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Ipilimumab

Updated: February 16, 2018.

OVERVIEW

Introduction

Ipilimumab is a human monoclonal antibody to cytotoxic T lymphocyte antigen-4 which acts as an immune checkpoint inhibitor increases immune reactivity and is used to treat metastatic malignant melanoma. Ipilimumab has major side effects, many of which can be serious and life threatening including acute liver injury.

Background

Ipilimumab (ip" i lim' ue mab) is a human recombinant monoclonal immunoglobulin G1 antibody to the cytotoxic T lymphocyte antigen-4 (CTLA-4) which is used in cancer immunotherapy. The CTLA-4 antigen is an important checkpoint molecule that modulates and down regulates T cell responses. Inhibition of CTLA on the surface of activated T cells prevents its binding to the costimulatory factor B7, which allows for a continued activation and proliferation of T cells. The subsequent enhancement of cytotoxic reactivity may play a beneficial role in cancer immunotherapy and can break immunological tolerance. In several large multicenter studies, ipilimumab therapy resulted in a prolongation of survival in patients with advanced, metastatic or unresectable malignant melanoma, and a proportion of patients had a long term remission. Ipilimumab was approved for use in advanced malignant melanoma in the United States in 2009, the first monoclonal checkpoint inhibitor approved for use in treating neoplastic diseases. Ipilimumab has also been evaluated in several other forms of cancer, including breast, colon, renal cell and pancreatic cancer, alone and in combination with other checkpoint inhibitors such as nivolumab (anti-PD-1). Ipilimumab is available in liquid solution in 50 and 200 mg vials (5 mg/mL) under the brand name Yervoy. The typical regimen is 3 mg/kg as an intravenous infusion every 3 weeks for a total of four doses. Ipililmumab is also approved for adjuvant therapy of melanoma where it is given in higher doses long term. Side effects are common and can be severe, life threatening and even fatal. As many as 70% of treated patients develop immune related side effects as a result of immune enhancement including enterocolitis, dermatitis, endocrinopathy, neuropathy, nephritis and hepatitis. Most of these reactions respond to immunosuppressive therapy. Early recognition and prompt management of these side effects is an integral component of proper use of ipilimumab.

Hepatotoxicity

Mild-to-moderate serum aminotransferase elevations are not uncommon (10% to 50%) during ipilimumab therapy, but are usually self-limited and resolve even with continuing cyclic therapy. Serum ALT elevations above 5 times the upper limit of normal (ULN) occur in 1% to 5% of patients, and a proportion of these individuals (~1%) develop clinically apparent liver injury that can be severe. The onset of injury is usually after 2 to 4 cycles, 3 to 9 weeks after initiation of treatment. The pattern of enzyme elevation is most frequently

hepatocellular, but can be mixed, particularly at the onset of injury. Liver histology demonstrates an acute hepatitis-like pattern with focal or confluent necrosis and prominent lymphocytic infiltrates of activated T cells, which is compatible with an immune mediated hepatic injury. Fibrin ring granulomas have been described in some cases and considered somewhat pathognomic of ipilimumab hepatic immune injury. Despite features of immune-mediated injury, autoantibodies are usually not present. Restarting ipilimumab can result in recurrence of injury, although corticosteroid treatment may block recurrence.

The effects of anti-CTLA-4 inhibition on hepatitis B have not been reported, as enrollment criteria in the clinical trials of ipilimumab have usually excluded patients with hepatitis B or C or preexisting liver disease. However, it is possible that anti-CTLA-4 treatment would exacerbate chronic hepatitis B and C by enhancing T cell cytotoxicity to viral antigens.

Likelihood score: A (very likely cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism of liver injury due to ipilimumab is likely to be immunologically mediated and some cases have appeared to respond to corticosteroid or immunosuppressive therapy, allowing for continuation of ipilimumab therapy.

