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Clinical features and treatment response in patients with immune checkpoint inhibitor associated cholangiopathy

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ABSTRACT

Background: Immune mediated biliary injury (ICI-cholangiopathy) is a rare toxicity in patients treated with immune checkpoint inhibitors (ICI) and clinical characteristics, treatment responses and optimal management remain poorly characterised. This study aimed to characterize clinical profiles and treatment response in ICI-cholangiopathy.

Methods: Patients treated with anti-PD-1, PDL-1 or CTLA-4 therapy between January 2010 and December 2025 were included in this retrospective study. Patients with ICI-cholangiopathy were identified from patients with significant elevation in cholestatic liver enzymes (R value <2) within 12 months of ICI exposure and clinical records were reviewed.

Results: Of 5103 patients treated with ICI during the study period, 14 patients developed ICI-cholangiopathy (0.3%). Median age was 71 years and most (64%) were male. Most common primary malignancy was lung cancer (57%) and most were treated with pembrolizumab (71%). Most patients (8, 57%) had abnormal biliary imaging, with the majority reporting intra- and extra-hepatic biliary wall thickening and dilatation. All patients were treated with immunosuppression. ALP normalised over 3-6 months in 10 patients (71%; termed acute ICI-c) and improved but remained elevated < 2.5 x ULN in 4 (29%, chronic ICI-c). There were no significant differences in age, sex, primary cancer type, presence of liver metastases, duration of ICI therapy, or extent of ALP or ALT elevation at ICI-c diagnosis between patients with acute or chronic ICI-c. Patients with acute ICI-c improved faster than patients with chronic ICI-c (median time to ALP < 2.5 x ULN 16.5 vs 270 days, $p = 0.007$). Percent ALP reduction at 7 days distinguished patients with acute and chronic ICI-c (area under the receiver operating characteristic curve (AUROC) 0.92 (95% CI 0.63 – 0.99, $p < 0.0001$)). An optimal cut-off of ≤20% ALP reduction at treatment day 7 was identified.

Conclusion: ICI-cholangiopathy, defined using biochemical criteria, is an uncommon complication of ICI treatment. Most patients (71%) respond to immunosuppression and normalise ALP over time. ALP reduction ≤20% at treatment day 7 may identify patients who will respond poorly to treatment, allowing management to be tailored accordingly. This approach should be evaluated in future prospective studies.

Introduction

Immune checkpoint inhibitors (ICI) are monoclonal antibodies that interfere with the inhibitory interaction between T-cell receptors (such as CTLA-4 and PD-1 receptors) and tissue ligands, including those found on tumor cells, thereby enhancing the anti-tumor activity of cytotoxic T-lymphocytes[1]. ICI have been transformative in treatment of a diverse range of cancers, extending survival in some patients and producing significant and durable tumour responses[2]. ICI are now standard of care for several malignancies, and their use continues to expand in combination with other anti-cancer therapies, and as further novel agents are developed[3].

Due to their immune-enhancing activity, ICIs are associated with immune-related adverse events that can involve virtually any organ system[3,4]. Checkpoint inhibitor-induced liver injury (ChILI) may affect up to 28% of ICI-treated patients[4-6]. ICI-hepatitis, characterized by a predominantly hepatocellular elevation of liver enzymes, is the most common presentation of ChILI[3,4]. ICI-cholangiopathy (ICI-c) is much less common, seen predominantly in patients receiving PD-1 or PD-L1 inhibitors[7,8]. Incidence is difficult to determine, due to both rarity and heterogeneity in terminology, but is estimated to occur in 0.05 – 3.3% of ICI-treated patients[5,9-13].

