3. Liver Transplantation

Table of Contents

3.1 Induction Therapy

Kim Y, et al. (2024). Evaluation of Induction Immunosuppression and Risk of Incisional Hernia After Liver Transplantation. J Surg Res. 2024 Feb;29(297):18-25. Retrieved from https://pubmed.ncbi.nlm.nih.gov/38428260/.

- This single-center retrospective study studied rates of incisional hernia after liver transplantation in patients who received either 500 mg IV methylprednisolone followed by a taper to oral prednisone 5 mg daily by 2 months post-transplant, or 20 mg IV basiliximab on postoperative day 0 and postoperative day 4 without corticosteroids. More patients in the basiliximab group developed postoperative incisional hernia within 5 years post-transplant (36.1% vs. 24.4%, p=0.03). BMI $\geq$ 30 (HR 2.67, 95% CI 1.7-4.3) and postoperative seroma (HR 2.03, 95% CI 1.1-3.9) of the abdominal wall were associated with an increased risk of developing incisional hernia within 5 years post-transplant. After propensity scoring, there was no difference in incisional hernia rates between groups (HR = 1.33, 95% CI 0.87-2.05, p=0.19).

Jung W, et al. (2023). T-cell specific antibody induction versus corticosteroid induction immunosuppression for liver transplant recipients: a meta-analysis. Sci Rep. 2023 Apr;13(1):6951. Retrieved from https://pubmed.ncbi.nlm.nih.gov/37117258/

- In this meta-analysis of T-cell depleting versus corticosteroid induction in liver transplant, eleven trials were included, with a total of 1683 patients. The primary outcome was biopsy-proven acute rejection, which had similar incidence between both groups (RR 0.85, 95% CI 0.72 to 1.01, p=0.06). A significant difference in rates of CMV infection, HCV recurrence, and hypertension were observed between groups, in favor of T-cell therapies.

Ruiz I, et al. (2022). Impact of Steroid Only Induction on Rejection in Simultaneous Liver-Kidney Transplantation. Prog Transplant. 2022 Dec;32(4):363-369. Retrieved from https://pubmed.ncbi.nlm.nih.gov/36062719/.

- This single center, retrospective, cohort study assessed induction with corticosteroids alone (N=41) versus basiliximab + corticosteroids (N=42) in simultaneous liver-kidney transplantation. The primary objective was biopsy-proven acute rejection at 3 months, which was found to be similar between groups (10% vs 7%, p=0.67). No differences in patient and graft survival were observed.

Cederborg A, et al. (2022). Renal function after liver transplantation: real-world experience with basiliximab induction and delayed reduced-dose tacrolimus. Dig Liver Dis. 2022 Aug;54(8):1076-1083. Retrieved from https://pubmed.ncbi.nlm.nih.gov/34965904/.

- Retrospective, cohort study that sought to evaluate change in renal function pre- vs post-transplant in patients receiving immunosuppression with either basiliximab induction, tacrolimus (trough goal 5-8 ng/mL) starting post-operative day 3, and mycophenolate or tacrolimus (trough goal 10-15 ng/mL) starting immediately post-operatively with corticosteroids. Patients with delayed initiation of tacrolimus exhibited higher mean eGFR (MDRD) at 3 and 12 months, compared to those who started tacrolimus immediately and with a higher trough goal. At 12 months, mean eGFR was 63.4 vs 56.8 mL/min/1.73m^2 (p=0.004), respectively. No difference in patient survival was observed (p=0.16); however, a reduction in BPAR at 12 months occurred with the delayed initiation of tacrolimus (21% vs 38%, p<0.001).

Boyd A, et al. (2021). Basiliximab with delayed tacrolimus improves short-term renal outcomes post-liver transplantation-a real-world experience. Transplant Proc. 2021 Jun;53(5):1541-1547. Retrieved from https://pubmed.ncbi.nlm.nih.gov/34074467/.

- Retrospective cohort analysis analyzing the impact of a renal-sparing strategy using basiliximab in conjunction with mycophenolate mofetil and corticosteroids from day 0 post-LT along with delayed introduction of tacrolimus vs tacrolimus, mycophenolate mofetil, and corticosteroids from the outset. The renal-sparing regimen was associated with significantly lower incidence of all-stage AKI at day 7 post-LT and less decline in renal function at 3 months. No further significant differences in renal outcomes were observed at other time points on follow-up to 1-year post-LT.

Kathirvel M, et al. (2021). Randomized trial of steroid free immunosuppression with basiliximab induction in adult live donor liver transplantation (LDLT). HPB (Oxford). 2021 May;23(5):666-674. Retrieved from https://pubmed.ncbi.nlm.nih.gov/33032883/.

- Randomized trial comparing basiliximab + TAC + AZA vs steroid + TAC + AZA. Incidence of post-transplant DM, hypertension, hypertriglyceridemia. No differences in BPAR, time to BPAR, patient, and graft survival amongst groups.

Nair A, et al. (2021). Induction therapy with antithymocyte globulin and delayed calcineurin inhibitor initiation for renal protection in liver transplantation: A multicenter randomized controlled phase II-b trial. Transplantation. 2022 May 1;106(5):997-1003. Retrieved from https://pubmed.ncbi.nlm.nih.gov/34319926/

- Open-label, multicenter, RCT comparing rATG induction with delayed CNI initiation (day-10) (n=55) to upfront CNI commencement (SOC: standard of care) (n=55) in patients at standard risk of postoperative renal dysfunction following liver transplant. A significant difference in change in creatinine was observed between rATG and SOC groups at 9-months but not at month-12. eGFR levels were comparable between cohorts at all-time points. Rates of biopsy-proven acute rejection at 1-year were similar between groups. rATG showed no significant adverse effects and survival at 12-months was comparable between groups.

Tovikkai C, et al. (2021). Delayed Calcineurin Inhibitor Introduction Without Antibody Induction in Liver Transplantation Is Safe and Helps Preserve Kidney Function. Transplant Proc. 2021 Mar;53(2):645-648. Retrieved from https://pubmed.ncbi.nlm.nih.gov/33358420/.

- Single-center, retrospective case-control study evaluating AKI in liver transplant recipients receiving delayed CNI delayed CNI protocol (study group) vs. immediate CNI protocol (control group). Patients with fulminant liver failure and were already on renal replacement therapy were excluded. Study group patients (n=30) received steroid induction, mycophenolate mofetil was added at the prescriber's discretion, and CNI administration was delayed 48 to 72 hours. The

control group (n=30) received CNI, MMF, and steroid induction and the CNI and MMF were continued post-transplant.

- AKI developed in 11 patients in the study group and in 20 patients in the control group (37% vs 66.7%; P = 0.02). There was no acute rejection observed in the first month in either group.

Anugwwom C, et al. (2021). Comparison of clinical outcomes of induction regimens in patients undergoing liver transplantation for acute liver failure. Liver Transpl. 2021 Jan;27(1):27-33. Retrieved from https://pubmed.ncbi.nlm.nih.gov/32578297/.

- Retrospective review of 3754 first-time liver transplant recipients comparing overall survival based on induction regimens grouped by steroid-only induction, use of antithymocyte globulin (ATG), or interleukin 2-receptor antibody. Compared with a steroid-only induction regimen, the addition of ATG is associated with worse overall survival after liver transplant for acute liver failure.

Hashim M, et al. (2020). Efficacy and safety of basiliximab as initial immunosuppression in liver transplantation: A single center study. Ann Hepatol. 2020 Sep-Oct;19(5):541-545. Retrieved from https://pubmed.ncbi.nlm.nih.gov/32768592/.

- Study of 89 patients given TAC + MMF + steroids vs basiliximab + MMF + delayed TAC followed for 6 months or until death. No significant differences in patient survival, graft dysfunction, BPAR, infection rate or type, or wound healing between both groups. Renal dysfunction was less in the basiliximab group.

Harada N, et al. (2020). Use of mycophenolate mofetil suspension as part of induction therapy after living-donor liver transplant. Exp Clin Transplant. 2020 Aug;18(4):485-490. Retrieved from https://pubmed.ncbi.nlm.nih.gov/32490763/.

- Retrospective review of 20 adult primary living-donor transplant recipients to evaluate recipient safety, tolerability, and pharmacokinetics of mycophenolate mofetil suspension compared with mycophenolate mofetil capsules as part of induction therapy after living-donor liver transplant. Mycophenolate mofetil suspension at 3000mg/day resulted in significantly higher AUC plasma concentration compared to capsules without increasing the risk for adverse events or rejection.

Best LM, et al. (2020). Induction immunosuppression in adults undergoing liver transplantation: a network meta-analysis. Cochrane Database Syst Rev. 2020 Jan 16;1:CD013203. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/31978255.

- Cochrane review of 25 randomized clinical trials evaluating induction regimens (glucocorticoids, anti-thymocyte globulin, basiliximab, daclizumab, alemtuzumab, or no induction) in liver transplant

recipients. Low-certainty evidence suggests basiliximab induction reduces mortality and graft failure compared with corticosteroid induction.

Bittermann T, et al. (2019). The use of induction therapy in liver transplantation is highly variable and is associated with post-transplant outcomes. Am J Transplant. 2019 Dec;19(12):3319-3327. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/31243887.

- Retrospective review comparing non-depleting induction vs depleting induction in 69,349 liver transplant recipients utilizing UNOS data. Only non-depleting induction was associated with a reduction in acute rejection. Both forms of induction were associated with a reduction in patient and graft loss, however, absolute difference was minimal.

Lange NW, et al. (2018). Delayed calcineurin inhibitor introduction and renal outcomes in liver transplant recipients receiving basiliximab induction. Clin Transplant. 2018 Dec;32(12):e13415. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/30276862.

- This retrospective review of 210 liver transplant recipients from 2007 through 2015 at New York Presbyterian Hospital/Columbia University assessed the impact of delaying CNIs with use of basiliximab induction on renal function between 4 groups with varying degrees of AKI post-transplant. By delaying therapeutic CNI (therapeutic levels of 6-10) by about 14 days post-transplant in all 4 groups with varying degrees of AKI, there was no difference in renal function past 90 days post-transplant.

Cillo U, et al. (2018). Identifying risk profiles in liver transplant candidates and implications for induction immunosuppression. Transplant Rev (Orlando). 2018 Jul;32(3):142-150. Retrieved from https://pubmed.ncbi.nlm.nih.gov/29709248/.

- A review article evaluating donor characteristics, recipient characteristics, and immunological characteristics that may warrant the use of induction therapy. This review evaluates literature available for use of different induction regimens and agents and the safety of using these agents.

Iesari S, et al. (2018). Tacrolimus and Single Intraoperative High-dose of Anti-T-lymphocyte Globulins Versus Tacrolimus Monotherapy in Adult Liver Transplantation: One-year Results of an Investigator-driven Randomized Controlled Trial. Ann Surg. 2018;268(5):776-783. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/30307410.

- This is a randomized controlled trial comparing tacrolimus monotherapy (TAC, n = 109) and tacrolimus plus a single, intraoperative, high-dose (9mg/kg), rabbit anti-T-lymphocyte globulin.

The primary endpoint evaluated was immunosuppression minimization to monotherapy with other endpoints including biopsy-proven rejection, clinical rejection, and patient and graft survival.

Zhang GQ, et al. (2017). Basiliximab application on liver recipients: a meta-analysis of randomized controlled trials. HBPD INT. 2017;16(2):139-146. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/28381376.

- Meta-analysis of 6 randomized controlled trials conducted from 1998 – 2015 examining the use of basiliximab induction in liver transplant recipients vs. steroid induction alone. Basiliximab induction was found to significantly reduce the incidence of post-transplant diabetes, in addition to lower observed rates of hypertension and biopsy prove acute rejection.

Montenovo MI, et al. (2017). Superior Patient and Graft Survival in Adult Liver Transplant with Rabbit Antithymocyte Globulin Induction: Experience with 595 Patients. Exp Clin Transplant. 2017 Aug;15(4):425-431. Retrieved from https://pubmed.ncbi.nlm.nih.gov/27309029/.

- Retrospective cohort study evaluating different induction protocols for liver transplant at the University of Washington from 1/2005-5/2012. There were identified 595 patients: 322 patients received rATG and 273 received IL2 receptor blocker. rTAG had lower rates of acute rejection and patient/graft survival was superior in the rATG group, up to 5 years.

Petite SE, et al. (2016). Antithymocyte Globulin Induction Therapy in Liver Transplant: Old Drug, New Uses. Ann Pharmacother. 2016;50(7):592-8. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27147705.

- MEDLINE literature search involving 9 studies reviewing the use of rATG induction therapy in liver transplant recipients. Patients receiving rATG induction tended to have improved renal function compared with patients not receiving induction. Rejection rates tended to be lower in recipients administered rATG.

Au KP, et al. (2015). Clinical factors affecting rejection rates in liver transplantation. Hepatobiliary Pancreat Dis Int. 2015;14(4):367-73. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26256080.

- This retrospective review of 788 liver transplant patients studied the relationship between acute cellular rejection (ACR) and various clinical factors. Liver transplant recipients with older age, chronic hepatitis B virus infection, living donor liver transplantation and use of interleukin-2 receptor antagonist on induction have fewer ACR.

Yoo MC, et al. (2015). Steroid-free Liver Transplantation Using Rabbit Antithymocyte Globulin Induction in 500 Consecutive Patients. Transplantation. 2015; 99(6):1231-5. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25539464.

- This report demonstrated the benefits of a steroid-free immunosuppression protocol using rabbit antithymocyte globulin (RATG) induction in orthotopic liver transplantation (OLT) with tacrolimus minimization 500 recipients

Halldorson JB, et al. (2015). Differential rates of ischemic cholangiopathy and graft survival associated with induction therapy in DCD liver transplantation. Am J Transplant. 2015;15(1):251-8. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25534449.

- This single center study used a Multivariable analysis demonstrating induction agents to be independently associated with graft survival and ischemic cholangiopathy free graft survival when analyzed against variables including donor age, fWIT, donor cold ischemia time and transplant era.

Garcia SM, et al. (2014). Impact of anti-thymocyte globulin during immunosuppression induction in patients with hepatitis C after liver transplantation. Dig Dis Sci. 2014;59(11):2804-12. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24865255.

- This study evaluated the 1- and 2-year patient survival and HCV recurrence rate in patients receiving ATG during the induction phase of immunosuppression after liver transplantation.

Kubal CA, et al. (2014). Crossmatch-positive liver transplantation in patients receiving thymoglobulin-rituximab induction. Transplantation. 2014;97(1):56-63. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24030603.

- This study reviewed the role of induction immunosuppression in positive crossmatch in liver transplantation. With the use of rabbit anti-thymocyte globulin ± rituximab induction, overall low rejection rates can be achieved in positive crossmatch liver transplantation.

Penninga L, et al. (2014). Antibody induction versus placebo, no induction, or another type of antibody induction for liver transplant recipients. Cochrane Database Syst Rev. 2014;(6):CD010253. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24901467.

- Cochrane review of 19 randomized clinical trials assessing immunosuppression with T-cell specific antibody induction compared with placebo, no induction, or another type of antibody induction in liver transplant recipients.

Penninga L, et al. (2014). Antibody induction versus corticosteroid induction for liver transplant recipients. Cochrane Database Syst Rev. 2014;(5):CD010252. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24880007.

- Cochrane review of 10 randomized clinical trials assessing immunosuppression with T-cell specific antibody induction versus corticosteroid induction in liver transplant recipients.

Turner AP, et al. (2013). Induction immunosuppression in liver transplantation: a review. Transpl Int. 2013 Jul;26(7):673-83. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/23651083.

- A review of antibody induction agents in liver transplantation, particularly the use of basiliximab in adults with renal function impairment allowing for delayed introduction of calcineurin-inhibitors.

Rostaing L, et al. (2012). Review article: use of induction therapy in liver transplantation. Transplant Rev (Orlando). 2012 Oct;26(4):246-60. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/22863028.

- Review of rationale, mechanisms, safety and evidence supporting various induction agents used in liver transplantation. Includes tables summarizing RCTs on induction.

Neumann U, et al. (2012). A Randomized Multicenter Study Comparing a Tacrolimus-Based Protocol with and without Steroids in HCV-Positive Liver Allograft Recipients. J Transplant. 2012;2012:894215. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/22690326.

- Comparison of induction with tacrolimus + daclizumab vs. tacrolimus + steroids. Primary endpoint, median HCV viral load at 12 months, was similar between groups.

Mangus R, et al. (2012). Immunosuppression induction with rabbit antithymocyte globulin with or without rituximab in 1000 liver transplant patients with long-term follow-up. Liver Transpl. 2012 Jul;18(7):786-95. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/22237953.

- Retrospective, single-center study comparing 3 induction methods: 1) rATG given in OR (n=166), 2) rATG given 48 hrs post-transplant (n=266), and 3) rATG given 48 hrs post-transplant + rituximab given 72 hrs post-transplant. No significant difference in 5-year survival was found between groups.

Ghanekar A, et al. (2012). Routine induction therapy in living donor liver transplantation prevents rejection by may promote recurrence of hepatitis C. Transplant Proceedings, 44, 1351-1356. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/22664014.

- Retrospective study in 184 LDLT patients who received either rATG or basiliximab for induction. Results showed significantly lower rates of rejection but higher rates of HCV recurrence in the rATG group.

Uemura T, et al. (2011). Outcome of induction immunosuppression for liver transplantation comparing anti-thymocyte globulin, daclizumab, and corticosteroid. Transpl Int. 2011 Jul;24(7):640-50. Retrieved from https://pubmed.ncbi.nlm.nih.gov/21429047/.

- Retrospective study evaluating ATG alone, ATG + steroids, daculizumab alone, or steroids alone for induction therapy. Overall graft survival in patients without HCV was similar with all agents. Inferior survival was seen in patients with HCV and use of ATG + steroids.

Klintmalm G, et al. (2011). A randomized, multicenter study comparing steroid-free immunosuppression and standard immunosuppression for liver transplant recipients with chronic hepatitis C. Liver Transpl. 2011 Dec;17(12):1394-403. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/21850690.

- Prospective RCT in 295 HCV patients comparing steroid-free induction (tacrolimus + mycophenolate mofetil + daclizumab) to tacrolimus + steroids and tacrolimus + mycophenolate mofetil + steroids. No significant differences found in ACR, HCV recurrence, patient survival, or graft survival at 2 years.

Levitsky J, et al. (2011). Alemtuzumab induction in non-hepatitis C positive liver transplant recipients. Liver Transpl. 2011 Jan;17(1):32-7. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/21254342.

- Retrospective case-control study comparing induction with alemtuzumab (n= 55) vs tacrolimus + steroid taper (n= 85). Alemtuzumab was associated with less hypertension and rejection but a higher rate of infections (due to increased number of viral infections). No significant differences in graft survival, patient survival, ACR, or renal dysfunction.

Selzner N, et al. (2010). The immunosuppressive pipeline: meeting unmet needs in liver transplantation. Liver Transpl. 2010 Dec;16(12):1359-72. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/21117245.

- Explores novel molecular targets for induction and maintenance immunosuppression, including CNI- free regimens.

Otero A, et al. (2009). A prospective randomized open study in liver transplant recipients: daclizumab, mycophenolate mofetil, and tacrolimus versus tacrolimus and steroids. Liver Transpl. 2009 Nov;15(11):1542-52. Retrieved from https://pubmed.ncbi.nlm.nih.gov/19877219/.

- Open-label, randomized study comparing TAC + steorid vs daculizumab + MMF + TAC. BPAR and time to BPAR was significantly reduced at 24 weeks in the daculizumab group. Overall survival outcomes were the same.

Boillot O, et al. (2009). Thymoglobulin induction in liver transplant recipients with a tacrolimus, mycophenolate mofetil, and steroid immunosuppressive regimen: a five-year randomized prospective study. Liver Transpl. 2009 Nov;15(11):1426-34. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19877264.

- Comparison of thymoglobulin induction (n=44) or no induction (n=49). No difference found in ACR or long-term survival, but higher rate of leukopenia in thymoglobulin group.

Bajjoka I, et al. (2008). Preserving renal function in liver transplant recipients with rabbit anti-thymocyte globulin and delayed calcineurin inhibitors. Liver Transpl. 2008 Jan;14(1):66-72. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18161842.

- Retrospective study comparing rATG induction and delayed CNI initiation (n=118) versus early initiation of CNI (n= 80). All patients received MMF and steroids. Patients in the rATG group had significantly lower serum creatinine and a trend toward lower rates of ACR at 12 months post-transplant.

Figueras J, et al. (2006). Daclizumab induction and maintenance steroid-free immunosuppression with mycophenolate mofetil and tacrolimus to prevent acute rejection of hepatic allografts. Transpl Int. 2006 Aug;19(8):641-8. Retrieved from https://pubmed.ncbi.nlm.nih.gov/16827681/.

- 6-month, open-label, multicenter, pilot study where patients were given daculizumab, MMF, TAC with steroid free regimen. Regimen showed similar rates of rejection, graft, and patient survival compared to standard of care regimen including steroids.

Nair S, et al. (2006). Induction with rabbit anti-thymocyte globulin versus induction with corticosteroids in liver transplantation: impact on recurrent hepatitis C virus infection. Transplantation. 2006 Feb 27;81(4):620-2. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16495812.

- HCV patients were randomized to receive either rATG (n=33) or methylprednisolone (n=31) induction. No significant difference was shown in patient survival or HCV recurrence rates at 6 months post-transplant.

Lin CC et al. (2005). The renal-sparing efficacy of basiliximab in adult living donor liver transplantation. Liver Transpl. 2005 Oct;11(10):1258-64. Retrieved from https://pubmed.ncbi.nlm.nih.gov/16184544/.

- To determine if basiliximab therapy improves post-operative renal function by delaying tacrolimus and decreasing dosing in living liver transplant patients vs no induction. Serum creatinine levels at second and third postoperative months were significantly lower in the induction group. The creatinine clearance rate in the induction group was higher at the third month post-transplant (median 72 vs. 57 ml/minute, P = 0.04). The incidences of acute cellular rejection, bacteremia, and cytomegalovirus infection were similar in both groups.

