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Lucy Meunier, Lina Hountondji, H el ene Jantzem, Jean-Luc Faillie, Alexandre Maria, Pascale Palassin, St ephanie Faure, Philine Witkowski-Durand-Viel, Xavier Quantin, Georges-Philippe Pageaux

► **To cite this version:**

Lucy Meunier, Lina Hountondji, H el ene Jantzem, Jean-Luc Faillie, Alexandre Maria, et al.. Cholangitis Induced by Immune Checkpoint Inhibitors: Analysis of Pharmacovigilance Data. *Clinical Gastroenterology and Hepatology*, 2024, 22 (7), pp.1542-1545.e4. 10.1016/j.cgh.2023.12.008 . hal-04960832

HAL Id: hal-04960832

<https://hal.science/hal-04960832v1>

Submitted on 21 Feb 2025

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Cholangitis Induced by Immune Checkpoint Inhibitors: Analysis of Pharmacovigilance Data



Immune checkpoint inhibitors (ICIs) are remarkable anticancer therapies that have revolutionized the oncological prognosis of many cancers.¹ The considerable efficacy of ICIs is associated with the onset of more- or less-serious, immune-related adverse effects (irAEs) affecting several organs, which can concern up to 70% of patients, owing to a loss of self-tolerance during the restoration of antitumor immunity.² Checkpoint inhibitor-induced liver injury (CHILI), which may occur in up to 25% of patients, is treated with steroids as first-line treatment, and immunosuppressive drugs as second-line treatment.³ Recently, ICI-induced cholangitis was described as an emerging irAE. Hence, Pi et al⁴ reviewed all 53 published cases of ICI-induced cholangitis and compared the different types of bile duct involvement. We recently described CHILI according to the biological profile: cholestatic, hepatocellular, or mixed.⁵ Cholestatic profiles were associated with macroscopic and/or microscopic bile duct damage, and time to resolution was significantly longer. More recently, Onoyama et al⁶ and Parlati et al⁷ described a poorer response to steroids in cases of biliary histologic damage or ICI-induced sclerosing cholangitis. The latest European Society for Medical Oncology guidelines include the management of cholangitis, which is succinct and still poorly documented.³ The aim of this study therefore was to analyze the cases of ICI-induced cholangitis reported in the French pharmacovigilance system to describe their clinical characteristics, evolution, and outcome.

Methods

We conducted a retrospective study of ICI-related cholangitis cases reported to the French pharmacovigilance system. All de-duplicated individual case safety report of cholangitis (Medical Dictionary for Regulatory Activities preferred term) reported with at least 1 ICI were selected. The case/noncase method was used to identify a potential disproportionate reporting signal, that is, a higher than expected number of adverse reaction reports compared with other reactions recorded in the international database, by calculating the reporting odds ratios (RORs).

The biological profile of cholangitis was defined by the ratio of serum alanine aminotransferase to alkaline phosphatase levels (R value = [alanine aminotransferase/upper limit of normal]/[alkaline phosphatase/upper limit of normal]), and can be categorized as hepatocellular (R >5), mixed (R = 2–5), or cholestatic (R <2).

Cholangitis severity was defined using the common terminology criteria for adverse events classification. We differentiated microscopic (liver biopsy) and macroscopic (imaging) cholangitis and their descriptions: cholangitis (inflammation), biliary dilatation, and sclerosing cholangitis.

Results

Among the 243 cases of cholangitis reported with at least 1 ICI drug in the international pharmacovigilance database, 80 cases were extracted from the French database. Twenty-seven cases were excluded because of a lack of data and 5 cases were excluded for differential diagnoses (lithiasis angiocholitis, tumor compression, primary sclerosing cholangitis, or primary biliary cholangitis at the cirrhosis stage). A total of 48 cases were analyzed, and their characteristics are presented in Table 1. The median time to onset of cholangitis was 5.7 months (minimum, 3 mo; maximum, 28.8 mo) (Supplementary Figure 1). In 31 (64.5%) patients, the detection of cholangitis was incidental; in the other patients, the symptoms were fever, jaundice, or pain.

