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Outcome of Hepatitis E Virus Infection in Patients With Inflammatory Arthritides Treated With Immunosuppressants

A French Retrospective Multicenter Study

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Abstract: The clinical presentation and outcome of hepatitis E virus (HEV) infection in inflammatory rheumatic diseases are unknown. We aimed to investigate the severity of acute HEV infection and the risk of chronic viral replication in patients with inflammatory arthritides treated with immunosuppressive drugs.

All rheumatology and internal medicine practitioners belonging to the Club Rhumatismes et Inflammation in France were sent newsletters asking for reports of HEV infection and inflammatory arthritides. Baseline characteristics of patients and the course of HEV infection were retrospectively assessed by use of a standardized questionnaire.

From January 2010 to August 2013, we obtained reports of 23 cases of HEV infection in patients with rheumatoid arthritis (n = 11), axial spondyloarthritis (n = 5), psoriatic arthritis (n = 4), other types of arthritides (n = 3). Patients received methotrexate (n = 16), antitumor necrosis factor α agents (n = 10), rituximab (n = 4), abatacept (n = 2), tocilizumab (n = 2), and corticosteroids (n = 10, median dose 6 mg/d, range 2–20). All had acute hepatitis: median aspartate and alanine aminotransferase levels were 679 and 1300 U/L, respectively. Eleven patients were asymptomatic, 4 had jaundice. The HEV infection diagnosis relied on positive PCR results for HEV RNA (n = 14 patients) or anti-HEV IgM positivity (n = 9). Median follow-up was 29 months (range 3–55). Treatment included discontinuation of immunosuppressants for 20 patients and ribavirin treatment for 5. Liver enzyme levels normalized and immunosuppressant therapy could be reinitiated in all patients. No chronic infection was observed.

Acute HEV infection should be considered in patients with inflammatory rheumatism and elevated liver enzyme values. The outcome of HEV infection seems favorable, with no evolution to chronic hepatitis or fulminant liver failure.

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Abbreviations: μmol/L = micromoles per day, AIDS = Acquired Immune Deficiency Syndrome, ALT = alanine aminotransferase, C.H. = centre hospitalier, C.H.R.U. = centre hospitalier régional universitaire, C.H.U. = centre hospitalo-universitaire, HCV = hepatitis C virus, HEV = hepatitis E virus, IgG = immunoglobulin G, IgM = immunoglobulin M, mg/d = milligrams per day, PCR = polymerase chain reaction, PT = prothrombin time, RA = rheumatoid arthritis, RNA = ribonucleic acid, U/L = units per liter, ULN = upper limit of normal.

Hepatitis E virus (HEV) infection is ubiquitous and is due to a small nonenveloped virus with a positive-sense, single-stranded RNA genome. The virus was discovered in the 1980s. Four major genotypes representing a single serotype have been recognized: HEV1 and HEV2 are restricted to humans and transmitted via contaminated water in developing countries; HEV3 and HEV4 infect humans, pigs, and other mammalian species and are responsible for sporadic cases of autochthonous HEV infection in Western countries. In this setting, HEV infection causes acute disease, mainly in middle-aged and older men. Such an infection might be mistaken for drug-induced liver injury.[1] Acute HEV infection might range in severity from subclinical to fulminant, in particular in the risk group of pregnant women, whose death rate in the course of HEV

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infection could approach 15% to 20%.[2,3] However, in the rest of the population and in immunosuppressed patients,[4] acute HEV infection is usually asymptomatic. Thus, in a French study of kidney transplant recipients, acute HEV infection was asymptomatic in 14 of 16 patients (87.5%).[5] Some extrahepatic manifestations of HEV infection were reported. Kamar et al[6] reported neurologic disorders among 126 patients with HEV infection: inflammatory polyradiculopathy (n = 3), Guillain-Barre syndrome (n = 1), bilateral brachial neuritis (n = 1), encephalitis (n = 1), and ataxia/proximal myopathy (n = 1). Hematological disorders, notably acute immune thrombocytopenia,[7] were also reported.