Yoshida EM, et al. (2005). Evaluation of renal function in liver transplant recipients receiving daclizumab (Zenapax), mycophenolate mofetil, and a delayed, low-dose tacrolimus regimen vs. a standard-dose tacrolimus and mycophenolate mofetil regimen: a multicenter randomized clinical trial. Liver Transpl. 2005 Sep;11(9):1064-72. Retrieved from https://pubmed.ncbi.nlm.nih.gov/16123958/.

- Randomized control trial evaluating daclizumab + delayed tac + steroids vs tac + steroids + MMF. No difference in patient survival or BPAR. Median MDRD eGFR favored daclizumab group at 1 week, 1 month, and 6 months.

Fung J, et al. (2005). Immunosuppression in liver transplantation: beyond calcineurin inhibitors. Liver Transpl. 2005 Mar;11(3):267-80. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15719409.

- Review of induction and maintenance immunosuppressant strategies, focusing on potential for CNI sparing regimens.

Boillot O, et al. (2005). Corticosteroid-free immunosuppression with tacrolimus following induction with daclizumab: a large randomized clinical study. Liver Transpl. 2005 Jan;11(1):61-7. Retrieved from https://pubmed.ncbi.nlm.nih.gov/15690537/.

- Open, randomized, multi-center 3-month study comparing TAC + steroids vs steroid free w/ daculizumab induction. Similar rates of rejection, patient survival, and graft survival. Lower rates of steroid-resistant rejection, CMV, and DM in the daculizumab group.

Liu CL, et al (2004). Interleukin-2 receptor antibody (basiliximab) for immunosuppressive induction therapy after liver transplantation: a protocol with early elimination of steroids and reduction of tacrolimus dosage. Liver Transpl. 2004 Jun;10(6):728-33. Retrieved from https://pubmed.ncbi.nlm.nih.gov/15162466/.

- Prospective evaluation to study potential benefit of IL2 induction with early steroid discontinuation w/ TAC + MMF. This was compared to a cohort of TAC + steroid standard of care patients. Lower incidences of post-operative DM ACR, cholesterol, and CMV in the IL2 induction group.

Tector AJ, et al. (2004). Promising early results with immunosuppression using rabbit anti-thymocyte globulin and steroids with delayed introduction of tacrolimus in adult liver transplant recipients. Liver Transpl. 2004 Mar;10(3):404-7. Retrieved from https://pubmed.ncbi.nlm.nih.gov/15004768/.

- Examined use of rATG with delayed TAC in liver transplant patients. 112 patients were included and 96% of patients were alive with a mean follow up of 12.9 ± 4.5 months, 6% of patients had acute rejection with no steroid rejection. rATG was safe to be given as induction for liver transplant recipients.

Lucey MR. (2002). Induction immunosuppression in hepatitis C virus-infected liver transplant recipients. Liver Transpl. 2002 Oct;8(10 Suppl 1):S44-6. Retrieved from https://pubmed.ncbi.nlm.nih.gov/12362297/.

- Review article discussing use of induction immunosuppression, evaluating available studies utilizing induction immunosuppression in HCV patients, and rationale to use induction or not.

Calmus Y, et al. (2002). Immunoprophylaxis with basiliximab, a chimeric anti-interleukin-2 receptor monoclonal antibody, in combination with azathioprine-containing triple therapy in liver transplant recipients. Liver Transpl. 2002 Feb;8(2):123-31. Retrieved from https://pubmed.ncbi.nlm.nih.gov/11862588/.

- Single-arm, open-label, multicenter study investigated the efficacy and tolerability of basiliximab w/ CSA + steroids + AZA maintenance. in 100 patients. At 6 months, the incidence of first acute biopsy-confirmed rejection episodes was 22.8%. No rejection episode was graded histologically as severe, and no patient required antibody therapy for the management of acute rejection but some required transition to TAC. No ADEs were reported.

Eason JD, et al. (2001). Steroid-free liver transplantation using rabbit anti-thymocyte globulin induction: results of a prospective randomized trial. Liver Transplantation, 7(8), 693-697. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11510013.

- First reported RCT comparing induction with rATG (n=36) versus methylprednisolone (n=35). Showed a trend toward lower rates of ACR, post-transplant diabetes and HCV recurrence in the rATG group.

3.2 Maintenance therapy

3.2.1 Calcineurin Inhibitors

Mulder MB, et al. (2024). Modifying Tacrolimus-related Toxicity After Liver Transplantation Comparing Life Cycle Pharma Tacrolimus Versus Extended-released Tacrolimus: A Multicenter, Randomized Controlled Trial. Transplant Direct. 2024;10(4):e1612. Retrieved from https://pubmed.ncbi.nlm.nih.gov/38481963/.

- Open-label, multicenter, randomized controlled trial comparing LCP-tacrolimus with ER-tacrolimus monotherapy in 105 liver transplant recipients. In the intention to treat analysis, LCP-tacrolimus was associated with a significantly lower rate of a composite of post-transplant diabetes mellitus, new-onset hypertension, or CKD (eGFR < 60 ml/min). However, no significant difference was found in the per protocol analysis. In both analyses, fewer patients on LCP-tacrolimus developed new-onset hypertension or CKD. There were no differences in rejection or graft/patient survival between groups.

Åberg F, et al. (2024). Cyclosporine vs. tacrolimus after liver transplantation for primary sclerosing cholangitis - a propensity score-matched intention-to-treat analysis. J Hepatol. 2024;80(1):99-108. Retrieved from https://pubmed.ncbi.nlm.nih.gov/37722533.

- Registry study using the European Liver Transplant Registry (ELTR) and SRTR to compare outcomes with tacrolimus vs. cyclosporine following adult liver transplantation for PSC. Propensity score matching was used to match tacrolimus-treated and cyclosporine-treated patients at a 3:1 ratio. Covariates included recipient/donor age, sex discordance, HCC/CC, ABO matching. Over a median follow-up of 7.4 years, patient and graft survival were better with tacrolimus compared to cyclosporine in the intention-to-treat population. In a Cox regression analysis, tacrolimus use was associated with a lower rate of a composite of death or re-transplant. Later transplant year and mycophenolate use in the first month post-transplant were independently associated with a lower rate of death or re-transplant while older donor age and recipient-donor sex mismatch were associated with a higher rate. The rate of acute rejections was 38% in both groups using SRTR data.

Mulder M, et al. (2023). Three-year results of renal function in liver transplant recipients on low-dose sirolimus and tacrolimus: a multicenter, randomized, controlled trial. Liver Transplantation. 2023 February. 29(2): p 184-195. Retrieved from https://pubmed.ncbi.nlm.nih.gov/36668691.

- Multi-center study addressing whether low-dose sirolimus and low-dose extended-release tacrolimus compared to normal-dose extended-release tacrolimus results in difference in renal function and comparable rates of rejection at 36 months post-transplantation. Chronic kidney disease (CKD) was similar between the 2 groups, but eGFR was higher in the interventional

group (mean eGFR 73.1±15 vs. 67.6±16 mL/min/1.73 m2, p=0.02). There were no differences in safety outcomes between groups.

Wohl D, et al. (2023). EnGraft: a multicentre, open-label, randomized, two-arm, superiority study protocol to assess bioavailability and practicability of Envarsus versus Advagraf in liver transplant recipients. Trials. 2023. 24(1): 325. Retrieved from https://pubmed.ncbi.nlm.nih.gov/37170284/

- Multicenter, randomized study comparing bioavailability and superiority of Envarsus versus Advagraf in de novo liver transplant recipients. The primary endpoint of dose-normalized trough level measured 12 weeks after randomization. Results not yet published.

Ruijter BN, et al. (2022). Tacrolimus 4-hour monitoring in liver transplant patients is non-inferior to trough monitoring: the randomized controlled FK04 trial. 2022 Dec;36(12):e14829. Retrieved from https://pubmed.ncbi.nlm.nih.gov/36193575/

- 50 patients were included in this open-label, blinded, randomized controlled trial. Interventions included tacrolimus C4 monitoring vs trough (C0) monitoring among liver transplant recipients. The primary endpoint was renal function at 12 weeks from randomization. No difference was observed between tacrolimus C4 monitoring and C0 monitoring methods; however, C4 monitoring does correlate well to AUC.

Meszaros M, et al. (2022). Impact of calcineurin inhibitor-free immunosuppression on de novo donor-specific antibody formation in liver transplant recipients. Liver Int. 2022 Feb 20. Epub ahead of print. Retrieved from https://pubmed.ncbi.nlm.nih.gov/35184373/.

- Multi-center study assessing development of de novo donor-specific HLA antibody (dnDSA) and allograft histopathological abnormalities in liver transplant recipients on CNI-free maintenance regimens. A total of 727 liver transplant recipients undergoing initial liver transplant had protocolized follow-up with dnDSA screening and allograft biopsy (at 1, 5 and 10 years).
- CNIs were withdrawn in 166 (22.8%) patients with or without conversion to mammalian target of rapamycin inhibitors and/or maintenance with mycophenolic acid. DSAs were present after withdrawal in 30.1% (50/166) patients on CNI-free immunosuppression vs. 16% (90/561) on CNI maintenance therapy ($p < 0.001$). Cumulative incidence of dnDSA 10 years after transplant was 20% in the CNI group vs. 28% in the CNI-free group ($p < 0.01$). dnDSAs were associated with histological graft abnormalities (significant allograft fibrosis or rejection) (HR 2.24, 95% CI 1.2-4.1; $p = 0.01$) but a CNI-free regimen did not impact graft histology in univariate Cox regression analysis.

Maurer M, et al. (2022). Reducing the Pill Burden: Immunosuppressant Adherence and Safety after Conversion from a Twice-Daily (IR-Tac) to a Novel Once-Daily (LCP-Tac) Tacrolimus Formulation in 161 Liver Transplant Patients. Biomedicines. 2022 Jan 26;10(2):272. Retrieved from https://pubmed.ncbi.nlm.nih.gov/35203481/.

- Single-center, prospective, non-randomized, single-arm 24 month observational study evaluating changes in adherence to immunosuppressive medications as well as efficacy and safety after conversion of stable liver transplant recipients from twice-daily immediate release Tacrolimus (IR-Tac) to a novel once-daily Tacrolimus (LCP-Tac) formulation. Medication adherence was evaluated using the BAASIS© (Basel Assessment of Adherence Scale to Immunosuppressives) questionnaire and a Visual Analog Scale (VAS) at specified intervals. Data on tacrolimus troughs, adverse events, and acute rejection or graft loss during the study were recorded.

Kang WH, et al. (2021). Efficacy and safety evaluation after conversion from twice-daily to once-daily tacrolimus in stable liver transplant recipients: A phase 4, open-label, single-center study. Transplant Proc. 2021 Nov 11;S0041-1345(21)00739-9. Online ahead of print. Retrieved from https://pubmed.ncbi.nlm.nih.gov/34776265/.

This prospective study analyzed graft function, drug compliance, and adverse reactions after switching regimen from twice-daily to once-daily tacrolimus in 101 stable liver transplant recipients for 24 weeks. No acute rejection was seen within 24 weeks as well as no chronic rejection, fatal deterioration of liver function, or death in any patient during the study period. After conversion, the trough level of tacrolimus decreased, and the mean ± standard deviation differences between the trough level and baseline level were 1.46 (±2.41) ng/mL, 0.43 (±2.08) ng/mL, and 0.07 (±2.73) ng/mL at 3, 12, and 24 weeks after conversion, respectively.

Maciel N, et al. (2021). Liver transplantation: Tacrolimus blood levels variation and survival, rejection and death outcomes. Arq Gastroenterol. Jul-Sep 2021;58(3):370-376. Retrieved from https://pubmed.ncbi.nlm.nih.gov/34705973/.

- Retrospective longitudinal study (n=127) investigating the association of tacrolimus blood levels with clinical outcomes late acute cellular rejection, death, patient survival and graft survival in patients undergoing liver transplantation. Increased risk of graft loss associated with increased standard deviations of tacrolimus blood levels may indicate the need for more rigorous and prospective monitoring of tacrolimus blood levels.

Friman S, et al. (2021). Long-term, prolonged-release tacrolimus-based immunosuppression in de novo liver transplant recipients: 5-year prospective follow-up of patients in the diamond study. Transplant

Direct. 2021 Jul 9;7(8):e722. eCollection 2021 Aug. Retrieved from https://pubmed.ncbi.nlm.nih.gov/34263020/.

- 5-y, prospective follow-up of a large patient cohort (n = 856) from the 24-wk DIAMOND study evaluating long-term graft survival in liver transplant recipients treated with prolonged-release tacrolimus-based immunosuppression. Renal function, graft survival, and patient survival were similar between treatment arms at 5 y post-transplant.

Choi D, et al. (2021). Evaluating the conversion to extended-release tacrolimus from immediate-release tacrolimus in liver transplant recipients. Eur J Gastroenterol Hepatol. 2021 Aug 1;33(8):1124-1128. Retrieved from https://pubmed.ncbi.nlm.nih.gov/34213506/.

- Retrospective study evaluating liver transplant recipients converted from immediate-release tacrolimus to extended-release tacrolimus. Among patients who switched formulations due to tremors, 88% noted significant improvement. No difference in SCr or GFR from baseline to 3 months post conversion and no episodes of ACR or CMV post conversion were seen.

Muta K, et al. (2021). Association between trough level of tacrolimus and change in estimated glomerular filtration rate 1 year after living donor liver transplantation. Ann Transplant. 2021 Feb 9;26:e928858. Retrieved from https://pubmed.ncbi.nlm.nih.gov/33558451/.

- Retrospective study of 191 living donor liver transplant recipients evaluating factors contributing to post-transplant eGFR changes. Tacrolimus trough level was associated with eGFR changes 1 year after LDLT. The adjusted dose of tacrolimus and combined use of other immunosuppressants may be important to maintain renal function after transplant.

Kahn J, et al. (2020). Immunosuppression with generic tacrolimus in liver and kidney transplantation-systematic review and meta-analysis on biopsy-proven acute rejection and bioequivalence. Transpl Int. 2020 Apr;33(4):356-372. Retrieved from https://pubmed.ncbi.nlm.nih.gov/31971288/.

- Systematic review and meta-analysis of to provide an overview of evidence for use of generic tacrolimus in liver and kidney transplant patients. 92.9% of studies reported the same or similar evidence of BPAR with generic vs brand TAC. De novo studies showed a significantly lower risk with generic TAC, conversion studies showed an increased risk.

Lim TY, et al. (2020). Sequential Cohort Analysis After Liver Transplantation Shows de Novo Extended Release Tacrolimus Is Safe, Efficacious, and Minimizes Renal Dysfunction. Transplant Direct. 2020 Jan 17;6(2):e528. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/32095514.

- Single-center, prospective sequential cohort analysis comparing clinical outcomes of liver transplant recipients receiving tacrolimus IR or de novo tacrolimus ER (Astagraf XL). Tacrolimus ER was associated with a reduction in new-onset CKD stage 3-4 compared with tacrolimus IR. Incidence of biopsy-proven acute rejection, patient and graft survival were similar between groups.

DuBay DA, et al. (2019). Pharmacokinetics of Once-Daily Extended-Release Tacrolimus Tablets Versus Twice-Daily Capsules in De Novo Liver Transplant. Clin Pharmacol Drug Dev. 2019 Nov;8(8):995-1008. Retrieved from https://pubmed.ncbi.nlm.nih.gov/30667591/.

- Phase II, randomized, open-label study, de novo liver transplant recipients were randomized to LCPT once daily vs IR BID TAC. Twenty-four-hour pharmacokinetic profiles were obtained on days 1, 7, and 14, with trough concentration and efficacy/safety monitoring through year 1. Similar proportion of patients reached therapeutic concertations and similar peak exposure. BPAR and ADEs were similar. This supports use of LCPT de-novo.

Dumortier J, et al. (2019). A Multicenter, Prospective, Observational Study of Conversion from Twice-Daily Immediate-Release to Once-Daily Prolonged-Release Tacrolimus in Liver Transplant Recipients in France: The COBALT Study. Ann Transplant. 2019 Aug 27;24:506-516. Retrieved from https://pubmed.ncbi.nlm.nih.gov/31451681/.

- Prospective, observational study in France between 7/2014-3/2016 describing use of prolonged-release tacrolimus with early <3 months vs later conversions 3-12 months. Only one patient required an additional visit due to conversion. Reasons for conversion included the physician's preference (56.3%), center practice (38.6%), and the dosing frequency (36.0%). Conversion was associated with a low rate of graft rejection, and no new safety issues were reported.

Lin S, et al. (2019). Tacrolimus Monotherapy in Recipients of Liver Transplant: A Single-Cent.er Experience. Transplant Proc. 2019 Jul - Aug;51(6):1920-1922. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/31399176.

- Single-center retrospective review evaluating outcomes of early tacrolimus monotherapy (<6 months post-transplant) in 100 liver transplant recipients. Compared with patients transitioned to monotherapy after 6 months post-transplant, there were no differences in rejection, CMV infection, renal impairment, or patient survival at 5 years follow-up.

Adam R, et al. (2019). Improved Survival in Liver Transplant Patients Receiving Prolonged-release Tacrolimus-based Immunosuppression in the European Liver Transplant Registry (ELTR): An Extension

Study. Transplantation. 2019;103(9):1844-1862. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/31343568.

- Retrospective analysis of European Liver Transplant Registry of long-term liver transplantation outcomes with prolonged-release tacrolimus (Astagraf) versus immediate-release tacrolimus-based immunosuppression. Analysis comprised up to 8-year data collected in an extension of the previously published ELTR study.

Lee ECgerard, et al. (2018). Safety and Efficacy of Once-Daily Prolonged-Release Tacrolimus in Living Donor Liver Transplantation: An Open-Label, Prospective, Single-Arm, Phase 4 Study. Ann Transplant. 2018;23:713-720. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/30310047.

- This is a phase 4 single-arm open-label prospective study assessing the efficacy and safety of conversion from twice-daily tacrolimus to once-daily prolonged-release tacrolimus in living donor LT recipients. Adherence was evaluated during outpatient visits after tacrolimus conversion, as well as acute rejection, graft loss, or patient death after Tac conversion

Shin M, et al. (2018). Once-daily, prolonged-release tacrolimus vs twice-daily, immediate-release tacrolimus in de novo living-donor liver transplantation: A Phase 4, randomized, open-label, comparative, single-center study. Clin Transplant. 2018;32(9):e13376. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/30098071

- Randomized, open-label, comparative, single-center, Phase 4, 24-week study comparing pharmacokinetics, safety, and efficacy of once-daily, prolonged-release tacrolimus with twice-daily, immediate-release tacrolimus in adult de novo living-donor liver transplant recipients in Korea.

Kim JM,et al. (2016). Conversion of once-daily extended-release tacrolimus is safe in stable liver transplant recipients: A randomized prospective study. Liver Transpl. 2016 Feb;22(2):209-16. Retrieved from https://pubmed.ncbi.nlm.nih.gov/26360125/.

- Evaluated the safety and efficacy of conversion from BID TAC to daily TAC ER in this randomized, prospective, controlled study included 91 patients who underwent liver transplant with data for at least 1 year. No incidences of BPAR, graft failure, or death were reported in either group at 24 weeks. Median TAC serum levels were 20% in conversion to ER TAC group. Liver function tests and renal function remained similar amongst groups.

Senft JD, et al. (2015). A Retrospective Comparison of Mycophenolate Mofetil with Low-Exposure Cyclosporine Versus Standard Cyclosporine Therapy in De Novo Liver Transplant Patients. Ann Transplant. 2015 Sep 12;20:539-43. Retrieved from https://pubmed.ncbi.nlm.nih.gov/26364728/.

- Evaluated 28 patients receiving CSA + MMF. Patients were characterized as low-exposure CSA <80 ng/mL trough vs standard exposure >80 ng/mL. BPAR occurred in 3 low-exposure CSA patients and 4 graft failures occurred. No difference in renal function occurred for patients with adequate baseline renal function. In patients with poor renal function at time of transplant, low-exposure CSA was favored.

Muduma G, et al. (2016). Systematic Review and Meta-Analysis of Tacrolimus versus Ciclosporin as Primary Immunosuppression After Liver Transplant. PLoS One. 2016 Nov 3;11(11):e0160421. Retrieved from https://pubmed.ncbi.nlm.nih.gov/27812112/.

- Systematic and meta-analysis identifying RCTs for TAC vs CSA between 1/2000-8/2014. TAC was associated with significantly less mortality and superior with regards to hypertension. TAC was inferior in regards to NODAT. No different in graft loss or acute rejection amongst groups.

Liu Z, et al. (2014). Tacrolimus-based versus cyclosporine-based immunosuppression in hepatitis C virus-infected patients after liver transplantation: a meta-analysis and systematic review. PLoS One. 2014 Sep 8;9(9):e107057. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4157850/.

- Meta-analysis evaluating TAC vs CSA regimens used in HCV patient after liver transplant. Mortality and graft loss were similar amongst groups. HCV recurrence, re=\-transplantation, and biopsies with histological presence of HCV wee similar amongst groups. TAC and CSA are effective regimens post-transplant.

Alloway RR, et al. (2014). Conversion from twice daily tacrolimus capsules to once daily extended-release tacrolimus (LCP-Tacro): phase 2 trial of stable liver transplant recipients. Liver Transpl. 2014 May;20(5):564-75. Retrieved from https://pubmed.ncbi.nlm.nih.gov/24493215/.

- Phase 2 trial transitioning patients from BID AC to LCPT. Mean conversion ratio was 0.71. AUC exposure was consistent at lower conversion dose. Six related ADEs and 1 possible rejection were seen. LCPT displayed significantly lower peak and peak-trough fluctuations.

Levy G, et al. (2014). REFINE: a randomized trial comparing cyclosporine A and tacrolimus on fibrosis after liver transplantation for hepatitis C. Am J Transplant. 2014 Mar;14(3):635-46. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24456049.

