 41 months. Overall survival rates at 1, 5 and 10 years were 87%, 78% and 72% respectively. Survival rates obtained in the second half of the cases (1999–2002) were sign. better than those obtained in the first half (1990–1998) (90% vs. 83% at 1 year and 81% vs. 76% at 5 years).	Increasing experience in liver transplant surgery and postoperative care allowed standardization of the procedure and expansion of the activity, with parallel improvement of the results.
65	(85)B.Eghtesad	<p><i>Immunosuppression for Liver Transplantation in HCV Infected Patients: Mechanism-Based Principles.</i></p> <p>Liver Transplantation, 2005</p>	Retrospectively analysis	Addresses the dilemma of optimal IS of patients with chronic HCV who underwent liver replacement under alternative management strategies	Analysed 42 HCV infected patients who underwent cadaveric LT under two strategies of IS: (1) daily TAC throughout and an initial cycle of high-dose prednisone (PRED) with subsequent gradual steroid weaning, or (2) intraoperative ATG and daily TAC that was later space weaned	After 36 +/- 4 months, patient and graft survival in the first group was 18/19 (94.7%) with no examples of clinically serious HCV recurrence. In the second group, the three-year patient survival was 52%, and graft survival was (39%); accelerated recurrent hepatitis was the principal cause of the poor results.	Since the anti-HCV response is unleashed when IS is weaned, treatment protocols that minimize disease recurrence in HCV-infected allograft recipients must balance the desire to reduce IS or induce allotolerance with the need to prevent antiviral immunopathology.

66	(86)K. Tanaka	<p><i>Comparison of Cyclosporine Microemulsion and Tacrolimus in 39 Recipients of Living Donor Liver Transplantation.</i></p> <p>Liver Transplantation, 2005</p>	randomized, prospective, multicenter, open-label study (LIS2T)	The first direct comparison of clinical outcomes using cyclosporine microemulsion (CsA-ME) with monitoring of blood concentration at 2 hours postdose (C2) and tacrolimus-based IS in LDLT.	39 Recipients of a LDLT of the 495 patients enrolled in LIS2T. Patients were randomized to CsA-ME(C2 monitoring) or tacrolimus and were administered corticosteroids with or without azathioprine. 23 LDLT received CsA-ME and 16 received tacrolimus.	By month 6, 9% CsA-ME and 19% of those receiving tacrolimus had lost their graft or died. 9 episodes of biopsy-proven ACR were reported: CsA-ME group (17%) and tacrolimus (31%). Serious adverse events; infections, CsA-ME group 61% and tacrolimus arm 81%. 12 patients in the CsA-ME arm (52%) and 5 in the tacrolimus arm (31%) discontinued the study prematurely.	CsA-ME C2 monitoring or tacrolimus both offer effective protection against rejection in LDLT while maintaining a good safety profile.
67	(87)P. E. Marik	<p><i>The hepatoadrenal syndrome: A common yet unrecognized clinical condition.</i></p> <p>Critical Care Medicine, 2010</p>	Clinical cohort study	As liver failure and sepsis are both associated with increased circulating levels of endotoxin and proinflammatory mediators and reduced levels of apoprotein-1/high-density lipoprotein, we postulated that adrenal failure may be common in patients with liver disease.	The study cohort included 340 patients with liver disease. LT at intensive care unit.	In vasopressor-dependent(VD) patients with adrenal insufficiency, hydrocortisone treatment was associated with a sign. reduction in the dose of norepinephrine at 24 hrs, whereas the dose of norepinephrine was sign. higher in those patients with adrenal failure not treated with hydrocortisone. In VD patients without adrenal insufficiency, treatment with hydrocortisone did not affect vasopressor d.	Patients with liver failure and patients post-LT have an exceedingly high incidence of adrenal failure, which may be pathophysiologically related to low levels of high-density lipoprotein. Treatment of patients with adrenal failure may improve outcome. High baseline serum Cortisol levels may be a maker of disease severity and portend a poor prognosis.

