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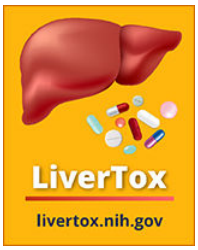

Transplant Agents

Updated: February 17, 2020.

OVERVIEW

Solid organ transplantation has been made possible by the development of potent immunosuppressive agents which block cellular rejection adequately for survival of the transplanted organ and induction of at least partial tolerance. The first regimens that were found to successfully prevent cellular rejection consisted of high doses of corticosteroids and an immunosuppressive antimetabolite such as azathioprine, 6-mercaptopurine or cyclophosphamide. These combinations allowed for the initial successes in renal, liver, lung and heart transplantation in the 1950s and 1960s. However, acute and chronic rejection as well as complications of high dose corticosteroid therapy remained major problems. The subsequent introduction of the calcineurin inhibitors, cyclosporine and tacrolimus in the 1980s placed organ transplantation on a solid basis, leading to its acceptance as the standard of care for end-stage kidney, liver, heart and lung disease. The further addition of the newer, more specific antiproliferative and immunosuppressive agents–mycophenolate mofetil (1995) and sirolimus (1999)–have further improved the management of patients after solid organ transplantation. All of these agents are associated with mild liver test abnormalities that occur early during therapy or shortly after transplantation and that resolve rapidly with dose modification. While these potent immunosuppressive agents all have some degree of liver toxicity, clinically significant injury is rare and has invariably been mild and rapidly reversible with dose modification or switching to another agent. These agents are often used in patients with underlying liver disease or who are receiving multiple potentially hepatotoxic drugs, so that their role in causing hepatic injury is not always clear.

The following drugs used to prevent transplant rejection are discussed separately. The references regarding the hepatotoxicity and safety of these agents are given together below.

- Antithymocyte Globulin
- Cyclosporine
- Mycophenolate
- Sirolimus
- Tacrolimus
- Monoclonal Antibodies

o Alemtuzumab

o Basiliximab

o Daclizumab

o Muromonab

- Plerixafor

ANNOTATED BIBLIOGRAPHY

References updated: 17 February 2020

Zimmerman HJ. Cyclosporine. Oncotherapeutic and immunosuppressive agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 697-8.

(Expert review of hepatotoxicity published in 1999; cyclosporine therapy was associated with a high rate of cholestatic liver enzyme elevations ranging from 4-86% and occasional instances of cholestatic hepatitis, some features of which were reproducible in animal models; tacrolimus, sirolimus, and mycophenolate are not discussed).

Reuben A. Hepatotoxicity of immunosuppressive drugs. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 569-92.

(Review of hepatotoxicity of immunosuppressive agents mentions that reports of hepatotoxicity of cyclosporine have decreased since the 1980s, perhaps because of monitoring of serum levels and lower doses used; liver injury from tacrolimus, sirolimus and mycophenolate is rare and usually rapidly reversible).

Krensky AM, Azzi JR, Hafler DA. Immnosuppressants and tolerogens. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 637-54.

(Textbook of pharmacology and therapeutics).

Klintmalm GB, Iwatsuki S, Starzl TE. Cyclosporin A hepatotoxicity in 66 renal allograft recipients. Transplantation 1981; 32:4 88-9.

(Among 66 renal transplant recipients on cyclosporine, 13 [17%] had rise of bilirubin above 2.0 [range 2.1-4.5] mg/dL, with minimal or no change in ALT or Alk P, and all episodes were mild and easily managed by dose reduction).

Kowdley KV, Keeffe EB. Hepatotoxicity of transplant immunosuppressive agents. Gastroenterol Clin North Am. 1995;24:991–1001. PubMed PMID: 8749908.

(Review of reports of hepatotoxicity from cyclosporine in form of mild hyperbilirubinemia, mild-to-moderate serum enzyme elevations and biliary sludge and stones).

Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver transplantation for acute liver failure from drug-induced liver injury in the United States. Liver Transpl. 2004;10:1018–23. PubMed PMID: 15390328.

(Among ~50,000 liver transplants reported to UNOS between 1990 and 2002, 270 [0.5%] were done for drug induced acute liver failure, 124 for acetaminophen and 137 for other drugs or toxins, but none for agents used to prevent transplant rejection).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology. 2008;135:1924–34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US collected between 2004 and 2008, none were attributed to cyclosporine, tacrolimus, sirolimus or mycophenolate).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology. 2010;52:2065–76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury, but none to an agent used to prevent transplant rejection).

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A, Chirino R, et al. Profile of idiosyncratic drug induced liver injury in Latin America: an analysis of published reports. Ann Hepatol. 2014;13:231–9. PubMed PMID: 24552865.

(Among 176 reports of drug induced liver injury from Latin America published between 1996 and 2012, one was attributed to mycophenolate but none to cyclosporine, sirolimus or tacrolimus).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52. e7.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, one case was attributed to cyclosporine, but none to tacrolimus, sirolimus, or mycophenolate mofetil).