- Multicenter, prospective, randomized, trial evaluating fibrosis development 12 months post-transplant for hepatitis C virus cirrhosis in 356 liver transplant recipients receiving either cyclosporine or tacrolimus. Fibrosis score >2 at month 12 was similar among both groups.

Yano I, et al. (2012). Significance of trough monitoring for tacrolimus blood concentration and calcineurin activity in adult patients undergoing primary living-donor liver transplantation. Eur J Clin Pharmacol. 2012 Mar;68(3):259-66. Retrieved from https://pubmed.ncbi.nlm.nih.gov/21969228/.

- Tacrolimus blood concentrations were evaluated in 14 living-donor liver transplant patients early post-transplant. Blood samples were taken at 1, 2, 4, 8, and 12 h after the morning administration of tacrolimus on POD 6 or 8 (at 1 week) and POD 20 or 22 (at 3 weeks). This study found that clearance of tacrolimus significantly increased at 3 weeks post-transplant vs 1 week. Trough concentrations did not differ. Each sampling point except 1-hour post-dose correlated well with AUC_{0-12}.

Kong Y, et al. (2011). Calcineurin-inhibitor minimization in liver transplant patients with calcineurin-inhibitor-related renal dysfunction: a meta-analysis. PLoS One. 2011;6(9):e24387. Retrieved from https://pubmed.ncbi.nlm.nih.gov/21931704/.

- Meta-analysis evaluating CNI trials. This found a significantly improved GFR in CNI minimization trials, SCr was minimally improved, but CrCl was unchanged. No differences in BPAR was seen and potential higher incidence of infections in the CNI minimization group.

Boudjema K, et al. (2011). Reduced-dose tacrolimus with mycophenolate mofetil vs. standard-dose tacrolimus in liver transplantation: a randomized study. Am J Transplant. 2011 May;11(5):965-76. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/21466650.

- The prospective, randomized, multicenter trial evaluated the impact of reduced-dose tacrolimus in combination with mycophenolate mofetil (experimental) compared to standard dose tacrolimus (control) in 195 liver transplant recipients. Rate of acute graft rejection and occurrence of renal dysfunction, arterial hypertension, or diabetes were lower in the experimental group.

Fischer L, et al. (2011). Pharmacokinetics for once-daily versus twice-daily tacrolimus formulations in de novo liver transplantation: a randomized, open-label trial. Liver Transpl. 2011 Feb;17(2):167-77. Retrieved from https://pubmed.ncbi.nlm.nih.gov/21280190/.

- 6-week, randomized, phase 2, multicenter, open-label, prospective trial in primary liver transplant recipients investigating tacrolimus daily vs BID regimens. At equivalent doses AUC was 50%

lower in daily vs BID group on day 1, by day 14 AUC was comparable le amongst treatment options. No changes in ADEs were seen.

Neuberger JM, et al. (2009). Delayed introduction of reduced-dose tacrolimus, and renal function in liver transplantation: the 'ReSpECT' study. Am J Transplant. 2009 Feb;9(2):327-36. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19120077.

- Prospective, randomized trial evaluating standard dose tacrolimus in combination with corticosteroids (n=183); reduced-dose tacrolimus, mycophenolate mofetil (MMF), and corticosteroids (n=170); and daclizumab induction with delayed introduction of reduced-dose tacrolimus, MMF, and corticosteroids (n=172) in liver transplant recipients who were without renal dysfunction in the pre-transplant setting. Estimated glomerular filtration rate decreased the least in the daclizumab induction group. Patient and graft survival were similar among all groups.

Beckebaum S, et al. (2009). Combined mycophenolate mofetil and minimal dose calcineurin inhibitor therapy in liver transplant patients: clinical results of a prospective randomized study. Transplant Proc. 2009 Jul-Aug;41(6):2567-9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19715976.

- Liver transplant recipients with chronic renal dysfunction are randomized to receive either calcineurin inhibitor therapy (N=30) or mycophenolate mofetil (MMF) in combination with reduced dose calcineurin inhibitor therapy (N=60). Serum creatinine significantly decreased and estimated glomerular filtration rate increased in the MMF group.

Moench C, et al. (2007). Tacrolimus monotherapy without steroids after liver transplantation--a prospective randomized double-blinded placebo-controlled trial. Am J Transplant. 2007 Jun;7(6):1616-23. Retrieved from https://pubmed.ncbi.nlm.nih.gov/17511685/.

- Prospective, randomized, double-blind, placebo-controlled trial of 110 liver transplant patients who were given tacrolimus without induction, 14 days of MP were given then patients were blinded to placebo vs steroid continuance. Steroids were stopped at 6 months. No differences patient survival, BPAR, CMV, HTN. Chronic rejection was seen in 2 patients in the placebo group. NODAT and hyperlipidemia was seen more frequently in the steroid group.

Levy G, et al (2006). 12-month follow-up analysis of a multicenter, randomized, prospective trial in de novo liver transplant recipients (LIS2T) comparing cyclosporine microemulsion (C2 monitoring) and tacrolimus. Liver Transpl. 2006 Oct;12(10):1464-72. Retrieved from https://pubmed.ncbi.nlm.nih.gov/17004259/.

- Open-label, multi-center trial, patients were randomized to receive CSA w/ C2 monitoring vs TAC with trough monitoring. Steroids were given without AZA. Graft survival, renal function, and HCV recurrence were similar amongst groups. Fewer mortality and graft loss for HCV patients occurred in the CSA vs TAC group. TAC patients required more anti-hyperglycemic therapies.

McAlister VC, et al. (2006). Cyclosporin versus tacrolimus as primary immunosuppressant after liver transplantation: a meta-analysis. Am J Transplant. 2006 Jul;6(7):1578-85. Retrieved from https://pubmed.ncbi.nlm.nih.gov/16827858/.

- Systematic review of RCTs to evaluate benefit and harmful effects of cyclosporine vs tacrolimus in liver transplant patients. Mortality, graft failure, and BPAR at 1-year were significantly reduced in the tacrolimus group.

Tanaka K, et al. (2005). Comparison of cyclosporine microemulsion and tacrolimus in 39 recipients of living donor liver transplantation. Liver Transpl. 2005 Nov;11(11):1395-402. Retrieved from https://pubmed.ncbi.nlm.nih.gov/16237691/.

- Compared C2 monitoring for cyclosporine to tacrolimus based immunosuppression in living liver transplant patients. This was a 6-month, randomized, prospective, multicenter, open-label study, patients were randomized to CSA + steroids or TAC + steroids. At 6 months, 9% of patients in CSA group lost graft and 19% in tacrolimus group, this was not statistically significant. BPAR was seen in 4 CSA patients and 5 TAC patients. C2 CSA monitoring and TAC trough monitoring seem effective.

González MG, et al. (2005). An open, randomized, multicenter clinical trial of oral tacrolimus in liver allograft transplantation: a comparison of dual vs. triple drug therapy. Liver Transpl. 2005 May;11(5):515-24. Retrieved from https://pubmed-ncbi-nlm-nih-gov/15838889/.

- Open-label, multicenter, prospective, and randomized trial was performed to assess efficacy and safety of TAC + steroids vs TAC + AZA + steroids. BPAR and HCV positive status was higher in the TAC + steroid group. 24-month graft and patient survival was decreased in TAC + AZA + steroids compared to TAC + steroids but this was not statistically significant.

Greig P, et al. (2003). Early steroid withdrawal after liver transplantation: the Canadian tacrolimus versus microemulsion cyclosporin A trial: 1-year follow-up. Liver Transpl. 2003 Jun;9(6):587-95. Retrieved from https://pubmed-ncbi-nlm-nih-gov/12783400/.

- Safety and efficacy of early steroid withdrawal in patients on TAC or micro CSA. Eligibility criteria for steroid withdrawal included freedom from acute rejection for a minimum of 3 months, and

prednisone <0.15 mg/kg/d. At 1 year, 75% of TAC and 63% of CSA patients were steroid-free. Patient survival and BPAR were similar amongst groups but graft survival was significantly higher in the TAC group. Renal function, ADEs, and infection were similar amongst both groups.

Jain A, et al. (2001). A prospective randomized trial of tacrolimus and prednisone versus tacrolimus, prednisone and mycophenolate mofetil in primary adult liver transplantation: a single center report. Transplantation. 2001 Sep 27;72(6):1091-7. Retrieved from https://pubmed-ncbi-nlm-nih-gov/11579306/.

- Open-label, single-center, prospective randomized trial study evaluating efficacy and toxicity of TAC + steroids vs TAC + steroids + MMF

Wiesner R. (1998). A long-term comparison of tacrolimus (FK506) versus cyclosporine in liver transplantation: a report of the United States FK506 Study Group. Transplantation. 1998 Aug 27;66(4):493-9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9734494.

- Randomized, multicenter trial evaluating tacrolimus compared to cyclosporine maintenance therapy in 529 liver transplant recipients. Biopsy-proven acute rejection at one year following transplant was significantly lower in the tacrolimus group. There was no difference in patient survival at 5 years following transplant.

U.S. Multicenter FK506 Liver Study Group. (1994). A comparison of tacrolimus (FK 506) and cyclosporine for immunosuppression in liver transplantation. N Engl J Med. 1994 Oct 27;331(17):1110-5. Retrieved from https://pubmed.ncbi.nlm.nih.gov/7523946/.

- Open-label, randomized, multicenter trial to compare the efficacy and safety of TAC vs CSA in 478 adults, 51 children. Patient and graft survival were similar among groups at 1 year. BPAR, corticosteroid-resistant rejection, and refractory rejection were lower in the TAC group at 1 year. Overall, tacrolimus was associated with significantly fewer episodes of acute, corticosteroid-resistant, or refractory rejection, but substantially more adverse events requiring discontinuation of the drug.

Todo S, et al. (1994). Single-center experience with primary orthotopic liver transplantation with FK 506 immunosuppression. Ann Surg. 1994 Sep;220(3):297-308; discussion 308-9. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1234382/.

- Compared TAC vs CSA, from 8/1989-12/1993 1391 received TAC which was compared to a historical control of 1213 patients on CSA. Overall survival was significantly higher in the TAC group-year graft survival was significantly higher in the TAC group and 4. Re-transplantation rates were lower in the TAC group. TAC was a better immunosuppresive agent than CSA.

3.2.2 Antimetabolites

Chiang HY, et al. (2023). Impact of sirolimus versus mycophenolate mofetil (MMF) on kidney function after calcineurin inhibitor (CNI) dose reduction in liver transplant recipients. Pharmaceuticals. 2023 Jul;16(8):1087. Retrieved from https://pubmed.ncbi.nlm.nih.gov/37631002/.

- Single-center, retrospective study of acute kidney disease (AKD) in patients who underwent living donor liver transplant. The use of MMF or sirolimus in combination with reduced dose CNI had similar risks of developing AKD. Sirolimus had a higher risk of developing >30% decline in eGFR than MMF.

Park J, et al. (2023). A Multicenter, Randomized, Open-Label Study to Compare the Efficacy and Safety of Tacrolimus and Corticosteroids in Combination With or Without Mycophenolate Mofetil in Liver Transplantation Recipients Infected With Hepatitis B Virus. Transplant Proc. 2023 Mar;55(2):387-395. Retrieved from https://pubmed.ncbi.nlm.nih.gov/36822884/.

- Multicenter, randomized, phase IV study with biopsy-proven acute cellular rejection occurring in 3.4 % of the study group containing MMF and not found in the control group, p = 0.468. Hepatitis B virus recurrence occurred in one patient in the control group. Serious adverse events did not differ between the two groups.

Zeng Q, et al. (2021). Mycophenolate mofetil enhances the effects of tacrolimus on the inhibitory function of regulatory T cells in patients after liver transplantation via PD-1 and TIGIT receptors. Immunopharmacol Immunotoxicol. 2021 Apr;43(2):239-246. Retrieved from https://pubmed.ncbi.nlm.nih.gov/33657960/.

- Investigated the effects of Tacrolimus and mycophenolate mofetil (MMF) on the inhibitory function of Tregs and explored the regulatory mechanism in patients after liver transplantation. Tacrolimus and MMF enhanced the function of Tregs by synergistically affecting PD-1 and TIGIT in liver transplant patients.

Tsai Y, et al. (2021). Effect of Mycophenolate Mofetil Therapy on Recurrence of Hepatocellular Carcinoma after Liver Transplantation: A Population-Based Cohort Study. J Clin Med. 2021 Apr 7;10(8):1558. Retried from https://pubmed.ncbi.nlm.nih.gov/33917215/.

- Cohort study of 1250 LTRs with HCC on the impact of mycophenolate on HCC recurrence. Increased HCC recurrence rates were observed (p = 0.03) following MMF administration; no

significant increase was demonstrated following cyclosporine, tacrolimus, or sirolimus administration. Significantly increased HCC recurrence rate following MMF administration with cumulative defined daily dose (cDDD) > 0.4893 compared with cDDD ≤ 0.4893 or no administration of MMF ($p < 0.0001$).

Tustumi F, et al. (2021). Safety and effectiveness of mycophenolate mofetil associated with tacrolimus for liver transplantation immunosuppression: A systematic review and meta-analysis of randomized controlled trials. Clinics (Sao Paulo). 2021 Mar 8;76:e2597. Retrieved from https://pubmed.ncbi.nlm.nih.gov/33681947/.

- This review aimed to evaluate the effectiveness and safety of tacrolimus associated with mycophenolate mofetil (MMF) in patients undergoing liver transplantation. Eight randomized trials were included. Patients undergoing liver transplantation who received tacrolimus plus MMF had similar adverse events when compared to patients receiving other evaluated immunosuppressive regimens and had a lower risk of acute rejection than those receiving in the monotherapy tacrolimus regimen.

Aguiar D, et al. (2017). Conversion from Calcineurin Inhibitor-Based Immunosuppression to Mycophenolate Mofetil in Monotherapy Reduces Risk of De Novo Malignancies After Liver Transplantation. Annals of transplantation. 2017 Mar 17;22:141-147. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/28302995.

- Retrospective review of adult liver transplant recipients at a Spanish center evaluating malignancy rates in patients maintained a mycophenolate monotherapy regimen. Patients converted to an immunosuppression regimen of mycophenolate monotherapy experienced less de novo malignancy, non-melanoma skin cancer and other malignancies compared to recipients with maintenance immunosuppression with calcineurin inhibitors.

Kaltenborn A, et al. (2013). Mycophenolate mofetil in liver transplantation: a review. Ann Transplant. 2013 Dec 18;18:685-96. Retrieved from https://pubmed.ncbi.nlm.nih.gov/24346057/.

- Review of properties, trials, and rationale to use mycophenolate in liver transplant.

Rodríguez-Perálvarez M, et al. (2012). Tacrolimus trough levels, rejection and renal impairment in liver transplantation: a systematic review and meta-analysis. Am J Transplant. 2012 Oct;12(10):2797-814. Retrieved from https://pubmed.ncbi.nlm.nih.gov/22703529/.

- Meta-analysis evaluating tacrolimus levels and rate of renal dysfunction and BPAR. Tacrolimus level current clinical consensus is > 10 ng/mL. Higher tacrolimus levels were associated with

renal dysfunction at 1 year with no increased incidence of BPAR (< 10 ng/mL tacrolimus level). Study determined tacrolimus levels of 6-10 ng/mL are appropriate.

Sańko-Resmer J, et al. (2012). Renal function, efficacy and safety postconversion from twice- to once-daily tacrolimus in stable liver recipients: an open-label multicenter study. Transpl Int. 2012 Mar;25(3):283-93. Retrieved from https://pubmed.ncbi.nlm.nih.gov/22239105/.

- Multicenter, open-label, phase III study evaluating renal function, safety, and efficacy with liver transplant patients converted from BID to once daily tacrolimus (Advagraf). 74.5% of patient did not require a dose conversion when transitioning to daily dosing, trough levels were reduced by 15% without any BPAR. Renal function demonstrated non-inferiority. Graft and patient survival were 100%. Low incidence of ADEs. Advagraf was save and effective for immunosuppression in liver transplant patients compared to BID tacrolimus.

Schmeding M, et al. (2011). Mycophenolate mofetil monotherapy in liver transplantation: 5-year follow-up of a prospective randomized trial. Transplantation. 2011 Oct 27;92(8):923-9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/21832958.

- The prospective, randomized trial evaluates maintenance immunosuppression consisting of either calcineurin inhibitor monotherapy or mycophenolate mofetil (MMF) monotherapy in 150 liver transplant recipients. Although no significant difference in acute rejection was identified between groups, the MMF monotherapy group had a trend to higher rejection rates. Chronic rejection was absent in both study groups and 5-year survival was similar among both groups.

Nashan B, et al. (2009). Pharmacokinetics, efficacy, and safety of mycophenolate mofetil in combination with standard-dose or reduced-dose tacrolimus in liver transplant recipients. Liver Transpl. 2009 Feb;15(2):136-47. Retrieved from https://pubmed.ncbi.nlm.nih.gov/19177449/.

- Randomized patients to receive standard tacrolimus 10-15 ng/mL goal vs reduced 5-8 ng/mL goal in combination with IV MMF followed by oral MMF + steroids. Pharmacokinetic sampling was performed after the last intravenous MMF dose, after the first oral MMF dose, and at selected times over 52 weeks. No significant differences between the tacrolimus standards vs reduced were seen in dose-normalized MPA values of the time to the maximum plasma concentration, maximum plasma concentration, or area under the curve.

Jain A, et al. (2008). Potential immunological advantage of intravenous mycophenolate mofetil with tacrolimus and steroids in primary deceased donor liver transplantation and live donor liver transplantation without antibody induction. Liver Transpl. 2008 Feb;14(2):202-9. Retrieved from https://pubmed.ncbi.nlm.nih.gov/18236395/.

- Study conducted to examine the rate of BPAR with TAC + IV MMF + steroids in liver transplant patients during 2005. Steroid bolus and rejection treatment only required in 6.1% of patients at 12 months (total 130 patients).

Jain A, et al. (2002). A prospective randomized trial of mycophenolate mofetil in liver transplant recipients with hepatitis C. Liver Transpl. 2002 Jan;8(1):40-6. Retrieved from https://pubmed.ncbi.nlm.nih.gov/11799484/.

- Evaluated use of MMF in HCV patients to determine if it is associated with a different rate of recurrence than other agents. Patients were randomized to received TAC + steroids vs TAC + steroids + MMF from 8/1995-5/1998. Patient survival, graft survival, and HCV recurrence were similar amongst groups.

Wiesner R, et al. (2001). A randomized double-blind comparative study of mycophenolate mofetil and azathioprine in combination with cyclosporine and corticosteroids in primary liver transplant recipients. Liver Transpl. 2001 May;7(5):442-50. Retrieved from https://pubmed.ncbi.nlm.nih.gov/11349266/

- Randomized double-blind trial evaluating liver transplant recipients treated with MMF (n – 278) or AZA (n = 287), both in combination with cyclosporine and corticosteroids. The incidence of acute rejection or graft loss was significantly higher in AZA patients (47.7% vs 38.5%, p <0.03) Steroid-resistant rejection occurred in 8.2% of AZA patients versus 3.8% in MMF patients (P <.02). Patient and graft survival rates at 1 year post-transplantation were similar.

Herrero JI, et al. (1999). Conversion of liver transplant recipients on cyclosporine with renal impairment to mycophenolate mofetil. Liver Transpl Surg. 1999 Sep;5(5):414-20. Retrieved from https://pubmed.ncbi.nlm.nih.gov/10477843/.

- Eleven patients with SCr > 1.5 mg/dL, normal liver graft function, and rejection free period of 1 year started MMF at 1000 mg PO BID while reducing CSA doses slowly. At the end of follow-up, 7 patients were off CSA, 2 were on reduced doses of CSA, 2 patients developed mild rejection and changed to TAC. SCr decreased in 7 patients free of CSA. MMF may allow for CSA reduction or DC to improve renal function.

Gavlik A, et al. (1997). Mycophenolate mofetil rescue therapy in liver transplant recipients: an extended follow-up. Transplant Proc. 1997 Nov;29(7):2971-2. Retrieved from https://pubmed.ncbi.nlm.nih.gov/9365633/.

- Patients were able to receive MMF in setting of rejection or steroid related toxicities between 9/1-11/30/1995 for 6 months. At the end of the trial some patients were still on MMF due to physician

preference, ongoing rejection, or to reduce tacrolimus/steroid doses. MMF may be a useful agent in controlling rejection and drug toxicities.

3.2.3 mTOR Inhibitors

Dumortier J, et al. (2024). Conversion from twice-daily everolimus to once-daily sirolimus in long-term stable liver transplant recipients. Transpl Immunol. 2024;83:102014. Retrieved from https://pubmed.ncbi.nlm.nih.gov/38395088/.

- Prospective, single-center trial that converted 108 stable liver transplant patients at a median of 14.8 years post-transplant from twice-daily everolimus to once-daily sirolimus. A 1:1 conversion was made with no sirolimus loading dose, followed by dose adjustment based on troughs. Sirolimus levels at 3 months post-conversion were 66% higher than pre-conversion everolimus levels using this 1:1 dosing conversion. By the end of follow-up, few patients (8.3%) had switched back to everolimus, mostly due to diarrhea. No cases of worsening renal function or rejection were observed. 87.1% of patients reported they preferred the sirolimus regimen.

De Simone P, et al. (2024). Everolimus Mitigates the Risk of Hepatocellular Carcinoma Recurrence after Liver Transplantation. Cancers (Basel). 2024;16(7):1243. Retrieved from https://pubmed.ncbi.nlm.nih.gov/38610921.

- Single-center retrospective review of 577 patients transplanted for HCC receiving either everolimus (+/- tacrolimus) or tacrolimus (+/- mycophenolate) for immunosuppression. Groups were balanced using inverse probability of treatment weighting. Everolimus could be introduced starting 1 month post-transplant to prevent HCC recurrence or due to tacrolimus adverse effects. After HCC recurrence, patients were switched to everolimus monotherapy where possible. Patients treated with tacrolimus had higher rates of death and HCC recurrence and were more likely to have multi-organ HCC involvement after recurrence. In the everolimus group, patients with HCC recurrence were more commonly on everolimus + tacrolimus combination therapy rather than everolimus monotherapy, had later everolimus initiation (median 52 vs. 30 days), shorter duration of everolimus treatment, and lower everolimus levels.