Although management algorithms involving immunosuppressive therapy are well established for ICI hepatitis, optimal management of ICI-c is less clearly defined and remains a significant management challenge for oncologists and hepatologists[3,4]. Greater understanding of immune -related biliary injury has been hampered by its low incidence and lack of a standardized definition or unified diagnostic approach. ICI-c is usually asymptomatic, identified initially by elevations in cholestatic liver enzymes on routine blood tests, but may be associated with a diverse range of radiological and histological findings. Imaging can be normal, or show abnormalities in the intra- and/or extra-hepatic bile ducts. These abnormalities include biliary strictures, dilatation, and/or duct wall thickening[11,14-16]. Histological findings may include portal inflammation with a predominance of CD8+ cytotoxic T cells, ductopenia, periductal fibrosis, cholestasis and lobular inflammation, although a small proportion of biopsies were unremarkable[11,14,16-18].

Existing reports have suggested that ICI-c responds poorly to immunosuppression[11,14,15]. A retrospective series of patients with ChILI undergoing liver biopsy found patients with histological biliary injury had a worse response to immunosuppression than patients with toxic/granulomatous histology[19]. However, these studies may be limited by selection or publication bias and not fully representative of treatment response across the spectrum of biochemical, radiological and histological phenotypes of ICI-c. More recently, a study from the French Pharmacovigilance database observed that 79% of patients with biochemically-defined ICI-c improved with immunosuppression, ursodeoxycholic acid (UDCA) or no specific treatment, and another small case series found that 60% of patients with biochemically defined ICI-c recovered following immunosuppression[10,20]. Therefore, the role of immunosuppressive treatment across the phenotypic spectrum of ICI cholangiopathy remains unclear.

The aim of this study was to better understand ICI-cholangiopathy, its frequency, clinical presentations and response to treatment, defining ICI-cholangiopathy using specific biochemical criteria to encompass the range of radiological and histological phenotypes of biliary injury associated with ICI therapy.

Methods

This was a retrospective, single centre study conducted at a tertiary academic centre (University Health Network (UHN), Toronto, Canada).

Patients included were treated with anti-PD-1, anti-PD-L1 and/or anti-CTLA-4 agents between January 2010 and December 2025 and were diagnosed and treated for ICI-c at UHN, with laboratory and imaging results available on the institutional electronic medical record (EMR). Patients who were treated for hepatocellular or mixed pattern ChILI, treated for ICI-c outside UHN, and/or did not have laboratory and imaging results available on the UHN EMR, were excluded.

Figure 1 summarises the process of patient selection. Electronic patient records were searched to identify all patients treated with anti-PD-1, anti-PD-L1 and/or anti-CTLA-4 agents during the study period. A subgroup of patients was identified with ≥Grade (G)2 elevation in ALT or ALP, according to CTCAE (version 5.0) criteria, within 12 months of first exposure to ICI therapy[21]. For this subgroup, clinical records were reviewed to identify patients in whom ChILI was diagnosed. The diagnosis of

ChILI and treatment decisions were made contemporaneously by the treating physician. Finally, for patients diagnosed and treated for ChILI, the R ratio was calculated to classify the pattern of liver injury (R = (ALT/ALT ULN)/(ALP/ALP ULN)). R >5.0 was classed as hepatocellular, R <2.0 as cholestatic, and R = 2.0 – 5.0 as mixed pattern liver injury[22]. R <2.0 was used to define patients with ICI-c.

Clinical records were reviewed for all patients diagnosed and treated for ICI-c. Information was collected on biochemical and histologic results, imaging findings, treatment, time to resolution, outcome of any further ICI exposure, duration of follow up and death. Resolution of ICI-c was defined as return of ALT/ALP to within the upper limit of normal or return to baseline, if the baseline ALT/ALP were abnormal. Biliary abnormalities on cross-sectional imaging were categorised anatomically as extrahepatic, intrahepatic or both; and descriptively as biliary duct wall thickening, strictures or dilatation.

The study protocol conforms to the 1975 Declaration of Helsinki and was reviewed and approved by UHN Research Ethics Board (REB). As this was a retrospective study, and many patients were no longer under active follow up, patient consent was waived following REB guidance.