According to the R ratio, all patients had a mixed or cholestatic pattern. A quarter of patients had jaundice (13 of 48), half of them with bilirubinemia greater than 50 $\mu\text{mol/L}$. The duration of treatment and the number of cycles were shorter in patients with a bilirubin level greater than 50 $\mu\text{mol/L}$ (260.8 [± 295.4] vs 150.3 [± 296.8] days; $P = .033$) (Supplementary Table 1). Twenty-three (47.9%) patients underwent liver biopsy. Among these patients, 19 (39.6%) had bile duct microscopic involvement. For some patients, the following signs also were associated: eosinophilic infiltrate, granulomatosis, sinusoidal dilatation, and biliary dystrophy. The number of infusions (8.41 [± 9.9] vs 21.2 [± 24.1]; $P = .003$) and the ICI treatment duration (155.4 [± 186.5] vs 380.9 [± 375.1] days; $P = .003$) were associated significantly with bile duct dilatation.

Abbreviations used in this paper: CHILI, checkpoint inhibitor-induced liver injury; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; ROR, reporting odds ratio; UDCA, ursodeoxycholic acid.

Most current article

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1542-3565

<https://doi.org/10.1016/j.cgh.2023.12.008>

Table 1. Characteristics of Patients With ICI-Induced Cholangitis

Characteristics	ICI-induced cholangitis cases, n = 48
Age, y, means (SD) (minimum–maximum)	64.2 (13.9) (14–86)
Gender, n (%)	
Male	24 (50)
Female	24 (50)
ICI class, n (%)	
PD-1	41 (85.4)
PDL-1	5 (10.4)
CTLA-4 + PD-1	2 (4.2)
ICI association, n (%)	
Monotherapy	39 (81.2)
ICI + chemotherapy	7 (14.6)
Cancer localization, n (%)	
Lung	29 (60.4)
Melanoma	13 (27.1)
Head and neck	2 (4.2)
Renal	2 (4.2)
Uterine leiomyoma	1 (2.1)
Astrocytoma	1 (2.1)
Treatment duration, d, means (SD) (minimum–maximum)	244.7 (295.0) (1–1627)
Number of infusions, means (SD) (minimum–maximum)	13.5 (17.9) (1–104)
Circumstances of finding, n (%)	
Biological follow-up evaluation/asymptomatic	31 (64.6)
Abdominal pain	7 (14.6)
Asthenia	4 (8.3)
Jaundice	4 (8.3)
Fever	1 (2.1)
Hyperthermia	1 (2.1)
Biological pattern, n (%)	
Cholestatic	34 (70.8)
Mixed	8 (16.7)
Not available	6 (12.5)
CTCAE grade, n (%)	
1	1 (2.1)
2	1 (2.1)
3	19 (39.6)
4	21 (43.8)
Not available	6 (12.5)
Macroscopic bile duct involvement, n (%)	
Yes	33 (73.3)
No	12 (26.7)
Bile duct dilatation, n (%)	
Yes	19 (39.6)
No	29 (60.4)
Type of macroscopic bile duct involvement, n (%)	
Cholangitis	18 (72.0)
Sclerosing cholangitis	7 (28.0)
Localization of bile duct involvement, n (%)	
Intrahepatic and extrahepatic	14 (43.8)
Extrahepatic	12 (37.5)
Intrahepatic	6 (18.8)
Liver biopsy, n (%)	
Yes	23 (47.9)
No	25 (52.1)
Microscopic cholangitis, n (%)	
Yes	19 (39.6)
No	3 (6.2)