Zhang L, et al. (2024). mTOR inhibitor reduces nontumour-related death in liver transplantation for hepatocellular carcinoma. Mol Biomed. 2024;5(1):9. Retrieved from https://pubmed.ncbi.nlm.nih.gov/38461206/.

- Multicenter, retrospective trial comparing sirolimus and sirolimus-free immunosuppressive regimens after liver transplantation for hepatocellular carcinoma. Overall survival was not significantly different between groups over a median of 47 months of follow-up, however survival

was significantly better in the subgroup of patients who exceeded the Milan criteria and were treated with sirolimus-containing compared to sirolimus-free regimens. The sirolimus group experienced fewer cases of non-tumour related causes of death compared to the sirolimus-free group.

Mulder, M et al. (2023). Health-related Quality of Life and Fatigue in Liver Transplant Recipients Receiving Tacrolimus Versus Sirolimus-based Immunosuppression: Results from a Randomized Trial. Transplantation. 2023 December; 107(12)2545-2553. Retrieved from https://pubmed.ncbi.nlm.nih.gov/38010321/

- Multicenter, randomized, controlled trial with liver transplant patients randomized to once-daily normal-dose tacrolimus or once daily combination therapy of low-dose sirolimus and tacrolimus. HRQoL and Fatigue Severity Score (FSS) were not significantly different between the groups. Patients reported the least problems in self-care and anxiety/depression and the most problems in pain/discomfort.

Cholongitas E, et al. (2023). Safety and efficacy of everolimus initiation from the first month after liver transplantation: A systematic review and meta-analysis. Clin Transplant. 2023 May;37(5):e14957. Retrieved from https://pubmed.ncbi.nlm.nih.gov/36880482/.

- This review and meta-analysis included seven studies published between 2010 and 2022. Everolimus therapy was initiated in 512 patients compared to calcineurin inhibitors in 494 patients. Overall, authors did not observe differences in rates of biopsy-proven acute rejection, hepatic artery thrombosis, or hepatocellular carcinoma recurrence.

Mulder MB, et al. (2023). Three-year results of renal function in liver transplant recipients on low-dose sirolimus and tacrolimus: a multicenter, randomized, controlled trial. Liver Transpl. 2023 Feb;29(2):184-195. Retrieved from https://pubmed.ncbi.nlm.nih.gov/36668691/.

- Multi-center study addressing whether low-dose sirolimus and low-dose extended-release tacrolimus compared to normal-dose extended-release tacrolimus results in difference in renal function and comparable rates of rejection at 36 months post-transplantation. Chronic kidney disease (CKD) was similar between the 2 groups, but eGFR was higher in the interventional group (mean eGFR 73.1±15 vs. 67.6±16 mL/min/1.73 m2, p=0.02). There were no differences in safety outcomes between groups.

Saliba F, et al. (2022). Five-year outcomes in liver transplant patients receiving everolimus with or without a calcineurin inhibitor: Results from the CERTITUDE study. Liver Int. 2022 Nov;42(11):2513-2523. Retrieved from https://pubmed.ncbi.nlm.nih.gov/35962772/.

- Reports 5 year outcomes of CERTITUDE trial which was an observational study comparing impacts of EVR vs TAC in liver transplant patients. Renal function preservation was more prominent in the EVR group but so was BPAR (mostly mild). No changes in overall renal function changes, cancer rates, or MACE occurred.

Sapisochin G, et al. (2022). Long-term effects of everolimus-facilitated tacrolimus reduction in living-donor liver transplant recipients with hepatocellular carcinoma. Ann Transplant. 2022 Nov; 27:e937988. Retrieved from https://pubmed.ncbi.nlm.nih.gov/36411723/.

- 117 living donor liver transplant recipients with history of primary hepatocellular carcinoma were included in this multicenter study. The interventions were either everolimus + reduced dose tacrolimus (n=56) or standard dose tacrolimus (n=61). Initial tacrolimus trough goals were 3-5 ng/mL vs 8-12 ng/mL in the reduced dose vs standard dose groups, respectively. No significant difference was observed in rates of HCC recurrence between groups; however, improved renal function was observed in the everolimus + reduced dose tacrolimus group.

Yan X, et al. (2022). Sirolimus or everolimus improves survival after liver transplantation for hepatocellular carcinoma: a systemic review and meta- analysis. Liver Transpl. 2022 Jun; 28(6):1063-1077. Retrieved from https://pubmed.ncbi.nlm.nih.gov/34919773/.

- In this review and meta-analysis, the primary endpoint was overall survival at 1, 2, 3, and 5 years post-transplant. Sirolimus or everolimus-based regimens were compared to those that lacked mTOR inhibitors. Overall survival was significantly improved in the mTOR inhibitor group starting at 2 years post-transplant.

Gomez-Bravo M, et al. (2022). Effects of everolimus plus minimized tacrolimus on kidney function in liver transplantation: REDUCE, a prospective, randomized controlled study. Rev Esp Enferm Dig. 2022 Jun; 114(6):335-342. Retrieved from https://pubmed.ncbi.nlm.nih.gov/35469409/.

- This was a phase III trial with interventions of everolimus + reduced dose tacrolimus (trough ≤ 5 ng/mL) vs MMF + standard dose tacrolimus (trough 6-10 ng/mL). No differences in clinical outcomes (acute rejection, death) were observed. Renal function, calculated as eGFR, increased throughout the study period of 52 weeks in the everolimus group but in not the MMF group.

Kang I, et al. (2021). Impact of everolimus on survival after liver transplantation for hepatocellular carcinoma. Clin Mol Hepatol. 2021 Oct;27(4):589-602. Retrieved from https://pubmed.ncbi.nlm.nih.gov/34293849/.

- Retrospective study evaluating 303 liver transplant recipients to investigate whether everolimus (EVR) affects long-term survival after liver transplantation (LT) in patients with hepatocellular carcinoma (HCC). Combined with CNIs, EVR has the potential to prolong long-term survival in patients undergoing LT for HCC.

Nashan B, et al. (2021). Early Everolimus-Facilitated Reduced Tacrolimus in Liver Transplantation: Results From the Randomized HEPHAISTOS Trial. Liver Transpl. 2022 Jun;28(6):998-1010. Retrieved from https://pubmed.ncbi.nlm.nih.gov/34525259/.

- 12-month, multicenter, controlled study evaluating early initiation of everolimus post-liver transplant. Patients randomized to receive TAC + steroids vs TAC + EVR at 7-21 days post-transplant. eGFR was numerically higher in the EVR group, eGFR change was also higher in the EVR group. ADEs and BPAR were similar amongst groups. Lower portion of patients discontinued EVR + TAC compared to tacrolimus alone.

Zhao Y, et al. (2021). Trends of rapamycin in survival benefits of liver transplantation for hepatocellular carcinoma. World J Gastrointest Surg. 2021 Sep 27;13(9):953-966. Retrieved from https://pubmed.ncbi.nlm.nih.gov/34621472/.

- Review discussing advances in mTOR inhibitor research in patients undergoing liver transplant for HCC.

Lee SG, et al. (2021). Efficacy and safety of everolimus with reduced tacrolimus in liver transplant recipients: 24-month results from the pooled analysis of 2 randomized controlled trials. Transplantation. 2021 Jul 1;105(7):1564-1575. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33741847/.

- Data from 2 randomized liver transplant trials (N = 772; H2304 [deceased donor, n = 488], H2307 [living donor, n = 284]) were pooled to further evaluate the efficacy and safety of everolimus with reduced tacrolimus (EVR + rTAC) versus standard tacrolimus (sTAC) regimen at month 24. EVR + rTAC versus sTAC showed comparable efficacy and safety with significantly better renal function, particularly in patients with normal/mildly decreased renal function (CKD stage 1/2) at randomization and a trend toward lower HCC recurrence in patients transplanted with HCC beyond Milan at month 24.

Kadry Z, et al. (2021). Renal protective effect of everolimus in liver transplantation: A prospective randomized open-label trial. Transplant Direct. 2021 Jun 8;7(7):e709. Retrieved from https://pubmed.ncbi.nlm.nih.gov/34124345/.

- Prospective, randomized, open-label trial comparing everolimus (EVR) and mycophenolic acid (MPA) with CNI and MPA immunosuppression. EVR with MPA resulted in significant long-term improvement in renal function and quality of life at 24 months after liver transplantation compared with standard CNI with MPA immunosuppression.

Schnitzbauer AA, et al. (2020). mTOR Inhibition Is Most Beneficial After Liver Transplantation for Hepatocellular Carcinoma in Patients With Active Tumors. Ann Surg. 2020 Nov; 272(5):855-862. Retrieved from https://pubmed.ncbi.nlm.nih.gov/32889867/.

- Data from 508 patients of the intention-to-treat SiLVER-trial analysis were included in exploratory univariate and multivariate models for overall survival (OS), DFS and a competing risk analysis for HCC recurrence. mTOR-inhibitor treatment with sirolimus for ≥3 months improves outcomes in LT for HCC, especially in patients with alpha-fetoprotein-evidence of higher tumor activity, advocating particularly for mTOR inhibitor use in this subgroup of patients.

Nogueras López F, et al. (2020). Impact of Everolimus-based Immunosuppression on Renal Function in Liver Transplant Recipients. Transplant Proc. 2020 Mar;52(2):556-558. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/32035673.

- Single-center, retrospective study evaluating renal function of 66 liver transplant recipients who received de novo everolimus in combination with tacrolimus minimization or withdrawal for baseline renal dysfunction. With 24 month follow-up, eGFR was significantly and persistently greater than baseline eGFR.

Grigg SE, et al. (2019). Systematic review with meta-analysis: sirolimus- or everolimus-based immunosuppression following liver transplantation for hepatocellular carcinoma. Aliment Pharmacol Ther. 2019;49(10):1260-1273. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/30989721.

- Systematic review with meta-analysis: sirolimus- or everolimus-based immunosuppression following liver transplantation for hepatocellular carcinoma

Saliba F, et al. (2019). Early Switch From Tacrolimus to Everolimus After Liver Transplantation: Outcomes at 2 Years. Liver Transpl. 2019 Dec;25(12):1822-1832. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/31631501.

- Two-year follow up of the SIMCER trial (early conversion from CNI to everolimus in combination with mycophenolate and prednisone). Continuation of everolimus was associated with preservation of renal function; however, only approximately 50% of patients were able to continue to everolimus therapy due to safety or efficacy concerns.

Wasilewicz MP, et al. (2019). Immunosuppressive treatment with everolimus in patients after liver transplant: 4 years of single-center experience. Pol Arch Intern Med. 2019 Oct 30;129(10):686-691. Retrieved from https://pubmed.ncbi.nlm.nih.gov/31502586/.

- Prospective, single-center trial of 108 liver transplant patient w/ CNI goal 3-6 ng/mL + EVR goal 3-5 ng/mL. CNI was discontinued at 4 months, EVR target 6/12 ng/mL. EVR was monotherapy in 29.6% of patients or EVR + CNI 70.4%. EVR withdrawn in 33% of patients due to ADRs. SCr improved in patients after to 3 months.

Jeng LB, et al. (2018). Efficacy and safety of everolimus with reduced tacrolimus in living-donor liver transplant recipients: 12-month results of a randomized multicenter study. Am J Transplant. 2018;18(6):1435-1446. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/29237235.

- Randomized multicenter, open-label study evaluating 284 living-donor liver transplant patients starting everolimus + reduced tacrolimus or continue standard tacrolimus. The primary endpoint was treated BPAR, and graft loss or death at 12 months post-transplant.

Yee ML, et al. (2017). Use of everolimus in liver transplantation. World J Hepatol. 2017 Aug 18;9(23):990-1000. Retrieved from https://pubmed.ncbi.nlm.nih.gov/28878864/.

- Overview of EVR, use in liver transplant, and studies conducted with EVR use in liver transplant.

De Simone P, et al. (2017). Use of Everolimus in Liver Transplantation: Recommendations From a Working Group. Transplantation. 2017 Feb;101(2):239-251. Retrieved from https://pubmed.ncbi.nlm.nih.gov/27495768/.

- EVR recommendations by a national consensus group, based on Delphi methodology for use in liver transplant grouped by renal function, time to EVR introduction, CNI reduction/elimination and risk of graft rejection, anti-proliferative effects of EVR, and management of EVR side effects.

Charlton M, et al. (2017). Everolimus Is Associated With Less Weight Gain Than Tacrolimus 2 Years After Liver Transplantation: Results of a Randomized Multicenter Study. Transplantation. 2017;101(12):2873-2882. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/28817434.

- Randomized multi-center study of patients in one of the following groups (1) everolimus + reduced tacrolimus (2) tacrolimus control (3) Tacrolimus elimination. Post hoc analysis completed evaluating weight change at 12 and 24 months, as well as vital signs, lipids, and laboratory parameters at 12 and 24 months.

Saliba F, et al. (2017). Efficacy and Safety of Everolimus and Mycophenolic Acid With Early Tacrolimus Withdrawal After Liver Transplantation: A Multicenter Randomized Trial (SIMCER). Am J Transplant. 2017;17(7):1843-1852. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28133906

- Randomized multi-center open-label trial of de novo liver transplant recipients receiving either to everolimus with low-exposure tacrolimus discontinued by month 4 or to tacrolimus-based therapy, both with basiliximab induction and enteric-coated mycophenolate sodium with or without steroids. Everolimus was associated with a significant improvement in renal function compared with CNI at 28 weeks post-transplant, however, a higher incidence of treated biopsy-proven acute rejection was observed.

Tarantino G, et al. (2016). Oncological Impact of M-Tor Inhibitor Immunosuppressive Therapy after Liver Transplantation for Hepatocellular Carcinoma: Review of the Literature. Front Pharmacol. 2016 Oct 21;7:387. Retrieved from https://pubmed.ncbi.nlm.nih.gov/27818634/.

- Systematic literature review of studies analyzing the oncological role of mTORs after liver transplant for HCC.

Sterneck M, et al. (2016). Long-term follow-up of five yr shows superior renal function with everolimus plus early calcineurin inhibitor withdrawal in the PROTECT randomized liver transplantation study. Clin Transplant. 2016 Jun;30(6):741-8. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27160359.

- Five-year follow up of the PROTECT study (early conversion from CNI to everolimus vs CNI). Conversion to everolimus resulted in better renal function and comparable patient and graft outcomes with long-term follow up.

Hüsing A, et al. (2015). Long-Term Renal Function in Liver Transplant Recipients After Conversion From Calcineurin Inhibitors to mTOR Inhibitors. Ann Transplant. 2015 Nov 26;20:707-13. Retrieved from https://pubmed.ncbi.nlm.nih.gov/26608590/.

- Retrospective review of patients from 1996-2010 who were switched from CNI regimen to mTOR regimen. Within 6 weeks of switching eGFR increased by 5.6 mL/min [95% confidence interval 2.6-8.7 mL/min, p<0.001]. BPAR occurred in 4 patients (5.1%). Cholesterol increased within the first 12 months.

Mocchegiani F, et al. (2014). Tacrolimus and Everolimus de novo versus minimization of standard dosage of Tacrolimus provides a similar renal function at one year after liver transplantation: a case-control matched-pairs analysis. Ann Transplant. 2014 Oct 27;19:545-50. Retrieved from https://pubmed.ncbi.nlm.nih.gov/25347718/.

- Case-control study evaluating TAC only vs TAC + EVR regimens in liver transplant patients. Patient survival, eGFR trends, and BPAR was similar in both groups.

Cholongitas E, et al. (2014). Mammalian target of rapamycin inhibitors are associated with lower rates of hepatocellular carcinoma recurrence after liver transplantation: a systematic review. Transpl Int. 2014 Oct;27(10):1039-49. Retrieved from https://pubmed.ncbi.nlm.nih.gov/24943720/.

- Systematic review of association of mTOR and HCC recurrence post-liver transplant.

Sterneck M, et al. (2014). Everolimus and early calcineurin inhibitor withdrawal: 3-year results from a randomized trial in liver transplantation. Am J Transplant. 2014 Mar;14(3):701-10. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24502384.

- Prospective, randomized trial in 203 liver transplant recipients receiving either everolimus with corticosteroids or cyclosporine/tacrolimus with corticosteroids. Glomerular filtration rate was significantly higher in the everolimus group by month 35 following randomization. No difference in biopsy-proven acute rejection, graft loss and death was seen between groups.

Asrani SK, et al. (2014). De novo sirolimus and reduced-dose tacrolimus versus standard-dose tacrolimus after liver transplantation: the 2000-2003 phase II prospective randomized trial. Am J Transplant. 2014 Feb;14(2):356-66. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24456026.

- Phase II, multicenter, randomized trial in 222 liver transplant recipients who received either standard-dose tacrolimus with corticosteroids or sirolimus, reduced-dose tacrolimus, in combination with corticosteroids. Patient and graft survival were significantly lower in the sirolimus group. Similar rates of acute cellular rejection were seen among both study groups.

Zhe AX, et al. (2014). Effect of Everolimus on Survival in Advanced Hepatocellular Carcinoma After Failure of Sorafenib: The EVOLVE-1 Randomized Clinical Trial. JAMA. 2014;312(1):57–67. Retrieved from https://jamanetwork.com/journals/jama/fullarticle/1884577.

- Everolimus, 7.5 mg/d, or matching placebo, both given in combination with best supportive care and continued until disease progression or intolerable toxicity. Per the 2:1 randomization scheme, 362 patients were randomized to the everolimus group and 184 patients to the placebo group. Everolimus did not improve overall survival in patients with advanced hepatocellular carcinoma whose disease progressed during or after receiving sorafenib or who were intolerant of sorafenib.

Teperman L, et al. (2013). Calcineurin inhibitor-free mycophenolate mofetil/sirolimus maintenance in liver transplantation: the randomized spare-the-nephron trial. Liver Transpl. 2013 Jul;19(7):675-89. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/23775875.

- Mycophenolate mofetil (MMF) and sirolimus combination therapy (n=148) is compared to MMF and calcineurin inhibitor (CNI) combination therapy (n=145) for preserving renal function in liver transplant recipients. The sirolimus group had a significantly greater improvement in glomerular filtration rate and increased rates of biopsy-proven acute rejection compared to CNI group. Patient survival was similar between both groups.

Saliba F, et al. (2013). Renal function at two years in liver transplant patients receiving everolimus: results of a randomized, multicenter study. Am J Transplant. 2013 Jul;13(7):1734-45. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/23714399.

- Multicenter, prospective, randomized trial evaluating everolimus with reduced-dose tacrolimus; standard-dose tacrolimus; or tacrolimus elimination in 719 liver transplant recipients. Composite endpoint of biopsy-proven acute rejection, graft loss or death was similar in the reduced-dose tacrolimus and standard-dose tacrolimus groups at 24 months. Patients in the tacrolimus elimination group experienced higher rates of treated biopsy proven acute rejection.

Menon KV, et al. (2013). Meta-analysis: recurrence and survival following the use of sirolimus in liver transplantation for hepatocellular carcinoma. Aliment Pharmacol Ther. 2013 Feb;37(4):411-9. Retrieved from https://pubmed.ncbi.nlm.nih.gov/23278125/.

- Systematic review and meta-analysis on SRL use in liver transplant for HCC. Rates of HCC were lower in the SRL group compared to CNIs. Recurrence-free survival was improved in the SRL group at 1, 3, and 5 years. Overall survival was also improved in the SRL group.

Fischer L, et al. (2012). A randomized, controlled study to assess the conversion from calcineurin-inhibitors to everolimus after liver transplantation--PROTECT. Am J Transplant. 2012 Jul;12(7):1855-65. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22494671.

- Multicenter, open-label, RCT evaluating the effect of early conversion from CNI to everolimus (4 weeks post-transplant) on renal function in 203 liver transplant recipients. At 1 year post-transplant, there was no difference in renal function, acute rejection, graft loss, or mortality in patients who transitioned to everolimus compared with those who continued on CNI.

De Simone P, et al. (2012). Everolimus with Reduced Tacrolimus Improves Renal Function in De Novo Liver Transplant Recipients: A Randomzied Controlled Trial (H2304). Am J Transplant. 2012 Nov;12(11):3008-20. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22882750.

- Prospective, multicenter, open-label study comparing three immunosuppression regimens in de novo liver transplant recipients: (i) everolimus with tacrolimus elimination, (ii) everolimus with reduced-exposure tacrolimus, and (iii) standard exposure tacrolimus. Group ii and iii had a similar composite outcome of treated biopsy proven acute rejection (tBPAR), graft loss or death at 12 months but group ii had less tBPAR than group iii. Group ii had improved GFR compared to group iii but had more discontinuation due to adverse events.

Masetti M, et al. (2012). Early withdrawal of calcineurin inhibitors and everolimus monotherapy in de novo liver transplant recipients preserves renal function. Am J Transplant. 2010 Oct;10(10):2252-62. Retrieved from https://pubmed.ncbi.nlm.nih.gov/20486905/.

- Randomized trial to evaluate renal function in CSA followed by EVR monotherapy vs CSA alone. CSA wad given for the first 10 days followed by EVR in combo with CSA for up to day 30 vs CSA ± MMF. No difference in survival or graft failure. Renal function and freedom from CKD 3 or higher was better in the EVR group.

Abdelmalek MF, et al. (2012). Sirolimus conversion regimen versus continued calcineurin inhibitors in liver allograft recipients: a randomized trial. Am J Transplant. 2012 Mar;12(3):694-705. Retrieved from https://pubmed.ncbi.nlm.nih.gov/22233522/.