STATISTICAL ANALYSIS

Descriptive statistics are presented as medians (ranges) for continuous variables, and counts (percentages) for non-continuous variables. Data were grouped according to resolution of ICI-c. For continuous variables, Mann-Whitney U test was used to assess for statistically significant differences between groups. For non-continuous variables, Chi squared or Fisher's exact tests were used. All tests were two-sided and a p value of <0.05 considered statistically significant. The diagnostic performance of percent decline in ALP after 7 days on treatment was assessed by receiver operating characteristic (ROC) curve analysis. Sensitivity, specificity, positive predictive values (PPVs), negative predictive values (NPVs), positive likelihood ratios (LR +ve), and negative likelihood ratios (LR −ve) for relevant cutoffs were also displayed. Cutoff for the percent decline in ALP after 7 days on treatment was derived by taking the point on the ROC where the combined value of sensitivity and specificity was highest. However, as the prevalence of treatment refractory ICI-c is very low in most published series, the optimal cutoff was also estimated using a prevalence rate of 0.1%, and assigning a higher cost to a false positive result than a false negative (cost of false positive to false negative 2:1). Statistical analyses were performed using MedCalc statistical software (version 23.5.2, Ostend, Belgium).

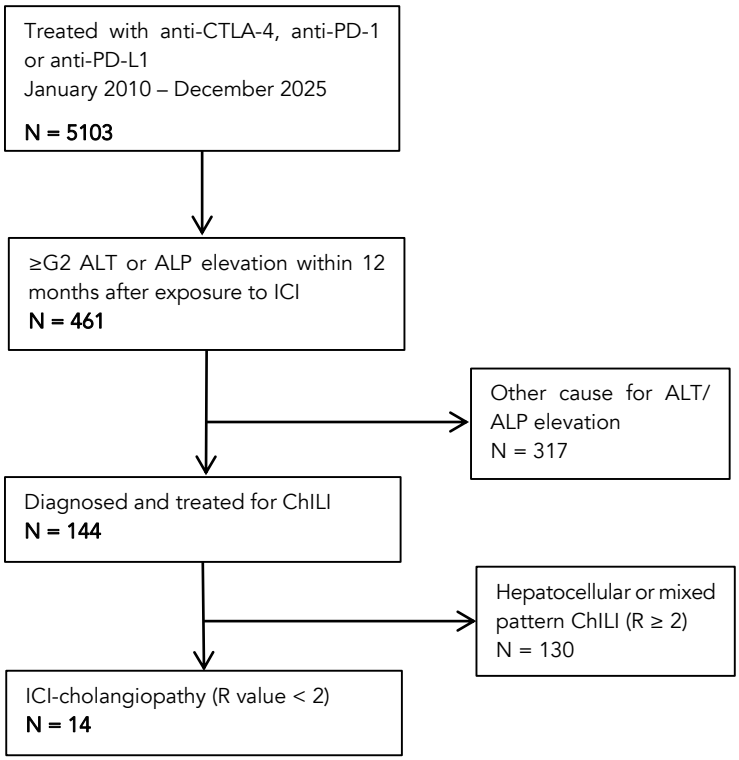

Figure 1. Flow diagram illustrating identification of patients with ICI-cholangiopathy for inclusion in the study. ALT, alanine aminotransferase; ALP, alkaline phosphatase; PD-1, programmed death protein 1; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD-L1, programmed death-ligand 1

Results

INCIDENCE AND CHARACTERISATION OF ICI-CHOLANGIOPATHY

During the study period, 5103 patients were treated with anti-PD-1, anti-PD-L1 and/or anti-CTLA-4 agents. Of those, 144 patients (2.8%) were diagnosed and treated for ChILI. Fourteen (0.2%) had biochemically-defined ICI-c.

Median age was 71 years (range 56 – 87) and most (9; 64%) were male. The majority (8; 57%) had non-small cell lung cancer (NSCLC) as the primary malignancy and most (10; 71%) had been treated with pembrolizumab. All patients had a normal or near-normal ALP at the time of initiation of ICI (median ALP 88 IU/mL, range 52 – 147). One patient presented with abdominal pain; the remainder were asymptomatic at the time of ICI-c diagnosis. Median peak ALT was 163 (range 64 – 531) and peak ALP was 917 (range 374 – 1272). The clinical characteristics of patients diagnosed with ICI-c are summarised in Table 1.

