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Abatacept

Updated: January 10, 2016.

OVERVIEW

Introduction

Abatacept is a recombinant fusion protein of the cell surface marker CTLA-4 and immunoglobulin that acts by interfering with T cell activation and is used to treat rheumatoid arthritis. Abatacept has been linked to a low rate of serum enzyme elevations during therapy, but has not been linked to cases of idiosyncratic, clinically apparent liver injury with jaundice. Because abatacept is a potent inhibitor of lymphocyte function, it may cause reactivation of chronic hepatitis B in susceptible patients.

Background

Abatacept (a bat' a sept) is a recombinant fusion protein that combines the extracellular domain of the cytotoxic T lymphocyte associated antigen-4 (CTLA-4) with the heavy chain fragment of immunoglobulin G. Abatacept blocks the actions of CTLA-4, which is important in the co-stimulatory pathway of activation of T cells. Blocking CTLA-4 inhibits maturation and activation of T cells, T cell proliferation and production of proinflammatory cytokines, such as tumor necrosis factor (TNF), interferon gamma and interleukin 2. Abatacept has been evaluated in several autoimmune inflammatory conditions, including rheumatoid and psoriatic arthritis, lupus erythematosis and inflammatory bowel disease. Abatacept was approved for use in the United States in 2005, but current formal indications are limited to rheumatoid arthritis and juvenile idiopathic arthritis. Abatacept is available under the brand name Orencia as a lyophilized power for intravenous administration in single use vials of 250 mg and as a solution for subcutaneous administration in single use syringes of 125 mg/mL. In adults, abatacept may be given subcutaneously (every week) or intravenously (at weeks 0, 2, 4 and then every 4 weeks) in doses based upon body weight ranging from 500 to 1000 mg. The dose in children is 10 mg/kg intravenously at weeks 0, 2, 4 and then every 4 weeks. Common side effects include infusion reactions of chills, fever and hypertension and nonspecific symptoms of headache, dizziness, body pain and rash. Acute hypersensitivity reactions occur in <1% of patients and anaphylaxis in <0.1%. Less common, but potentially severe side effects include an increased risk of infections and possibly reactivation of tuberculosis or hepatitis B.

Hepatotoxicity

In prelicensure controlled trials, serum ALT elevations occurred in 2% to 3% of abatacept and a similar proportion of placebo treated subjects. The elevations were usually mild-to-moderate in severity, asymptomatic and self-limited in course. ALT elevations above 5 times the upper limit of normal (ULN) occurred <1% of abatacept recipients, and only rare patients had to stop therapy because of serum enzyme elevations. Clinically apparent liver injury is not listed as a potential side effect in the product label for abatacept, but there has been at

least one case report of acute liver injury with symptoms or jaundice attributed to abatacept: a case of severe acute hepatitis accompanied by ANA positivity and a response to corticosteroid therapy (Case 1). Thus, abatacept may precipitate an acute autoimmune hepatitis but this is quite rare.

Abatacept is a potent immunosuppressive agent and reactivation of hepatitis B in susceptible patients is theoretically possible, but has not been reported despite considerable experience with its use in patients with inactive or resolved hepatitis B. Reactivation of hepatitis B typically occurs in patients who are HBsAg carriers with inactive liver disease. During early stages of the immunosuppressive therapy, levels of HBV DNA rise, followed by increases in serum ALT and AST and then symptoms and jaundice. The onset of liver injury is usually after 3 to 6 monthly injections of the immunomodulatory agent. Nevertheless, there have been no clear instances of reactivation of hepatitis B attributed to abatacept, and routine screening for hepatitis B and prophylaxis against reactivation is not recommended.

Likehood score: D (possible but rare cause of clinically apparent liver injury).

Mechanism of Injury

Abatacept is a recombinant human protein and as such is unlikely to be intrinsically hepatotoxic. Because it has immunomodulatory actions, it may cause reactivation of hepatitis B or induce an autoimmune liver reaction.

Outcome and Management

Abatacept has been linked to minor serum enzyme elevations and to rare instances of acute liver injury with jaundice. Discontinuation for serum enzyme elevations is rarely necessary, but should be done if the elevations are accompanied by symptoms or jaundice or for persistent ALT elevations of more than 5 times ULN. There is no information on cross sensitivity to liver injury between abatacept and other immunomodulatory cytokines.

Drug Class: Antirheumatic Agents

CASE REPORT

Case 1. Acute liver injury attributed to abatacept therapy.