- Large prospectively, open-label, randomized trial evaluating CNI to SRL immunosuppression for renal function preservation. Abrupt conversion from CNI to SRL occurred around 6-144 months post-transplant in 393 patients. Renal function was not different between groups. Non-inferiority was not met for graft loss or death in the sirolimus group and a higher rate of BPAR and discontinuation due to side-effects was seen at 12 months.

Liang W, et al. (2012). Sirolimus-based immunosuppression in liver transplantation for hepatocellular carcinoma: a meta-analysis. Liver Transpl. 2012 Jan;18(1):62-9. Retrieved from https://pubmed.ncbi.nlm.nih.gov/21964956/.

- Meta-analysis to determine if SRL could improve patient survival and decrease risk of tumor recurrence in patients w/ pre-transplant HCC. SRL based regimens improved overall survival at 1 and 5 years. SRL based regimens decreased tumor recurrence.

Saliba F, et al. (2011). Conversion to everolimus in maintenance liver transplant patients: a multicenter, retrospective analysis. Liver Transpl. 2011 Aug;17(8):905-13. Retrieved from https://pubmed.ncbi.nlm.nih.gov/21384525/.

- Retrospective study on 240 patients transitioned to EVR to assess efficacy and safety. Time to initiation was usually 4.9 ± 5.2 years. Renal functioned improved at start to month 12 in patients on EVR. Four patients developed BPAR. ADRs led to discontinuation in 12.9% of patients.

Asrani SK, et al. (2010). Use of sirolimus in liver transplant recipients with renal insufficiency: a systematic review and meta-analysis. Hepatology. 2010 Oct;52(4):1360-70. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/20815021.

- Eleven randomized controlled trials and observational trials are included in the meta-analysis to evaluate the impact of sirolimus on renal function in liver transplant recipients. Sirolimus use was associated with improved renal function. Sirolimus use was not associated with patient death, graft failure, and rejection.

Molinari M, et al. (2010). Multicentric outcome analysis of sirolimus-based immunosuppression in 252 liver transplant recipients. Transpl Int. 2010 Feb;23(2):155-68. Retrieved from https://pubmed.ncbi.nlm.nih.gov/19765266/.

- Retrospective study in 252 OLT who received SRL was compared to 291 who received CNI that assessed efficacy of SRL de novo post-liver transplant. Patient and graft survival were similar. HAT was higher in the CNI than SRL group. Biliary complications and incisional hernias were similar amongst groups. SRL was safe and effective.

De Simone P, et al. (2009). Conversion from a calcineurin inhibitor to everolimus therapy in maintenance liver transplant recipients: a prospective, randomized, multicenter trial. Liver Transpl. 2009 Oct;15(10):1262-9. Retrieved from https://pubmed.ncbi.nlm.nih.gov/19790150/.

- Prospective, randomized, multicenter, 6-month study with additional 6-month follow up evaluated EVR + CNI reduction vs CNI only impaired renal function in liver transplant patients.80% of patients on everolimus discontinued CNI. There was no statistical difference in renal function amongst groups. BPAR was no different in each groups. Data demonstrate that everolimus allows for discontinuation or reduction of CNI exposure in liver allograft recipients without a loss of efficacy.

De Simone P, et al. (2009). Conversion to everolimus monotherapy in maintenance liver transplantation: feasibility, safety, and impact on renal function. Transpl Int. 2009 Mar;22(3):279-86. Retrieved from https://pubmed.ncbi.nlm.nih.gov/19054383/.

- 12-month results of a prospective trial of CNI to EVR conversion which was 0.75 mg PO BID, withdrawal of antimetabolites, and a 50% reduction in CNI with a complete stop within 4 weeks. Patient and graft survival was 100% and success rate was 75%. Ten patients, 25% were treatment failures: BPAR 10%, transaminitis in HCV patients 7.5%, cholangitis 2.5%, 5% persistent pruritus or oral ulcers. EVR likely had renal function benefit. Conversion from CNI to EVL is feasible in 75% of the cases and associated with improvement in renal function for patients with higher baseline CrCl.

Watson CJ, et al. (2007). A randomized controlled trial of late conversion from calcineurin inhibitor (CNI)-based to sirolimus-based immunosuppression in liver transplant recipients with impaired renal function. Liver Transpl. 2007 Dec;13(12):1694-702. Retrieved from https://pubmed.ncbi.nlm.nih.gov/18044728/.

- Single-center, randomized, controlled trial of 27 patients at least 6 months post liver transplant randomized to stay on CNI vs transition to SRL. Significant improvement in GFR change following conversion from CNI to SRL wat 3 months and 1 year. Skin rash and mouth ulcers were most common ADRs in the SRL group.

Levy G, et al. (2006). Safety, tolerability, and efficacy of everolimus in de novo liver transplant recipients: 12- and 36-month results. Liver Transpl. 2006 Nov;12(11):1640-8. Retrieved from https://pubmed.ncbi.nlm.nih.gov/16598777/.

- One hundred and nineteen liver allograft recipients were randomized to 1 of 4 groups: everolimus 0.5 mg bid, everolimus 1.0 mg bid, everolimus 2 mg bid, or placebo. Patients also received CSA. Trends toward less BPAR in EVR groups than placebo but not significant. ADRs were higher in the EVR group especially with > 4 mg/day. EVR is an appropriate agent for immunosuppression.

Zaghla H, et al. (2006). A comparison of sirolimus vs. calcineurin inhibitor-based immunosuppressive therapies in liver transplantation. Aliment Pharmacol Ther. 2006 Feb 15;23(4):513-20. Retrieved from https://pubmed.ncbi.nlm.nih.gov/16441472/.

- Retrospective review SRL only, CNI only, or CNI + SRL. Patient and graft survival were similar. BPAR rates were similar. Renal function was similar at 1 month post-transplant. SRL alone and in combo with CNI appears to be safe.

3.2.4 Co-Stimulation Blockade

Klintmalm, G, et al. (2022). Belatacept Treatment of Recurrent Late-onset T Cell-mediated Rejection/Antibody-mediated Rejection With De Novo Donor-specific Antibodies in a Liver Transplant Patient. Transplant Direct. 2022 Jun 24;8(7):e1076. Retrieved from https://pubmed.ncbi.nlm.nih.gov/35774420/.

- In this single-center, single-patient case report, the authors report the case of a 20-year-old female status post liver transplant secondary to Alagille's syndrome who experienced multiple cases of steroid-resistant T-cell mediated rejection and DSA development within the first 3.5 years post-transplant. The patient was initiated on belatacept at 3 years and 5 months post-transplant at 5 mg/kg monthly. LFTs normalized and had remained normal since belatacept initiation, and had not experienced additional episodes of TCMR at the time of publication.

Cristea O, et al. (2021). Belatacept conversion in kidney after liver transplantation. Transplant Direct. 2021 Oct 22;7(11):e780. Retrieved from https://pubmed.ncbi.nlm.nih.gov/34712780/.

- Retrospective review of 8 patients who underwent kidney after liver transplant and were treated with belatacept-based immunosuppression and transient CNI therapy. All patients tolerated belatacept therapy without any patient deaths or graft losses. No episodes of rejection, de novo donor-specific antibody formation, or major systemic infections were observed, and all patients demonstrated preserved liver and excellent renal allograft function.

Klintmalm G, et al. (2014). Belatacept-based immunosuppression in de novo liver transplant recipients: 1-year experience from a phase II randomized study. Am J Transplant. 2014 Aug;14(8):1817-27. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25041339.

- Phase II RCT evaluating de novo belatacept in liver transplant recipients. Patients were randomized to one of five treatment arms (1. basiliximab + belatacept high dose [HD] + mycophenolate mofetil (MMF), 2. belatacept HD + MMF, 3. belatacept low dose [LD] + MMF, 4. tacrolimus + MMF, or 5. tacrolimus alone). Due to an increase in death and graft loss with belatacept users, the study was terminated early after 12 months.

LaMattina JC, et al. (2014). Safety of belatacept bridging immunosuppression in hepatitis C-positive liver transplant recipients with renal dysfunction. Transplantation. 2014 Jan 27;97(2):133-7. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24342980.

- Retrospective review evaluating the use of belatacept at a single center in seven liver transplant recipients with hepatitis C virus. Patient survival, graft survival, and biopsy-proven acute rejection episode are among the endpoints evaluated.

3.2.5 Other

Khorsandi SE, Heaton N (2016). Optimization of immunosuppressive medication upon liver transplantation against HCC recurrence. Translational gastroenterology and hepatology. 2016 Apr 6;1:25. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/28138592.

- Review of evidence evaluating the impact of immunosuppression agents on hepatocellular cancer recurrence and oncological survival.

Wei Q, et al. (2016). Efficacy and Safety of a Steroid-Free Immunosuppressive Regimen after Liver Transplantation for Hepatocellular Carcinoma. Gut Liver. 2016 Jul 15;10(4):604-10. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4933422/.

- Enrolled 66 HBV-HCC patients to receive no steroids after liver transplant vs 132 SOC patients. No differences were observed at 1-year, 3-year, 5-year patient or tumor-free survival rates between both groups. 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 ($p<0.001$). HBV recurrence was lower in the steroid free group.

Manousou P, et al. (2014). Reduced fibrosis in recurrent HCV with tacrolimus, azathioprine and steroids versus tacrolimus: randomised trial long term outcomes. Gut. 2014 Jun;63(6):1005-13. Retrieved from https://pubmed.ncbi.nlm.nih.gov/24131637/.

- Evaluated evidence of fibrosis at a median 8 years follow-up post liver transplant for HCC with use of TAC triple therapy (AZA, pred) vs TAC monotherapy. No significant preoperative, peri-operative or postoperative differences between groups were found. Stage 4 fibrosis was reached in more patients in the monotherapy groups and slower progression was seen in the triple therapy group. pHTN higher in monotherapy vs triple therapy. More patients decompensated in the monotherapy group.

Gu J et al. (2014). Role of steroid minimization in the tacrolimus-based immunosuppressive regimen for liver transplant recipients: a systematic review and meta-analysis of prospective randomized controlled trials. Hepatol Int. 2014 Mar 20;8(2):198-215. Retrieved from https://pubmed.ncbi.nlm.nih.gov/24765218/.

- Systemic review and meta-analysis to evaluate the efficacy and safety of early steroid withdrawal or steroid avoidance in TAC immunosuppression. Graft and patient survival were similar upt to 5 years. Acute and chronic rejection were similar amongst groups.

Watt KD, et al. (2012). Impact of sirolimus and tacrolimus on mortality and graft loss in liver transplant recipients with or without hepatitis C virus: an analysis of the Scientific Registry of Transplant Recipients Database. Liver Transpl. 2012 Sep;18(9):1029-36. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/22641474.

- The current study analyzes the Scientific Registry of Transplant Recipients Database to identify risk factors for mortality and graft loss in liver transplant recipients with or without hepatitis C virus indication for transplant.

Klintmalm GB, et al. (2011). A randomized, multicenter study comparing steroid-free immunosuppression and standard immunosuppression for liver transplant recipients with chronic hepatitis C. Liver Transpl. 2011 Dec;17(12):1394-403. Retrieved from https://pubmed.ncbi.nlm.nih.gov/21850690/.

- Randomized, prospective, multicenter trial comparing safety and efficacy of steroid-free immunosuppression (daclizumab + TAC + MMF vs TAC + MMF+ steroids or TAC + steroids in hepatitis C patients. At 2 years no difference in ACR, HCV recurrence, patient survival, or graft survival rates.

Manousou P, et al. (2009). Outcome of recurrent hepatitis C virus after liver transplantation in a randomized trial of tacrolimus monotherapy versus triple therapy. Liver Transpl. 2009 Dec;15(12):1783-91. Retrieved from https://pubmed.ncbi.nlm.nih.gov/19938143/.

- Evaluated 103 patients with HCV cirrhosis as indication for liver transplant, 54 patients were on TAC monotherapy vs 49 on TAC + AZA + steroids. Steroids were tapered by 3-6 months. During a mean follow-up of 53.5 months, 9 monotherapy patients and 6 triple therapy patients died, and 5 monotherapy patients and 4 triple therapy patients underwent retransplantation. Stage 4 fibrosis was found in 17 patients in TAC monotherapy group vs 10 patients in TAC + AZA + steroids group, slower progression to stage 4 was seen in TAC + AZA + steroids group.

Chen ZS, He F, Zeng FJ, Jiang JP, Du DF, Liu B. Early steroid withdrawal after liver transplantation for hepatocellular carcinoma. World J Gastroenterol. 2007 Oct 21;13(39):5273-6. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4171311/.

- Evaluated impact of early steroid withdrawal on the incidence of rejection, tumor recurrence, and complications after liver transplant for HCC. 45 patients receiving liver transplant from 4/2003-6/2005 were divided into steroid withdraw or steroid continuance. No difference was seen in rejection, mean tacrolimus trough levels, liver and kidney function at 6 months , 6-month recurrence rate of carcinoma and 1-year survival rate. Blood sugar and cholesterol were lower in the steroid withdraw group at 1 year.

Berenguer M, et al. (2007). Immunosuppression with calcineurin inhibitors with respect to the outcome of HCV recurrence after liver transplantation: results of a meta-analysis. Liver Transpl. 2007 Jan;13(1):21-9. Retrieved from https://pubmed.ncbi.nlm.nih.gov/17192906/.

- Systematic review and meta-analysis evaluating TAC vs CSA immunosuppression in HCV patients. No difference in mortality, graft survival, BPAR, corticosteroid resistant rejection, or fibrosing cholestatic hepatitis.

3.3 ABO-Incompatible Liver Transplantation

Hirukawa K, et al. (2023). Long-term outcomes following ABO-incompatible living donor liver transplantation for acute liver failure: a single-center experience of over 20 years. Surg Today. 2023 Oct;53(10:1160-1172. Retrieved from https://pubmed.ncbi.nlm.nih.gov/37272972/.

- Retrospective, single center study of ABO incompatible living donor liver transplant recipients whose etiology for transplant was acute liver failure (N=5) or non-acute liver failure (N=33). The ABO incompatible protocol is as follows. In the preoperative period, rituximab, CNI, steroids, antimetabolites, and plasma exchange were given. Intra-operatively, splenectomy was performed. Postoperatively, patients received portal infusion therapies, with a target ABO antibody titer of ≤ 1:128. Maintenance immunosuppression was continued with CNI, steroids, and antimetabolites. However, for patients with urgent indication for liver transplant (in the acute liver failure group), this protocol could not always be followed with respect to intervention timing. The median number of days from rituximab administration to liver transplant differed significantly between groups (2 days vs 13 days, $p<0.001$). 5-year survival outcomes were similar between both groups (80.0% vs 77.9%).

Spaggiari M, et al. (2023). Single-dose eculizumab as part of a modified desensitization protocol for ABO-incompatible living donor liver transplantation. Liver Transplantation. 2023 Aug;29(8):906-910. Retrieved from https://pubmed.ncbi.nlm.nih.gov/36876445/.

- In this single center case report, a patient with acute liver failure received an ABO incompatible liver transplant and was desensitized with a single dose of eculizumab 900 mg IV prior to transplant. Concomitant splenectomy was performed at the time of transplant. Induction immunosuppression consisted of anti-thymocyte globulin (rabbit) with 1.5 mg/kg IV once daily starting intraoperatively and continued daily through day 4. Maintenance immunosuppression was continued with tacrolimus (trough goal 8-10 ng/mL), mycophenolate sodium, and a steroid taper. She required plasmapheresis with IVIG post-transplant due to mild AMR and cholestasis on her

biopsy. The patient has continued to progress well post-transplant through month 7 (when this paper was published) without any further complications.

Rhu J, et al. (2023). Pretransplant mycophenolate mofetil may be associated with reduced intrahepatic cholangiopathy in ABO-incompatible liver transplantation. Liver Transplantation. 2023 Aug;29(8):849-860. Retrieved from https://pubmed.ncbi.nlm.nih.gov/36695301/.

- This study included ABO incompatible living donor liver transplant recipients from 2010 to 2022 (N=234) and, in November of 2020, pretransplant mycophenolate mofetil was added to the immunosuppression protocol. The primary outcome was incidence of intrahepatic cholangiopathy, which occurred in 14 patients total. Laparoscopic hepatectomy with pretransplant mycophenolate mofetil was associated with lower risk of intrahepatic cholangiopathy, with similar results as donors who received open surgery without mycophenolate mofetil.

Egawa H, et al. (2023). Current Status of ABO-incompatible Liver Transplantation. Transplantation. 2023 Feb 1;107(2):313-325. Retrieved from https://pubmed.ncbi.nlm.nih.gov/35849558/.

- Discussing potential options, protocols, and medications in Japan and Asia for living donor living transplantation for ABO-incompatible transplant.

Lee W, et al. (2022). Quick preparation of ABO-incompatible living donor liver transplantation for acute liver failure. Clin Transplant. 2022 Mar;36(3):e14555. Retrieved from https://pubmed.ncbi.nlm.nih.gov/34874071/.

- In this prospective, single center study the regimen of bortezomib, plasma exchange, and rituximab for urgent preparation of acute liver failure transplant recipients (N=8) for ABO incompatible living donation was assessed. One patient died from AMR 6 months post-transplant, and 12-month patient/graft survival was 75%.

Puri Y, et al. (2022). ABO-Incompatible Living Donor Liver Transplant From a Blood Type A2 Donor to a Type B Recipient: A Note of Caution. Exp Clin Transplant. 2022 Jan;20(1):100-103. Retrieved from https://pubmed.ncbi.nlm.nih.gov/34763633/.

- Case report of 48-year-old male patient with blood group type B who underwent ABO-incompatible liver transplant of a right lobe liver graft from a type A2 living donor. The recipient's anti-A isohemagglutinin (AAI) titers were checked preoperatively and were serially measured on a daily basis postoperatively. Immunosuppression included tacrolimus, MMF, and corticosteroids. Authors describe AAI titer trend and management of subsequent severe acute AMR which included conventional therapeutic plasma exchange (TPE), immunoadsorption, and splenectomy.

Skogsberg U, et al. (2022). Excellent outcome following emergency deceased donor ABO-incompatible liver transplantation using rituximab and antigen specific immunoadsorption. Scand J Gastroenterol. 2022 Jan;57(1):50-59. Retrieved from https://pubmed.ncbi.nlm.nih.gov/34541993/.

- Single-center evaluation of outcomes in 20 ABOi DDLTs using the center's antibody reducing immunosuppressive protocol for patients in urgent need of liver transplant. There were 12 non-A2 donors (A1=8, B = 3, AB = 1) and 8 A2-donors. Immunosuppression consisted of rituximab (n = 20) and basiliximab (n = 15) or anti-thymocyte globulin (n = 4), intravenous immunoglobulin (IVIG; n = 6), tacrolimus, prednisolone and mycophenolate mofetil. Fifteen patients were treated with IA (antigen specific immunoadsorption; n = 14) or both IA and plasmapheresis (PP; n = 1) pre-transplant and 18 patients were treated with IA (n = 15) or both IA and PP (n = 3) post-transplant. Patient and graft survival and complications were compared to a 1:4 case matched control group of ABO-identical or compatible (ABOid/c) DDLT. The 1-, 3- and 5-year patient and graft survival rates were 85, 85 and 78% for the ABOi recipients and not significantly different compared to ABOid/c controls. Only one ABOi patient developed antibody-mediated rejection.

Gan K, et al. (2021). Clinical outcomes after ABO-incompatible liver transplantation: A systematic review and meta-analysis. Transpl Immunol. 2021 Dec;69:101476. Retrieved from https://pubmed.ncbi.nlm.nih.gov/34601097/.

- Meta-analysis based on observational studies that included outcomes at at least 1 year for 2137 ABOi-LT and 8646 ABOc-LTs. The short-term and long-term outcomes were worse after ABOi-DDLT than ABOc-DDLT in the all-cause mortality, death-censored graft survival, and complication incidence rate. However, the same outcomes were essentially comparable between ABOi-LDLT vs. ABOc-LDLT cohorts.

Lee TB, et al. (2021). ABO-incompatible living donor liver transplantation with a simplified desensitization and immunosuppression protocol: A single-center retrospective study. Exp Clin Transplant. 2021 Jul;19(7):676-685. Retrieved from https://pubmed.ncbi.nlm.nih.gov/34325624/.

- Retrospective review of 20 ABO-incompatible living donor liver transplant cases that utilized rituximab 2-3 weeks prior to transplant, subsequent plasma exchanges, basiliximab administration, and IVIG protocol. No patients had biopsy-confirmed antibody-mediated rejection. No bacterial or fungal infections were observed. Biliary anastomotic stricture was observed in 9 patients.

Zhang Y, et al. (2021). A novel MSC-based immune induction strategy for ABO-incompatible liver transplantation: a phase I/II randomized, open-label, controlled trial. Stem Cell Res Ther. 2021 Apr 16;12(1):244. Retrieved from https://pubmed.ncbi.nlm.nih.gov/33863383/.

- Prospective study evaluating safety and feasibility of using mesenchymal stem cells (MSC) to replace rituximab in ABO-incompatible transplant. No severe ADRs were observed during the trial. MSC yielded better results than ritiuximab as the biliary complications (0% vs 45.5%) and infection (9.1% vs 81.8%) were significantly decreased in the MSC group. The 2-year graft and recipient survival between both groups was similar.

Oh J, et al. (2020). Immunologic strategies and outcomes in ABO-incompatible living donor liver transplantation. Clin Mol Hepatol. 2020 Jan;26(1):1-6. Retrieved from https://pubmed.ncbi.nlm.nih.gov/30909688/.

- Review of literature for past and current immune strategies for desensitization and to provide outcomes for ABO-incompatible transplant in living donor liver transplant.

Yadav DK, et al. (2019). ABO-Incompatible Adult Living Donor Liver Transplantation in the Era of Rituximab: A Systematic Review and Meta-Analysis. Gastroenterol Res Pract. 2019 Jun 11;2019:8589402. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6594289/.

