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Daclizumab

Updated: November 10, 2017.

OVERVIEW

Introduction

Daclizumab is a humanized monoclonal antibody to CD25, the alpha subunit of the IL2 receptor on T lymphocytes, which was used in the past to treat and prevent acute cellular rejection after solid organ transplantation and is currently approved as a second line therapy of refactory relapsing multiple sclerosis. Daclizumab has been linked to occasional mild-to-moderate serum enzyme elevations during therapy, and to rare but potentially severe and fatal instances of immune mediated, clinically apparent liver injury.

Background

Daclizumab (da kliz' ue mab) is a humanized monoclonal immunoglobulin G1 antibody to the alpha subunit of the IL2 receptor (CD25). The IL2 receptor is found on T cells and its engagement results in activation and proliferation of T cells and generation of proinflammatory cytokines. Inhibition of the receptor by antibody results in prevention of activation and inhibition of T cell responses. Daclizumab has been shown to be effective in reducing in incidence of acute rejection after renal, liver, heart and lung transplantation. Daclizumab was approved for use in preventing acute rejection after renal transplantation in 1997 and was used largely as a part of induction regimens at and around the time of transplant. However, daclizumab was subsequently withdrawn by the sponsor in 2007 because of market factors rather than toxicity or lack of efficacy. Subsequently daclizumab was evaluated as therapy of several autoimmune conditions and was shown to decrease relapses in patients with refractory, relapsing multiple sclerosis. Daclizumab was reintroduced in 2016 with indications being second line therapy for refractory multiple sclerosis in 2016. Daclizumab is available in liquid solution in single use syringes or autoinjectors of 150 mg (150 mg/mL) under the brand name Zinbryta. The recommended dose is 150 mg subcutaneously once monthly. Side effects of daclizumab when used as therapy of multiple sclerosis can include infusion reactions, chills, fever, skin rash, fatigue, leukopenia and infections. Less common, but potentially severe adverse events include immune mediated disorders, severe infections, depression, suicidal ideation and hypersensitivity reactions including anaphylaxis.

Hepatotoxicity

When given as a part of induction therapy for solid organ transplantation, daclizumab was not linked to instances of serum enzyme elevations or clinically apparent liver injury. While adverse events at the time of organ transplantation are common, they were not found to be more frequent in patients receiving induction therapy with daclizumab than in those given conventional immunosuppressive regimens.

In contrast, in studies of long term daclizumab therapy for autoimmune conditions such as multiple sclerosis, transient and asymptomatic elevations of serum aminotransferase levels were reported in up to one third of

patients, and rose to above 5 times ULN in 4% to 6% of daclizumab vs 1% of placebo and 3% of interferon beta treated subjects. These serum enzyme elevations were usually transient and asymptomatic, but in rare instances led to jaundice and symptomatic acute liver injury. In preregistration clinical trials, 0.3% of patients treated with daclizumab for more than 6 months developed hepatitis with autoimmune features, and at least one patient died despite discontinuation of the monoclonal antibody therapy. The onset of the clinically apparent liver injury was usually within 1 to 6 months after starting the monthly injections, but some cases arose shortly after discontinuation of treatment. The clinical features of the liver injury suggested an immune mediated hepatitis with marked elevations in serum aminotransferase levels sometimes accompanied by autoantibody formation, increased immunoglobulin levels or liver biopsy histology demonstrating acute hepatocellular injury with lymphocytic infiltrates including plasma cells. Because of these reports, daclizumab product labels include a black box warning about hepatic injury, recommend prospective monitoring before, during and for several months after treatment, and state that daclizumab is contraindicated in patients with preexisting liver disease.

Likelihood score: C (probable cause of clinically apparent liver injury).

Daclizumab is a potent immunosuppressive agent and may be capable of causing reactivation of chronic hepatitis B. However, its use in prevention of organ rejection as well as therapy of refractory multiple sclerosis has not been linked to cases of reactivation. In trials of daclizumab in multiple sclerosis and uveitis, cases of reactivation of hepatitis B or worsening of hepatitis C were not reported, but patients with coexisting hepatitis B or C were typically excluded from early phase trials.

Drug Class: Monoclonal Antibodies, Transplant Agents, Multiple Sclerosis Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Daclizumab – Zinbryta®

DRUG CLASS

Transplant Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Daclizumab	**152923-56-3**	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 10 November 2017

Reuben A. Hepatotoxicity of immunosuppressive drugs. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2011, pp. 569-91.

