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Infliximab in steroid-refractory immune-related hepatitis does not demonstrate hepatotoxicity and may shorten time on steroids

Elias Burri ,[1,2] Joanna Mangana,[1,2] Phil F Cheng,[1,2] Alia Schneider,[3] Achim Weber,[3,4] Reinhard Dummer ,[1,2] Egle Ramelyte[1,2]

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[1]Department of Dermatology, University Hospital of Zurich, Zurich, Switzerland
[2]Medical Faculty, University of Zurich, Zurich, Switzerland
[3]Department of Pathology and Molecular Pathology, University Hospital Zurich, Zurich, Switzerland
[4]Institute of Molecular Cancer Research, University of Zurich, Zurich, Switzerland

Correspondence to
Dr Egle Ramelyte;
egle.ramelyte@usz.ch

ABSTRACT

Background Immune-related hepatitis (irHepatitis) is a relatively common immune-related adverse event (irAE) of checkpoint inhibitors. Often, it responds well to steroids; however, in refractory cases, further therapy is needed. Anti-tumor necrosis factor (TNF) antibodies are used for management of multiple irAEs, but there are little data in irHepatitis. Here, we report on safety and efficacy of infliximab in 10 cases of steroid-refractory irHepatitis.

Methods We retrospectively reviewed patients treated with infliximab for steroid-refractory grade ≥3 irHepatitis at the Department of Dermatology, University Hospital Zurich. The positive response to infliximab was defined as no further increase in alanine aminotransferase (ALT)/aspartate aminotransferase (AST) above 50% than at the time of first infliximab infusion and control of irHepatitis without therapies other than steroids and infliximab.

Results 10 patients with steroid-resistant irHepatitis grade ≥3 were treated with infliximab 5 mg/kg, of whom 7 (70%) responded positively. In two cases, the liver values increased over 50% before the irHepatitis could be controlled. In another case, therapies other than infliximab and steroids were given. At the median follow-up of 487 days, 90% of the patients demonstrated resolved irHepatitis without AST/ALT elevation following infliximab infusions.

Conclusions Treatment of irHepatitis with infliximab did not result in hepatotoxicity and led to long-lasting positive response in 9 of 10 of the cases. Further research is needed to evaluate the role of anti-TNF antibodies in management of irHepatitis.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Infliximab is not recommended in steroid-refractory immune-related hepatitis as there is the suspicion that it could trigger hepatitis.

WHAT THIS STUDY ADDS

⇒ We showed in 10 cases that there have been no safety signals in using infliximab in immune-related hepatitis and that it may shorten time on steroids.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ After this, further studies may take infliximab into the guidelines for treating steroid-refractory immune-related hepatitis.

BACKGROUND

Immune checkpoint inhibitors (ICIs) are used in the treatment of several tumors, especially in melanoma. ICIs can deliver long-lasting responses but also cause immune-related adverse events (irAEs).[1] Liver irAEs vary in severity from mild to life-threatening. Immune-related hepatitis (irHepatitis) is diagnosed and graded based on the elevation of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The predominant histological pattern is a pan-lobular hepatitis similar to an autoimmune hepatitis and rarely, ring granulomas.[2] The risk of grade (G) ≥3 irHepatitis is 1–2% with anti-PD1/anti-PDL1 and >10% with combination anti-CTLA4/PD1.[3] The onset of irHepatitis ranges between 6 and 14 weeks following treatment initiation with immunotherapy; however, it varies greatly.[4] The risk factors for developing irHepatitis are unknown yet.[5]

Due to lack of prospective trials, current guidelines for management of irHepatitis are based on expert opinion. For G≥3 ICI hepatitis, the guidelines recommend discontinuation of ICI, administration of high-dose (1–2 mg/kg/day methylprednisolone equivalents) systemic corticosteroids and consideration of adding a second immunosuppressive agent (eg, mycophenolate mofetil (MMF)) if there is insufficient improvement after 3–5 days of corticosteroid treatment.[4 6 7] In most cases, irHepatitis responds well to treatment with corticosteroids[8] with various time to resolution. The median time from diagnosis of G3–4 irHepatitis to improvement to G1 was 42 days (range 8–182) in 24 analyzed patients.[9] Recent studies show that doses of

corticosteroids higher than 1 mg/kg/day appear to have no additional benefit regarding the time to resolution.[10]