Table 1. Continued

Characteristics	ICI-induced cholangitis cases, n = 48
CHILI first-line treatment, n (%)	
Steroids	23 (47.9)
UDCA	10 (20.8)
No treatment	15 (31.2)
CHILI second-line treatment, n (%)	
Steroids	1 (2.1)
MMF	1 (2.1)
UDCA	3 (6.2)
Steroid bolus	1 (2.1)
No treatment	42 (87.5)
Outcomes, n (%)	
Improvement	38 (79.2)
Recurrence after rechallenge	3 (6.3)
Death	4 (8.3)

CHILI, checkpoint inhibitor–induced liver injury; CTCAE, common terminology criteria for adverse events; CTLA-4, cytotoxic T-lymphocyte–associated protein-4; ICI, immune checkpoint inhibitor; MMF, mycophenolate mofetil; PD-1, programmed cell death receptor-1; PDL-1, programmed cell death ligand-1; UDCA, ursodeoxycholic acid.

Regarding cholangitis management, 24 (50%) patients received steroids, 13 (27.1%) received ursodeoxycholic acid (UDCA), and 15 patients improved without treatment. Only 1 patient received mycophenolate mofetil. ICI was rechallenged in 6 patients and cholangitis recurred in 3 patients. Four (8.3%) patients died, 2 of them owing to liver injury.

Disproportionality analyses showed that cholangitis cases were reported 18 times more frequently with ICI drugs than with all other drugs (ROR, 18.07; 95% CI, 15.85–20.59), and 7 times more than with all antineoplastic agents (ROR, 7.02; 95% CI, 6.13–8.03). As a positive control, the disproportionality analysis of cholangitis cases reported with ketamine, a drug well known to induce cholangitis, retrieved a strong significant pharmacovigilance signal (ROR, 27.81; 95% CI, 17.49–44.22).

Discussion

This study, based on French pharmacovigilance data, analyzed 48 cases of ICI-induced cholangitis. This was a large series of patients with original data, providing new information on this poorly described type of CHILI. All cases of cholangitis had a cholestatic or mixed biological pattern with a predominance of alkaline phosphatases. In our cohort, almost half of all cholangitis cases occurred after 6 months of ICI treatment. The time to onset is longer than described for hepatitis or other irAEs, which generally occur in the first 3 months of treatment.^{5,8} All CHILI cases were exposed to anti-programmed cell death ligand-1, suggesting that inhibition of programmed cell death receptor-1 signaling is involved in the pathophysiology of cholangitis.

Disproportionality analyses showed a signal of over-reporting of ICI-induced cholangitis compared with other antineoplastic drugs. The increase in reporting of cholangitis observed with ICI was close to that observed with ketamine, our positive control.⁹

Our data suggest that the microscopic bile ducts may be affected initially, followed by macroscopic bile ducts in case of prolonged treatment. These results also may lead to performing a liver biopsy in cases of cholestasis, to detect ICI-induced cholangitis lesions at an early stage, and thus introduce treatment more rapidly.

Nearly 40% of patients presented with a concurrent irAE associated with cholangitis. Colitis often is involved, suggesting a common spectrum associating cholangitis and colitis, with shared pathophysiological mechanisms, as in the case of inflammatory bowel disease and primary sclerosing cholangitis.

Regarding management, an association between ICI-induced cholangiopathy and steroid-resistant hepatitis already has been reported in the literature.^{4,7,10} Approximately a quarter of patients improved spontaneously without treatment and a quarter improved with UDCA. These alternatives to steroids (therapeutic abstention or UDCA) already were suggested by our group.⁵ The latest European Society for Medical Oncology guidelines³ propose using UDCA for the management of cholangitis, without specifying its place in relation to steroids. UDCA probably is under-prescribed in the treatment of ICI-induced cholangitis and should be recommended as first-line therapy, with or without steroids, considering its excellent benefit-risk balance.