Recent efforts to develop and standardize the HEV serology led to data showing increasingly recognized cases of HEV infection. HEV infection might correspond to about 10% of cases of non-A–D acute viral hepatitis in Western countries among nontravelers.[8]

Another feature of HEV is its ability to cause chronic infection, defined as a persistent infection lasting >6 months, usually in severely immunocompromised patients.[9] In 3 well-known circumstances of immunodeficiency—AIDS, kidney or liver transplantation, and haematological malignancies—HEV infection can develop into chronic infection.[10,11] In liver transplant recipients,[12] chronic infection with HEV can result in HEV-related cirrhosis.[13] However, little is known about the incidence and severity of acute and chronic HEV infection in patients with inflammatory rheumatic diseases. We therefore addressed this issue of HEV infection in patients receiving treatment for inflammatory arthritides.

PATIENTS AND METHODS

This retrospective multicenter study was initiated by the Club Rhumatismes et Inflammation, a section of the Society of Rheumatology in France. All rheumatology and internal medicine practitioners belonging to the club (nearly 2400 physicians) were sent 3 newsletters over 12 months asking for reports of HEV infection and inflammatory rheumatism. Informed consent was given by all enrolled patients. No ethical approval was requested, since it is not required for noninterventional retrospective studies in France. Practitioners were sent a standardized and anonymized questionnaire to collect information on baseline characteristics of patients and the course of HEV infection. Inclusion criteria in the study were (1) diagnosis of inflammatory rheumatism according to international criteria, (2) treatment with an immunosuppressive drug, and (3) detection of specific IgM antibodies against HEV or HEV RNA in serum and/or stools with tests performed in 2 national reference centers in Paris and Toulouse, as previously described.[14–16] Patients with positive IgG antibodies and negative IgM antibodies and negative PCR results for HEV RNA were excluded because the presence of IgG antibodies indicated only that HEV was seroprevalent in those patients. Chronic HEV infection was defined by continued PCR detection of HEV RNA in serum or stools for >6 months.

RESULTS

Patient Characteristics

The main characteristics of patients are provided in Table 1. Cases for 23 patients (10 men; median age at diagnosis 51 years [range 26–79 years]) were reported between January 2010 and August 2013. Most patients did not have any other comorbidity; only 1 patient showed excessive consumption of alcohol and none had chronic liver disease. Three patients had type II diabetes, 2 had arterial hypertension, and 10 were overweight.

In total, 11 patients had rheumatoid arthritis (RA), 5 axial spondyloarthritis, 4 psoriatic arthritis, and 1 each juvenile idiopathic arthritis, discoid lupus with Jaccoud arthropathy and undifferentiated arthritis. Median disease duration was 15 years (range 1.5–34 years). Overall, 18 patients received a biologic drug, including an antitumor necrosis factor α agent (n = 10), rituximab (n = 4), abatacept (n = 2), and tocilizumab (n = 2); 16 received methotrexate, 4 leflunomide, and 1 cyclosporine. In all, 15 patients received both a biologic drug and a conventional immunosuppressive drug; 10 received corticosteroids (median dose 6 mg/d, range 2–20 mg/d).

Clinical Presentation of HEV

Overall, 21 cases were autochthonous. Two patients had traveled out of France in the 3 months preceding infection, 1 to Spain (patient 9) and the other to Morocco (patient 17). The patient who had traveled to Spain, along with 3 family members had become infected with HEV by eating contaminated chorizo. Seven patients lived in the northern part of France and 16 in the southern part.