(Review of hepatotoxicity of immunosuppressive agents mentions rituximab and problems of reactivation of hepatitis B, but also states that "the biological immunosuppressants are largely free from hepatotoxicity, with the exception of the TNF alpha antagonists").

Chabner BA, Barnes J, Neal J, Olson E, Mujagiv H, Sequist L, Wilson W, et al. Targeted therapies: tyrosine kinase inhibitors, monoclonal antibodies, and cytokines. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1731-53.

(Textbook of pharmacology and therapeutics).

Vincenti F, Kirkman R, Light S, Bumgardner G, Pescovitz M, Halloran P, Neylan J, et al. Interleukin-2-receptor blockade with daclizumab to prevent acute rejection in renal transplantation. Daclizumab Triple Therapy Study Group. N Engl J Med 1998; 338: 161-5. PubMed PMID: 9428817.

(Among 260 patients undergoing renal transplantation treated with cyclosporine, azathioprine and prednisone with or without daclizumab, acute rejection was less common with daclizumab induction therapy [22% vs 35%] and there was no increase in opportunistic infections or adverse events; no mention of ALT elevations or hepatotoxicity).

New monoclonal antibodies to prevent transplant rejection. Med Lett Drugs Ther 1998; 40 (1036): 93-4. PubMed PMID: 9774964.

(Concise review of the efficacy and safety of basiliximab and daclizumab, two monoclonal antibodies to the IL2 receptor, shortly after their approval for use in transplantation in the US; no mention of ALT elevations or hepatotoxicity for either).

Heffron TG, Pillen T, Smallwood GA, Welch D, Oakley B, Romero R. Pediatric liver transplantation with daclizumab induction. Transplantation 2003; 75: 2040-3. PubMed PMID: 12829908.

(Among 81 children undergoing liver transplantation, the rate of acute rejection was lower with daclizumab induction therapy than without [15% vs 50%] and no adverse events were reported).

Nussenblatt RB, Thompson DJ, Li Z, Chan CC, Peterson JS, Robinson RR, Shames RS, et al. Humanized anti-interleukin-2 (IL-2) receptor alpha therapy: long-term results in uveitis patients and preliminary safety and activity data for establishing parameters for subcutaneous administration. J Autoimmun 2003; 21: 283-93. PubMed PMID: 14599854.

(Among 10 patients with severe uveitis treated with varying doses of daclizumab [every 2-6 weeks, intravenously or subcutaneously], 7 were maintained on therapy for 4 years, 2 of whom had minor transient serum ALT elevations which were considered only possibly related to the monoclonal antibody therapy).

Sellers MT, McGuire BM, Haustein SV, Bynon JS, Hunt SL, Eckhoff DE. Two-dose daclizumab induction therapy in 209 liver transplants: a single-center analysis. Transplantation 2004; 78: 1212-7. PubMed PMID: 15502722.

(Among 352 liver transplant recipients, the 209 who received daclizumab induction therapy had lower rates of acute rejection [25% vs 39%] and hepatitis C recurrent rates were similar; no mention of hepatotoxicity).

Morris JA, Hanson JE, Steffen BJ, Chu AH, Chi-Burris KS, Gotz VP, Gordon RD. Daclizumab is associated with decreased rejection and improved patient survival in renal transplant recipients. Clin Transplant 2005; 19 (3): 340-5. PubMed PMID: 15877795.

(Analysis of SRTR database on renal transplant recipients receiving daclizumab [n=8203] or no induction treatment [n=25368] in the US between 1998 and 2003 found lower reported rates of rejection with daclizumab [13% vs 17% after 3 years] and improved patient and graft survival, with no excess mortality from malignancy or opportunistic infections).

Rostaing L, Cantarovich D, Mourad G, Budde K, Rigotti P, Mariat C, Margreiter R, et al.; CARMEN Study Group. Corticosteroid-free immunosuppression with tacrolimus, mycophenolate mofetil, and daclizumab induction in renal transplantation. Transplantation 2005; 79: 807-14. PubMed PMID: 15818323.

(Among 538 renal transplant recipients followed for at least 6 months, there were no differences in rates of acute rejection, patient or graft survival or in overall safety between those given daclizumab induction therapy and corticosteroid avoidance or standard immunosuppressive treatment).

Mottershead M, Neuberger J. Daclizumab. Expert Opin Biol Ther 2007; 7: 1583-96. PubMed PMID: 17916050.