[Modified from: Iwanaga N, Origuchi T, Terada K, Ueki Y, Kamo Y, Kinoshita N, Yonemitsu N, et al. Rheumatoid arthritis complicated with severe liver injury during treatment with abatacept. Mod Rheumatol 2014; 24: 874-6. PubMed Citation]

A 61 year old Japanese woman with Sjögren syndrome and rheumatoid arthritis developed epigastric pain and nausea after four infusions of abatacept. She had been treated previously with methotrexate, infliximab, adalimumab, tacrolimus and tocilizumab without a lasting response. She had no history of liver disease, drug allergies, risk factors for viral hepatitis or alcohol abuse. Physical examination showed jaundice and epigastric tenderness. Laboratory tests show a total bilirubin of 15.2 mg/dL (12.1 mg/dL direct) with an ALT of 2217 U/L, AST 4310 U/L, alkaline phosphatase 1388 U/L and prothrombin time index 50%. Tests for hepatitis A, B (including HBV DNA) and C were negative, as were IgM antibodies to cytomegalovirus and Epstein Barr virus. The ANA was positive (1:1280), IgG was elevated (2,030 mg/dL) and rheumatoid factor was present (56.8 IU/mL), but SMA and AMA were negative. Over the next few weeks, she worsened with serum bilirubin rising to 24 mg/dL, prothrombin activity falling to 40% and appearance of hepatic encephalopathy and ascites. She was treated with high doses of methylprednisolone and plasma exchange. She was evaluated for emergency liver transplantation, but then began to improve spontaneously. Over the next several months, liver tests improved and were normal 6 months later.

Key Points

Medication:	Abatacept (500 mg, four intravenous infusions)
Pattern:	Mixed (R=4.6)
Severity:	4+ (jaundice, hospitalization, abnormal INR, hepatic coma)
Latency:	~6 weeks
Recovery:	~8 weeks
Other medications:	None concurrently

Comment

This case is an example of an acute hepatitis with a "mixed" pattern of serum enzyme elevations and severe course arising after 4 to 6 weeks of abatacept therapy of rheumatoid arthritis. Other common causes of acute liver injury were excluded. Tests for hepatitis B documented that the hepatitis was not due to reactivation. Autoimmune features were present, including high titers of ANA and elevations in IgG levels, but these might also have been present because of the underlying disease. Nonetheless, the course and outcome are most compatible with an autoimmune hepatitis induced by the immunomodulatory agent. This reaction must be quite rare.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Abatacept – Orencia®

DRUG CLASS

Antirheumatic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Abatacept	332348-12-6	Recombinant Protein	Not Available

ANNOTATED BIBLIOGRAPHY

References updated:10 January 2016

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 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).

Kremer JM, Westhovens R, Leon M, Di Giorgio E, Alten R, Steinfeld S, Russell A, et al. Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. N Engl J Med 2003; 349: 1907-15. PubMed PMID: 14614165.

(Among 339 patients with rheumatoid arthritis not responding adequately to methotrexate who were treated with 1 of 2 doses of abatacept or placebo for six months, response rates were 60% with higher doses of abatacept, 42% with lower doses, and 35% with placebo, while rates of adverse events were similar and no serious adverse event was attributed to drug; no mention of ALT elevations or hepatotoxicity).

Genovese MC, Becker JC, Schiff M, Luggen M, Sherrer Y, Kremer J, Birbara C, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. N Engl J Med 2005; 353: 1114-23. PubMed PMID: 16162882.

(Among 389 patients with rheumatoid arthritis not responding to anti-TNF agents who were treated with abatacept or placebo for 6 months, clinical responses occurred with 50% of abatacept vs 20% of placebo recipients and overall rates of side effects were similar, although abatacept recipients were more likely to have infections [38% vs 32%] and acute infusion reactions [5% vs 3%]).

Abatacept (Orencia) for rheumatoid arthritis. Med Lett Drugs Ther 2006; 48 (1229): 17-8. PubMed PMID: 16498306.

(Concise review of the mechanism of action, efficacy, safety and costs of abatacept for rheumatoid arthritis; mentions adverse events of increased rates of infections, especially when combined with anti-TNF agents).

Schiff M, Keiserman M, Codding C, Songcharoen S, Berman A, Nayiager S, Saldate C, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis 2008; 67: 1096-103. PubMed PMID: 18055472.

(Among 416 patients with rheumatoid arthritis not responding to methotrexate who were treated with abatacept, infliximab or placebo for 6 months, clinical responses were similar for abatacept and infliximab and side effect rates were similar).

Khraishi M, Russell A, Olszynski WP. Safety profile of abatacept in rheumatoid arthritis: a review. Clin Ther 2010; 32: 1855-70. PubMed PMID: 21095481.