In total, 11 of the 23 cases were clinically asymptomatic and HEV infection was suspected because of liver enzyme elevation; 8 patients reported asthenia, which was the only symptom in 2 of them. The other symptoms were jaundice (n = 4), pain in the right hypochondriac region (n = 4), fever (n = 3), skin eruption (n = 3, including a bullous eruption [patient 3] and purpura [patient 11]), pruritus (n = 2), and arthralgia (n = 1). In 1 patient (patient 9), concomitant to HEV infection, a bilateral Parsonage–Turner syndrome developed (also called bilateral brachial neuritis or neuralgic amyotrophy), and was proven by electroneuromyography.

Laboratory Presentation of HEV

Liver biology tests and virology tests at diagnosis of HEV infection are provided in Table 2. All patients had acute elevated aspartate and alanine aminotransferase (ALT) levels, and 11 also had moderate cholestasis. Median aspartate and ALT levels were 679 and 1300 U/L, respectively. The diagnosis of acute HEV infection relied on positive PCR results for HEV RNA in blood (n = 13 patients) and/or stools (n = 3 patients), positive IgM antibodies without PCR assessment (n = 4), or positive IgM antibodies with negative PCR results for HEV RNA (n = 5). The viral genotype for 8 patients was 3c for 3 and 3f for 5. No other etiology for the hepatitis could be found, specially no coinfection with hepatitis A, B, or C.

Two patients had a liver failure with decreased prothrombin time (PT). A 49-year-old woman (patient 11) with RA for 10 years received tocilizumab, methotrexate (15 mg/week), and corticosteroids (3 mg/day). The PT was 46% with ALT level 79-fold the upper limit of normal (ULN) and associated with cholestasis (bilirubin level up to 400 μmol/L). For the other patient (patient 17), a 61-year-old man with RA for 12 years and receiving rituximab and corticosteroids (3 mg/day), the PT was 57% with an ALT level 8-fold the ULN.

Outcome of HEV Infection

All patients had a follow-up of at least 3 months, and all recovered. The median reported follow-up was 29 months (range 3–55 months). Liver enzyme levels normalized within

TABLE 1. Patient Characteristics

			Treatments				
Patient/ Age/Sex	**Disease Duration, y**	**Rheumatic Inflammatory Disease**	**MTX: Delivery, mg/wk**	**Other DMARDs, mg/d**	**Biologic/mg**	**Corticosteroids, mg/d**	**NSAIDs**
1/30/F	30	JIA	O/20		Infliximab	6	Naproxen
2/54/F	23	AS			Adalimumab/40 per wk		
3/62/M	7	PA	SC/20				
4/52/F	34	AS	IM/10		Infliximab/600 per 7 wk		
5/62/F	31	RA	O/15		Infliximab/200		Naproxen
6/25/F	2	PA	O/10			20	
7/70/M	1.5	Undifferentiated arthritis	O/17.5			5	
8/72/M	19	RA	SC/20	Leflunomide/MD	Rituximab/1000		Celecoxib
9/30/F	5	PA		Cyclosporine/250			Naproxen
10/38/M	5	AS		Leflunomide/20	Infliximab/460 per 6 wk	4.5	
11/49/F	10	RA	O/15		Tocilizumab/32 per 4 wk	3	
12/69/F	25	RA		Leflunomide/20	Abatacept/750 per 4 wk	5	
13/40/M	17	AS			Etanercept		
14/79/F	7	Jaccoud arthropathy	MD/10			2	
15/35/M	25	AS	MD/15		Infliximab		
16/69/M	20	RA	MD/15		Rituximab		
17/61/M	12	RA		Leflunomide/MD	Rituximab	3	
18/53/F	32	RA	MD/15		Abatacept/750 per 4 wk		Meloxicam
19/44/F	8	RA	O/12.5		Rituximab		Flurbiprofen
20/55/F	2	RA	O/20		Etanercept/50 per wk		
21/60/F	26	RA	O/15		Adalimumab/40 per 2 wk	4	
22/61/M	3	PA			Adalimumab/40 per 2 wk		Diclofenac
23/59/M	6	RA	MD/15		Tocilizumab/4 mg/kg per 4 wk	7	

AS = axial spondyloarthritis, DMARDs = disease-modifying antirheumatic drugs, IM = intramuscular, JIA = juvenile idiopathic arthritis, MD = missing data, MTX = methotrexate, NSAIDs = Nonsteroidal anti-inflammatory drugs, O = oral, PA = psoriatic arthritis, RA = rheumatoid arthritis, SC = subcutaneous.