68	(33)M. Vivarelli	<p><i>Analysis of Risk Factors for Tumor Recurrence After Liver Transplantation for Hepatocellular Carcinoma: Key Role of Immunosuppression.</i></p> <p>Liver Transplantation, 2005</p>	Retrospectively analysis.	Confirm recent observations about the relationship between IS and the recurrence of HCC after LT.	70 consecutive HCC patients who underwent LT and received cyclosporine (CsA)-based IS. CsA was associated with steroids in 26 patients and steroids and azathioprine in 44 patients.	HCC recurred in 7 patients (10.0%). Different IS schedules or the cumulative dosage of steroids and azathioprine did not influence HCC recurrence that was associated instead with CsA exposure. The relationship between CsA exposure; various clinical.	High CsA exposure favors tumor recurrence; CsA blood levels should be kept to the effective minimum in HCC patients. In the presence of pathologic and histologic risk factors, specific IS protocols should be considered
69	(88)A. Marcos	<p><i>Use of Alemtuzumab and Tacrolimus Monotherapy for Cadaveric Liver Transplantation: With Particular Reference to Hepatitis C Virus.</i></p> <p>Transplantation, 2004</p>	Cohort Study	Further suggested that the efficacy of minimalistic treatment could be enhanced by preoperative recipient conditioning with an antilymphoid antibody preparation.	76 adults;38 HCV-, 38 HCV+, were infused with 30 mg alemtuzumab before primary cadaveric LT and maintained afterward on daily monotherapy unless breakthrough rejection mandated additional agents.	The overall incidence of rejection was similar with the two strategies of IS. With follow-ups of 14 to 22 months, patient and primary graft survival in HCV- cases are 97% and 90%, respectively, with alemtuzumab depletion plus minimal immunosuppression versus 71% and 70%, respectively,	With or without HCV, 62% of the 64 surviving lymphoid-depleted patients are on spaced IS, and four patients receive no IS. Lymphoid depletion with alemtuzumab and minimalistic maintenance IS is a practical strategy of liver transplantation in HCV- recipients but not HCV+ recipients

70	(89)A. Ramji	<p><i>Late Acute Rejection After Liver Transplantation: The Western Canada Experience.</i></p> <p>Liver Transplantation, 2002</p>	Retrospective review	Determine the incidence, predictive factors, and outcomes of LAR, of adult LT recipients in Western Canada from 1989 to 2000	415 patients	LAR occurred in 23% of patients >180 days posttrans-plantation. Median follow-up was 402 days; 79% of LAR episodes were graded mild. At the time of LAR, 33% were on a steroid taper. A total of 73% of LAR episodes were treated with pulse intravenous steroids, and 5% were steroid-resistant.	There was a trend toward increased chronic rejection in patients who developed LAR. LAR is common and occurs after > 1 year post transplantation. Patients undergoing LT for viral etiologies seem to have a lower risk of LAR. There may be an increased risk of chronic rejection in those developing LAR.
71	(12)G. Therapondos	<p><i>Cardiac Function After Orthotopic Liver Transplantation and the Effects of Immunosuppression: A Prospective Randomized Trial Comparing Cyclosporin (Neoral) and Tacrolimus.</i></p> <p>Liver Transplantation, 2002</p>	Prospective randomized trial.	investigated the cardiac function of patients on tacrolimus (T) compared with those on cyclosporin (C) IS after OLT	Randomized 40 adult patients with cirrhosis to either T or C with azathioprine and prednisolone IS and followed up on them for 3 months after OLT. All had detailed clinical, biochemical, lectro-cardiographic and echocardiographic assessments at regular intervals.	Abnormalities in cardiac function were common after OLT and sign. deterioration in left ventricular diastolic function was demonstrable up to 3 months in both patient groups. Cardiac function was similar in the T and C. Reduced heart rate variability (HRV) and higher mean BNP levels were identified in the T group. The percentage increase in posterior wall thickness was higher in the T group.	Cardiac dysfunction as shown by worsening echocardiographic measures of left ventricular diastolic function and by clinical cardiac events is common in the first 3 months after OLT in patients with cirrhosis. HRV and BNP values in the T group were worse than in the C group, but this was not translated to an increase in cardiac clinical events in this study.