LUCY MEUNIER

Department of Hepatogastroenterology and Liver Transplantation
 Universitary Hospital Centre Montpellier
 University of Montpellier
 Montpellier, France, and
 Institute for Regenerative Medicine and Biotherapy
 University of Montpellier
 Montpellier, France

LINA HOUNTONDI

Department of Hepatogastroenterology and Liver
Transplantation
Universitary Hospital Centre Montpellier
University of Montpellier
Montpellier, France

HÉLÈNE JANTZEM

Department of Pharmacovigilance
Universitary Hospital Centre Brest
Brest, France

JEAN LUC FAILLIE

Department of Medical Pharmacology and
Toxicology
Universitary Hospital Centre Montpellier
University of Montpellier
Montpellier, France, and
Desbrest Institute of Epidemiology and Public
Health, INSERM
University of Montpellier
Montpellier, France

ALEXANDRE MARIA[§]

Internal Medicine and Immuno-Oncology
Institute for Regenerative Medicine and Biotherapy
Universitary Hospital Centre Montpellier
University of Montpellier
Montpellier, France

PASCALE PALASSIN[§]

Department of Medical Pharmacology and
Toxicology
Universitary Hospital Centre Montpellier
University of Montpellier
Montpellier, France

MONRIO GROUP**Supplementary Material**

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at <http://doi.org/10.1016/j.cgh.2023.12.008>.

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[§]Authors share co-senior authorship

Acknowledgments

The authors would like to thank the Uppsala Monitoring Centre (UMC) (VigiBase) and French network of regional pharmacovigilance centers (RFCRPV), for collecting and providing the data. The opinions and conclusions in this study are not necessarily those of the various centers or of the World Health Organization.

The MonRIO group includes: Stéphanie Faure,¹ Philine Witkowski-Durand-Viel,² Xavier Quantin,² and Georges Philippe Pageaux¹ from the ¹Department of Hepatogastroenterology and Liver Transplantation, Universitary hospital center (CHU) Montpellier, University of Montpellier, Montpellier, France and the ²Department of Medical Oncology, Montpellier Cancer Institute, CHU Montpellier, University of Montpellier, Montpellier, France.

Conflicts of interest

The authors disclose no conflicts.

Supplementary Materials and Methods

Data Collection

Data were extracted from the French pharmacovigilance database, which collects all adverse drug reactions occurring spontaneously and reported since 1985 to the French public pharmacovigilance system (30 regional centers), currently more than 1.2 million drug adverse reactions. All adverse drug reaction reports have been analyzed and recorded by specialized pharmacologists using the Medical Dictionary of Regulatory Activities (version 25.0) classification and include detailed clinical characteristics such as medical history; clinical course of the adverse drug reaction; laboratory, histologic, and imaging results; diagnoses; management; and, most of the time, the evolution of the adverse drug reaction. All de-duplicated individual case safety reports of cholangitis (Medical Dictionary for Regulatory Activities preferred term) reported with at least 1 ICI (including nivolumab, ipilimumab, pembrolizumab, atezolizumab, avelumab, cemiplimab, durvalumab, tremelimumab, spartalizumab, relatlimab, and dostarlimab) were selected.

To perform disproportionality analyses, individual case safety reports of cholangitis (preferred term) reported worldwide with at least 1 ICI also were extracted from the World Health Organization international pharmacovigilance database: VigiBase. These data are not sufficiently detailed for a clinical description but are suitable for statistical analyses. The case/noncase method was used to identify a potential disproportionate reporting signal, that is, a higher than expected number of adverse reaction reports compared with other reactions recorded in the database, by calculating ROR. The cases were all reports of cholangitis that occurred and the noncases were all the other drug-related adverse reactions recorded in this global database. Exposure to ICI (narrow standardized drug grouping) was compared between cases and noncases with all other drugs and with all other antineoplastic agents. As a positive control, a disproportionality analysis for cholangitis cases also was performed with ketamine, which is well known to induce cholangitis. A signal of disproportionate reporting

was considered if the 95% CI lower limit of the ROR exceeded 1.