- Systematic review and meta-analysis of 9 studies (retrospective or prospective) evaluating the safety and effectiveness of rituximab in ABO-incompatible living donor liver transplantation. No differences were observed when comparing graft or patient survival at 1, 3, or 5 years' post-transplant for ABOi vs ABOc groups, however, ABOi transplant recipients had higher rates of biliary complications, CMV infection and AMR.

Lee EC, et al. (2017). Outcomes after liver transplantation in accordance with ABO compatibility: A systematic review and meta-analysis. World J Gastroenterol. 2017;23(35):6516-6533. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/29085201.

- Systematic review and meta-analysis of 21 retrospective studies including 8247 total patients (1494 ABO-incompatible and 6753 ABO-compatible liver transplant recipients). ABOi transplant recipients were noted to have lower 1, 3, and 5-year graft survival, as well as an increased incidence of AMR, chronic rejection, CMV, and surgical complications, as compared to ABO-compatible recipients.

Jun IG, et al. (2016). Comparison of acute kidney injury between ABO-compatible and ABO-incompatible living donor liver transplantation: A propensity matching analysis. Liver Transpl. 2016 Dec;22(12):1656-1665. Retrieved from https://pubmed.ncbi.nlm.nih.gov/27595780/.

- Retrospective study evaluating incidence of AKI following ABO incompatible living donor liver transplant 11/2008-12/2014. A total of 271 patients were reviewed, AKI occurred in 184 (67.9%) of patients according to KDIGO criteria. AKI was more common in ABO-incompatible transplant compared to ABO-compatible transplant (67.0% versus 48.2%; P < 0.001). There was no difference in graft failure, mortality, and post-operative dialysis.

Kim JM, et al. (2016). Case-matched comparison of ABO-incompatible and ABO-compatible living donor liver transplantation. Br J Surg. 2016 Feb;103(3):276-83. Retrieved from https://pubmed.ncbi.nlm.nih.gov/26695115/.

- Forty-seven ABO-I LDLT procedures were included. Ninety-four patients who had ABO-C LDLT were selected as a comparator group. The incidence of cytomegalovirus, bacterial and fungal infections during the first 3 months was similar after ABO-I LDLT and ABO-C LDLT. The 1-, 2- and 3-year patient survival rates after ABO-I LDLT and ABO-C LDLT were 89% *vs* 87%, 85% *vs* 83%, and 85% *vs* 79% respectively.

Song GW, et al. (2016). ABO-Incompatible Adult Living Donor Liver Transplantation Under the Desensitization Protocol With Rituximab. Am J Transplant. 2016 Jan;16(1):157-70. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26372830.

- Retrospective review of 235 adult patient undergoing adult donor living donor liver transplantation. The desensitization protocol included a single dose of rituximab and total plasma exchange. Three-year graft and patient survival rates were comparable to those of the ABOc group, however, 17 patients experienced AMR that manifested as diffuse intrahepatic biliary stricture; six cases required retransplantation, and three patients died.

Morimoto H, et al. (2016). Different sensitivity of rituximab-treatment to B-cells between ABO-incompatible kidney and liver transplantation. Hepatobiliary Surg Nutr. 2016 Apr;5(2):91-7. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27085793.

- Study showing B-cell and T-cell immune responses in both KT and LT recipients. Investigated the kinetics of proportions of peripheral blood B-cell subsets in transplant recipients to compare the susceptibility to rituximab of ABO-I KT and LT. Rituximab has differing B-cell sensitivity between KT and LT recipients and a minimal effect on the alloreactive T-cell responses in KT and LT recipients.

Ikegami T, et al. (2016). Feasible usage of ABO incompatible grafts in living donor liver transplantation. Hepatobiliary Surg Nutr. 2016 Apr;5(2):91-7. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4824747/.

- Five year follow up study of 19 patients receiving ABOi-LDLTs using plasmapheresis and rituximab for desensitization. ABOi-LDLTs had increased incidence of cytomegalovirus infection (52.6% vs. 22.9%), other post-transplant complications including bacterial sepsis and acute rejection were not different. The 5-year graft survival rate was 87.9% in ABOi-LDLTs and 80.3% in non-ABOi-LDLTs.

Lee CF, et al. (2015). Adult Living Donor Liver Transplantation Across ABO-Incompatibility. Medicine (Baltimore). 2015 Oct;94(42):e1796. Retrieved from https://pubmed.ncbi.nlm.nih.gov/26496313/.

- Evaluate ABO incompatible living donor liver transplant with two designed regimens. Regimen one was when isoagglutinin IgG and IgM titers were ≤ 64 were then given rituximab 375 mg/m^2 POD1. Regimen two was wen isoagglutinin titers were >64, rituximab 375 mg/m^2 was given preoperative ± plasmapheresis and boosted on POD1. These were compared to ABO compatible liver transplant patients. Survival rates were similar amongst both groups, biliary complications occurred more frequently in the ABO incompatible group.

Zhou J, et al. (2015). ABO-incompatible liver transplantation for severe hepatitis B patients. Transpl Int. 2015 Jul;28(7):793-9. Retrieved from https://pubmed.ncbi.nlm.nih.gov/25630359/.

- Retrospective review of 22 patients with severe Hepatitis B(SHB) in whom were performed emergency liver transplantation from ABO-incompatible donors. Although the 1-, 3-, 5-year graft and patient survival rates of ABOi were lower than that of ABO-compatible group, the results suggested that ABOi liver transplantation might be a life-saving procedure for patients with SHB as a promising alternative operation when ABO-c donors are not available and bridges the second opportunity for liver retransplantation.

Yasuda M, et al. (2015). The changes in treatment strategies in ABOi living donor liver transplantation for acute liver failure. J Med Invest. 2015;62(3-4):184-7. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26399345.

- Review of changes in treatment strategies in ABOi LDLT for acute liver failure. The desensitization protocol for ABOi barrier included Case #1; local infusion + plasma exchange (PE), Case #2; local infusion + rituximab + PE, Case #3 and #4; rituximab + PE, and Case #5; rituximab + PE under high-flow continuous hemodiafiltration. The patients of Case #2 and #3 received rituximab within 7 days before LDLT and experienced antibody-mediated rejection.

Rituximab-based ABOi-LDLT given at least 2 weeks prior to transplant, most-recently under high-flow hemodiafiltration for treating encephalopathy, is a feasible option for applying LDLT for ALF.

Detry O. (2015). Should ABO-incompatible deceased liver transplantation be reconsidered? Transpl Int. 2015 Jul;28(7):788-9. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25847352.

- A retrospective review of the literature highlighting results in ABO-incompatible deceased donor liver transplantation in adult recipients. Both groups conclude that ABOi DDLT might be life-saving and might be used in urgent cases.

Thorsen T, et al. (2015). Liver transplantation with deceased ABO-incompatible donors is life-saving but associated with increased risk of rejection and post-transplant complications. Transpl Int. 2015 Jul;28(7):800-12. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25736519.

- Uncontrolled, retrospective, observational study in 61 patients receiving ABOi LT. Results show non-A2 grafts are associated with inferior graft survival and increased risk of rejection, vascular and biliary complications. ABOi LT performed with A2 grafts is associated with good long-term graft survival and can be used safely in urgent cases.

Egawa H, et al. (2014). Impact of rituximab desensitization on blood-type-incompatible adult living donor liver transplantation: a Japanese multicenter study. Am J Transplant. 2014 Jan;14(1):102-14. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24279828.

- Uncontrolled, retrospective, observational study in 381 ABO-incompatible living-donor liver transplant (LDLT) recipients comparing desensitization with or without rituximab. Rituximab was associated with significantly lower rates of antibody-mediated rejection (AMR).

Muth B, et al. (2013). Use of apheresis in solid organ transplantation. J Infus Nurs. 2013 Sep-Oct;36(5):329-33. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24006111.

- Overview of use of apheresis, including management of associated complications.

Wu J, et al. (2011). Recipient outcomes after ABO-incompatible liver transplantation: a systematic review and meta-analysis. PLoS One. 2011 Jan 25;6(1):e16521. Retrieved from https://pubmed.ncbi.nlm.nih.gov/21283553/.

- Systematic review of ABO-incompatible liver transplant vs ABO-compatible liver transplant which showed no statistical different in pediatric graft survival rate and pediatric + adult survival rate. ABO-incompatible liver transplant graft survival was lower than ABO-compatible in adults. BPAR

and biliary complications post-operatively were higher in the ABO-incompatible group.

Tanabe M, et al. (2010). Current progress in ABO-incompatible liver transplantation. Eur J Clin Invest. 2010 Oct;40(10):943-9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/20636381.

- Review article describing mainly progress in ABO-incompatible liver transplant since 1998, highlighting improved survival seen since the introduction of rituximab prophylaxis in 2003.

Testa G, et al. (2008). Adult living-donor liver transplantation with ABO-incompatible grafts. Transplantation. 2008 Mar 15;85(5):681-6. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18337660.

- Report of 5 ABO-incompatible LDLT recipients treated with plasmapheresis and IVIG pre-transplant, followed by thymoglobulin induction splenectomy. At 43 months post-transplant, 4 of 5 patients were alive with their original grafts. The 5th patient died of multi-organ failure 4 months after transplant; cause of organ failure was not determined. Overall results suggest favorable outcomes in ABO-incompatible LDLT.

Egawa H, et al. (2007). B-cell surface marker analysis for improvement of rituximab prophylaxis in ABO-incompatible adult living donor liver transplantation. Liver Transpl. 2007 Apr;13(4):579-88. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/17394164.

- Prospective study in 30 ABO-incompatible LDLT patients treated with hepatic artery infusion (HAI) only or HAI with rituximab prophylaxis. Rituximab was associated with a trend toward lower rates of humoral rejection and lower peak IgG titers.

Hanto D, et al. (2003). ABO-incompatible liver transplantation with no immunological graft losses using total plasma exchange, splenectomy, and quadruple immunosuppression: evidence for accommodation. Liver Transpl. 2003 Jan;9(1):22-30. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12514769.

- Retrospective study of 14 ABO-incompatible liver transplants treated with a protocol including total plasma exchange pre- and post-transplant, splenectomy at time of transplant and quadruple immunosuppression. Five-year patient and graft survival rates were 71.4% and 61.2%, respectively. No antibody-mediated rejections occurred.

3.4 Management of Rejection

Maddur H, et al. (2024). Rejection in liver transplantation recipients. J Clin Exp Hepatol. 2024 Jul-Aug;14(4):101363. Retrieved from https://pubmed.ncbi.nlm.nih.gov/38495462/.

- Review article describing the diagnosis, presentation, and management trends of rejection in liver transplant recipients

Shamsaeefar A, et al. (2024). Factors Associated with Chronic Rejection in Liver Transplant Recipients: A Retrospective Cohort Study From Shiraz Organ Transplant Center. Exp Clin Transplant. 2024;22(2):114-119. Retrieved from https://pubmed.ncbi.nlm.nih.gov/38511982.

- Single-center retrospective review of 178 adult liver transplant recipients over an average of 7 years of follow-up that evaluated risk factors for chronic rejection. The chronic rejection group differed significantly from the control group in the following ways: younger recipient and donor age, autoimmune hepatitis as the most common underlying etiology vs. viral hepatocellular carcinoma in the control group, higher rate of recipient male sex, higher rate of donor-recipient sex concordance, greater number of acute rejection episodes, and longer cold ischemia time. In a Cox proportional hazards model, only recipient male sex and recipient-donor sex concordance were significantly associated with chronic rejection. Chronic rejection was associated with a nonsignificant decrease in patient survival, significantly more hospital readmissions, and a nonsignificant increase in retransplant rate.

Sarwar R, et al. Acute cellular rejection in liver transplantation recipients following vaccination against coronavirus disease 2019: A case series. Liver Transpl. 2022 Aug;28(8):1388-1392. Retrieved from https://pubmed.ncbi.nlm.nih.gov/35243757/.

- Case series of 5 LTs developing biopsy-proven ACR following COVID-19 vaccination (3 received Moderna 2 received Pfizer-BioNtech). Two patients had a history of ACR at 40 days and 418 days post-LT (195 and 370 days prior to the first dose of vaccination, respectively). Three patients had elevation in liver enzymes after the first dose of vaccination but they eventually received a second dose without complication and all patients completed their vaccination series.
- Three patients had RAI 5 out of 9 and the other 2 had 3 out of 9 and 2 patients required admission for ACR treatment. All patients were initially treated with high dose IV methylprednisolone for 3 days and 3 patients started on additional immunosuppressive medications. Liver enzymes returned to normal (or baseline) in all patients. No patients required readmission to hospital, died or developed graft failure and no patients developed symptomatic COVID-19 infection during the follow-up period after vaccination and treatment of ACR.

De Martin E, et al. (2022). The optimal immunosuppression management to prevent early rejection after liver transplantation: A systematic review of the literature and expert panel recommendations. Clin Transplant. 2022 Oct;36(10):e14614. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35143096.

- Systematic review performed to identify immunosuppression regimens to minimize early ACR following LT and provide expert panel recommendations. Studies from January 2000 onward focusing on early ACR were included. Rates of early renal dysfunction and infection were evaluated. Thirty-seven studies met inclusion criteria (23 randomized controlled trials, 14 retrospective or prospective observational comparative or noncomparative studies). Several sources of biases which potentially confound conclusions were identified: heterogeneity in immunosuppression protocols, higher serum tacrolimus levels than currently used in clinical practice, differences in the definition of ACR. Expert panel recommendations are provided based on review of included studies.

Komagome MM, et al. (2022). Refractory Acute Antibody Mediated Rejection in Liver Transplant After Desensitization of Preformed Donor Specific Antibody-Validity of Bortezomib and Everolimus: A Case Report. Transplant Proc. 2022 Jan-Feb;54(1):147-152. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34974892/.

- Case report of living donor liver transplantation (LDLT) complicated with severe acute antibody-mediated rejection (aAMR) despite desensitization with rituximab and plasma exchange before LDLT for preformed donor-specific anti-human leukocyte antigen antibody (DSA). Immunosuppressive regimen included steroids and tacrolimus. Re-administration of rituximab followed by 4 courses of plasma exchange failed to treat aAMR. The DSA mean fluoro-intensity was successfully suppressed after bortezomib was administered however impaired serologic liver function test and cholestasis remained. LFTs and cholestasis in the graft were improved after everolimus was administered and the recipient was discharged on POD 196.

Perottino G, et al. (2022). Biomarkers of rejection in liver transplantation. Curr Opin Organ Transplant. 2022 Apr 1;27(2):154-158. Retrieved from https://pubmed.ncbi.nlm.nih.gov/35232928/.

- Review of recent progress in the field of biomarker discovery in liver allograft rejection. Developments include blood genomic assays measuring miRNA, mRNA and donor-derived cell-free DNA. Additionally, serum levels of cytokines, proteoforms, donor-specific antibodies and immunophenotyping have shown promising results in predicting rejection pre and/or post-transplant. The findings discussed in the studies outlined in the review are promising in the potential to improve patient management, reduce complications from over- or under-immunosuppression, and ultimately enhance outcomes.

Lee T, et al. (2022). Steroid-Resistant Rejection in Liver Transplant: A Single-Center Study for Risk Factor and Second-Line Treatment. Transplant Proc. 2022 Mar;54(2):443-449. Retrieved from https://pubmed.ncbi.nlm.nih.gov/35101321/.

- A 10-year, single-center, retrospective cohort study describing steroid-resistant rejection (SRR) and steroid-sensitive rejection (SSR) and comparing the effect of the SRR treatment methods. Of 663 cases, 124 patients (18.7%) with biopsy-proven rejection were analyzed. Multivariate analysis was performed on risk factors of SRR at first rejection. CMV infection and total bilirubin at first rejection and numbers of rejection were significant results. Both overall survival and allograft survival rate of SSR are higher than SRR ($P < .001$). Of second-line treatment patients, 13 patients (54.2%) recovered, and 11 patients (45.8%) failed to recover. Survival was the highest in patients using antithymocyte globulin and in patients with liver re-transplant.

Cuervo F, et al. (2021). Progress and challenges in diagnosis and treatment of rejection following liver transplantation. Curr Opin Organ Transplant. 2021 Dec 1;26(6):669-674. Retrieved from https://pubmed.ncbi.nlm.nih.gov/34581291/.

- Discusses recent studies with preliminary results regarding utilizing non-invasive biomarkers such as quantification of dd-cfDNA, mRNA microarray profiling of differentially expressed genes, and characterization of cytokine responses and immunophenotypic shifts to aid in diagnosis and treatment of allograft rejection.

Lee B, et al. (2021). Antibody-mediated rejection of the liver allograft: An update and a clinico-pathological perspective. J Hepatol. 2021 Nov;75(5):1203-1216. Retrieved from https://pubmed.ncbi.nlm.nih.gov/34343613/.

- Review article discussing the recent advances in the clinical diagnosis and treatment of antibody-mediated rejection in liver transplantation, as well as some of the histopathologic features (on liver biopsy tissue) of acute and chronic antibody mediated rejection.

Baradaran H, et al. (2021). Antibody-Mediated Rejection in Adult Liver Transplant Recipients: A Case Series and Literature Review. J Clin Pharmacol. 2022 Feb;62(2):254-271. Retrieved from https://pubmed.ncbi.nlm.nih.gov/34480762/.

- A literature review of 24 case series containing 64 liver transplant recipients with antibody-mediated rejection investigating treatment management for mild and moderate to severe acute antibody-mediated rejection

Del Bello A, et al. (2020). Outcome of Liver Transplant Patients With Preformed Donor-Specific Anti-Human Leukocyte Antigen Antibodies. Liver Transpl. 2020 Feb;26(2):256-267. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/31612580.

- Multi-center, retrospective analysis of 142 liver transplant recipients with preformed DSAs evaluating impact of induction therapy and transplant outcomes. Preformed DSA was associated with significantly higher rates of acute rejection but not patient survival.

Vionnet J, et al. (2019). Donor-specific antibodies in liver transplantation. Gastroenterol Hepatol. 2020 Jan;43(1):34-45. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/31810796.

- Review article of the impact of pre-formed donor specific antibodies and de novo anti-human leukocyte antigen donor-specific antibodies in liver transplantation, as well as strategies to overcome the issue

Charlton M, et al. (2018). International Liver Transplantation Society Consensus Statement on Immunosuppression in Liver Transplant Recipients. Transplantation. 2018;102(5):727-743. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29485508.

- Recommendations of the International Liver Transplantation Society (ILTS) Consensus guidelines on T-cell mediated rejection and antibody mediated rejection in liver transplant recipients are presented in this consensus findings article.

Kim PT, et al. (2016). Prevention and treatment of liver allograft antibody-mediated rejection and the role of the 'two-hit hypothesis'. Curr Opin Organ Transplant. 2016 Apr;21(2):209-18. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/26918881.

- This article reviews prevention and treatment strategies for acute and chronic antibody-mediated rejection (AMR).

Del Bello A, et al. (2016). Donor-specific antibodies and liver transplantation. Hum Immunol. 2016 Nov;77(11):1063-1070. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/26916836.

- This article reviews the implications and impact of preformed and de novo DSAs in liver transplantation and outlines potential management.

Oleary J, et al. (2014). The role of donor-specific HLA alloantibodies in liver transplantation. Am J Transplant. 2014 Apr;14(4):779-87. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/24580828.

- This article addresses the concerns surrounding the misunderstandings of the role of donor specific antibodies in liver transplantation. Experts were consulted to pool common theories and clinical experience. The findings suggest that AMR is typically overlapped with ACR in liver transplantation and those patients undergoing simultaneous liver-kidney transplant are at higher

risk for AMR post-transplant. DSA identification prior to transplant which persist post-liver transplant increase the risk for AMR as well.

Hübscher SG. (2012). Antibody-mediated rejection in the liver allograft. Curr Opin Organ Transplant. 2012 Jun;17(3):280-6. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/22569512.

- This article reviews the pathology of antibody-mediated rejection (AMR) focusing on recent studies which have improved our understanding of the clinicopathological features and diagnostic approaches.

Fosby B, et al. (2012). Recurrence and rejection in liver transplantation for primary sclerosing cholangitis. World J Gastroenterol. 2012 Jan 7;18(1):1-15. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/22228965.

- This review article focuses on the epidemiology, pathogenesis, treatment and the possible influence of rejection on the risk of recurrent disease in the liver allograft.

Levitsky J, et al. (2012). Risk for immune-mediated graft dysfunction in liver transplant recipients with recurrent HCV infection treated with pegylated interferon. Gastroenterology. 2012 May;142(5):1132-1139.e1. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/22285805.

- 52 liver transplant recipients with hepatitis C were assessed for the incidence of, risk factors for, and outcomes of PEGIGD. PEG-IGD has high morbidity and mortality and is not associated with increased rates of virologic response and is recommended to be avoided due to an increased risk of rejection.

Paterno F, et al. (2012). Bortezomib for acute antibody-mediated rejection in liver transplantation. Am J Transplant. 2012 Sep;12(9):2526-31. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/22681986.

- Case report of three liver transplant recipients with ABO-compatible refractory AMR. Treatment with bortezomib resulted in normalization of liver function tests, resolution of C4d deposition and decrease in DSA.

Togashi J, et al. (2011). Basiliximab as therapy for acute rejection after liver transplantation for hepatitis C virus cirrhosis. Biosci Trends. 2011;5(2):57-60. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/21572248.

- Due to the controversy in utilizing steroids in liver transplant recipients experiencing rejection due to reactivation of diseases, basiliximab was studied. Authors concluded that basiliximab can be

safely used as rescue therapy for ACR without significant adverse effects in patients who underwent liver transplantation for HCV cirrhosis.

Neil D, et al. (2010). Current views on rejection pathology in liver transplantation. Transpl Int. 2010 Oct;23(10):971-83. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/20723179.

- This article addresses the differences between acute and chronic rejection with regard to pathophysiology and clinical presentation. A discussion on antibody-mediated rejection is also present in this review.

Shaked A, et al. (2009). Incidence and Severity of Acute Cellular Rejection in Recipients Undergoing Adult Living Donor or Deceased Donor Liver Transplantation. Am J Transplant. 2009 Feb;9(2):301-8. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/19120082.