72	(27)S. Saigal	<p><i>Evidence of Differential Risk for Posttransplantation Malignancy Based on Pretransplantation Cause in Patients Undergoing Liver Transplantation.</i></p> <p>Liver Transplantation, 2002</p>	Retrospective study.	Determine risk factors, clinical characteristics, and outcomes of de novo nonlymphoid malignancies after liver transplantation from a large single-center series.	All patients undergoing LT at the King's College Hospital, between Jan 1988 - Dec 1999 were analyzed retrospectively for the development of de novo malignancy in the post-transplantation period	Of 1,140 patients undergoing 1,271 LT, 30 patients (2.6%) developed de novo nonlymphoid malignancy after LT. Skin cancers were the most common (n = 13), followed by oropharyngeal, carcinoma bladder carcinoma, acute leukemia, breast carcinoma(n = 2), and various other malignancies (n = 9)..	Although the incidence of de novo nonlymphoid malignancy after LT is low, patients who underwent LT for alcoholic cirrhosis appear to have an increased risk for developing post LT malignancy
73	(90)Y. Calmus	<p><i>Immunoprophylaxis With Basiliximab, a Chimeric Anti-Interleukin-2 Receptor Monoclonal Antibody, in Combination With Azathioprine-Containing Triple Therapy in Liver Transplant Recipient.</i></p> <p>Liver Transplantation, 2002</p>	Single-arm, open-label, multicentre study. Cohort.	Efficacy and tolerability of basiliximab immunoprophylaxis in adult patients undergoing first elective liver transplantation.	101 patients (70 HCV- patients, 31 HCV+ patients) were administered basiliximab, 20mg, by iv. bolus injection the day of transplantation (day 0) and day 4. In addition; triple IS therapy.	At 6 months, the incidence of first acute biopsy-confirmed rejection episodes was 22.8%. Rejections were more frequent in the HCV-positive (29%) than HCV-negative subgroup (20%). No rejection episode. Patient and graft survival rates at 12 months were 90.1% and 88.1%.5 malignancies were reported at 12 months: of these, 3 malignancies predated LT surgery.	Basiliximab caused no injection-site reactions, anaphylaxis, or cytokine release syndrome. Compared with earlier studies, the addition of basiliximab immunoprophylaxis to triple IS therapy provides increased efficacy in reducing the incidence of acute rejection episodes, with no clinically significant increase in adverse events.

74	(91)J. Hunt	<p><i>Histological Recurrence and Progression of Hepatitis C After Orthotopic Liver Transplantation: Influence of Immunosuppressive Regimens.</i></p> <p>Liver Transplantation, 2001</p>	A blinded retrospective review of clinical, serological, and histopathologic features	Examines long-term clinical and liver histological features at and after OLT to elucidate factors predictive of hepatitis C recurrence and progression after OLT.	65 patients who underwent OLT for hepatitis C and Non A Non B hepatitis was conducted.	Histological recurrence of HCV was seen in 43/65 patients, with progression in 19 patients. Histological findings in the native liver and post-OLT biopsy specimen at the time of recurrence showed no correlation with HCV recurrence and progression. Patients treated with AZA-containing IS regimens experienced less recurrence (6/17 v 37/48 patients) and progression (1/17 vs 18/48) than those without AZA.	No difference was seen between patients treated with cyclosporine vs those administered FK506. The grade of inflammation in the native liver at the time of OLT and time of recurrence is not predictive of progression. AZA containing regimens reduce histological recurrence and progression of HCV in post-OLT.
75	(92)A. J. Bathgate	<p><i>The Prediction of Acute Cellular Rejection in Orthotopic Liver Transplantation.</i></p> <p>Liver Transplantation and Surgery, 1999</p>	Case report study	The occurrence of acute cellular rejection after orthotopic liver transplantation is common. At present, no allowance is made in IS regimens for parameters other than weight.	121 consecutive patients receiving their primary allograft to determine if there are pre-transplantation factors predicting the occurrence of acute cellular rejection after transplantation.	ACR was more likely to occur in younger patients. ACR was increased in transplant recipients from donors aged <30 and >50 years. ACR was less likely to occur in patients who underwent LT for alcoholic liver disease. Chronic rejection was significantly increased in women and those patients who experienced recurrent acute rejection.	It may be possible to individualize IS regimens on the basis of pretransplantation characteristics.

76	(93)G. V. Papatheodoridis	<i>Longitudinal variation in hepatitis C virus (HCV) viraemia and early course of HCV infection after liver transplantation for HCV cirrhosis: the role of different immunosuppressive regimens.</i>	Clinical study, case report.	Evaluate the fluctuation of HCV viraemia and the early course of infection, and their relation to the type of IS in HCV transplant patients	47 HCV transplant patients, serum HCV RNA were taken pretransplant, at 1 and 2 weeks, 3 and 12 months after transplant. Initial IS triple (cyclosporin, azathioprine, predn) in 31, double (cyclosporin, predn) in five, and single (cyclosporin or tacrolimus) in 11.	At 3 months, HCV RNA levels were higher in patients with single than with triple or double initial therapy. At 12 months, HCV RNA levels correlated only with duration of prednisolone treatment and were relatively higher in patients with triple compared with single initial IS.	HCV RNA levels at three months after transplant are higher in patients treated with single initial IS therapy, but at 12 months are higher in patients with longer duration of steroid treatment. HCV viraemia at 12 months seems to be particularly important, as its levels are strongly correlated with the severity of fibrosis.