1 month for 12 patients, 3 months for 9 patients (including the 2 patients with liver failure), and 4 months for 2 patients.

PCR tests were repeated for 14 patients who previously had positive results, and all were negative within 3 months after HEV infection. Among the 9 patients with a diagnosis based on positivity for IgM antibodies, 4 were not retested, 3 were IgM negative, and 2 remained IgM positive (1 month and 7 months after diagnosis, both with a negative PCR result 1 month after diagnosis). The time of active infection was estimated as the time from the first day of increased liver enzyme level and the day of the first negative PCR result for HEV RNA in blood and/or stools. Median time of active infection, estimated for 13 patients, was 6 weeks (range 19 days–11 weeks). After a first negative PCR result for HEV RNA, 7 patients had at least 1 other PCR test. No viral reactivation was observed, with a minimal follow-up of 3 months.

Treatment With Ribavirin

Treatment for HEV infection included an antiviral treatment with ribavirin for only 5 patients, which lasted 1 to 24 weeks.

Patient 9 had psoriatic arthritis previously treated with cyclosporine. The discontinuation of the immunosuppressive treatment triggered a major clinical flare-up, with synovitis and pustular psoriasis. That patient was the one who developed the bilateral Parsonage–Turner syndrome. Because a new immunosuppressive treatment had to be initiated and to counter this severe HEV infection, the physician decided to treat with ribavirin for 26 weeks. The viremia was undetectable within 7.5 weeks.

Patient 4 had axial spondyloarthritis treated with infliximab. At diagnosis of HEV, ribavirin treatment was introduced. However, the antiviral drug was stopped after 1 week, when the first PCR test for HEV RNA was negative, showing a short period of viremia.

Patient 16 was a 68-year-old man with RA for 20 years who received methotrexate and rituximab. The elevated liver enzyme levels (19-fold ULN aspartate aminotransferase and 24-fold ULN ALT) occurred 5 months after the last rituximab infusion. The patient received ribavirin for 3 months. The HEV load disappeared within 8 weeks.

In patients 1 and 3, who were followed by the same hepatologist, PCR testing for HEV RNA was performed weekly, and ribavirin was stopped when results were negative.

Outcome and Therapeutic Management of Inflammatory Rheumatic Disease

Therapeutic management is summarized in Table 3. Treatment of HEV infection included the discontinuation of

TABLE 2. Liver Biochemical and Virological Tests

	Liver Biological Tests					Virological Tests					
								Positive HEV RNA			
Patient	AST IU/L	ALT IU/L	Abnormal PAL and GGT Results	Bilirubin μmol/L	Prothrombin Time %	IgM Positive	IgG Positive	Blood	Stool	Genotype	Time With Positive RNA (wk)
1	264	591	−	6	77	+	+	+	/	3f	4
2	58	121	−	/	81	+	+	−	−	/	4
3	584	1190	+	28	99	+	−	+	/	3c	7
4	72	142	−	8	91	+	−	+	/	/	3
5	357	841	/	174	100	+	+	+	−	/	4
6	88	88	−	6	100	+	+	−	−	/	0
7	3430	3170	+	65	99	+	+	+	+	3c	6
8	1712	1518	−	74	67	+	/	/	/	/	/
9	338	769	+	11	80	+	+	+	+	3f	7.5
10	76	151	−	5	116	+	+	−	/	/	/
11	4889	3552	+	375	46	+	−	+	/	3f	6
12	865	1905	−	39	112	+	+	+	/	3f	6
13	1351	2342	+	92	78	+	/	/	/	/	/
14	1387	1787	−	40	75	+	+	/	/	/	/
15	230	351	/	/	/	+	−	−	/	/	/
16	679	1095	+	13	93	−	+	/	+	/	10.5
17	290	353	+	22	57	+	/	+	/	/	8
18	783	1750	+	9	94	+	+	+	/	/	9
19	853	1364	−	8	100	−	−	+	/	3c	9.5
20	981	1386	+	17	86	+	/	−	/	/	4
21	1468	2373	+	32	100	+	/	+	/	3f	8
22	537	1300	+	140	100	+	/	/	/	/	/
23	1077	1750	/	32	100	+	+	+	/	/	4