Outcome and Management

Guidelines for management of patients receiving ipilimumab recommend monitoring of liver test results before starting therapy and at the time of each infusion. Corticosteroid therapy is recommended for patients who develop serum aminotransferase elevations above 5 times the ULN, initiating therapy with high doses of intravenous methylprednisolone, switching to oral prednisone after 1 to 2 days, and continuing tapering doses for at least 30 days. Most cases of hepatitis due to ipilimumab resolve with prompt institution of immunosuppressive therapy. In some more protracted and resistant instances, adding a second agent to corticosteroids, such as antithymocyte globulin, tacrolimus, azathioprine or mycophenolate mofetil, has resulted in resolution of the injury. The few fatal cases that have been reported occurred in patients who had other severe immune related adverse events (Stevens Johnson syndrome, capillary leak syndrome) or who had a delay in starting corticosteroid therapy. Restarting ipilimumab after severe liver injury requiring corticosteroid therapy is usually promptly followed by recurrence of liver injury and is not recommended.

Drug Class: Antineoplastic Agents, Monoclonal Antibodies, Checkpoint Inhibitors

CASE REPORT

Case 1. Clinically apparent, acute liver injury due to ipilimumab.

[Modified from Case 5 in: Kleiner DE, Berman D. Pathologic changes in ipilimumab-related hepatitis in patients with metastatic melanoma. Dig Dis Sci 2012; 57: 2233-40. PubMed Citation]

A 43 year old man with metastatic melanoma developed erythema, rash and elevations in serum enzymes 3 days after a third infusion of ipilimumab. He had no history of liver disease, and all liver tests had been normal before starting ipilimumab therapy. Serum ALT was 173 U/L (4 times ULN) and Alk P 131 (1.1 times ULN), while bilirubin levels were normal. The absolute eosinophil count was raised (889/μL) and antinuclear antibody was reactive (2.4 by ELISA), but smooth muscle antibody was not present, and immunoglobulin levels were normal. Over the next few days, liver tests worsened with ALT rising to 2860 U/L, Alk P 410 U/L and total bilirubin 2.2 mg/dL. A liver biopsy showed an acute hepatitis superimposed upon fatty liver disease with steatosis, slight ballooning degeneration, occasional Mallory bodies and slight fibrosis. Initiation of oral prednisone therapy was followed by a slow improvement in enzymes, which fell into the normal range approximately 5 months after

onset. Prednisone was later stopped without recurrence of liver injury. He died of progressive metastatic melanoma one year later.

Key Points

Medication:	Ipilimumab
Pattern:	Mixed initially (R=3.7), hepatocellular at peak (R=20.2)
Severity:	1+ (symptoms and liver enzyme elevations without frank jaundice)
Latency:	6 weeks
Recovery:	5 months
Other medications:	None mentioned

Comment

The clinical presentation 10 days after a third infusion of ipilimumab and approximately 90 days after starting therapy was typical of the hepatic injury from this monoclonal antibody. Despite discontinuing further infusions, the liver injury worsened and was eventually treated with low doses of corticosteroids, with a slow but eventually complete response.

CASE REPORTS SUBMITTED TO LIVERTOX

Clinical cases of drug-induced liver injury that have been submitted to LiverTox ("Submit a Case Report") are available for review. Most of these reference cases are from the Drug-Induced Liver Injury Network, but others are from users of LiverTox who have submitted data from an actual clinical case. All cases have been reviewed and cleared of personal identifiers and a brief comment added by the LiverTox editors. Click on the following link to view the submitted case reports that have been made publically available.

Submitted Cases on Ipilimumab

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Ipilimumab – Yervoy®

DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Ipilimumab	**477202-00-9**	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 16 February 2018

Abbreviations: CTLA-4, cytotoxic T lymphocyte-associated antigen-4; PD-1, programmed cell death receptor-1.

Zimmerman HJ. Drugs used to treat rheumatic and musculospastic disease. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 517-54.

(Expert review of hepatotoxicity published in 1999; well before the availability of most monoclonal antibody therapies).

Reuben A. Biological immunosuppressives. Hepatotoxicity of immunosuppressive drugs. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 580-2.