- This review article discusses risk factors for acute rejection and different management strategies from different transplant centers. The reported incidence of acute cellular rejection is also reported.

3.5 Hepatic Diseases

3.5.1 Acute Hepatic Necrosis

Popescu M, et al. (2024) The Use and Potential Benefits of N-Acetylcysteine in Non-Acetaminophen Acute Liver Failure: An Etiology-Based Review. Biomedicines. 2024;12(3):676. Retrieved from https://pubmed.ncbi.nlm.nih.gov/38540289.

- This review article describes the rationale for use of N-acetylcysteine in acute liver failure and summarizes the existing evidence for NAC use for various etiologies of acute liver failure.

Fernández J, et al. (2024) Bridging the critically ill patient with acute to chronic liver failure to liver transplantation. Am J Transplant. 2024 Mar 26:S1600-6135(24)00223-5. Retrieved from https://pubmed.ncbi.nlm.nih.gov/38548058.

- This brief review article discusses the management of patients with acute on chronic liver failure in the pre-, peri-, and post-transplant phases of care, including management of certain etiologies and complications of acute on chronic liver failure.

Kesar V, et al. (2022). Liver Transplantation for Acute Liver Injury in Asians Is More Likely Due to Herbal and Dietary Supplements. Liver Transpl. 2022 Feb;28(2):188-199. Retrieved from https://pubmed.ncbi.nlm.nih.gov/34370392/.

- Authors used UNOS LT data to analyze severe herbal and dietary supplement (HDS)-induced acute liver injury in the US and identify epidemiologic differences between patients with HDS drug-induced liver injury (DILI) and non-HDS DILI. A subanalysis was performed for transplanted patients, including longitudinal changes. Of 1875 patients waitlisted, 736 (39.2%) underwent LT. The proportion of Asian patients in the HDS DILI group was significantly higher vs. the non-HDS DILI group (17.4% versus 3.8%; P < 0.001). Excluding acetaminophen cases, the proportion of Black patients in the HDS DILI vs. non-HDS group was significantly lower (8.7% versus 25.3%; P < 0.001). Waitlisted patients with HDS DILI were significantly older (median age, 38 years for HDS DILI versus 31 years for non-HDS DILI; P = 0.03). The number of patients requiring LT for HDS DILI increased significantly over time with >70% of cases occurring in the last 10 years (2010-2020) compared with the prior 15 years (1994-2009; Ptrend = 0.001). Ethnicity may help in identifying the cause of severe acute DILI, a growing problem as more patients experiment with HDS.

Karvellas C, et al. (2021). Liver Transplantation in Acute-on-chronic Liver Failure. Transplantation. 2021 Jul 1;105(7):1471-1481. Retrieved from https://pubmed.ncbi.nlm.nih.gov/33208692/.

- Review article discussing the role of liver transplant in acute-on-chronic liver failure including prognosis scores, critical care management of patients awaiting liver transplant, donor issues, and post-liver transplant outcomes in acute-on-chronic liver failure.

Stravitz RT, et al. (2019). Acute liver failure. Lancet. 2019;394(10201):869-881. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/31498101.

- Review article describing common causes, diagnosis, management, prognosis, as well as long-term outcomes after transplant. A brief review of available evidence is also included.

Wang D, et al. (2013). Advances in the management of acute liver failure. World J Gastroenterol. 2013 Nov 7;19(41):7069-77. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24222950.

- Review article which focuses on etiologies of acute liver failure and the management of various complications. The role of liver transplantation in this population is also discussed.

Gulmez S, et al. (2013). Transplantation for acute liver failure in patients exposed to NSAIDs or paracetamol (acetaminophen): the multinational case-population SALT study. Drug Saf. 2013 Feb;36(2):135-44. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/23325533.

- Study designed to estimate population rates of NSAID associated acute liver failure leading to transplantation. 9479 patients total across 52 centers were registered for transplantation with 600

of them actually leading to transplantation. Of these 600, 301 had received either NSAID or paracetamol therapy within 30 days of transplantation.

Banares R, et al. (2013). Extracorporeal albumin dialysis with the molecular adsorbent recirculating system in acute-on-chronic liver failure: the RELIEF trial. Hepatology. 2013 Mar;57(3):1153-62. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/23213075.

- 189 patients were randomized to receive molecular adsorbent recirculating system (MARS) or to standard medical therapy. No significant difference was seen between the two groups with respect to 28-day survival. When confounders were controlled, patients who received MARS also did not have a significantly beneficial effect over standard medical therapy. However, in patients with severe HE, MARS may have a role in decreasing the grade of diseases more rapidly than standard medical therapy without additional adverse effects.

Lee W, et al. (2012). Introduction to the revised American Association for the Study of Liver Diseases Position Paper on acute liver failure 2011. Hepatology. 2012 Mar;55(3):965-7. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/22213561.

- Guidelines review from the American Association for the Study of Liver Diseases. Etiology of acute liver failure and therapeutic management are discussed.

Reuben A, et al. (2010). Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology. 2010 Dec;52(6):2065-76. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/20949552.

- Cases of idiosyncratic drug-induced liver failure are discussed. Long-term outcomes, such as transplant-free survival and overall survival are also discussed as well.

Lee W, et al. (2009). Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. Gastroenterology. 2009 Sep;137(3):856-64, 864.e1. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19524577.

- 173 patients with non-acetaminophen induced acute liver failure were stratified to receive either intravenous NAC (N=81) or placebo (N=92). Overall survival was 70% in the NAC group and 66% in the placebo group (p=0.283). Transplant-free survival however, was significantly better in those that received NAC (40%) vs. those that received placebo (27%); p=0.043. This benefit was seen in patients with coma grades I-II, suggesting that more advanced coma grades (worse encephalopathy) did not benefit from NAC with regards to survival.

Larson, A et al. (2005). Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology. 2005 Dec;42(6):1364-72. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/16317692.

- Review article which discusses the epidemiology of acute liver failure secondary to acetaminophen toxicity. Overall survival, median dose ingested, and intentional vs. unintentional overdose data are discussed.

Schiodt F, et al. (2003). Viral hepatitis-related acute liver failure. Am J Gastroenterol. 2003 Feb;98(2):448-53. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/12591067

- Review article which discusses the incidence of viral-hepatitis induced acute liver failure. This article discusses the incidence of transplant free-survival rate as well as transplant rate differentiation between different subsets of viral hepatitis.

3.5.2 Biliary Atresia

Lu X, et al. (2023). Effect of Adjuvant Steroid Therapy in Type 3 Biliary Atresia: A Single-Center, Open-Label, Randomized Controlled Trial. Ann Surg. 2023 Jun 1;277(6):e1200-e1207. Retrieved from https://pubmed.ncbi.nlm.nih.gov/35170539/.

- Open-label randomized control trial where participants either received post-operative treatment with or without 10-12 weeks of adjuvant steroid treatment. Participants jaundice free without liver transplantation was significantly higher in the adjuvant steroid arm (54.1% vs 31.0%, p=0.0015). Survival time with the adjuvant steroid arm was significantly longer.

Kakos C, et al. (2021). Management of biliary atresia: To transplant or not to transplant. World J Transplant. 2021 Sep 18;11(9):400-409. Retrieved from https://pubmed.ncbi.nlm.nih.gov/34631471/.

- This review article discusses conditions which favor native liver survival after kasai procedure and the ones which optimize a positive liver transplant outcome. It also discusses pathophysiology of biliary atresia and transition of care.

Uto K, et al. (2019). A multicenter study of primary liver transplantation for biliary atresia in Japan. Pediatr Surg Int. 2019;35(11):1223-1229. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/31535197.

- Multi-center study conducted of the first nationwide survey in Japan to assess the status of primary liver transplant for biliary atresia in over 2800 patients.

Kasahara M, et al. (2017). Liver transplantation for biliary atresia: a systematic review. Pediatr Surg Int. 2017;33(12):1289-1295. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/28983725.

- Systematic review of liver transplantation for biliary atresia.

Davenport M, et al. (2013). Steroids in biliary atresia: single surgeon, single centre, prospective study. J Hepatol. 2013 Nov;59(5):1054-8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/23811305.

- This primary article observes the difference in outcomes in patients with biliary atresia who received steroid therapy vs. those that did not. 153 infants underwent portoenterostomy. Afterwards, patients were divided into three groups, low dose steroid (prednisolone 2mg/kg/day), high dose steroid (prednisolone 5mg/kg/day), and no steroids. A significant difference was seen between groups with respect to decreases in bilirubin and AST between the high dose steroids vs. no steroid groups. There was also an increase in the clearance of jaundice between those patients that received steroids and those that did not. This study supports the use of steroids in infants immediately post portoenterostomy.

Moreira R, et al. (2012). Biliary atresia: a multidisciplinary approach to diagnosis and management. Arch Pathol Lab Med. 2012 Jul;136(7):746-60. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/22742548.

- This review article discusses the diagnosis and management of biliary atresia. The main points of discussion include pathophysiology, kasai's procedure, and the role of liver transplantation.

Davenport M, et al. (2007). Randomized, double-blind, placebo-controlled trial of corticosteroids after Kasai portoenterostomy for biliary atresia. Hepatology. 2007 Dec;46(6):1821-7. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/17935230.

- This clinical trial evaluated the use of steroids as adjuvant therapy after Kasai's procedure. Patients were randomized to receive placebo or 2mg/kg/day of prednisolone on day 7 to 21 and then 1mg/kg/day on day 22 to day 28. There was a statistically significant difference in bilirubin levels with much lower levels seen in the steroid group at 1 month (66 vs. 92 mmol/L; p=0.06). However, no difference was seen at 6 months (p=0.56) or 12 months (p=0.3). The need for liver transplantation at 6 and 12 months was also not statistically significant (p=0.99, p=0.47, respectively). The authors concluded that the rates of reduction in bilirubin were only apparent in the immediate post-operative period (1 month), but did not sustain a long term effect.

3.5.3 Malignant Neoplasms

Rodríguez-Espinosa D, et al. (2024). Long-Term Outcomes of Incidental Liver Malignancies in Simultaneous Liver-Kidney Transplant Recipients. Transplant Proc. 2024;56(2):330-334. Retrieved from https://pubmed.ncbi.nlm.nih.gov/38350821.

- Single-center retrospective review of all SLKs performed between May 1993-April 2022 to evaluate post-transplant outcomes in the setting of incidental liver malignancy. Out of 108 SLK transplants, 13 (12.7%) of patients with incidental explant carcinoma, of which 12/13 were HCC. 41% of HCC tumors found were > 2 cm. There were 2 cases of intrahepatic cholangiocarcinoma. mTOR inhibitors were not used routinely - only 3/13 patients were switched to an mTOR inhibitor-containing regimen. A patient with cholangiocarcinoma experienced recurrence and metastatic disease leading to death. There were no other recurrences or deaths attributed to carcinoma. The study found no differences in 5-year patient survival and liver/kidney rejection between the carcinoma and no carcinoma groups. The authors speculate that the reduced amount of immunosuppression that SLK recipients receive may have contributed to the 0% rate of HCC recurrence observed.

Durkin C, et al. (2023). Induction Immunosuppression Does Not Worsen Tumor Recurrence After Liver Transplantation for Hepatocellular Carcinoma. Transplantation. 2023 Jul;107(7):1524-1534. Retrieved from https://pubmed.ncbi.nlm.nih.gov/36695564/.

- This retrospective registry study aimed to assess the impact of induction agents on HCC recurrence and patient survival. Groups included no antibody induction (N=17688, 78.48%), non-depleting induction (N=2984, 13.24%), and depleting induction (N=1863, 8.27%). Overall, no significant differences in HCC burden were observed across induction groups. Improved overall survival at 5 years was demonstrated with non-depleting induction vs either no antibody induction or depleting induction (81% vs 78% vs 79%, respectively). Upon specifically analyzing the exception group (patients with HCC who qualified for exception points through MELD), non-depleting induction was significantly associated with decreased all-cause mortality (HR 0.88, 95% CI -.80-0.97, p=0.01).

Rodríguez-Perálvarez M, et al. (2022). Cumulative exposure to tacrolimus and incidence of cancer after liver transplantation. Am J Transplant. 2022 Jun;22(6):1671-1682. Retrieved from https://pubmed.ncbi.nlm.nih.gov/35286761/.

- Multicenter, case-control study to evaluate effect of maintenance IS in post-liver transplant malignancy. 2,495 patients were evaluated with TAC immunosuppression, 425 (19.7%) developed malignancy, these were matched to similar patients without malignancy. Predictors of post-liver transplant malignancy were older age, male sex, smoking habit, and alcoholic liver

disease. Increased cumulative exposure to tacrolimus (CET) was a predictor of malignancy. Tacrolimus minimization monitored by CET may help modulate immunosuppression.

Abrahamsson J, et, al. (2022). Reduced calcineurin inhibitor exposure with antibody induction and recurrent hepatocellular carcinoma after liver transplantation. Scand J Gastroenterol. 2022 Mar;57(3):325-332. Retrieved from https://pubmed.ncbi.nlm.nih.gov/34871120/.

- Evaluated the impact on HCC recurrence of an immunosuppression protocol introduced in 2010 with interleukin-2 receptor antibody (IL-2RA) induction and delayed-introduction of reduced-dose tacrolimus with mycophenolate. A total of 235 patients (mean MELD 13, 57% within Milan criteria) were included. The cumulative 5-yr HCC recurrence rate in LT before and after 2010 were 28.6% and 19.7%, respectively. IL-2RA induction had no independent effect on HCC recurrence. High tacrolimus exposure (mean 20-day tacrolimus concentration ≥8ng/mL) was associated with increased HCC recurrence risk on univariable analysis (HR 2.22, 95% CI 1.23-4.01, p = .008), but was non-significant on multivariable analysis (p = .17). Outside Milan criteria, high tacrolimus exposure was significant for HCC recurrence (HR 3.68, 95% CI 1.34-10.11, p = 0.012) independently of tumor characteristics and AFP level. This was confirmed on multivariable propensity score-adjusted analysis. Further studies are needed to confirm if early tacrolimus-minimization strategies can help reduce HCC recurrence rates and help extend transplant criteria.

Khajeh E, et al. (2022). Statin use is associated with the reduction in hepatocellular carcinoma recurrence after liver surgery. BMC Cancer. 2022 Jan 21;22(1):91. Retrieved from https://pubmed.ncbi.nlm.nih.gov/35062904/.

- Meta-analysis of 9 retrospective studies analyzing the effect of statins on recurrence of hepatocellular carcinoma after liver surgery. Findings suggest statins decrease the recurrence rate of hepatocellular carcinoma after liver transplantation or resection.

Karakaya E, et al (2022). Treatment of Posttransplant Hepatocellular Carcinoma Recurrence. Exp Clin Transplant. 2022 Jan;20(1):59-61.Retrieved from https://pubmed.ncbi.nlm.nih.gov/35060449/.

- Retrospective analysis of 72 liver transplants performed in response to hepatocellular carcinoma (HCC). HCC recurred in 7 patients (9.7%; 5 adult, 2 pediatric). Except for one patient, all were in the late diagnosis group. Mean survival in the early diagnosis group was longer than in the late diagnosis group. During follow-up, 11 patients died from recurrence and distant metastasis.

Muhammad H, et al. (2021). Hepatocellular Carcinoma and the Role of Liver Transplantation: A Review. J Clin Transl Hepatol. 2021 Oct 28;9(5):738-748. Retrieved from https://pubmed.ncbi.nlm.nih.gov/34722189/.

- A comprehensive PubMed/MEDLINE review of 120 studies that outlines the various selection criteria for LT, discuss the outcomes of LT in HCC patients, and explore future directions of LT for HCC.

Orfanoudaki E, et al. (2021). Immunoproliferative Small Intestinal Disease in a Liver Transplant Recipient: A Case Report and Literature Review. Exp Clin Transplant. 2021 Jun;19(6):620-623. Retrieved from https://pubmed.ncbi.nlm.nih.gov/34085608/.

- Case report and literature review of which of immunoproliferative small intestinal disease which is an extranodal marginal zone B-cell lymphoma. Patient was an 18 year old with diarrhea and weigh loss. Immunosuppression was switched to EVR from TAC and patient achieved remission.

Mehta N, et al. (2021). Liver Transplantation Criteria for Hepatocellular Carcinoma, Including Posttransplant Management. Clin Liver Dis (Hoboken). 2021 Jun 4;17(5):332-336. Retrieved from https://pubmed.ncbi.nlm.nih.gov/34136137/.

- Review article describing strategies to help refine selection criteria for liver transplant in patients with HCC, and post-transplant management.

Verna EC, et al. (2020). Liver transplantation for hepatocellular carcinoma: Management after the transplant. Am J Transplant. 2020 Feb;20(2):333-347. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31710773.

- This review discusses risk factors for HCC recurrence, surveillance modalities, HCC prevention and treatment strategies after liver transplantation.

Kulik L, et al. (2018). Therapies for patients with hepatocellular carcinoma awaiting liver transplantation: A systematic review and meta-analysis. Hepatology. 2018;67(1):381-400. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/28859222.

- Systematic review and meta-analysis of 63 studies including pre-liver transplant patients with hepatocellular carcinoma. Reviews data available describing outcomes of various approaches to HCC management, including observation vs. therapy, transplant alone vs. transplant with bridging, and transplant without down-staging vs. transplant following down staging to within Milan Criteria.

Rizvi S, et al. (2018). Cholangiocarcinoma - evolving concepts and therapeutic strategies. Nat Rev Clin Oncol. 2018;15(2):95-111. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5819599/.

- Extensive review of cholangiocarcinoma, including epidemiology, anticipated outcomes, standards of care based on anatomical subtype, surgical approach and consideration of transplant, use of newer immunotherapies, and emerging investigational therapies.

Campos GR, et al. (2017). Study of factors affecting the incidence of skin cancer in patients after liver transplant. An Bras Dermatol. 2017 Jul-Aug;92(4):492-498. Retrieved from https://pubmed.ncbi.nlm.nih.gov/28954097/.

- Retrospective study to evaluate factors that influence skin cancer in liver transplant patients from 1997-2010. Predictors included diabetes in the third year after transplant, not using tacrolimus in the first year after transplant, and actinic keratosis.

Carenco C, et al. (2016). Solid, non-skin, post-liver transplant tumors: Key role of lifestyle and immunosuppression management. World J Gastroenterol. 2016 Jan 7;22(1):427-34. Retrieved from https://pubmed.ncbi.nlm.nih.gov/26755888/.

- Review discussing incidence and risk of cancer at specific sites including evaluating primary literature.

Geissler EK, et al. (2016). Sirolimus Use in Liver Transplant Recipients With Hepatocellular Carcinoma: A Randomized, Multicenter, Open-Label Phase 3 Trial (SiLVER Trial). Transplantation. 2016;100(1):116-25. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26555945.

- Randomized, open-label study of 525 liver transplant recipients with hepatocellular carcinoma (HCC) randomized to maintenance immunosuppression incorporating either sirolimus or continuing standard of care. The primary endpoint of recurrence free survival (RFS) occurred in 218 (85.2%) of the treatment/sirolimus group and 233 (92.5%) of the control group at 1-year post-transplant (p=0.01). However, this difference became non-significant at 2 –years. Benefit in RFS was most pronounced in those considered low-risk based on Milan Criteria.

Carenco C, et al. (2015). Chanques G, Ursic-Bedoya J, Jaber S, Larrey D, Navarro F, Pageaux GP. Incidence of solid organ cancers after liver transplantation: comparison with regional cancer incidence rates and risk factors. Liver Int. 2015 Jun;35(6):1748-55. Retrieved from https://pubmed.ncbi.nlm.nih.gov/25488375/.

- Single-center study from 1991-2008 including 465 liver transplant patients who had survived 1 year or more post-transplant to assess incidence of de novo solid organ cancers after liver transplant. 65 (13.9%) of patients experienced de novo solid cancer with incidence risk of 3.7. Significant increased relative risks were observed for digestive, oesophageal, colorectal, oral and

lung cancers, but not for genito-urinary and breast cancers. 43 patients died (66.1%), 41 from cancer. Pre-transplant smoking and obesity were risk factors. 55 (17%) of patients were on tacrolimus, exposure level was a risk factor for de novo solid cancers.

Yao D, et al. (2014). A review of the clinical diagnosis and therapy of cholangiocarcinoma. J Int Med Res. 2014 Feb;42(1):3-16. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24366497.

- This review article serves as a reference for the diagnosis and clinical management of cholangiocarcinoma. Being the second most common primary hepatic malignancy worldwide, this article will provide a reference as to the common treatment strategies.

Wimmer CD, et al. (2013). Impact of cyclosporine versus tacrolimus on the incidence of de novo malignancy following liver transplantation: a single center experience with 609 patients. Transpl Int. 2013 Oct;26(10):999-1006. Retrieved from https://pubmed.ncbi.nlm.nih.gov/23952102/.

- Study was to determine whether CSA vs TAC affects long-term tumor incidence by evaluating de novo malignancies in 609 liver transplant patients from 1985-2007. During 3,765 patients years of follow up, 87 de novo malignancies occurred in 71 patients (mean age 47.5 ± 13.3 years, mean time after liver transplantation 5.7 ± 3.7 years). Cumulative incidence of de novo malignancies was 34.7% in liver transplant patients vs 8.9% in the non-transplant population over 15 years. Most common tumors were nonmelanoma skin cancers. Risk factors for cancer were male gender, recipient age, and tacrolimus-based immunosuppression.

Pompili M, et al. (2013). Bridging and down staging treatments for hepatocellular carcinoma in patients on the waiting list for liver transplantation. World J Gastroenterol. 2013 Nov 21;19(43):7515-30. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24282343.

- This review article describes various strategies for managing hepatocellular carcinoma before and after liver transplantation. Treatment strategies such as radiofrequency ablation, transarterial chemoembolization, and other therapies are described in detail. Many primary articles are also referenced throughout this review. This will serve as a reference for those who wish to expand their exposure to standard management of HCC pre and post-liver transplantation.