/ = missing data, − = no, + = yes, ALT = alanine aminotransferase, AST = aspartate aminotransferase, HEV = Hepatitis E Virus, RNA = RiboNucleic Acid, GGT = γ-glutamyl transpeptidase, PAL = alkaline phosphatase, IU/L = international unit per liter.

immunosuppressants in 20 of 23 patients. Biologic therapy was discontinued in all but 3 patients: adalimumab was maintained in 1 patient (without ribavirin treatment), infliximab was maintained in 1 patient receiving ribavirin for 1 week, and the third patient had a new cycle of rituximab 3 months after HEV infection when HEV RNA became undetectable. Methotrexate was maintained in 2 patients, both receiving ribavirin (3 months and 1 week) and was introduced simultaneously with ribavirin (6 months) in 1 patient previously receiving cyclosporine. Corticosteroids were discontinued in 2 of 10 patients. In 2 other patients, corticosteroids were introduced because of flare of the rheumatic disease after discontinuation of biologic therapy (doses of 20 and 40 mg/day).

Information on rheumatic disease activity after discontinuation of immunosuppressants was available in 22 patients. Eleven of them experienced a flare of the rheumatic disease after discontinuation of their treatment. The median time between the treatment discontinuation and the flare-up was 4 weeks (range 1 day–10 weeks).

Among the 20 patients who discontinued immunosuppressants, an immunosuppressant could be reinitiated in all of them. The median time to biologic and methotrexate discontinuation was 12 (range 4–20) and 11.5 weeks (1–16), respectively. For all the patients, the rheumatic disease was controlled after resumption of their immunosuppressive treatment.

DISCUSSION

We report 23 cases of HEV infection in patients with inflammatory arthritides treated with immunosuppressants. All had acute hepatitis. The HEV infection diagnosis was based on positive PCR detection for HEV RNA in the serum and/or stools or anti-HEV IgM antibodies. Treatment included discontinuation of immunosuppressants for 20 patients and ribavirin treatment for 5. Some patients underwent a flare of their arthritides after discontinuation of immunosuppressants. In all patients, liver enzyme levels normalized and immunosuppressant therapy could be reinitiated. No chronic infection was observed. Even in patients whose immunosuppressive therapy was continued and in those under immunosuppressive treatment with a long half-life (as rituximab), no complication of HEV infection was observed. Acute HEV infection should be considered in patients with inflammatory rheumatism and elevated liver enzyme levels. The outcome of HEV infection seems favorable, with no evolution to chronic hepatitis or fulminant liver failure.

In the present study, 2 patients with RA and HEV infection were previously reported as case reports.[17–18]

Our epidemiological and biological characteristics of HEV infection are consistent with current knowledge of this infection. The course of acute HEV was found to be cytolytic rather than cholestatic, and liver cytolysis predominantly concerned