(Review of hepatotoxicity of immunosuppressive agents; mentions that "the biological immunosuppressants are largely free from hepatotoxicity, with the exception of the TNF alpha antagonists"; ipilimumab is not specifically discussed).

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).

Phan GQ, Yang JC, Sherry RM, Hwu P, Topalian SL, Schwartzentruber DJ, Restifo NP, et al. Cancer regression and autoimmunity induced by cytotoxic T lymphocyte-associated antigen 4 blockade in patients with metastatic melanoma. Proc Natl Acad Sci U S A 2003; 100: 8372-7. PubMed PMID: 12826605.

(Initial study of anti-CTLA-4 therapy in 14 patients with melanoma, 6 of whom developed clinically apparent immune adverse reactions, including one with hepatitis arising after the third infusion [ALT 6820 U/L], resolving over the ensuing 4 months with corticosteroid therapy: Case 1).

O'Day SJ, Maio M, Chiarion-Sileni V, Gajewski TF, Pehamberger H, Bondarenko IN, Queirolo P, et al. Efficacy and safety of ipilimumab monotherapy in patients with pretreated advanced melanoma: a multicenter single-arm phase II study. Ann Oncol 2010; 21: 1712-7. PubMed PMID: 20147741.

(In a clinical trial of ipilimumab in 155 patients with metastatic melanoma, 109 patients [70%] suffered an immune related adverse event, including 14 [9%] with a liver related event, 2 of which were severe and 1 fatal).

Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, Gonzalez R, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010; 363: 711-23. PubMed PMID: 20525992.

(Controlled trial of ipilimumab vs a glycoprotein-100 vaccine vs both in 676 patients with metastatic melanoma from 125 centers in 13 countries found ipilimumab therapy prolonged median survival from 6.4 to 10.0 months, but that adverse events were common and usually immune mediated; ALT elevations [>5 times ULN] occurred in 0.5-0.8% of ipilimumab treated patients, but in none of controls).

Di Giacomo AM, Biagioli M, Maio M. The emerging toxicity profiles of anti-CTLA-4 antibodies across clinical indications. Semin Oncol 2010; 37: 499-507. PubMed PMID: 21074065.

(Review of immune related adverse events including hepatitis associated with ipilimumab therapy; recommends stopping therapy for grade 3 toxicity [ALT >5 times ULN] and initiating corticosteroids for at least 30 days).

Robert C, Thomas L, Bondarenko I, O'Day S, M D JW, Garbe C, Lebbe C, Baurain JF, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 2011; 364: 2517-26. PubMed PMID: 21639810.

(Trial of ipilimumab and dacarbazine vs dacarbazine alone in 502 patients with metastatic melanoma found ALT elevations in 33% on the combination vs 6% on dacarbazine alone, and ALT values above 5 times ULN in 16% vs 0.7%, but no deaths due to liver failure).

Ipilimumab (Yervoy) for metastatic melanoma. Med Lett Drugs Ther 2011; 53 (1367): 51-2. PubMed PMID: 21701442.

(Concise review of the pharmacology, efficacy and safety of ipilimumab as therapy of metastatic melanoma shortly after its approval in the US; common side effects are diarrhea, nausea, fatigue, pruritus, rash and colitis; immune related side effects can include hepatitis; cost of a single dose averages $30,000).

Chmiel KD, Suan D, Liddle C, Nankivell B, Ibrahim R, Bautista C, Thompson J, Fulcher D, Kefford R. Resolution of severe ipilimumab-induced hepatitis after antithymocyte globulin therapy. J Clin Oncol 2011; 29: e237-40. PubMed PMID: 21220617.

(61 year old man with melanoma developed fever and rash 10 days after a second dose of ipilimumab [bilirubin 1.2 mg/dL, ALT 2521 U/L, Alk P 275 U/L, ANA negative], rapidly improving on high doses of methylprednisolone, but relapsing when dose was reduced [bilirubin peak 3.8, ALT 6362 U/L], ultimately responding to addition of antithymocyte globulin and mycophenylate).