(Review of the mechanism of action, pharmacology, efficacy and safety of daclizumab; no mention or discussion of hepatotoxicity or ALT elevations).

Otero A, Varo E, de Urbina JO, Martín-Vivaldi R, Cuervas-Mons V, González-Pinto I, Rimola A, et al. A prospective randomized open study in liver transplant recipients: daclizumab, mycophenolate mofetil, and tacrolimus versus tacrolimus and steroids. Liver Transpl 2009; 15: 1542-52. PubMed PMID: 19877219.

(Among 157 patients underlying liver transplantation treated with induction therapy using daclizumab or a standard corticosteroid containing regimen, acute rejection was more frequent with standard therapy [27% vs 12% within 24 weeks], but patient and graft survival and rates of hepatitis C recurrence were similar).

Wynn D, Kaufman M, Montalban X, Vollmer T, Simon J, Elkins J, O'Neill G, et al.; CHOICE investigators. Daclizumab in active relapsing multiple sclerosis (CHOICE study): a phase 2, randomised, double-blind, placebo-controlled, add-on trial with interferon beta. Lancet Neurol 2010; 9: 381-90. PubMed PMID: 20163990.

(Among 230 patients with relapsing multiple sclerosis who were treated with beta interferon with or without daclizumab, "common adverse events were equally distributed across groups", but serious adverse events were more common in daclizumab treated subjects; no mention of ALT elevations or hepatotoxicity).

Kandus A, Arnol M, Omahen K, Oblak M, Vidan-Jeras B, Kmetec A, Bren AF. Basiliximab versus daclizumab combined with triple immunosuppression in deceased donor renal transplantation: a prospective, randomized study. Transplantation 2010; 89: 1022-7. PubMed PMID: 20075788.

(Among 212 patients given induction therapy before renal transplantation with either basiliximab or daclizumab, there were no differences in rates of rejection, graft or patient survival or adverse events; no mention of ALT elevations or hepatotoxicity).

Cai J, Terasaki PI. Induction immunosuppression improves long-term graft and patient outcome in organ transplantation: an analysis of United Network for Organ Sharing registry data. Transplantation 2010; 90: 1511-5. PubMed PMID: 21057388.

(Since 2003, most solid organ transplant recipients have received induction therapy, and analyses of the UNOS registry for this period shows highest rates of patient and graft survival with alemtuzumab [89% 5 year patient survival] as compared to antithymocyte globulin [89%], basiliximab [84%], daclizumab [77%], steroids [75%] or no induction [71%]).

Hanaway MJ, Woodle ES, Mulgaonkar S, Peddi VR, Kaufman DB, First MR, Croy R, et al. INTAC Study Group. Alemtuzumab induction in renal transplantation. N Engl J Med 2011; 364: 1909-19. PubMed PMID: 21591943.

(Among 474 patients undergoing renal transplantation and given alemtuzumab or convention induction therapy, acute rejection rates during the first 3 years were lower with alemtuzumab than basiliximab in low risk patients [15% vs 24%], but were similar with alemtuzumab and antithymocyte globulin in high risk patients [30% vs 24%]).

Klintmalm GB, Davis GL, Teperman L, Netto GJ, Washburn K, Rudich SM, Pomfret EA, et al. A randomized, multicenter study comparing steroid-free immunosuppression and standard immunosuppression for liver transplant recipients with chronic hepatitis C. Liver Transpl 2011; 17: 1394-403. PubMed PMID: 21850690.

(Among 295 patients undergoing liver transplantation for chronic hepatitis C treated with daclizumab, mycophenolate and tacrolimus or a corticosteroid-containing regimen without daclizumab, there were no differences between groups in graft or patient survival or in biochemical and histological severity of recurrent hepatitis C).

Wroblewski K, Sen HN, Yeh S, Faia L, Li Z, Sran P, Gangaputra S, et al. Long-term daclizumab therapy for the treatment of noninfectious ocular inflammatory disease. Can J Ophthalmol 2011; 46: 322-8. PubMed PMID: 21816251.

(Among 39 patients with chronic uveitis treated with daclizumab for an average of 40 months, skin toxicity was the most common adverse event, but did not prevent continuation of therapy; mentions elevated liver function tests, but no details given and no other mention of hepatotoxicity or discontinuations for liver toxicity).