In case of no improvement on steroids, second-line treatment with following therapies have been reported: MMF 500–100 mg,[11–13] azathioprine 1–2 mg/kg/day,[14 15] 6-mercaptorpurine 1 mg/kg/day,[2] ciclosporin 100 mg two times per day,[14] antithymocyte globulin 1.5 mg/kg,[16 17] tacrolimus (targeting blood levels 8–10 ng/mL),[10 18] tocilizumab 4 mg/kg/dose,[19] and plasmapheresis.[20] Second-line therapies are also important to shorten time on high-dose steroids to reduce their side effects.

Anti-tumor necrosis factor (TNF) antibodies are used in management of multiple irAEs. However, the use in irHepatitis is not recommended due to sparse reports of adverse events like drug-induced liver injury (DILI).[21–23] Also, American Society of Clinical Oncology and European Society for Medical Oncology guidelines do not recommend giving anti-TNF antibodies.[4 7] Among anti-TNF agents, infliximab is associated most frequently with DILI, developing in 1 of 120 patients who received this drug, mostly after four infusions (median 98 days after start infliximab). However, the indication therefore was mostly rheumatological disorders.[24] It is important to note that a single dose is often sufficient in management of irAEs. Until now, there is only one study reporting safety of infliximab in management of irAEs with none of the 56 reported patients showing an increase of ALT or AST at 4 weeks after the first infusion.[25] The use of infliximab in irHepatitis is limited to single case reports.[10 18 26]

In this study, we analyzed the safety and efficacy of infliximab in a single-institution series of patients with steroid-refractory G≥3 irHepatitis.

METHODS

After approval of the Local Ethics Committee, we collected retrospective data from electronic medical records (KISIM V.5.3.1.5). Patients were included if they received infliximab for steroid-resistant G≥3 irHepatitis at the Skin Cancer Unit of Department of Dermatology, University Hospital Zurich, Switzerland, between January 2015 and September 2022, and had a follow-up of at least 1 month after the resolution of irHepatitis, defined as AST/ALT G≤1. All patients have received ICIs for melanoma.

irHepatitis was defined as ALT and/or AST elevation in patients treated with ICIs (anti-PD1 alone or in combination with other ICIs or kinase inhibitors) with the absence of other probable causes of liver injury, including viral hepatitis, ischemia, or toxicity of coexistent medications known to cause DILI. The cases were graded according to the Common Terminology Criteria of Adverse Events V.5.[27] Steroid-resistant irHepatitis was defined as irHepatitis not showing AST/ALT decrease after 3–5 days. The positive response to infliximab was defined as no further increase in ALT/AST above 50% than at the time of first infliximab infusion and control of hepatitis without further treatment besides steroids. There is currently no generally accepted definition for response to therapy in the literature.

The descriptive data are reported as medians and ranges for continuous data, and frequencies and percentages for categorical data. The time between two time points (eg, diagnosis of any grade irHepatitis and outcomes such as resolution to G1 irHepatitis) is reported in days, rounded to full numbers.

RESULTS

10 patients with steroid-resistant irHepatitis G≥3 were treated with infliximab 5 mg/kg at our department. Median age at first onset of irHepatitis was 64.5 years, 60% of the patients were male. 70% of patients were receiving the first-line treatment, two had second-line treatment and one had more than two treatment lines for melanoma. Most common ICI was the combination of ipilimumab/nivolumab (60% of patients). 50% of patients had G3 irHepatitis and 50% of patients had G4. Patient characteristics are reported in table 1. Two patients had irAEs preceding irHepatitis of interest, which were treated with systemic steroids (online supplemental table 1). 80% of patients had other irAEs during the course of irHepatitis (online supplemental table 2). In 60% of patients, a liver biopsy was performed, all displaying histologic changes consistent with irAE (figure 1 and online supplemental figure 1).