Hanaizi Z, van Zwieten-Boot B, Calvo G, Lopez AS, van Dartel M, Camarero J, Abadie E, Pignatti F. The European Medicines Agency review of ipilimumab (Yervoy) for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy: summary of the scientific assessment of the Committee for Medicinal Products for Human Use. Eur J Cancer 2012; 48: 237-42. PubMed PMID: 22030452.

(Summary of safety and efficacy results of ipilimumab forming the basis of approval in Europe; ALT elevations were reported to occur in only 1-2% of patients, with onset of hepatic injury [which can be fatal] after 3-9 weeks).

Kleiner DE, Berman D. Pathologic changes in ipilimumab-related hepatitis in patients with metastatic melanoma. Dig Dis Sci 2012; 57: 2233-40. PubMed PMID: 22434096.

(Clinical and histological features of 5 patients with liver injury due to ipilimumab; 3 men and 2 women, ages 43 to 76 years, arising after 2 to 4 courses, 39-71 days after initial dose [peak bilirubin 1.5-5.1 mg/dL, ALT 326-3070 U/L, Alk P 206-427 U/L], only one had autoantibodies, resolving with immunosuppressive therapy within 1-4 months; one had recurrence on rechallenge; liver biopsies showed acute hepatitis usually with prominent inflammation, interface hepatitis and confluent necrosis: Case 1).

Weber JS, Kähler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol 2012; 30: 2691-7. PubMed PMID: 22614989.

(Review of the immune related adverse events associated with ipilimumab therapy and their management mentions that hepatotoxicity occurs in 3-9% of patients, usually with asymptomatic increases in ALT and bilirubin, but some with symptoms; authors recommend use of high doses of corticosteroids for 2 days followed by tapering doses to at least 30 days, multiple courses may be necessary and ipilimumab should not be restarted).

Prieto PA, Yang JC, Sherry RM, Hughes MS, Kammula US, White DE, Levy CL, et al. CTLA-4 blockade with ipilimumab: long-term follow-up of 177 patients with metastatic melanoma. Clin Cancer Res 2012; 18: 2039-47. PubMed PMID: 22271879.

(Among 177 patients with metastatic melanoma treated with ipilimumab, 33 had a long term objective response and 15 a complete response).

Voskens CJ, Goldinger SM, Loquai C, Robert C, Kaehler KC, Berking C, Bergmann T, et al. The price of tumor control: an analysis of rare side effects of anti-CTLA-4 therapy in metastatic melanoma from the Ipilimumab Network. PLoS One 2013; 8: e53745. PubMed PMID: 23341990.

(Retrospective review of adverse reactions seen in 752 patients with metastatic melanoma treated with ipilimumab in 19 major cancer centers in Europe; 120 events were summarized including 11 involving the liver, which usually presented 3-6 weeks after starting therapy, with marked elevations in serum enzymes; one fatal case described in detail).

Anderson L, Bhatia V. Ipilimumab immune-related adverse reactions: a case report. S D Med 2013; 66 (8): 315-7. PubMed PMID: 24175496.

(Abstract: a case of autoimmune hypophysitis during ipilimumab therapy).

Kim KW, Ramaiya NH, Krajewski KM, Jagannathan JP, Tirumani SH, Srivastava A, Ibrahim N. Ipilimumab associated hepatitis: imaging and clinicopathologic findings. Invest New Drugs 2013; 31: 1071-7. PubMed PMID: 23408334.

(Six patients with ipilimumab hepatitis, ages 44-82 years, five men and one woman, treated with 2-4 cycles presenting with fatigue, fever and nausea [bilirubin 0.5-19.6 mg/dL, ALT 168-975 U/L], resolving within 34-147 days of stopping, many were treated with corticosteroids).

Ribas A, Hodi FS, Callahan M, Konto C, Wolchok J. Hepatotoxicity with combination of vemurafenib and ipilimumab. N Engl J Med 2013; 368: 1365-6. PubMed PMID: 23550685.