77	(94)R. M. Ghobrial	<i>Orthotopic Liver Transplantation for Hepatitis C: Outcome, Effect of Immunosuppression, and Causes of Retransplantation During an 8-Year Single-Center Experience.</i> ANNALS OF SURGERY, 1999	Single-center retrospective review study.	Determine the outcome of orthotopic liver transplantation (OLT) for end-stage liver disease caused by hepatitis C virus (HCV).	8-year period 374 patients underwent LT for HCV (79.6% received one OLT; 20.4% required re-OLT). Median follow-up was 2 years. IS was based on cyclosporine in 190 patients and tacrolimus in 132 patients. 3 group; therapy switched from cyclosporine to tacrolimus or vice versa.	5-year patient survival rates were 85%, 81%, and 75%, respectively. In patients requiring re-OLT, there was no difference in the 1-year patient survival rate after re-OLT when cyclosporine (60%), tacrolimus (63%), or cyclosporine/ tacrolimus (56%) was used for primary therapy	There are no distinct advantages to the use of cyclosporine vs tacrolimus IS when patient and graft survival are considered. Re-OLT is an important option in the treatment of recurrent HCV and should be performed early in the course of recurrent disease. Survival after re-OLT is not distinctively affected by cyclosporine or tacrolimus primary immunotherapy. The incidence of re-OLT for recurrent HCV or chronic rejection is low after either tacrolimus or cyclosporine therapy.

11.3 Summary of GRADE

<p>Reference: Klintmalm GB, Washburn WK, Rudich SM, Heffron TG, Teperman LW, Fasola C, et al. Corticosteroid-free immunosuppression with daclizumab in HCV(+) liver transplant recipients: 1-year interim results of the HCV-3 study. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2007;13(11):1521-31.</p>			<p>Study design: Open-label, randomized, prospective</p>	
			<p>Grade - quality</p>	<p>III</p>
<p>Purpose</p>	<p>Material and methods</p>	<p>Results</p>	<p>Discussion and comments</p>	
<p>Evaluate the effect of corticosteroid-free IS HCV+ LT recipients following LT.</p>	<p>LT recipients >18 yr with end-stage liver disease caused by chronic HCV infection. Patients excluded from the study: - Previously received or receiving an organ transplant other than a liver. - Received a liver from a hepatitis B core antibody-positive or a hepatitis C antibody-positive donor, or from an ABO blood group-incompatible organ donor. - Fulminant liver failure, HBV surface antigen+. - Restricted to the ICU, or could not be administered a calcineurin inhibitor within the first 72 hours following LT were.</p>	<p>At 1 yr, 64.1%, 63.4%, and 69.4% of patients achieved the composite primary endpoint of freedom from rejection, freedom from HCV recurrence, and freedom from treatment failure, respectively. Excellent patient and graft survival did not differ significantly among treatment arms. Freedom from HCV recurrence at 1 yr was 6.2%, 6.1%, and 4.3% in Arms 1, 2, 3. Freedom from rejection was significantly higher in Arm 3 vs. 1.</p>	<p><i>Defined population:</i> Yes. Is the selection representative for the population: Yes. <i>Does responders deviate from not-responders:</i> No. <i>Standardized data analysis:</i> The Kaplan-Meier product-limit method. <i>Objective criteria of outcome:</i> A Cox proportional hazards model was used to assess the impact of known or suspected risk factors on HCV recurrence at day 395. <i>Adequate methods in computer analysis:</i> Yes. <i>Defined purpose:</i> Yes. <i>Exclusion and inclusion:</i> Yes. <i>Were Arm 1, 2 and 3 similar at the beginning:</i> Yes. <i>The randomization has worked:</i> Yes. <i>Randomization procedure:</i> 312 patients were enrolled and randomized in a 1:1:2 ratio among 3 treatment groups. <i>Blinded.</i> For the recurrence analysis, patients were censored at the last known time at which a biopsy showed no recurrence of hepatitis C infection, if the biopsy was conducted outside of a protocol biopsy visit window. <i>Groups treated equally beyond the intervention?</i> Yes. <i>Primary endpoint:</i> freedom from treatment failure (death, graft loss, or study withdrawal by day 365), freedom from rejection, and freedom from HCV recurrence. <i>Results: Recession:</i> There were no withdrawals from Arm 1. Over the first yr of follow up, 4 patients withdrew from Arm 2, and 7 from Arm 3. In Arm 2, 3 of the 4 patients withdrew consent, while 4 of 7 patients in Arm 3 were lost to follow-up. <i>Can results be transferred to practice?</i> Yes. <i>All outcomes measured?</i> Yes. <i>Are the benefits worth the disadvantage/costs?</i> Benefits of this regimen included a significantly reduced incidence of acute rejection, potentially important because of its demonstrated association with HCV disease recurrence. <i>Other literature that strengthens the results?</i> Yes; Our findings that are consistent with those of some other studies reveal no detectable impact of corticosteroid avoidance on HCV recurrence 1 yr after transplantation <i>The Authors:</i> All transplant surgeons from different centres in USA. <i>Plausible explanations on the results:</i> No.</p>	