(Systematic review of the literature on safety of abatacept including analysis of 7 placebo controlled trials and 5 with long term follow up; no mention of ALT elevations of hepatotoxicity).

Ruperto N, Lovell DJ, Quartier P, Paz E, Rubio-Pérez N, Silva CA, Abud-Mendoza C, et al.; Paediatric Rheumatology International Trials Organization and the Pediatric Rheumatology Collaborative Study Group. Long-term safety and efficacy of abatacept in children with juvenile idiopathic arthritis. Arthritis Rheum 2010; 62: 1792-802. PubMed PMID: 20191582.

(Among 153 children with juvenile idiopathic arthritis treated with abatacept in a long term extension study, none developed a severe hepatic adverse reaction; no mention of ALT elevations).

Genovese MC, Covarrubias A, Leon G, Mysler E, Keiserman M, Valente R, Nash P, et al. Subcutaneous abatacept versus intravenous abatacept: a phase IIIb noninferiority study in patients with an inadequate response to methotrexate. Arthritis Rheum 2011; 63: 2854-64. PubMed PMID: 21618201.

(Among 1457 patients with rheumatoid arthritis treated with either intravenous or subcutaneous abatacept for 6 months, both beneficial responses and adverse events were similar in the two groups; no mention of ALT elevations or hepatotoxicity).

Mease P, Genovese MC, Gladstein G, Kivitz AJ, Ritchlin C, Tak PP, Wollenhaupt J, et al. Abatacept in the treatment of patients with psoriatic arthritis: results of a six-month, multicenter, randomized, double-blind, placebo-controlled, phase II trial. Arthritis Rheum 2011; 63: 939-48. PubMed PMID: 21128258.

(Among 170 patients with psoriatic arthritis treated with 1 of 3 doses of abatacept or placebo for 6 months, response rates were 33%, 48% and 42% in the abatacept and 19% in the placebo group, and side effects were slightly higher with high dose abatacept; no mention of ALT elevations or hepatotoxicity).

Drugs for rheumatoid arthritis. Treat Guidel Med Lett 2012; 10 (117): 37-44; PubMed PMID: 22538522.

(Concise review of therapy of rheumatoid arthritis mentions that abatacept can cause acute infusion reactions and probably increases the risk for serious infections, but not tuberculosis).

Grasland A, Sterpu R, Boussoukaya S, Mahe I. Autoimmune hepatitis induced by adalimumab with successful switch to abatacept. Eur J Clin Pharmacol 2012; 68: 895-8. PubMed PMID: 22205272.

(35 year old woman with seronegative arthritis developed rise in ALT [from 18 to 266 U/L, ANA 1:80, SMA 1:320] two months after starting adalimumab, which fell to normal on stopping prednisone therapy and did not recur on starting abatacept).

Sandborn WJ, Colombel JF, Sands BE, Rutgeerts P, Targan SR, Panaccione R, Bressler B, et al. Abatacept for Crohn's disease and ulcerative colitis. Gastroenterology 2012; 143: 62-69.e4. PubMed PMID: 22504093.

(Pooled results from 4 controlled trials of abatacept in inflammatory bowel disease showing little evidence of efficacy and an increase in adverse events compared to placebo; no mention of ALT elevations or hepatotoxicity).

Weinblatt ME, Moreland LW, Westhovens R, Cohen RB, Kelly SM, Khan N, Pappu R, et al. Safety of abatacept administered intravenously in treatment of rheumatoid arthritis: integrated analyses of up to 8 years of treatment from the abatacept clinical trial program. J Rheumatol 2013; 40: 787-97. PubMed PMID: 23588946.

(Analysis of pooled results from 8 clinical trials of intravenous abatacept including data on 3173 patients for up to 8 years of treatment found no increase in rates of adverse events with long term therapy; no mention of ALT elevations or hepatotoxicity).

Westhovens R, Kremer JM, Emery P, Russell AS, Alten R, Barré E, Dougados M. Long-term safety and efficacy of abatacept in patients with rheumatoid arthritis and an inadequate response to methotrexate: a 7-year extended study. Clin Exp Rheumatol 2014; 32: 553-62. PubMed PMID: 25005467.

(Analysis of long term open-label extension study of abatacept in 219 patients with psoriasis, of whom 114 were still receiving drug after 7 years, found sustained clinical benefits and no increase in rates of adverse events; no mention of ALT elevations or hepatotoxicity and no episodes of tuberculosis).