(In a pilot study of the combination of vemurafenib and ipilimumab in 10 patients with metastatic melanoma, serum ALT or AST elevations ≥5 times ULN arose within 13-36 days of starting therapy in 6 patients, all of which were asymptomatic and reversible, which resolved within 4-12 days with corticosteroid therapy, recurring in one patient on restarting ipilimumab).

Minter S, Willner I, Shirai K. Ipilimumab-induced hepatitis C viral suppression. J Clin Oncol 2013; 31: e307-8. PubMed PMID: 23690418.

(42 year old man with melanoma and chronic hepatitis C was treated with four courses of ipilimumab and had improvements in serum ALT [192 U/L to normal] and HCV RNA levels [398,938 to <12 IU/mL] during therapy that was partially sustained thereafter [ALT 39 U/L, HCV RNA 1558 IU/mL]).

Bernardo SG, Moskalenko M, Pan M, Shah S, Sidhu HK, Sicular S, Harcharik S, et al. Elevated rates of transaminitis during ipilimumab therapy for metastatic melanoma. Melanoma Res 2013; 23: 47-54. PubMed PMID: 23262440.

(Among 11 patients with malignant melanoma treated with ipilimumab, 6 [54%] developed some degree of ALT elevation after 1 to 4 courses, but only one had values above 5 times ULN and all resolved with temporary delay in therapy).

Weber JS, Dummer R, de Pril V, Lebbé C, Hodi FS; MDX010-20 Investigators. Patterns of onset and resolution of immune-related adverse events of special interest with ipilimumab: detailed safety analysis from a phase 3 trial in patients with advanced melanoma. Cancer 2013; 119: 1675-82. PubMed PMID: 23400564.

(In clinical trials of ipilimumab in 676 patients with melanoma, immune related adverse events occurred in ~60% of patients arising 3-9 weeks after starting and often mild, but severe in 12% and fatal in 1%, including one case of acute liver failure).

Fecher LA, Agarwala SS, Hodi FS, Weber JS. Ipilimumab and its toxicities: a multidisciplinary approach. Oncologist 2013; 18: 733-43. PubMed PMID: 23774827.

(Thorough review of side effects of ipilimumab therapy of melanoma states that common adverse events include fatigue, nausea, vomiting, diarrhea, fever, headache, dizziness, rash and pruritus occurring in 70-88% of patients, and that hepatotoxicity occurs in 2-9% that can be self-limited, but also can be severe and require corticosteroid therapy).

McDermott D, Haanen J, Chen TT, Lorigan P, O'Day S; MDX010-20 Investigators. Efficacy and safety of ipilimumab in metastatic melanoma patients surviving more than 2 years following treatment in a phase III trial (MDX010-20). Ann Oncol 2013; 24: 2694-8. PubMed PMID: 23942774.

(Among 676 patients with melanoma enrolled in the phase III trial of ipilimumab, 94 [20%] survived for 2 years and 42 [16%] for 3 years; late onset immune related adverse events occurred in 11 patients [14%], but were usually mild and none were hepatic).

Ascierto PA, Simeone E, Sileni VC, Pigozzo J, Maio M, Altomonte M, Del Vecchio M, et al. Clinical experience with ipilimumab 3 mg/kg: real-world efficacy and safety data from an expanded access programme cohort. J Transl Med 2014; 12: 116. PubMed PMID: 24885479.

(Among 855 patients with melanoma treated with ipilimumab in an expanded access program, 19 [2%] developed "liver toxicity", which led to stopping therapy in 1 patient and death from hepatitis in another).

Postow MA, Chesney J, Pavlick AC, Robert C, Grossmann K, McDermott D, Linette GP, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med 2015; 372: 2006-17. PubMed PMID: 25891304.

(Trial of ipilimumab with or without nivolumab in 142 patients with melanoma found higher rates of response but also side effects with the antibody combination, ALT elevations occurring in 22.3% vs 4.3% and values above 5 times ULN in 10.5% vs 0%, but there were no deaths from liver injury).