irHepatitis occurred at median of 31 days (range 4–145), or two infusions after start of ICIs (range 1–3). The course of the irHepatitis can be seen in figure 2. In 70% of cases, therapy with oral corticosteroids was started at the time of diagnosis; in one case, treatment was started after 28 days. The reason for the delayed start of corticosteroids after 28 days was a slow dynamics of ALT elevation. In the first 7 days of therapy, patients were administered with average 1.28 mg/kg/day of prednisolone equivalent. After 7 days or next measurement, the average increase in ALT/AST in average was 113% (range −47% to +765%). The highest value (peak) of ALT was documented after median of 22 days (range 2–94) after irHepatitis diagnosis. All patients were treated with intravenous steroids after insufficient effect of oral steroids and prior to start of infliximab. The median time to the start of infliximab was 17 days (range 7–78) after irHepatitis diagnosis. Most of the patients (60%) received one dose of infliximab (table 2).

The median time to resolution to irHepatitis G1 was 44 days (range 22–112) from the diagnosis of irHepatitis and 26 days (range 12–49) from the start of infliximab (table 2). 70% responded positively to infliximab. Among the non-responders (30%), in one case, there was an increase in ALT/AST of 433% within 16 days after infliximab administration. After another infusion of infliximab and an increase in steroids, the values fell again. In the second non-responder, ALT/AST increased by 77% 19 days after the first infliximab infusion. After increasing the steroids, the irHepatitis could be controlled again. In the third case, tocolizumab was administered once 3 days after the first dose of infliximab. The steroids were tapered to ≤20 mg/day in a median of 72 days (range

Table 1 Patient characteristics

Characteristic	Overall, n=10
Age at onset of irHepatitis, median (range)	64.5 years (32–86)
Gender distribution, patients	
Male	6
Female	4
Therapy at onset of irHepatitis, patients	
Anti-PD1+anti-CTLA4 (ipilimumab/nivolumab)	6
Anti-PD1	1
Anti-PD1+anti-CTLA4+anti-TIGIT	1
Anti-PD1+anti-LAG3+IDO1 inhibitor	1
Anti-PDL1+vemurafenib/cobimetinib	1
Treatment line, patients	
First	7
Second	2
Third and more	1
Liver metastasis at onset of irHepatitis, n	3
Grade of irHepatitis at infliximab, patients	
Grade 3	5
Grade 4	5
Other irAEs preceding irHepatitis, patients	
No	8
Yes	2
Other irAEs during irHepatitis, n	
No	2
Yes	8
1 irAE	5
≥2 irAEs	3

irAE, immune-related adverse event; irHepatitis, immune-related hepatitis.

37–139). At the median follow-up of 487 days (range 33–1208) after first infliximab infusion, 90% of the patients demonstrated no further AST/ALT increase after the first irHepatitis, despite a rechallenge of ICI in 60%. One patient developed increase of AST/ALT at 206 days after first infliximab infusion after a rechallenge of ICI. Because of the temporal correlation with the rechallenge and response to steroids, we interpreted this as an irHepatitis and not late-onset infliximab-induced hepatotoxicity.

DISCUSSION

To our best knowledge, we report the largest systematic study on safety and efficacy of infliximab in G3–4 steroid-resistant irHepatitis. Seven patients responded positively to infliximab and in six cases only one infusion of infliximab was administered. At a median follow-up of 487 days after the first infliximab infusion, only one patient has developed an ICI rechallenge-related increase of AST/ALT values.