Table 1. Characteristics of patients with ICI-cholangiopathy who were included in the study. irAE, immune-related adverse event; HNSCC, head and neck squamous cell carcinoma; RCC, renal cell cancer.

ID	Age (years) Sex	Primary cancer	Liver metastases	Bone metastases	ICI	Other irAE	Peak ALT (IU/mL)	Peak ALP (IU/mL)	R-value
LT1	82 M	NSCLC	Yes	Yes	Pembrolizumab	Epiglottitis	105	657	0.48
LT2	76 M	NSCLC	No	No	Pembrolizumab	Thyroid	192	526	1.10
LT3	71 M	NSCLC	No	No	Pembrolizumab	None	92	627	0.44
LT4	62 M	NSCLC	No	No	Pembrolizumab	None	146	1018	0.43
LT5	77 M	HNSCC	No	No	Pembrolizumab	None	356	852	1.25
LT6	71 M	Urothelial	No	No	Nivolumab	None	358	982	1.09
LT7	56 F	Melanoma	Yes	No	Nivolumab, Ipilimumab	Optic neuritis	531	1175	1.36
LT8	78 M	HNSCC	Yes	No	Pembrolizumab	Pneumonitis	64	734	0.26
LT9	70 M	RCC	Yes	No	Nivolumab, Ipilimumab	None	99	1272	0.23
LT10	87 M	Melanoma	Yes	No	Pembrolizumab	None	336	1092	0.92
LT11	70 F	NSCLC	No	Yes	Nivolumab	None	430	1160	1.11
LT12	82 F	NSCLC	No	Yes	Pembrolizumab	Pneumonitis	137	374	1.10
LT13	78 F	NSCLC	No	No	Pembrolizumab	Colitis	142	617	0.69
LT14	64 F	NSCLC	No	No	Pembrolizumab	Arthritis	180	1189	0.45

Thirteen patients had CT or MRI imaging at diagnosis. Five patients (38%) had normal imaging. Six (46%) had both intra-and extra-hepatic biliary abnormalities on imaging and 2 (15%) had intrahepatic biliary abnormalities only. Most patients with abnormal imaging had both duct dilatation and biliary wall thickening (6; 75%); 1 (13%) had isolated intrahepatic duct dilatation and 1 (13%) had biliary duct strictures and dilatation.

Three patients in this cohort underwent liver biopsy (Table 2). Indications for biopsy were diagnostic clarification (patient LT6) and poor response to immunosuppression (patients LT2 and LT9). Patient LT2 showed minimal histological changes (mild portal inflammation, focal biliary degenerative changes, reactive ductules) despite concurrent imaging showing intrahepatic biliary strictures and dilatation, consistent with a sclerosing cholangitis phenotype. Patient LT6 showed features of an immune-mediated cholangitis, with bile duct atrophy, focal duct loss and active lymphocytic injury. Patient LT9 showed features reminiscent of

large duct biliary obstruction, with periportal bile infarcts and mixed portal inflammatory infiltrate with neutrophils, biliary degenerative changes with focal necrosis. Mild to moderate lobular hepatitis was also seen.

Table 2: summary of histology findings for patients with ICI-c who underwent liver biopsy.