Zimmer L, Vaubel J, Mohr P, Hauschild A, Utikal J, Simon J, Garbe C, et al. Phase II DeCOG-study of ipilimumab in pretreated and treatment-naïve patients with metastatic uveal melanoma. PLoS One 2015; 10 (3): e0118564. PubMed PMID: 25761109.

(Among 53 patients with metastatic uveal melanoma treated with ipilimumab, response rates were poor and side effects were common, ALT elevations occurred in 7% and were above 5 times ULN in 4%).

Hodi FS, Lee S, McDermott DF, Rao UN, Butterfield LH, Tarhini AA, Leming P, et al. Ipilimumab plus sargramostim vs ipilimumab alone for treatment of metastatic melanoma: a randomized clinical trial. JAMA 2014; 312: 1744-53. PubMed PMID: 25369488.

(Among 245 patients with metastatic melanoma treated with ipilimumab with or without sargramostim [GM-CSF] found improved objective responses with the combination and lower rates of severe adverse events, ALT elevations above 5 times ULN occurring in 5.1% vs 5.8% of patients).

Ravi S, Spencer K, Ruisi M, Ibrahim N, Luke JJ, Thompson JA, Shirai K, et al. Ipilimumab administration for advanced melanoma in patients with pre-existing Hepatitis B or C infection: a multicenter, retrospective case series. J Immunother Cancer 2014; 2: 33. PubMed PMID: 25317333.

(Among 9 patients with metastatic melanoma and either chronic hepatitis C [n=4] or B [n=5] treated with ipilimumab, viral levels and serum ALT levels did not change in a consistent manner; most with hepatitis B were on antiviral prophylaxis).

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, 49 cases were attributed to antineoplastic agents, one of which was due to ipilimumab).

Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, Daud A, et al.; KEYNOTE-006 investigators. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med 2015; 372: 2521-32. PubMed PMID: 25891173.

(Among 834 patients with advance melanoma treated with pembrolizumab [Pem: 10mg/kg every 2 or 3 weeks] or ipilimumab [Ipil: 3 mg/kg every 3 weeks], 6 month progression free survival was higher with Pem [47% and 46%] than Ipil [26.5%] and adverse events were less; thyroiditis was more common with Pem, whereas colitis and hypophysitis were more common with Ipil; ALT elevations occurred in 3% [Pem] vs 3.5% [Ipil] and were above 5 times ULN in 0.2% vs 0.8%).

Ahmed T, Pandey R, Shah B, Black J. Resolution of ipilimumab induced severe hepatotoxicity with triple immunosuppressants therapy. BMJ Case Rep 2015; 2015. PubMed PMID: 26174726.

(50 year old woman with metastatic melanoma developed fever and liver test abnormalities after a first infusion of ipilimumab [bilirubin 0.9 rising to 1.8 mg/dL, ALT 640 to 4700 U/L, Alk P 366 to 604 U/L], treated with corticosteroids and then ATG and mycophenolate and resolving in 4 weeks, not restarted).

Johncilla M, Misdraji J, Pratt DS, Agoston AT, Lauwers GY, Srivastava A, Doyle LA. Ipilimumab-associated Hepatitis: Clinicopathologic characterization in a series of 11 cases. Am J Surg Pathol 2015; 39: 1075-84. PubMed PMID: 26034866.

(Among 11 patients with metastatic melanoma treated with ipilimumab who developed liver injury and had liver biopsy, age range 33-71 years, 10 men, arising after 1-4 doses, all with ALT elevations and 3 with jaundice [bilirubin 0.7 to 15.6 mg/dL, ALT 185 to 3075, Alk P 48 to 453 U/L], 9 biopsies showed panlobular or central hepatitis, one showed NASH, one cholangitis; all resolved in 2-12 weeks with corticosteroid therapy).