Gold R, Giovannoni G, Selmaj K, Havrdova E, Montalban X, Radue EW, Stefoski D, et al.; SELECT study investigators. Daclizumab high-yield process in relapsing-remitting multiple sclerosis (SELECT): a randomised, double-blind, placebo-controlled trial. Lancet 2013; 381 (9884): 2167-75. PubMed PMID: 23562009.

(Among 621 patients with relapsing multiple sclerosis treated with daclizumab [150 or 300 mg] or placebo subcutaneously once weekly for 52 weeks, patients on daclizumab had fewer relapses, but rates of skin toxicity [18-22% vs 13%] and infections [50-54% vs 44%] were more common; rates of ALT elevations were similar [33-37% vs 34%], but were above 5 times ULN in 2% vs <1%).

Giovannoni G, Gold R, Selmaj K, Havrdova E, Montalban X, Radue EW, Stefoski D, et al.; SELECTION Study Investigators. Daclizumab high-yield process in relapsing-remitting multiple sclerosis (SELECTION): a multicentre, randomised, double-blind extension trial. Lancet Neurol 2014; 13: 472-81. PubMed PMID: 24656609.

(Among 517 patients with multiple sclerosis who participated in the SELECT trial [Gold 2013] and were enrolled in an extension study, one developed hepatitis after stopping and restarting daclizumab, ALT levels rising to 195 U/L after 8 weeks and 638 U/L at 12 weeks at which time serum bilirubin levels rose and symptoms of liver failure appeared, with increased IgG levels and liver histology at autopsy suggesting autoimmune hepatitis).

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. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 5 cases were attributed to monoclonal antibodies, but none to daclizumab).

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/761029Orig1s000MedR.pdf

(FDA medical review of daclizumab describing the hepatic adverse events observed in the preregistration trials in multiple sclerosis which included 7 cases [0.3%] of suspected autoimmune hepatitis including one death among the 2236 patients in the safety assessment).

Giovannoni G, Kappos L, Gold R, Khatri BO, Selmaj K, Umans K, Greenberg SJ, et al. Safety and tolerability profile of daclizumab in patients with relapsing-remitting multiple sclerosis: An integrated analysis of clinical studies. Mult Scler Relat Disord 2016; 9: 36-46. PubMed PMID: 27645341.

(Analysis of safety of daclizumab based upon six clinical studies and 2236 treated patients including ALT elevations at least 3 times ULN which occurred in 10% and were mostly asymptomatic and self-limiting, not recurring with

continuation or restarting therapy, but accounting for drug discontinuation in 5% of subjects and qualifying as a serious adverse event in 1%).

Gold R, Radue EW, Giovannoni G, Selmaj K, Havrdova E, Stefoski D, Sprenger T, et al. Safety and efficacy of daclizumab in relapsing-remitting multiple sclerosis: 3-year results from the SELECTED open-label extension study. BMC Neurol 2016; 16: 117. PubMed PMID: 27461166.

(Among 410 patients with multiple sclerosis enrolled in an extension study of daclizumab with 854 patient-years of exposure, hepatic adverse events occured in 15% that were serious in 1%; ALT or AST elevations above 3 times ULN occurred in 9%, above 5 times ULN in 4%, and 2 patients developed hepatitis with jaundice).

Daclizumab (Zinbryta) for multiple sclerosis. Med Lett Drugs Ther 2016; 58 (1503): 117-9. PubMed PMID: 27603962.

(Concise summary of the mechanism of action, clinical efficacy, safety and costs of daclizumab shortly after its approval for use in relapsing multiple sclerosis in the US; mentions that it has a black box warning regarding liver injury, that it is contraindicated in patients with liver disease, and that liver tests should be monitored monthly during treatment and 6 months after the last dose).

Herwerth M, Hemmer B. Daclizumab for the treatment of relapsing-remitting multiple sclerosis. Expert Opin Biol Ther 2017; 17: 747-53. PubMed PMID: 28286970.

(Review of the mechanism of action, clinical efficacy and safety of daclizumab as therapy of multiple sclerosis concludes that "given its substantial effectiveness, daclizumab can be an attractive option for patients with highly active MS").

Risk of severe liver injury with daclizumab (Zinbryta). Drug Ther Bull 2017; 55: 110. PubMed PMID: 28978627.

(Warning on the risk of severe liver injury from daclizumab from the Medicines and Healthcare Products Regulatory Agency mentioning 4 cases under review).