<p>Conclusion</p>				
<p>Corticosteroid-free regimen of tacrolimus and MMF following daclizumab induction is safe and effective in HCV+ LT recipients</p>				
<p>Country</p>	<p>USA</p>			
<p>Year of Data sampling:</p>	<p>2007</p>			
	<p>Patients received tacrolimus and corticosteroids (Arm 1; n=80); tacrolimus, corticosteroids, and MMF (Arm 2; n=79); or daclizumab induction, tacrolimus, and MMF (Arm 3; n= 153).</p>			

Reference: Llado L, Fabregat J, Castellote J, Ramos E, Xiol X, Torras J, et al. Impact of immunosuppression without steroids on rejection and hepatitis C virus evolution after liver transplantation: results of a prospective randomized study. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2008;14(12):1752-60.			Study design: Prospective Randomized Study	
			Grade - quality	III
Purpose	Material and methods	Results	Discussion and comments	
Evaluate the influence of a steroid-free IS on hepatitis C virus recurrence	198 LT patients were randomized to receive IS with basiliximab and cyclosporine, either with prednisone (St-group) or without prednisone (NoSt-group).	The rejection rate was 19% (St: 21% vs. NoSt: 17%). Patients in the St group had more bacterial infections (59% vs 38%) 97% of all patients had histological HCV recurrence. The % of accumulated biopsies with gr. 4 portal inflammation at 6 months, 1 year, 2 years were, 23%, 49%, and 49% in the NoSt group, vs. 33%, 55%, and 69% in the St group. For grade 3/4 fibrosis at 6 m, 1 y, 2 y were 0%, 8%, and 22% for the NoSt group, vs. 8%, 19%, and 31% for the St group.	<p><i>Defined population:</i> Yes. <i>Is the selection representative for the population:</i> Yes. <i>Does responders deviate from not-responders:</i> Patient demographics and baseline characteristics of the HCV-infected patients were similar between the groups. <i>Response rate:</i> after this 2-year analysis we think that antiviral treatment did not probably had influence in our results because rate of response was low and similar between groups. <i>Standardized data analysis:</i> Student t test or nonparametric tests as indicated. Categorical data were analyzed using the chi-square test or Fisher's exact test as required. Analyses of survival were based on Kaplan-Meier estimates and survival curves were compared by means of the log-rank test. A P value <0.05 was considered significant. <i>Objective criteria of outcome:</i> Yes, The primary endpoints of the study were biopsy-proven acute rejection incidence and patient and graft survival. The secondary endpoints were the incidence of adverse events, both infections and metabolic decompensations (mainly de novo diabetes mellitus and hypertension), and the incidence and severity of hepatitis C recurrence. <i>Defined purpose:</i> Yes. <i>Exclusion and inclusion:</i> Yes. <i>Similar groups at the beginning:</i> Yes. <i>The randomization has worked:</i> Yes. <i>Randomization procedure:</i> Within each center, eligible patients were randomized at the beginning of surgery using sealed envelopes and stratification into 2 cohorts: HCV-negative and HCV-positive. <i>Blinded:</i> No. <i>Groups treated equally beyond the intervention?</i> Yes. <i>Primary endpoint?</i> Incidence of biopsy-proven acute rejection was 19%, with no differences between the groups. <i>Results:</i> Actuarial patient and graft survival rates were similar between groups. <i>Can results be transferred to practice?</i> Yes. <i>All outcomes measured?</i> Yes. <i>Are the benefits worth the disadvantage/costs?</i> Reduces both metabolic complications and bacterial infection. <i>Other literature that strengthens the results?</i> Meta-analysis has shown that HCV recurrence is lower with steroid avoidance, although no individual trial reached statistical significance. Few prospective randomized studies have evaluated the influence of steroid-free IS on HCV recurrence; only 2 studies included protocol biopsies, and their follow-up was limited to 1 year. <i>Plausible explanations on the results:</i> Not accounted for in this article.</p>	
Conclusion	The group of 89 HCV-infected patients got biopsies for 2 years after LT. This group of HCV patients are the patients evaluated in the present study.			