Morales RE, Shoushtari AN, Walsh MM, Grewal P, Lipson EJ, Carvajal RD. Safety and efficacy of ipilimumab to treat advanced melanoma in the setting of liver transplantation. J Immunother Cancer 2015; 3: 22. PubMed PMID: 26082835.

(67 year old man with liver transplant for hepatitis C developed metastatic melanoma treated with 4 doses of ipilimumab and 2 weeks later had ALT elevations without jaundice that resolved without corticosteroids or antirejection therapy).

Hofmann L, Forschner A, Loquai C, Goldinger SM, Zimmer L, Ugurel S, Schmidgen MI, et al. Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy. Eur J Cancer 2016; 60: 190-209. PubMed PMID: 27085692.

(Review of the major immune mediated side effects of anti-PD-1 therapy, with characteristics of 11 cases of hepatitis due to pembrolizumab or nivolumab, arising 1-4 weeks after initial infusions, resolving mostly with corticosteroid therapy and stopping drugs).

Weber JS, Postow M, Lao CD, Schadendorf D. Management of adverse events following treatment with anti-programmed death-1 agents. Oncologist 2016; 21: 1230-40. PubMed PMID: 27401894.

(Review of immune mediated adverse events from anti-PD-1 therapy and their management; ALT elevations are reported in 2-4% of patients with higher rates with combinations; recommend stopping therapy if ALT elevations are above 5 times ULN or bilirubin is raised and use of methylprednisolone, but merely delay in therapy and increased frequency of monitoring if ALT elevations are above 3 times but below 5 times ULN).

Koelzer VH, Rothschild SI, Zihler D, Wicki A, Willi B, Willi N, Voegeli M, et al. Systemic inflammation in a melanoma patient treated with immune checkpoint inhibitors-an autopsy study. J Immunother Cancer 2016; 4: 13. PubMed PMID: 26981243.

(35 year old woman with refractory metastatic melanoma received 4 infusions of ipilimumab and 4 cyclces of nivolumab with partial response only and death, autopsy showing necrotic melanoma metastases and CD8+ T cell infiltrates in many organs, including liver).

Spänkuch I, Gassenmaier M, Tampouri I, Noor S, Forschner A, Garbe C, Amaral T. Severe hepatitis under combined immunotherapy: resolution under corticosteroids plus anti-thymocyte immunoglobulins. Eur J Cancer 2017; 81: 203-5. PubMed PMID: 28641200.

(49 year old woman with metastatic melanoma developed abdominal pain after 3 cycles of ipilimumab and nivolumab [bilirubin 5.5 mg/dL, ALT 722 U/L, Alk P 449 U/L], responding slowly to methylprednisolone and ATG, and then tolerating pembrolizumab therapy without recurrence).

Yildirim S, Deniz K, Doğan E, Başkol M, Gürsoy Ş, Özkan M. Ipilimumab-associated cholestatic hepatitis: a case report and literature review. Melanoma Res 2017; 27: 380-2. PubMed PMID: 28489679.

(45 year old man with refractory metastatic melanoma developed jaundice 7 days after a 4th dose of ipilimumab [bilirubin 8.5 mg/dL, ALT 96 U/L, Alk P 678 U/L, GGT 1320 U/L], resolving slowly with corticosteroid therapy).

Tanaka R, Fujisawa Y, Sae I, Maruyama H, Ito S, Hasegawa N, Sekine I, et al. Severe hepatitis arising from ipilimumab administration, following melanoma treatment with nivolumab. Jpn J Clin Oncol 2017; 47: 175-8. PubMed PMID: 28173241.

(59 year old man with refractory metasatic melanoma treated with 11 doses of nivolumab developed severe hepatitis after one dose of ipilimumab with fever, chills and fatigue [bilirubin 2.1 rising to 12.6 mg/dL, ALT 1623 U/L, Alk P 1306 U/L, INR 1.45], eventually improving with high doses of methylprednisolone and mycophenolate).