Cheah Y, et al. (2012). Liver Transplantation for Hepatocellular Carcinoma: An Appraisal of Current Controversies. Liver Cancer. 2012 Nov;1(3-4):183-9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24159583.

- This review article describes criteria for liver transplantation in patients with HCC and discusses Milan criteria. Other areas discussed include living donor liver transplantation for HCC and

expanding Milan criteria in the setting of an increased incidence of HCC. Many patients are unable to undergo surgical resection due to location of tumors or due to high perioperative mortality risk. This article describes alternative strategies in managing this patient population.

Finn RS. (2012). Current and Future Treatment Strategies for Patients with Advanced Hepatocellular Carcinoma: Role of mTOR Inhibition. Liver Cancer. 2012 Nov;1(3-4):247-56. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24159589.

- This review article discusses the role of mTOR inhibitors in patients with advanced HCC. The mechanism of the anti-proliferative effect that mTOR inhibitors possess to have positive outcomes in patients with HCC is explained

Lewandowski R, et al. (2009). A Comparative Analysis of Transarterial Downstaging for Hepatocellular Carcinoma: Chemoembolization Versus Radioembolization. Am J Transplant. 2009 Aug;9(8):1920-8. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/19552767.

- This primary article evaluates the use of chemoembolization (TACE) vs. radioembolization (Y90) for the management of HCC. The objective of this study was to see if the effects of TACE vs. Y90 were better or worse in downstaging HCC to allow patients to be listed for liver transplantation. 43 patients were treated with TACE and 43 patients were treated with Y90 procedures. Median tumor size at baseline was similar (5.7cm vs. 5.6cm) in TACE vs. Y90 groups. Event-free survival was significantly better in the Y90 group (17.7 vs. 7.1 months; p=0.0017). Overall survival was also significantly better in the Y90 group (41.6 vs. 19.2 months, p=0.008). The authors concluded that Y90 seemed to provide better downstaging response rates than TACE.

Maddala Y, et al. (2004). Drop-Out Rates of Patients with Hepatocellular Cancer Listed for Liver Transplantation: Outcome with Chemoembolization. Liver Transpl. 2004 Mar;10(3):449-55. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15004776.

- This primary article discusses the use of chemoembolization in patients with HCC on the waiting list for liver transplantation. The aim of this study was to assess the dropout rate of patients who were removed from the waiting list due to resolution of disease from chemoembolization. The dropout rate at 6 months was 15% (8 patients dropped out of the waiting list out of 54 total). This study reflects alternative options to the management of HCC aside from liver transplant, due to the rising incidence of disease and lack of transplantable organs.

3.5.4 Metabolic Diseases

Czarnecka K, et al. (2024). MASH Continues as a Significant Burden on Metabolic Health of Liver Recipients. Transplant Proc. 2024 Feb 24:S0041-1345(24)00133-7. Retrieved from https://pubmed.ncbi.nlm.nih.gov/38403537/.

- Retrospective study that evaluated differences in post-transplant metabolic abnormalities and weight gain in patients who underwent transplant for MASH vs. non-MASH indications. Metabolic syndrome was diagnosed post-transplant more often in patients in the MASH vs. non-MASH group ($p<0.01$). Patients transplanted for MASH had a BMI at baseline, and experienced more pronounced weight gain than those transplanted for non-MASH indications. MASH etiology of liver disease, weight at 1 year post-transplant and older age at transplant were found to be independent predictors of new onset metabolic syndrome.

Paklar L, et al. (2023). The outcomes of liver transplantation in severe metabolic dysfunction-associated steatotic liver disease patients. Biomed. 2023 Nov;11(11):3096. Retrieved from https://pubmed.ncbi.nlm.nih.gov/38002096/.

- Review of literature surrounding MASH vs. non-MASH post-transplant outcomes, complications and future directions.

Lonardo A, et al. (2022). Metabolic mechanisms for and treatment of NAFLD or NASH occurring after liver transplantation. Nat Rev Endocrinol. 2022 Oct;18(10):638-650. Retrieved from https://pubmed.ncbi.nlm.nih.gov/35840803/.

- Review article discusses NAFLD and NASH before and after liver transplant, risk factors after liver transplant, and treatment strategies, including management of cardiometabolic comorbidities, tailored immunosuppression, lifestyle changes, and pharmacotherapy for NAFLD.

Horiuchi K, et al. (2022). Prevalence of fatty liver disease after liver transplantation and risk factors for recipients and donors. Ann Hepatol. 2022 Mar-Apr;27(2):100670. Retrieved from https://pubmed.ncbi.nlm.nih.gov/35051631.

- A total of 108 liver transplant recipients were enrolled. On evaluation of 88 prospective living donors, fatty liver was observed in 21 patients. After LT, 28 of 105 recipients (26.7%) developed FLD. FLD was more common in patients with a high body mass index (BMI) and dyslipidemia (both $p < 0.01$), primary nonalcoholic steatohepatitis ($p = 0.02$), after living-donor LT ($p = 0.03$) and everolimus (EVL) use ($p = 0.08$). Factors predictive of FLD included EVL use and a high BMI (hazard ratios = 3.00 and 1.34; $p = 0.05$ and $p < 0.01$, respectively). Development of FLD did not have a negative impact on LT outcome; the 5-year survival rate was 92.6%.

Sastre L, et. al. (2022). Results of a multidisciplinary strategy to improve the management of cardiovascular risk factors after liver transplant. Liver Transpl. 2022 Aug;28(8):1332-1344. Retrieved from https://pubmed.ncbi.nlm.nih.gov/35224857/.

- Analysis of a multidisciplinary strategy to manage cardiovascular risk factors (CVRF) 12 months after LT in the post-intervention cohort (n=150) compared to a control cohort (n=100). At 12 months, significantly more patients in the post-intervention cohort had measured blood pressure, HbA1c and HDL/LDL-cholesterol. Blood pressure and HbA1c were within target in more patients with HTN and diabetes, respectively in the post-intervention cohort. Median total cholesterol levels were lower in the post-intervention cohort. At 2 years, the incidence of cardiovascular events was 14% in the control and 6% in the post-intervention cohort (p=0.063).

Litwin T, et al. (2022). Liver transplantation as a treatment for Wilson's disease with neurological presentation: a systematic literature review. Acta Neurol Belg. 2022 Apr;122(2):505-518. Retrieved from https://pubmed.ncbi.nlm.nih.gov/35080708/.

- Systematic review of the outcomes of liver transplantation as a treatment for Wilson’s disease with neurological symptoms. Of 302 patients, 71.2% had major improvement.

Salman H, et al. (2022). Biochemical testing for the diagnosis of Wilson's disease: A systematic review. J Clin Lab Anal. 2022 Feb;36(2):e24191. Retrieved from https://pubmed.ncbi.nlm.nih.gov/34951059/.

- Systematic review of 9 studies analyzing the diagnostic accuracy for Wilson’s disease of biochemical tests. Study reports sensitivity and specificity of hepatic copper, 24-hour urinary copper, and ceruloplasmin using the Leipzig criteria.

Shetty A, et al. (2021). Nonalcoholic Fatty Liver Disease after Liver Transplant. J Clin Transl Hepatol. 2021 Jun 28;9(3):428-435. Retrieved from https://pubmed.ncbi.nlm.nih.gov/34221929/.

- Review article that describes the risk factors associated with recurrent and de novo NAFLD, natural course of the disease, and management strategies after liver transplantation.

Ando Y, et al. (2021). Nonalcoholic Fatty Liver Disease and Recent Guideline Updates. Clin Liver Dis (Hoboken). 2021 Feb 1;17(1):23-28. Retrieved from https://pubmed.ncbi.nlm.nih.gov/33552482/

- Summarizes updated guideline and guidance recommendations for the management of adult NAFLD

Patel D, et al. (2021). Alpha-1 antitrypsin deficiency liver disease. Transl Gastroenterol Hepatol. 2021 Apr 5;6:23. Retrieved from https://pubmed.ncbi.nlm.nih.gov/33824927/.

- Review article that discusses clinical presentation, pathophysiology, diagnosis, prognosis and management, and liver transplant and outcomes of alpha-1 antitrypsin deficiency liver disease

VanWagner LB, et al. (2020). Blood pressure control according to clinical practice guidelines is associated with decreased mortality and cardiovascular events among liver transplant recipients. Am J Transplant. 2020 Mar;20(3):797-807. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31730286.

- Longitudinal cohort study of 602 liver transplant recipients assessing the effect of blood pressure control on cardiovascular events and mortality. Achieving blood pressure control (<140/<90 mmHg) was associated with a reduction in cardiovascular events and improved survival.

Cotter TG, et al. (2020). Nonalcoholic Steatohepatitis After Liver Transplantation. Liver Transpl. 2020 Jan;26(1):141-159. Retrieved from https://pubmed.ncbi.nlm.nih.gov/31610081/.

- This review discusses pre- and post-transplant management considerations for patients with end stage liver disease due to NASH.

Sheka AC, et al. (2020). Nonalcoholic Steatohepatitis: A Review. JAMA. 2020 Mar 24;323(12):1175-1183. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/32207804.

- This review discusses the epidemiology, diagnosis and management of NASH.

Jenssen T, et al. (2019). Post-transplant diabetes mellitus in patients with solid organ transplants. Nat Rev Endocrinol. 2019;15(3):172-188. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/30622369.

- This review discusses current evidence on PTDM in patients receiving kidney, heart, liver and lung transplants.

Wong VW, et al. (2019). Emerging medical therapies for non-alcoholic fatty liver disease and for alcoholic hepatitis. Transl Gastroenterol Hepatol. 2019;4:53. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/31463412.

- This review article discussed the novel therapeutic agents and current status of ongoing clinical trials with agents for the treatment of non-alcoholic fatty liver disease and/or alcoholic hepatitis.

Mitchell EL, et al. (2017). Liver Disease in Alpha-1 Antitrypsin Deficiency: Current Approaches and Future Directions. Curr Pathobiol Rep. 2017;5(3):243-252. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/29399420.

- Review of the liver disease caused by alpha-1 antitrypsin deficiency. This review includes a discussion on pathogenesis, epidemiology, diagnostic testing, and recent therapeutic developments.

Kanwar P, et al. (2014). Metal Storage Disorders Wilson Disease and Hemochromatosis. Med Clin North Am. 2014 Jan;98(1):87-102. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24266916.

- This review article discusses the details of diagnosis, treatment, stratification, and survival data in patients with Wilson's disease and hemochromatosis.

Said A, et al. (2013). Non-alcoholic fatty liver disease and liver transplantation: Outcomes and advances. World J Gastroenterol. 2013 Dec 28;19(48):9146-55. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24409043.

- This review article discusses the details of treatment of NAFLD and recurrence after transplantation. The incidence of transplantation rates as well as long-term outcomes after transplant is discussed.

Teckman J. (2013). Liver Disease in Alpha-1 Antitrypsin Deficiency: Current Understanding and Future Therapy. COPD. 2013 Mar;10 Suppl 1:35-43. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/23527737.

- This review article discusses the details of diagnosis, pathophysiology, and clinical management of alpha-1-antitrypsin deficiency and its effect on the liver.

Deugnier Y, et al. (2011). Pathology of Hepatic Iron Overload. Semin Liver Dis. 2011 Aug;31(3):260-71. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/21901656.

- The description of diagnosis and etiologies are presented in this review article. Genetic variations of disease are also discussed as well as some treatment options.

Gan, E et al. (2011). Natural History and Management of HFE-Hemochromatosis. Semin Liver Dis. 2011 Aug;31(3):293-301. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/21901659.

- This review articles discusses commonly raised issues relating to the current natural history, diagnosis, and management of HH patients.

Johncilla M, et al. (2011). Pathology of the Liver in Copper Overload. Semin Liver Dis. 2011 Aug;31(3):239-44. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/21901654.

- This review article discusses copper iron overload and its mechanism in causing liver injury.

Rosencrantz R, et al. (2011). Wilson Disease: Pathogenesis and Clinical Considerations in Diagnosis and Treatment. Semin Liver Dis. 2011 Aug;31(3):245-59. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/21901655.

- This review article discusses the details of diagnosis, treatment, stratification, and survival data in patients with Wilson's disease.

3.5.5 Cholestatic Liver Disease/Cirrhosis and Non-Cholestatic Cirrhosis

Henson JB, et al. (2024). Post-Transplant Management and Complications of Autoimmune Hepatitis, Primary Biliary Cholangitis, and Primary Sclerosing Cholangitis including Disease Recurrence. Clin Liver Dis. 2024;28(1):193-207. Retrieved from https://pubmed.ncbi.nlm.nih.gov/37945160.

- This review article summarizes the management of patients transplanted for autoimmune liver diseases, including pharmacologic strategies to reduce the risk of recurrent liver diseases.

van Hooff MC, et al. (2024). Treatment in primary biliary cholangitis: Beyond ursodeoxycholic acid. Eur J Intern Med. 2024 Feb 2:S0953-6205(24)00037-2. Retrieved from https://pubmed.ncbi.nlm.nih.gov/38307734.

- This review article summarizes the available evidence for pharmacologic treatment options for PBC, including ursodeoxycholic acid, farnesoid X receptor agonists, PPAR agonists, and corticosteroids.

Carbone M, et al. (2023). Liver Transplantation for Primary Sclerosing Cholangitis (PSC) With or Without Inflammatory Bowel Disease (IBD)-A European Society of Organ Transplantation (ESOT) Consensus Statement. Transpl Int. 2023;36:11729. Retrieved from https://pubmed.ncbi.nlm.nih.gov/37841645.

- This consensus statement addresses the management of patients transplanted for PSC, including a discussion of unique immunosuppression considerations in these patients and the use of treatments for IBD, including biologics, before and after transplant.

Dumortier J, et al. (2022). Posttransplant immune-mediated cholangiopathies. Curr Opin Gastroenterol. 2022 Mar 1;38(2):98-103. Retrieved from https://pubmed.ncbi.nlm.nih.gov/35098931/.

- Review of clinical implications and diagnostic issues of post-transplant immune-related cholangiopathies. Immune-mediated cholangiopathies post-transplant can be biliary lesions due to recurrence of PBC or PSC or rejection. Diagnostic workup takes into consideration indication for LT, delay since transplantation, biological abnormalities, imaging clinical context as well as biopsy of the graft.

Montano-Loza AJ, et al. (2022). Risk factors and outcomes associated with recurrent autoimmune hepatitis following liver transplantation. J Hepatol. 2022 Jul;77(1):84-97. Retrieved from https://pubmed.ncbi.nlm.nih.gov/35143897/.

- International, multicenter cohort analysis of liver transplant recipients to identify risk factors associated with recurrent AIH and the association between recurrent disease and patient and graft survival (n=736).
- 5-year and 10-year recurrence rate was 20% and 31%, respectively. Age at LT ≤42 years, use of MMF post-transplant, donor and recipient sex mismatch and high IgG pre-transplant were associated with higher risk of AIH recurrence.
- Recurrent AIH was significantly associated with graft loss and death.

Vuppalanchi R, et al. (2022). Proof-of-concept study to evaluate the safety and efficacy of saroglitazar in patients with primary biliary cholangitis. J Hepatol. 2022 Jan;76(1):75-85. Retrieved from https://pubmed.ncbi.nlm.nih.gov/34487750/.

- Prospective, multicenter, randomized, double-blind, placebo-controlled phase II proof-of-concept trial of 37 patients with PBC who were either resistant or intolerant to ursodeoxycholic acid were randomized to saroglitazar 4 mg (n=13), 2 mg (n=14), or placebo (n=10) for 16 weeks. Saroglitazar was associated with rapid and sustained improvements in alkaline phosphatase level at both 2 mg and 4 mg daily dosing. Further studies evaluating a daily dose of 2 mg and 1 mg are underway due to higher incidence of elevated liver enzymes observed with 4 mg dose.

Liu X, et al. (2022) Efficacy and safety of immune-modulating therapy for primary sclerosing cholangitis: A systematic review and meta-analysis. Pharmacol Ther. 2022 Sep;237:108163. Retrieved from https://pubmed.ncbi.nlm.nih.gov/35271884/.

- Systematic review and meta-analysis of 21 studies (6 RTCs and 15 observational studies) analyzing the efficacy and safety of immunomodulators in patients with PSC. In subgroup

analysis, immunosuppressants (MMF, methotrexate, and tacrolimus) appeared to be most effective with the significant reduction in ALP and AST levels, but had the highest incidence of severe AEs (24.9%). Glucocorticoids (budesonide, prednisolone) moderately reduced ALP level with the lowest incidence of severe AEs (6.1%). Immunomodulators were associated with improvement in ALP, especially in patients with elevated ALP and AST levels at baseline.

Prokopič M, et al. (2021). Management of primary sclerosing cholangitis and its complications: an algorithmic approach. Hepatol Int. 2021 Feb;15(1):6-20. Retrieved from https://pubmed.ncbi.nlm.nih.gov/33377990/.

- Review article on PSC pathogenesis and an algorithmic approach to diagnostic procedures and recommendations for the management of PSC and its complications, as well as promising treatment options subject to current clinical trials.

Hasegawa S, et al. (2021). Cholestatic Liver Disease: Current Treatment Strategies and New Therapeutic Agents. Drugs. 2021 Jul;81(10):1181-1192. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34142342/.

- Review article that discusses the general natural history of PBC and PSC, and provides information on the latest drug therapies currently available and those that are under investigation.

Montano-Loza AJ, et al. (2019). Factors Associated With Recurrence of Primary Biliary Cholangitis After Liver Transplantation and Effects on Graft and Patient Survival. Gastroenterology. 2019 Jan;156(1):96-107.e1. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/30296431.

- Multicenter, international cohort study assessing incidence and risk of PBC recurrence after liver transplantation. PBC recurred in 22% at 5 years and 36% at 10 years post-transplant. Risk factors for recurrence included age <50 years at time of diagnosis, age <60 years at time of transplant, tacrolimus use, and elevated bilirubin or alkaline phosphatase at 6 months post-transplant.

Pena Polanco NA, et al. (2017). Cholestatic Liver Diseases After Liver Transplant. Clin Liver Dis. 2017 May;21(2):403-420. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/28364821.

- Review article that discusses disease recurrence post-transplant and outcomes associated with disease recurrence.

Bosch A, et al. (2015). Preventive administration of UDCA after liver transplantation for primary biliary cirrhosis is associated with a lower risk of disease recurrence. J Hepatol. 2015 Dec;63(6):1449-58. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26282232.

- Multi-center retrospective cohort study evaluating preventative administration of ursodeoxycholic acid (UDCA) on PBC recurrence post-transplant in 90 liver transplant recipients. Preventative UDCA was associated with reduced risk of PBC recurrence after transplant.

Liou IW. (2014). Management of end-stage liver disease. Med Clin North Am. 2014 Jan;98(1):119-52. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24266918.

- The current article reviews various complications associated with end-stage liver disease and treatments for managing complications.

Bjornsson ES, et al. (2013). Drug-induced cholestasis. Clin Liver Dis. 2013 May;17(2):191-209. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/23540497.

- The current article describes risk factors, pathophysiology, and drugs more commonly associated with drug-induced cholestasis occurrence.

Hirschfield GM, et al. (2010). Pathogenesis of cholestatic liver disease and therapeutic approaches. Gastroenterology. 2010 Nov;139(5):1481-96. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/20849855.

- The current article reviews the pathophysiology of cholestasis at the molecular level and provides a brief description of treatment options for managing cholestasis.

Neuberger J. (2003). Liver transplantation for primary biliary cirrhosis: indications and risk of recurrence. J Hepatol. 2003 Aug;39(2):142-8. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/12873808.

- Review article that discusses PBC, outcomes after transplant and PBC recurrence post-transplant.

Hofmann AF. (2002). Cholestatic liver disease: pathophysiology and therapeutic options. Liver. 2002;22 Suppl 2:14-9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12220297.

- The current article reviews the pathophysiology of the development of cholestasis and treatment options for managing cholestasis.

3.6 Miscellaneous

3.6.1 Machine Perfusion

Meurisse N, et al. (2023) Effect of a combined drug approach on the severity of ischemia-reperfusion injury during liver transplant: a randomized clinical trial. JAMA Netw Open. 2023 Feb; 6(2):e230819. Retrieved from https://pubmed.ncbi.nlm.nih.gov/36853611/.

- In this open-label, randomized controlled trial, liver transplant recipients were randomized to either the standard cold preservation method vs the standard method with a combined drug approach (epoprostenol ex situ in portal vein along with the following medications which were administered to recipient prior to procurement: a-tocopherol, melatonin, antithrombin III, infliximab, apotransferrin, recombinant erythropoietin-b, C1 inhibitor, and glutathione). The primary outcome was peak AST within 72 hours, which did not differ between groups.

Markmann JF, et al. (2022). Impact of Portable Normothermic Blood-Based Machine Perfusion on Outcomes of Liver Transplant: The OCS Liver PROTECT Randomized Clinical Trial. JAMA Surg. 2022 Mar;157(3):189-198. Retrieved from https://pubmed.ncbi.nlm.nih.gov/34985503/.

- First evidence (multicenter, randomized clinical trial) to suggest that normothermic machine perfusion for deceased donor livers is associated with reduced ischemia reperfusion injury, which contributed to reduced early organ dysfunction and increased utilization of DCD donors.

3.6.2 Donor Interventions

Pagano D, et al. (2022). Donor simvastatin treatment is safe and might improve outcomes after liver transplantation: a randomized clinical trial. Transplantation. 2022 Dec;106(12):2379-2390. Retrieved from https://pubmed.ncbi.nlm.nih.gov/35862782/.

- This is a double-blind, randomized, prospective trial that assessed the incidence of patient and graft survival at 90- and 180-days post-transplant in recipients of DBD liver transplants. The intervention group of donors were given one dose of simvastatin 80 mg prior to procurement, whereas the control group did not receive a statin. Recipients of liver transplants from donors in the intervention group demonstrated significantly improved survival at 6 months post-transplant (p=0.0435).