IS without steroids in HCV patients is safe, reduces bacterial infections and metabolic complications, and improves histological short-term evolution of HCV recurrence				
Country				
Spania				
Year of Data sampling:				
April 2001 - September 2004				

Reference: O'Grady JG, Hardy P, Burroughs AK, Elbourne D. Randomized controlled trial of tacrolimus versus microemulsified cyclosporin (TMC) in liver transplantation: poststudy surveillance to 3 years. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2007;7(1):137-41.			Study design: Randomized Controlled Trial	
			Grade - quality	III
Purpose	Material and methods	Results	Discussion and comments	
The 1-year results of the tacrolimus vs. microemulsified cyclosporin (TMC) study found a benefit with tacrolimus IS after primary LT in adults with respect to freedom from graft loss and immunological failure. This is further 2 years for poststudy surveillance.	The study population comprised adults undergoing their first liver transplant in any of the eight centers in the United Kingdom or Republic of Ireland. Sample size calculation indicated that 596 patients (298 in each group) would be needed to detect a 10% difference in the composite primary endpoint at 1 year from 70–80% (tacrolimus) with 80% power and a two-tail alpha error of 5%.	The data after 3 years confirms the significant difference between tacrolimus and cyclosporin with tacrolimus less likely to meet the composite primary endpoint (log rank p = 0.01; relative risk 0.75; 95% CI 0.60–0.95; p = 0.016). However, freedom from death or retransplantation no longer achieves statistical significance (relative risk 0.79; 95% CI 0.62–1.02; p = 0.065). A total of 62.1% of patients randomized to tacrolimus were alive at 3 years with their original graft and still on their allocated study medication, as compared with only 41.6% in the cyclosporin limb (p < 0.001). No difference was detected between tacrolimus and cyclosporin in HVC+ patients with the available data.	<p><i>Defined population:</i> Yes. <i>Is the selection representative for the population:</i> Yes. <i>Does responders deviate from not-responders:</i> No.</p> <p><i>Standardized data analysis:</i> Kaplan-Meier estimates and comparing differences using the log rank test. Other comparisons between treatment groups are presented as estimates of effect sizes (relative risks of difference of means) with 95% confidence intervals (CIs) and chi-squared, Fisher's exact, Mann-Whitney U or t-tests, where appropriate. <i>Objective criteria of outcome:</i> Yes. <i>Defined purpose:</i> Yes. <i>The randomization has worked:</i> Yes. <i>Randomization procedure:</i> The integrity of the randomization process was preserved for a further 2 years for poststudy surveillance. Patients were randomized to either tacrolimus or microemulsified cyclosporin. <i>Blinded?</i> Yes. <i>Groups treated equally beyond the intervention?</i> Yes.</p> <p><i>Primary endpoint?</i> By 3 years, patients immunosuppressed with tacrolimus were less likely to meet the composite primary endpoint (log rank p = 0.01; relative risk 0.75; 95%, CI [0.60 to 0.95] chi-squared p = 0.016). <i>Results:</i> During the poststudy surveillance period there were 20 new deaths in the tacrolimus limb (8% of those at risk) and 8 new deaths in the cyclosporin limb (3.5% of those at risk), resulting in the overall number of deaths being 71 and 80, respectively. There were 9 deaths at 3 years in the tacrolimus group (20%) versus 15 (26%) in the cyclosporin group. <i>Can results be transferred to practice?</i> Yes. <i>All outcomes measured:</i> The data collected during the poststudy surveillance was not as comprehensive as during the first 12 months of the study. In particular, detailed data on rejection episodes, drug levels and toxicity that did not lead to a change in the immunosuppressive regimen were not collected. <i>Are the benefits worth the disadvantage / costs?</i> benefits of tacrolimus-based IS over cyclosporin using C0 monitoring. <i>Other literature that strengthens the results?</i> Yes. <i>The Authors:</i> Members of the UK and the Republic of Ireland Liver Transplant Study Group. <i>Plausible explanations on the results:</i> Yes.</p>	
Conclusion	No difference was found between tacrolimus and cyclosporin in HCV+ patients with the data. TMC study confirms after 3 years of follow-up the benefits of tacrolimus > cyclosporin.			