Patient	Portal inflammation	Cholangitis	Duct injury	Duct loss	Ductular reaction	Periductal fibrosis	Interface hepatitis	Lobular hepatitis
LT2	mild	none	focal	none	focal	none	none	none
LT6	moderate	moderate	moderate	mild	moderate	moderate	mild	moderate
LT9	moderate	moderate	moderate	mild	moderate	moderate	mild	mild

MANAGEMENT OF ICI-CHOLANGIOPATHY

All patients diagnosed with ICI-c were initially treated with corticosteroids. Most (10, 71%) received prednisone at an initial dose of 1 mg/kg methylprednisolone equivalents (mpe)/day. Two patients (14%) received an initial dose of 2mg/kg mpe/day. One patient was treated with dexamethasone 4mg/day and one patient with budesonide 9mg/day. Second line treatment with mycophenolate mofetil (MMF) was added in 5 patients (36%) after median 49 days (range 14-116), for poor response to corticosteroids (N=3), or relapse during corticosteroid taper (N=2). Seven patients (50%) were treated with UDCA, either concurrent with corticosteroids (N = 2) or due to poor corticosteroid response (N = 4). In 1 patient, UDCA was used as first line treatment, and corticosteroids added due to poor response. ALP improved in all patients and normalised/returned to previous baseline in 10 patients (71%; termed "acute ICI-c"). In 4 patients (29%), G1/G2 ALP elevation persisted at the end of follow up ("chronic ICI-c").

A comparison of characteristics of patients with acute and chronic ICI-c is shown in Table 3. There were no significant differences in age, sex, primary cancer type, presence of liver metastases, duration of ICI therapy, or extent of ALP or ALT elevation at ICI-c diagnosis. Chronic ICI-c patients had a slightly higher peak bilirubin than acute ICI-c, and were treated with higher corticosteroid doses. Duration of corticosteroid therapy was numerically higher in chronic ICI-c, although did not reach statistical significance in this small cohort. Three patients with acute ICI-c relapsed during corticosteroid taper, prolonging the course of treatment. When these patients are removed from the analysis, patients with chronic ICI-c were exposed to corticosteroids for significantly longer than acute ICI-c (median 48 days (10-107) vs 133.5 days (83-289), $p = 0.024$).

Two patients in each of the acute ICI-c and chronic ICI-c groups developed steroid-associated adverse events, including infection (N = 2), vertebral fracture and impaired glycemic control requiring hospital admission (each N = 1).

Table 3. Comparison of patients who responded to treatment for ICI-cholangiopathy with patients who did not respond. Continuous variables and given as median (range); non-continuous variables are given as N (%).

	Acute ICI-c (N = 10)	Chronic ICI-c (N = 4)	P value
Age (years)	77.5 (56-87)	70 (62-76)	0.118
Sex (M:F)	6:4	3:1	1.000
Primary cancer:			
NSCLC	4	4	
HNSCC	3	0	
Melanoma	2	0	
Genitourinary	1	1	
Liver metastases present	5 (50)	1 (25)	0.580
ICI type (anti-PD-1:other)	9:1	3:1	0.505
Duration of ICI (days)	202.5 (28-954)	329.5 (56-801)	0.839

	Acute ICI-c (N = 10)	Chronic ICI-c (N = 4)	P value
Peak ALT	161 (64-531)	169 (99-430)	0.839
Peak ALP	793 (374-1189)	1089 (526-1272)	0.454
Peak bilirubin	14.5 (11-49)	34 (22-44)	**0.027**
Corticosteroid dose (mg/kg mpe/day)	1 (0.14 – 1)	1.5 (1-2)	**0.033**
MMF prescribed	3 (30)	2 (50)	0.580
UDCA prescribed	4 (40)	3 (75)	0.559
Time to ALP <G1 (days)	16.5 (6-115)	270 (71-664)	**0.007**
Corticosteroid therapy (days)	51 (10-196)	133.5 (83-289)	0.110
Steroid associated AE	2 (20)	2 (50)	0.520
ALP at 1 month	261 (104-690)	405 (230-561)	0.217
ALP at 3 months	153 (89-595)	349 (348-388)	0.050
ALP at 6 months	100 (80-187)	393 (285-447)	**0.014**

Comparing imaging findings at diagnosis and follow up, there were no apparent differences in anatomical distribution of biliary abnormalities, or characterisation of bile duct injury on imaging, between those with acute ICI-c and chronic ICI-c (Figure 2). Two patients with acute ICI-c had persistent biliary abnormalities on follow up imaging (mild intrahepatic duct dilatation), despite biochemical resolution.