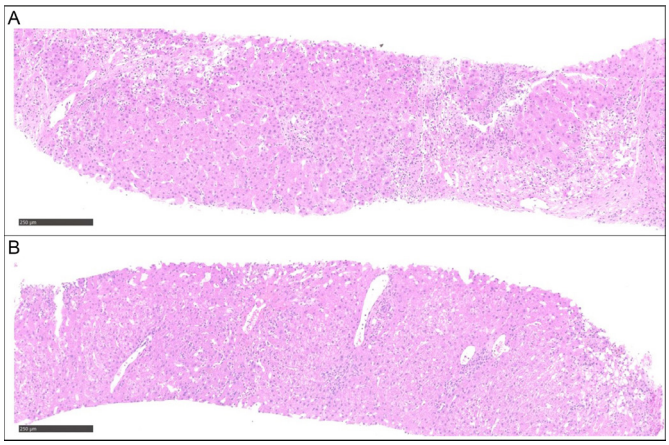

Figure 1 Liver biopsy findings: (A) patient 3: severe acute hepatitis with confluent necrosis predominantly in zone 3 (25% of parenchyma) associated with lobular collapse and few fibrous septa; (B) patient 8: hepatitis with confluent necrosis predominates in zone 3 associated with lobular collapse.

In patients with steroid-resistant irHepatitis, further immunosuppressive therapies are needed to control the irAE. As large clinical trials are still missing, current irAE management guidelines are mostly based on expert opinion or small case reports. For G≥3 steroid-resistant irHepatitis, a second immunosuppressive agent (eg, MMF) is recommended.[4 6 7] However, other drugs, such as anti-TNF antibodies, including infliximab, are known to have anti-inflammatory effects by downregulating endothelial cell expression of leukocyte adhesion molecules, inhibiting the induction of synovial production of interleukin (IL)-6, IL-8 and prostaglandin, and inhibition of the induction of macrophage of proinflammatory phenotype.[28] Given the lack of larger studies, supporting the use of MMF in steroid-resistant irHepatitis and our experience of insufficient efficacy of MMF, we decided to give infliximab as second immunosuppressive agent. Moreover, patients often presented with concurrent irAEs along with irHepatitis, so we chose infliximab with intention to treat all of occurring irAEs.

Given the report of hepatotoxicity with infliximab, their application in treatment of irHepatitis is limited. Hepatotoxicity was reported after a median of 98 days or four infusions of anti-TNF antibodies for mainly rheumatological disorders.[24] We did not see infliximab-induced hepatotoxicity as with the median follow-up of 487 days. In our cohort, only one patient had an increase of ALT/AST, which occurred after rechallenge of ICI, hence was diagnosed as irHepatitis and not infliximab-induced hepatotoxicity because of the temporal correlation with the rechallenge. Importantly, in majority of our patients (60%), only one infusion of infliximab was administered, suggesting that reported hepatotoxicity could be dose or exposure related. Indeed, there is until now no published evidence that infliximab induces hepatotoxicity in a

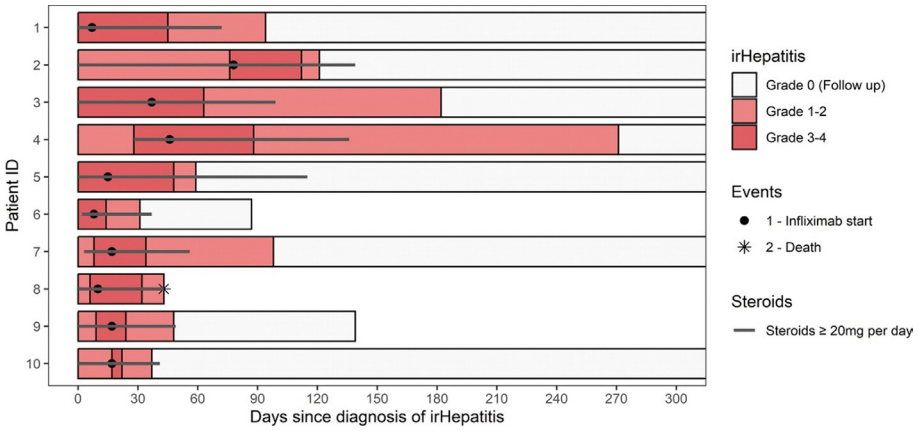

Figure 2 Clinical course of patients with steroid-refractory immune-related hepatitis (irHepatitis). Each starting bar on the y-axis shows one patient and on the x-axis, the number of days since the start of the diagnosis of irHepatitis. The different colored bars show how long each degree of hepatitis has existed. The line shows how long the patient was treated with more than 20 mg/day of steroids. The black dot indicates the time of the first administration of infliximab. The star indicates the death of a patient.

dose-limited setting used in management for irAEs, or that infliximab may aggravate steroid-refractory irHepatitis and our analysis did not detect any safety signals.