Characterization of Cholangitis

For all cases, the duration of ICI treatment, time to onset of cholangitis, etiologic assessment of cholangitis, imaging and histologic data in the event of liver biopsy, treatments administered, and clinical and laboratory result evolution were collected. In the presence of a differential diagnosis more plausible than ICI-induced cholangitis, such as lithiasis, bacterial infection, or pre-existing autoimmune disease, the case was excluded from the analysis.

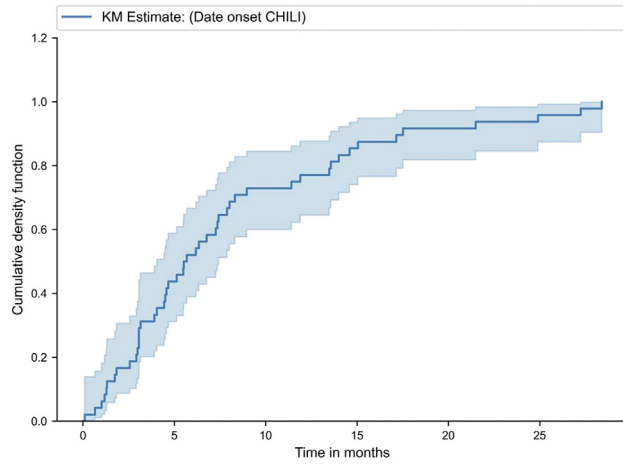
Cholangitis severity was defined using the common terminology criteria for adverse events classification: alanine aminotransferase level greater than 3-fold the upper limit of normal (common terminology criteria for adverse events grade 1), alanine aminotransferase level greater than 3- to 5-fold the upper limit of normal (common terminology criteria for adverse events grade 2), alanine aminotransferase level greater than 5- to 20-fold the upper limit of normal (common terminology criteria for adverse events grade 3), or alanine aminotransferase level greater than 20-fold the upper limit of normal (common terminology criteria for adverse events grade 4) in participants with previous normal liver laboratory tests.

Statistical Analysis

Descriptive statistics are presented as medians (ranges) or means (\pm SD) for quantitative variables, and as frequencies (percentages) for qualitative variables. The α risk was set to 5% and 2-tailed tests were used. Statistical analyses were performed with EasyMedStat (version 3.27; www.easymedstat.com).

Ethical Considerations

Institutional Review Board statement: Neither ethics committee approval nor informed consent was required for this observational study based on anonymous pharmacovigilance data.



Supplementary Figure 1. Time to onset of checkpoint inhibitor-induced liver injury (CHILI) after immune checkpoint inhibitor (ICI) initiation. This figure presents the time to onset (in months) of ICI-induced cholangitis as a function of the time since the start of ICI. At 3 months, the CHILI-free survival was 77.1% (95% CI, 62.5–86.6), and at 6 months, the CHILI-free survival was 47.9% (95% CI, 33.3–61.1). KM, Kaplan–Meier.

Supplementary Table 1. Comparison of ICI-Induced Cholangitis Cases With or Without Jaundice (Bilirubinemia >50 $\mu\text{mol/L}$)