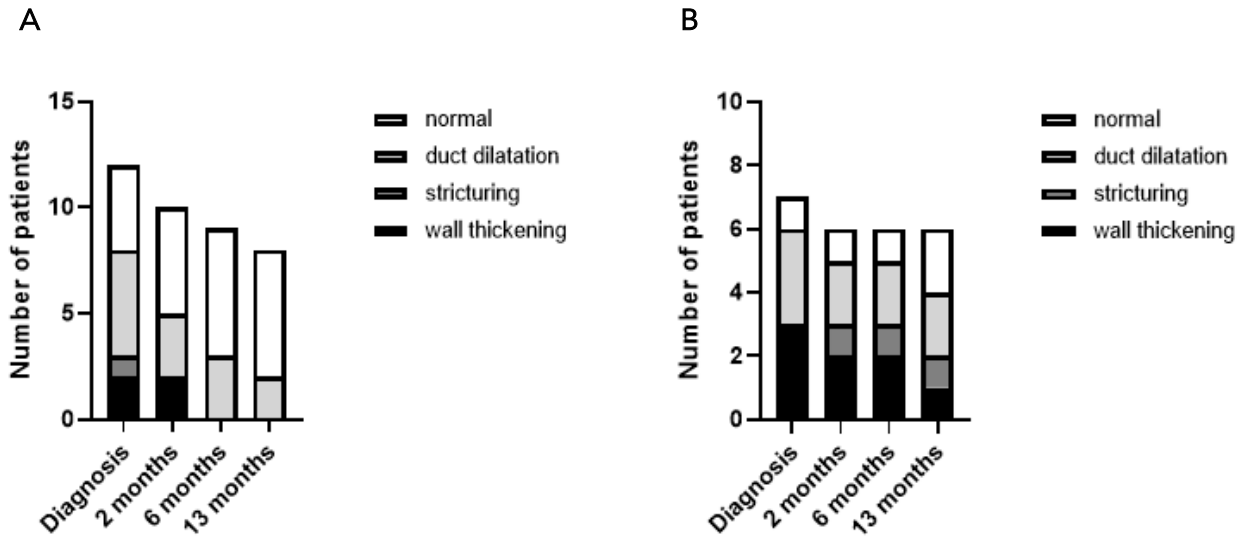

Figure 2. Progression of imaging abnormalities from diagnosis of ICI-cholangiopathy, at median 2 months, 6 months and 13 months after diagnosis, in patients with acute ICI-c (A) and chronic ICI-c (B).

Of the 3 patients who underwent liver biopsy, 1 patient had acute ICI-c (patient LT6) and 2 had chronic ICI-c (LT2 and LT9). In this very small cohort, there were no apparent differences in histological findings between acute and chronic ICI-c.

PREDICTORS OF RESOLUTION OF ICI-CHOLANGIOPATHY

Comparing initial response to corticosteroids, acute ICI-c patients showed a greater reduction in ALP 7 days after starting immunosuppression, compared to chronic ICI-c (ALP reduction at treatment day 7 of 40% (23%-71%) for acute ICI-c, vs. 21.5% (-10%-27%) for chronic ICI-c, $p = 0.016$). The AUROC for percent reduction in ALP at 7 days was 0.92 (95% CI 0.63 – 0.99, $p < 0.0001$), suggesting good diagnostic accuracy to distinguish acute from chronic ICI-c. Youden index J of 0.667 was associated with a criterion of ≤27% decline in ALP at day 7. However, this represents the optimal criterion value only when disease prevalence is 50%, equal weight is given to sensitivity and specificity, and costs of various decisions are ignored. The overall prevalence of chronic ICI-c is very low, approximately 0.05-3.3% in published series [5,7,11-13], and the "cost" of a false

positive may be higher than a false negative, if this leads to premature discontinuation of immunosuppression. Estimating prevalence at 0.1%, and assigning a "cost" of false positive:false negative as 2:1, the optimal cut-off to predict chronic ICI-c was calculated at ≤20% reduction in ALP at 7 days of treatment. Sensitivity, specificity, positive predictive values (PPVs), negative predictive values (NPVs), positive likelihood ratios (LR +ve), and negative likelihood ratios (LR −ve) for relevant cutoffs are shown in Table 4.