Table 2 The course of irHepatitis

Measurements	Results
Days from irHepatitis diagnosis until	
Peak ALT, median (range)	22 (2–94)
Start of infliximab, median (range)	17 (7–78)
PDN ≤20 mg/day, median (range)	72 (37–139)
Baseline ALT and AST, median (range)	94 (31–271)
Days from infliximab infusion until	
ALT and AST resolution to G1, median (range)	26 (12–49)
PDN ≤20 mg/day, median (range)	61 (24–100)
Days to resolution to G1 from	
Diagnosis of irHepatitis, median (range)	44 (22–112)
Peak ALT, median (range)	21 (10–47)
Start of infliximab, median (range)	26 (12–49)
Median follow-up after infliximab infusion, days (range)	487 (64–1208)
Normal ALT and AST values at last follow-up, patients	9
Received doses of infliximab (% of patients)	
1	6 (60)
2	3 (30)
3	1 (10)

The only patient who did not have normal values at last follow-up has succumbed to disease progression before resolution of irHepatitis.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; G, grade; irHepatitis, immune-related hepatitis; PDN, prednisone; Peak, the highest value of ALT since first diagnosis of irHepatitis.

However, it should be noted that short after the first infusion of infliximab, ALT/AST increased by more than 50% in two cases. We saw this increase in the context of irHepatitis due to timing and not as a infliximab-induced hepatotoxicity. In one of these two cases, infliximab was continued with no further escalations of ALT/AST.

In our cohort of 10 steroid-resistant cases treated with infliximab, the time from diagnosis of irHepatitis back to G1 was 44 days (range 22–112). In the literature, for irHepatitis management with steroids, the reported time for resolution of G3–4 irHepatitis ranges from 37.5 to 68 days[29–33] (table 3).

It should be considered that the patterns of response to these therapies are not well defined and the reported outcomes are heterogeneous. A study on patients with irHepatitis G3–4 reported the median time from irHepatitis diagnosis until improvement to G1: in four patients who did not receive steroids, it was 17 days (range, 6–41); in 12 patients who received steroids, it was 40 days (range 14–91); and in 19 patients with intravenous and oral steroids, it was 42 days (range 8–182). This study also reported on five patients who required a second immunosuppressive—tacrolimus—and improved to G1 irHepatitis at a median time of 42 days (range 33–135)[9] (table 3). Our results with the median of 44 (22–112) days from irHepatitis to G1 suggest infliximab not to be inferior to tacrolimus as a second-line therapy.

Our results are in the range of the reported data with steroid-sensitive and steroid-resistant cases. In management of irAEs, not only the resolution of the irAE, but also the time on immunosuppressive doses of steroids, is important. Patients with immunosuppressive doses of prednisone (PDN) have inferior outcomes compared with patients without them.[34 35] As without the second immunosuppressive agent, steroid-resistant cases would be exposed to PDN for undetermined time, our data suggest that infliximab could be effective in shortening time on steroids in treatment of irHepatitis. In patients with metastatic disease without a complete response,