Mirza S, Hill E, Ludlow SP, Nanjappa S. Checkpoint inhibitor-associated drug reaction with eosinophilia and systemic symptom syndrome. Melanoma Res 2017; 27: 271-3. PubMed PMID: 28146044.

(46 year old man with refractory metastatic melanoma developed fever, rash and liver test abnormalities while receiving ipilimumab and nivolumab, but also 1 week after a course of levofloxacin [bilirubin and Alk P not given, ALT 116 U/L, eosinophils 1400/uL], resolving with corticosteroid therapy and stopping monoclonal antibodies).

Bunchorntavakul C, Reddy KR. Drug hepatotoxicity: newer agents. Clin Liver Dis 2017; 21: 115-34. PubMed PMID: 27842767.

(Review of hepatotoxicity of agents newly approved for use in the US including ipilimumab which is associated with ALT elevations in 3-9% of patients [above 5 times ULN in 0.5% to 1.5%], most of which are self-limited in course; however, clinically apparent, largely hepatocellular, injury can also occur, especially when combined with dacarbazine or vemurafenib, usually responding to corticosteroid therapy, but rare deaths from hepatic failure have been reported).

Everett J, Srivastava A, Misdraji J. Fibrin ring granulomas in checkpoint inhibitor-induced hepatitis. Am J Surg Pathol 2017; 41: 134-7. PubMed PMID: 27792061.

(Fibrin ring granulomas were found in liver biopsies from 2 patients with metastatic melanoma treated with ipilimumab who developed fever, rash and elevated liver tests after 3 infusions [bilirubin 0.5 and 0.2 mg/dL, ALT 130 and 643 U/L, Alk P 264 and 70 U/L], resolving with corticosteroid therapy).

Weber J, Mandala M, Del Vecchio M, Gogas HJ, Arance AM, Cowey CL, Dalle S, et al.; CheckMate 238 Collaborators. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. N Engl J Med 2017; 377: 1824-35. PubMed PMID: 28891423.

(Among 905 patients with malignant melanoma after surgical resection given adjuvant therapy for at least 18 months, progression free survival was less with ipilimumab than nivolumab [60.8% vs 70.5% at 12 months] and side effects were greater [serious adverse events in 43% vs 18%] including ALT elevations [15% vs 6% which were above 5 times ULN in 5.7% vs 1.1%]).

Huffman BM, Kottschade LA, Kamath PS, Markovic SN. Hepatotoxicity after immune checkpoint inhibitor therapy in melanoma: natural progression and management. Am J Clin Oncol 2018; 41 (8): 760-5. PubMed PMID: 28749795.

(Among 218 pateints treated with various checkpoint inhibitors at the Mayo Clinic over a 5 year period, 17 developed hepatotoxicity [12 after ipilimumab alone], with onset after median of 52 days [16-151 days] and resolving mostly with corticosteroid therapy after 31 days [6-56 days]).

Dueland S, Guren TK, Boberg KM, Reims HM, Grzyb K, Aamdal S, Julsrud L, et al. Acute liver graft rejection after ipilimumab therapy. Ann Oncol 2017; 28: 2619-20. PubMed PMID: 28961840.

(67 year old woman with ocular melanoma underwent liver transplantation and later had metastases to graft, developed liver test abnormalities 3 weeks after stopping immunosuppression [sirolimus and mycophenolate] and receiving one infusion of ipilimumab [ALT 750 U/L], biopsy showing acute rejection).

Zen Y, Yeh MM. Hepatotoxicity of immune checkpoint inhibitors: a histology study of seven cases in comparison with autoimmune hepatitis and idiosyncratic drug-induced liver injury. Mod Pathol 2018 Feb 5. [Epub ahead of print] PubMed PMID: 29403081.

(Liver histology in 7 cases of hepatotoxicity from checkpoint inhibitors [2 ipilimumab, 7 nivolumab] showed lobular hepatitis with prominence of CD8+ lymphocytes in most, with less eosinophilic infiltration and bile plugs than typical drug induced hepatitis and less plasma cell infiltration and portal inflammation than autoimmune hepatitis).