Table 4. Performance of percent reduction in ALP at treatment day 7 to identify acute vs chronic ICI-c, at a range of cutoffs.

AUROC (95% CI)	Cutoff (%)	Sens. (%)	Spec (%)	PPV (%)	NPV (%)	LR +ve	LR -ve
0.92 (0.63-0.99)	≤20	50	100	100	99.9		0.50
	≤23	75	88.9	70	100	6.75	0.28
	≤26	75	77.8	30	100	3.37	0.32
	≤27	100	66.7	30	100	3.00	0.00
	≤45	100	0	10		1.00	

OUTCOMES

No patients in the chronic ICI-c group received further ICI. Of four patients with acute ICI-c rechallenged with ICI, only one experienced recurrent cholangiopathy. Four patients, all of whom also experienced other organ irAEs, did not receive further ICI due to concerns regarding further toxicity. One patient maintained stable disease, and 1 patient did not receive further anti-cancer therapy due to disease progression. Over a median follow up period of 13.1 months (range 2.5 – 64.4), 4 patients died, all from cancer progression (3 in the acute ICI-c group and 1 in the chronic ICI-c group). None died of complications related to liver disease.

Discussion

In this retrospective, observational study, we identified patients with biochemically-defined ICI-c from a large cohort of ICI-treated patients. Using specific biochemical inclusion criteria, reflective of real-world clinical practice, we aimed to identify different phenotypes of ICI-c and patterns of treatment response. We found that ICI-c is an uncommon complication of ICI therapy, comprising only 10% of our cohort of patients with ChILI. The frequency of cholestatic ChILI in this study is somewhat lower than that reported by others from the UK, France and Japan (17-37%)[5,23,24], and may reflect regional and/or temporal differences in cancer prevalence and treatment practices. Our observation that ICI-c affected only 0.9% of ICI treated patients is broadly aligned with others, who have reported an incidence of ICI-c of 0.05-3.3%, defined using a variety of biochemical, imaging and histological criteria[5,9-13]. Congruent with the observations of others, we found that ICI-c was strongly associated with anti-PD-1 therapies, especially pembrolizumab.

There are conflicting reports in the published literature regarding response of ICI-c to immunosuppression. For example, systematic reviews of published case reports indicated that although biliary enzymes may improve, only a minority of patients (8.5 – 11.5%) respond completely to immunosuppression[14,15]. In contrast, a review of cases from the French pharmacovigilance database indicated that a majority of patients (79%) diagnosed with ICI-cholangitis improved, some without any specific therapy. However, this cohort included patients with mixed as well as cholestatic hepatitis, and the degree of improvement versus resolution was not described[20].

All patients in this study received immunosuppression, and liver injury resolved over 3-6 months in most patients (71%; acute ICI-c). In the remaining patients ALP improved, especially during the first month after diagnosis, but did not normalise/return to previous baseline (chronic ICI-c). There appeared to be little additional benefit from second line immunosuppression (MMF) or anti-cholestatic therapy (UDCA). Causes of ALP elevation may be multifactorial in patients with metastatic cancer. However, following a detailed review, no other cause for persistent ALP elevation was identified in these patients. ALP was normal or near-normal at baseline and rose acutely at the time of diagnosis of ICI-c. Bone metastases were present in 1 patient but without ALP elevation prior to the diagnosis of ICI-c, and did not progress during follow up. There were no identified

exposures to other medications associated with cholestatic liver injury[25]. Biliary imaging abnormalities were present in 3 of the 4 patients at diagnosis and persisted during follow up. Therefore, chronic ICI-c was adjudicated as the most likely cause for persistent ALP elevation in these patients.