Table 3 Comparison with other studies

Study	Grade of irHepatitis	Patients	Intervention	Outcome
Tew *et al*[9]	G3–4	19 patients	Corticosteroids only	Days from irHepatitis diagnosis to G1, median 42 (range 8–182)
		5 patients	Corticosteroids and second line tacrolimus	Days from irHepatitis diagnosis back to G1, median 42 (range 33–135)
Li 2022[37]	G3–4	87 patients	High-dose corticosteroids	Days from irHepatitis diagnosis until steroid <10 mg/day, median 60 (range 40–85)
		128 patients	Low-dose corticosteroids	Days from irHepatitis diagnosis until steroid dose <10 mg/day, median 44 (range 32–70)
Patrinely *et al*[30]	Any grade	164 patients	Corticosteroids only, 35 patients treated second line, 30 with MMF, 3 tacrolimus, 1 infliximab, 1 MMF+abatacept	Days from irHepatitis diagnosis until resolution=median 52
Romanski *et al*[32]	G3–4	43 patients	Corticosteroids only, 2 patients treated second line with MMF	Days from irHepatitis diagnosis until complete resolution=median 53 (for grade 3), median 68 (for grade 4)
Smith *et al*[33]	Any grade	31 patients	Corticosteroids only, 1 patient second line with infliximab	Days from irHepatitis diagnosis until resolution, median 43
	G3–4			Days from irHepatitis diagnosis until resolution, median 60
Gauci *et al*[29]	G3–4	21 patients	Corticosteroids only	Days from irHepatitis diagnosis until resolution, median 37.5
Riveiro-Barciela *et al*[31]	G3–4	28 patients	Corticosteroids only and 10 patients treated second line with MMF	Days from irHepatitis diagnosis until resolution, median 45

G, grade; irHepatitis, immune-related hepatitis; MMF, mycophenolate mofetil.

resumption of therapy is often considered. The guidelines recommend considering resumption of once PDN ≤10 mg.[7] A shorter time on steroids for irHepatitis could lead to faster rechallenge of ICIs.

The risk of recurrence of irAEs upon ICI resumption is not negligible. A cohort study of 24 079 irAEs assessed the risk of irAE recurrence upon rechallenge. The therapy used for initial irAE management was not considered; however, the OR for irHepatitis recurrence upon rechallenge of ICI was 3.38.[36] In our cohort, after recovery of irHepatitis, the ICI was resumed in six patients and only one of the patients showed an increase of AST/ALT with G3 irHepatitis, which responded well to steroids. A prophylactic therapy may be considered for patients requiring a rechallenge of ICI; however, the agent with the least immunosuppressive and best protective properties is yet to be identified.

Limitations of our study are the small number of cases and the retrospective design. In addition, even though other causes of hepatitis, such as viral infection or hepatotoxic medication, were excluded, in 40% of the cases, a liver biopsy was not performed, which means that other reasons for hepatopathy cannot be completely ruled out. Overlapping histological diseases have also led to discussion regarding the diagnosis as patient 9 had concurrent metabolic-associated fatty liver disease or alcoholic steatohepatitis at the same time as irHepatitis. However, due to the dynamics of the transaminases and response to immunosuppressive therapies, we assigned the diagnosis to irHepatitis. Such cases reflect the real-life population and to our opinion, aid in improving patient outcomes.

CONCLUSION

To our knowledge, this is the largest cohort of patients with steroid-resistant irHepatitis treated with infliximab. Our data suggest that given in dose-limited setting, infliximab does not show hepatotoxicity or other unexpected safety signals and leads to improvement of irHepatitis. Our study is a small retrospective monocentric study relying on the interpretation of clinical notes with an inherent reporting bias; hence, larger studies are needed to assess the role of infliximab as the second-line immunosuppressive therapy in irHepatitis.

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Contributors EB collected the data for the study, interpreted the results and wrote the manuscript. ER was the senior author of this study, developed the concept, designed the study, interpreted the results, and helped write the manuscript. PFC helped in collecting the data for the study. AS and AW re-evaluated and documented archival liver biopsies included in this study. RD, JM, and AW reviewed the manuscript. All authors read and approved the final manuscript. ER acts as guarantor.

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Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and was approved by Ethik-Komission Universität-Zürich (no: 2014-0193). The patients made a general declaration when they entered the hospital that their data could be used, but not specifically for this study. The Ethics Committee then decided that the data could be used in this study.

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ORCID iDs
Elias Burri http://orcid.org/0009-0002-4092-1093
Reinhard Dummer http://orcid.org/0000-0002-2279-6906

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