Takeuchi T, Matsubara T, Urata Y, Suematsu E, Ohta S, Honjo S, Abe T, et al.; Japan Abatacept Study Group. Phase III, multicenter, open-label, long-term study of the safety of abatacept in Japanese patients with rheumatoid arthritis and an inadequate response to conventional or biologic disease-modifying antirheumatic drugs. Mod Rheumatol 2014; 24: 744-53. PubMed PMID: 24754273.

(Among 217 Japanese patients with rheumatoid arthritis treated intravenously with abatacept for an average of 3 years, response rates ranged from 61-81% and were sustained; ALT elevations occurred in 11.5%, but none were considered serious; no mention of reactivation of hepatitis B and no patient developed tuberculosis).

Furie R, Nicholls K, Cheng TT, Houssiau F, Burgos-Vargas R, Chen SL, Hillson JL, et al. Efficacy and safety of abatacept in lupus nephritis: a twelve-month, randomized, double-blind study. Arthritis Rheumatol 2014; 66: 379-89. PubMed PMID: 24504810.

(Among 298 patients with lupus nephritis treated with 2 doses of abatacept or placebo for 12 months, response rates were similar in all three groups, and adverse events were similar except for higher rates of infection with abatacept; no mention of ALT elevations or hepatotoxicity).

Iwanaga N, Origuchi T, Terada K, Ueki Y, Kamo Y, Kinoshita N, Yonemitsu N, et al. Rheumatoid arthritis complicated with severe liver injury during treatment with abatacept. Mod Rheumatol 2014; 24: 874-6. PubMed PMID: 24611764.

(61 year old woman with Sjögren syndrome and rheumatoid arthritis developed nausea after 4 infusions of abatacept [bilirubin 15.2 mg/dL, ALT 2217 U/L, Alk P 1388 U/L, prothrombin activity 50%, ANA 1:1280], progressing to hepatic failure, treated with corticosteroids and plasma exchange, and ultimately resolving within 2 months of onset).

Alten R, Kaine J, Keystone E, Nash P, Delaet I, Genovese MC. Long-term safety of subcutaneous abatacept in rheumatoid arthritis: integrated analysis of clinical trial data representing more than four years of treatment. Arthritis Rheumatol 2014; 66: 1987-97. PubMed PMID: 24782324.

(Among 1879 patients with rheumatoid arthritis treated with subcutaneous abatacept for an average of 2.2 years in 5 clinical trials, serious adverse events included serious infections [1.8% per year], malignancy [1.3%], autoimmune conditions [1.4%], injection site reactions [1.7%], and 4 cases of tuberculosis, one fatal; ALT elevations occurred in 2.4% of patients, but there were no liver related serious adverse events).

Lovell DJ, Ruperto N, Mouy R, Paz E, Rubio-Pérez N, Silva CA, Abud-Mendoza C, et al.; Pediatric Rheumatology Collaborative Study Group and the Paediatric Rheumatology International Trials Organisation. Long-term safety, efficacy, and quality of life in patients with juvenile idiopathic arthritis treated with intravenous abatacept for up to seven years. Arthritis Rheumatol 2015; 67: 2759-70. PubMed PMID: 26097215.

(Among 153 children [ages 6-17 years] with juvenile idiopathic arthritis treated with abatacept in 43 centers for up 7 years, 30 [20%] had a serious adverse event [mostly infections and autoimmune events], but none were liver related; ALT elevations not mentioned).

Padovan M, Filippini M, Tincani A, Lanciano E, Bruschi E, Epis O, Garau P, et al. Safety of abatacept in rheumatoid arthritis with serological evidence of past or present hepatitis B virus infection. Arthritis Care Res (Hoboken) 2015 Nov 10. [Epub ahead of print] PubMed PMID: 26555747.

(Among 51 patients wtih rheumatoid arthritis and HBsAg and 21 with anti-HBc without HBsAg who were treated with abatacept for up to 4 years, none developed HBV reactivation or de novo HBsAg even though most [76%] did not receive antiviral prophylaxis).

Harigai M, Ishiguro N, Inokuma S, Mimori T, Ryu J, Takei S, Takeuchi T, et al. Postmarketing surveillance of the safety and effectiveness of abatacept in Japanese patients with rheumatoid arthritis. Mod Rheumatol 2016: 1-8. PubMed PMID: 26635183.

(Among 3882 Japanese patients wtih rheumatoid arthritis treated with abatacept for an average of 6 months, liver test abnormalities were reported in 0.75% and were considered serious in 0.05%, but no death was due to liver disease and there was no mention of hepatitis or reactivation of hepatitis B).