Characteristics	ICI-induced cholangitis without jaundice, n = 41	ICI-induced cholangitis with jaundice, n = 7	P value
Age, y, means (SD)	65.4 (\pm 12.2)	57.0 (\pm 21.1)	.560
Gender, n (%)			>.999
Men	20 (48.8%)	4 (57.1%)	
Women	21 (51.2%)	3 (42.9%)	
ICIs, n (%)			.539
Atezolizumab	2 (4.9%)	0 (0.0%)	
Cemiplimab	1 (2.4%)	0 (0.0%)	
Durvalumab	2 (4.9%)	1 (14.3%)	
Nivolumab	26 (63.4%)	3 (42.9%)	
Nivolumab + ipilimumab	2 (4.9%)	0 (0.0%)	
Pembrolizumab	8 (19.5%)	3 (42.9%)	
ICI class, n (%)			>.999
CTLA-4 + PD-1	2 (4.9%)	0 (0.0%)	
PD-1	35 (85.4%)	6 (85.7%)	
PDL-1	4 (9.8%)	1 (14.3%)	
ICI association, n (%)			.072
Combination therapy	2 (4.9%)	0 (0.0%)	
ICI + chemotherapy	4 (9.8%)	3 (42.9%)	
Monotherapy	35 (85.4%)	4 (57.1%)	
Cancer localization, n (%)			.015
Head and neck	2 (4.9%)	0 (0.0%)	
Lung	27 (65.9%)	2 (28.6%)	
Melanoma	11 (26.8%)	2 (28.6%)	
Other cancers	0 (0.0%)	2 (28.6%)	
Renal	1 (2.4%)	1 (14.3%)	
Treatment duration, d, means (SD)	260.8 (\pm 295.4)	150.3 (\pm 296.8)	.033
Microscopic cholangitis, n (%)			.650
No	3 (7.3%)	0 (0.0%)	
Yes	15 (36.6%)	4 (57.1%)	
Macroscopic bile duct involvement, n (%)			.362
Yes	29 (76.3%)	4 (57.1%)	
No	9 (23.7%)	3 (42.9%)	
Type of macroscopic bile duct involvement, n (%)			.548
Cholangitis	16 (76.2%)	2 (50.0%)	
Sclerosing cholangitis	5 (23.8%)	2 (50.0%)	
Bile duct dilatation, n (%)			.219
Yes	18 (43.9%)	1 (14.3%)	
No	23 (56.1%)	6 (85.7%)	
Localization of bile duct involvement, n (%)			.651
Extrahepatic	10 (35.7%)	2 (50.0%)	
Intrahepatic	5 (17.9%)	1 (25.0%)	
Intrahepatic and extrahepatic	13 (46.4%)	1 (25.0%)	
CHILI first-line treatment, n (%)			.651
No treatment	14 (34.2%)	1 (14.3%)	
Steroids	19 (46.3%)	4 (57.1%)	
UDCA	8 (19.5%)	2 (28.6%)	
CHILI second-line treatment, n (%)			.420
No treatment	36 (87.8%)	6 (85.7%)	
Steroids	0 (0.0%)	1 (14.3%)	
UDCA	3 (7.3%)	0 (0.0%)	
Steroid bolus	1 (2.4%)	0 (0.0%)	
MMF	1 (2.4%)	0 (0.0%)	

Supplementary Table 1. Continued

Characteristics	ICI-induced cholangitis without jaundice, n = 41	ICI-induced cholangitis with jaundice, n = 7	P value
Outcomes, n (%)			.229
Death	2 (4.9%)	2 (28.6%)	
Improvement	33 (80.49%)	5 (71.43%)	
Recurrence	3 (7.32%)	0 (0.0%)	
CHILI pattern, n (%)			.563
Cholestatic	29 (70.7%)	5 (71.4%)	
Mixed	6 (14.6%)	2 (28.6%)	
CTCAE grade, n (%)			.596
1	1 (2.4%)	0 (0.0%)	
2	1 (2.4%)	0 (0.0%)	
3	17 (41.5%)	2 (28.6%)	
4	16 (39.0%)	5 (71.4%)	
Other immune adverse event, n (%)			.219
Yes	18 (43.9%)	1 (14.3%)	
No	23 (56.1%)	6 (85.7%)	

Bolded entries indicate significant P value $\leq .05$.

CHILI, checkpoint inhibitor-induced liver injury; CTCAE, common terminology criteria for adverse events; CTLA-4, cytotoxic T-lymphocyte-associated protein-4; ICI, immune checkpoint inhibitor; MMF, mycophenolate mofetil; PD-1, programmed cell death receptor-1; PDL-1, programmed cell death ligand-1; UDCA, ursodeoxycholic acid.