Country	England and Ireland.			
Year of Data sampling:	May 1997 – April 1999			

Reference: Therapondos G, Flapan AD, Dollinger MM, Garden OJ, Plevris JN, Hayes PC. Cardiac function after orthotopic liver transplantation and the effects of immunosuppression: a prospective randomized trial comparing cyclosporin (Neoral) and tacrolimus. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2002;8(8):690-700.			Study design: Prospective randomized trial.	
			Grade - quality	II
Purpose	Material and methods	Results	Discussion and comments	
Investigated the cardiac function of patients on tacrolimus (T) compared with those on cyclosporin (C) IS after OLT.	Randomized 40 adult patients with cirrhosis to either T or C with azathioprine and prednisolone IS and followed up on them for 3 months after OLT. All had detailed clinical, biochemical, electro-	Abnormalities in cardiac function were common after OLT and sign. deterioration in left ventricular diastolic function was demonstrable up to 3 months in both patient groups. Cardiac function was similar in the T and C. Reduced HRV and higher mean BNP levels were identified in the T group. The percentage increase in posterior wall thickness was higher in the T group. There were three deaths; two patients randomized to T, a total of 11 deaths (including the three described previously) from a variety of causes. Cardiac events: Two patients suffered intraoperative cardiac arrests (see later) at reperfusion, and a further eight patients suffered clinically significant cardiac events. These were all episodes of pulmonary edema within the first 7 post-operative days (T = 4, C = 4). HRV and BNP data may suggest a degree of diastolic impairment and increase in LV wall thickness in the T patients, the clinical relevance of these findings remains unclear.	Defined population: Yes. Is the selection representative for the population: Yes. Does responders deviate from not-responders: No. <i>Standardized data analysis:</i> All data were analysed on an intention-to-treat basis up to the point of withdrawal from the study using the SPSS statistical package. Student's t-test was used to compare normally distributed variables and chi-square test for categoric variables. <i>Objective criteria of outcome:</i> The aforementioned investigations were repeated at weeks 1, 2, 4, 8, and 12. Clinical event and inpatient stay were recorded. C and T blood levels were recorded with target levels. <i>Adequate methods in computer analysis:</i> Yes. <i>Defined purpose:</i> Yes. <i>Were C and T-group similar at the beginning:</i> Yes. <i>The randomization has worked:</i> Yes. <i>Blinded?</i> No. <i>Groups treated equally beyond the intervention?</i> Yes. <i>Results:</i> BNP may prove to be a predictor of cardiac complications in this setting, although because of the small number of patients, these results should be interpreted cautiously. BNP levels were found to be significantly higher in the T group from week four onward and may reflect a mild degree of LV hypertrophy. <i>Can results be transferred to practice?</i> Unclear. <i>All outcomes measured?</i> Yes. <i>Are the benefits worth the disadvantage/ costs?</i> Although T may theoretically adversely affect the cardiac profile of these patients, it has to be remembered that perhaps the benefit gained by its use in patients with steroid-resistant rejection (3 in study) outweighs the potential complications of its use. <i>Other literature that strengthens the results?</i> Yes. Both the European and the United States Multicenter Liver Study groups; fewer patients with HT in the T group when compared with the C group (European, 35 vs 42%; United States, 47% vs 56%), although the differences were not statistically sign. <i>Plausible explanations on the results:</i> Might be, because of the small group of patients in this study.	
Conclusion	Elected to use electrocardiography (ECG), detailed echocardiography, heart rate variability (HRV) indices, and brain natriuretic peptide (BNP) levels to study cardiac function. HRV indices (rMSSD and sNN50) have been shown to be decreased in patients with chronic heart failure. Patients with acute liver failure; those undergoing multiple organ transplantation or reLT; and patients with systemic infection, renal insufficiency, AB0 blood group incompatibility, and previous history of malignancy were excluded.			
Cardiac dysfunction as shown by worsening echocardiographic measures of left ventricular diastolic function and by clinical cardiac events is common in the first 3 months after OLT in patients with cirrhosis. HRV and BNP values in the T group were worse than in the C group, but this was not translated to an increase in cardiac clinical events in this study.				