TABLE 3. Therapeutic Management

	Biologic			Conventional Immunosuppressant			
		Discontinuation			Discontinuation		Ribavirin Duration
Patient	Type	Yes/No	Duration (wk)	Type	Yes/No	Duration (wk)	(wk)
1	Infliximab	Y	12	MTX	Y	12	4
2	Adalimumab	N					
3				MTX	Y	12	5
4	Infliximab	N		MTX	N		1
5	Infliximab	Y	12	MTX	Y	12	
6				MTX	Y	6	
7				MTX	Y	4	
8	Rituximab	N		MTX, LFN	Y	8	
9				Cyclosporine	Y	Replaced by Etanercept	26
10	Infliximab	Y	6.5	LFN	N		
11	Tocilizumab	Y	20	MTX	Y	16	
12	Abatacept	Y	16	LFN	Y	16	
13	Etanercept	Y	4				
14				MTX	Y	6	
15	Infliximab	Y	16	MTX	Y	16	
16	Rituximab	N		MTX	N		12
17	Rituximab	N		LFN	Y	11.5	
18	Abatacept	Y	15	MTX	Y	15	
19	Rituximab	Y	No second infusion at day 15	MTX	Y	Replaced by Leflunomide	
20	Etanercept	Y	11	MTX	Y	11	
21	Adalimumab	Y	11	MTX	Y	5	
22	Adalimumab	Y	MD				
23	Tocilizumab	Y	10	MTX	Y	8	

LFN = leflunomide, MD = Missing Data, MTX = methotrexate, N = No, Y = Yes.

ALT. The duration of liver cytolysis was most frequently <3 months.

Nearly half of the patients reported in the present study were totally asymptomatic, emphasizing the need to specifically look for HEV in the checkup of elevated liver enzymes in patients with inflammatory arthritides, regardless of the symptoms.

One patient had a neurologic manifestation of HEV infection. Neurologic symptoms associated with HEV have been reported in up to 5.5% of HEV infection in immunocompetent and immunocompromised patients. Recently a study found HEV infection in 10% of group of 47 patients with neuralgic amyotrophy,[19] making HEV one of the most common etiology of brachial neuritis.

For all reported cases of HEV, the outcome was favorable within 3 months, with or without antiviral treatment with ribavirin. No fulminant hepatic failure was reported.

Treatment of HEV infection in patients receiving treatment for inflammatory arthritides is not codified. The present study gives some indication of how to manage this infection. Immunosuppressive treatment was discontinued in most of our patients. The evolution of viral infection was monitored with PCR tests of HEV RNA in blood and/or stools. Immunosuppressive therapy could be resumed after a negative PCR result for HEV RNA in blood and/or stools. Only a few patients received antiviral treatment with ribavirin, by analogy with HCV infection.[20] Ribavirin was prescribed when liver enzyme levels were particularly elevated and/or when the activity of the inflammatory arthritides required immunosuppressive drugs.

Another feature of HEV is its ability to cause chronic infection, defined as a persistent infection lasting >6 months, usually in severely immunocompromised patients.[9] In liver transplant recipients,[12] chronic infection with HEV can result in HEV-related cirrhosis.[13] In patients with inflammatory arthritides, no chronic infection was observed in the present study. The duration of the patient follow-up was sufficient to establish the resolution of the HEV infection, but the absence of reactivation of HEV infection must be confirmed in the longer term.

The main limitations of this study are its retrospective nature and the various procedures used to perform the diagnosis and monitoring of HEV infection. Diagnosis of acute HEV infection was based on positive PCR results or IgM positivity. Some patients were IgM positive, but the first PCR result for HEV RNA was negative. In these patients with elevated liver enzyme levels, the diagnosis of acute HEV is completely reliable because of the high specificity of IgM detection.[21] A short period of viremia explains the negative PCR result, often performed after serology findings.

In conclusion, given the increasingly diagnosed autochthonous HEV infection in some countries, HEV infection could be suspected in patients with inflammatory arthritides and elevated liver enzyme levels. The present study of a limited number of patients with acute HEV infection does not suggest a particular severity or risk of chronicity of this infection in patients with inflammatory arthritis treated with immunosuppressants. Further larger studies are needed to evaluate longer-term outcomes.

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