Most patients had radiological features of cholangitis at ICI-c diagnosis, although 6 (43%), one of whom developed chronic ICI-c, had normal biliary imaging both at diagnosis and follow up. We observed no apparent differences in the distribution or type of abnormal imaging findings between acute and chronic ICI-c. Numerically more patients with chronic ICI-c had persistent imaging abnormalities over 6-13 months of follow up than patients with acute ICI-c, although 2 patients with acute ICI-c had persistent mild intrahepatic duct dilatation on imaging approximately one year after diagnosis, despite normalisation of ALP. This is consistent with other reports of persistent radiologic abnormalities despite biochemical and clinical resolution[7,11,14]. Neither of these patients were rechallenged with further ICI therapy, and the clinical significance of persistent radiological abnormalities remains unclear.

No patient in this study received third line immunosuppression. Of the patients with ICI-c, one patient had imaging showing intra- and extrahepatic biliary strictures with no evidence of ongoing immune-mediated hepatitis or cholangitis on liver biopsy (LT2), so further immunosuppression was not indicated. In the other 3 patients, immunosuppression was tapered when ALP reached Grade 1 and was not re-introduced, as ALP remained stable despite withdrawal of immunosuppression. There is little data on efficacy of second or third line immunosuppression in ICI-c, although one case report suggested little benefit from addition of tacrolimus to corticosteroids and MMF[11]. Recently, Tocilizumab has shown benefit in some patients with treatment refractory ChILI, including mixed and cholestatic phenotypes[26,27], and this may represent an additional treatment strategy.

Management guidelines for ICI-c remain sparse, and based on limited data[3,4]. Several authors advocate for early liver biopsy, to identify features of immune-mediated cholangitis and guide further management[11,19,28]. However, liver biopsy is an invasive test which carries some risk and may introduce delays in care. We found that ≤20% reduction in ALP after 7 days of immunosuppressive treatment identifies patients who respond poorly to therapy (chronic ICI-c). This cut-off could be incorporated into future management algorithms. For example, patients with >20% reduction in ALP at treatment day 7 are likely to respond well and should continue treatment. Patients with ≤20% reduction in ALP at treatment day 7 could be considered for liver biopsy to guide escalation to second/third line immunosuppression, if histology demonstrates ongoing immune-mediated cholangitis. In patients without histological evidence of immune-mediated inflammation, immunosuppression could be withdrawn, reducing the risk for corticosteroid-associated side effects in patients who are unlikely to benefit.

There are several limitations to this study. The retrospective design is associated with inherent bias. Classification of events as ChILI was based on clinician judgement and cannot be fully verified retrospectively. Access to data outside our institution was limited due to privacy regulations. Management of ChILI was at the treating clinician's discretion, leading to some heterogeneity in treatment. The number of instances of ICI-c was small, limiting the analysis. In particular, only 3 patients underwent a liver biopsy, limiting evaluation of the role of histology in diagnosis/management of ICI-c.

Conclusions

This study demonstrates that most patients with biochemically-defined ICI-c respond well to treatment with immunosuppression, with resolution of liver injury within 3-6 months. However, up to 30% of patients may develop chronic ICI-c, characterised by improvement in ALP but failure of normalisation. A reduction in ALP by ≤ 20% at treatment day 7 may predict patients who will respond poorly to treatment and help to guide further investigation and management, in particular to minimise prolonged corticosteroid exposure and associated side effects in patients with a low likelihood of response. This approach warrants evaluation in further prospective studies.

Conflict of Interest Statement:

ESG consults for GlaxoSmithKline, is on Speaker's Bureau for Incyte and has received grant/research support from Regenta Therapeutics, GlaxoSmithKline, AstraZeneca, and Tempus. PB has received honoraria from AstraZeneca and Merck and is on a Data Safety Monitoring Board for Bristol Myers Squibb (no financial remuneration). NL has received grant/research support from Merck, AstraZeneca, Bristol Myers Squibb and Roche, and educational travel funding from Merck and AstraZeneca. ARL, FS, RB and MC have no conflicts of interest to declare.

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