Country				
Scotland				
Year of Data sampling:				
Sept 1996 – June 1998				

Reference: Saliba F, Fischer L, de Simone P, Bernhardt P, Bader G, Fung J. Association Between Renal Dysfunction and Major Adverse Cardiac Events After Liver Transplantation: Evidence from an International Randomized Trial of Everolimus-Based Immunosuppression. <i>Annals of transplantation</i> . 2018;23:751-7.			Study design: Prospective randomized trial	
			Grade - quality	
Purpose	Material and methods	Results	Discussion and comments	
Prospective evidence is lacking regarding the association between renal dysfunction and cardiovascular events after LT.	Two-year prospective trial of <i>de novo</i> LTx recipients randomized at 30 days post-transplant to (i) everolimus [EVR]/reduced tacrolimus [EVR/rTAC] (ii) EVR with tacrolimus discontinued [TAC Elimination] or (iii) standard tacrolimus [TAC Control]. Patients were required to have eGFR 30 mL/min/1.73 m ² at study entry and at the point of randomization, with urine protein excretion <1.0 g/day.	By month 24 post-transplant, 32/716 patients had major cardiac event (4.5%): 4.1%, 2.2% and 7.0% of patients in the EVR/rTAC, TAC Elimination and TAC Control groups, respectively (p=0.043). The cumulative eGFR was 119 706, 123 082, and 105 946 mL in the EVR/rTAC, TAC Elimination, and TAC Control groups, respectively, corresponding to a mean eGFR AUC of 82.4, 83.0, and 71.9 mL/min/1.73 m ² . Mean eGFR AUC was inversely associated with time to first major cardiac event: [95% CI -0.0000078; -0.000024] (p<0.001) At randomization, 38.8% of patients had diabetes and 22.3% had a history of cardiac disorders, with a similar distribution of both parameters between treatment groups.	<p><i>Defined population:</i> Yes. <i>Is the selection representative for the population:</i> Yes. The study population had similar mean baseline eGFR values to the general liver transplant population. <i>Does responders deviate from not-responders:</i> Yes. A number of uremic-specific cardiovascular risk factors have been identified in the general population, including anemia, hyperparathyroidism, hyperhomocysteinemia, high lipoprotein(a) levels, and low vitamin C which would be expected to apply equally in LTx recipients with poor renal function. <i>Standardized data analysis:</i> (see method). Notably, both the EVR/rTAC and TAC Elimination groups were associated with a sign. reduction in risk for major cardiac events vs standard CNI therapy based on Kaplan-Meier analysis, but with a more marked effect for the TAC Elimination. <i>Objective criteria of outcome:</i> Yes. <i>Adequate methods in computer analysis:</i> Yes. <i>Defined purpose:</i> Yes. <i>Exclusion and inclusion:</i> Yes. <i>Were group i and ii similar at the beginning:</i> Yes. <i>The randomization has worked:</i> Yes. <i>Blinded?</i> Yes. <i>Groups treated equally beyond the intervention?</i> Yes. <i>Primary endpoint?</i> Defined. <i>Results:</i> A significant direct cardioprotective effect seems unlikely. Despite evidence that switching to a mammalian target of mTOR inhibitor reduces left ventricular remodelling after heart transplantation, early conversion to everolimus has not been found to exert a clinically relevant effect on ventricular mass in kidney transplantation. <i>Can results be transferred to practice?</i> Yes. <i>All outcomes measured?</i> Yes. <i>Are the benefits worth the disadvantage/ costs?</i> It should be noted that although the randomized PROTECT study found no increase in biopsy-proven acute rejection when CNI elimination was performed more gradually and basiliximab induction was given, continuation of a reduced-exposure CNI regimen after introducing everolimus may overall be a more appropriate option than CNI withdrawal. <i>Other literature that strengthens the results?</i> Yes. Organ Procurement and Transplant Network (OPTN).</p>	
Conclusion	IS regimen based on everolimus with TAC withdrawal, or to a lesser extent TAC reduction, improves both renal function and the risk of major cardiac events compared to standard treatment with TAC. Selection of an everolimus-based IS may be advantageous in avoiding major cardiac events in LTx recipients with renal dysfunction			
Country	France, Germany, USA Italy, Switzerland.			
Year of Data sampling:	719 patients were randomized and formed the ITT population (EVR/rTAC 245, TAC Elimination 231, TAC Controls 243). To evaluate trends in renal function from randomization to month 24, eGFR values documented at each study visit (months 1, 2, 3, 4, 5, 6, 9, 12, 18, and 24) were used to calculate the area under the curve (30), using the standard trapezoidal rule.			
	Jan 2008 – April 2012			