Is Screening for Hepatitis B and Hepatitis C Useful in Patients with Recent-Onset Polyarthritis? The ESPOIR Cohort Study

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ABSTRACT. ***Objective.*** To evaluate the seroprevalence of hepatitis B (HBV) and C (HCV) in patients living in France with recent-onset polyarthritis suggesting rheumatoid arthritis.

Methods. The 813 patients in the ESPOIR cohort were screened for anti-HCV antibodies and HBs antigen.

Results. Seroprevalence was 0.86% for HCV (n = 7) and 0.12% for HBV (n = 1). HCV-related arthritis was diagnosed in 4 (0.5%) patients; no patient had HBV-related arthritis. HCV-seropositive patients had significantly higher transaminase levels (ALAT, 41.5 IU vs 23.2 IU, p = 0.02; and ASAT, 39.2 IU vs 21.8 IU, p = 0.001) but only 2 patients had ASAT or ALAT levels > 40 IU. No significant differences were found for anti-CCP antibodies, C-reactive protein, erythrocyte sedimentation rate, or other test. HCV seroprevalence was significantly higher in the subgroup with history of blood transfusion than in other patients (3.7% vs 0.42%, p = 0.02). Two of the 7 HCV positive patients and the single patient with confirmed hepatitis B infection were born in areas with higher prevalence of viral hepatitis (Togo, Senegal, Vietnam). Positive hepatitis status was known before study inclusion in 4 of the 7 HCV-positive patients and in the HBV-positive patient.

Conclusion. The prevalence of HBV and HCV in a population of patients with recent-onset polyarthritis suggestive of RA was not greater than expected based on data from the general population in the same geographic area. Routine HBV and HCV serological testing did not contribute substantially to the diagnosis of recent-onset polyarthritis. Although advisable before initiating immunosuppressive or hepatotoxic drugs, serological testing for HCV and HBV is unnecessary in routine diagnostic evaluation of recent-onset polyarthritis. (J Rheumatol First Release June 15 2009; doi:10.3899/jrheum.081308)

Key Indexing Terms:
RECENT-ONSET ARTHRITIS RHEUMATOID ARTHRITIS
HEPATITIS B HEPATITIS C SEROLOGY

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Recent-onset polyarthritis may indicate infection, metabolic disorder, or systemic disease such as rheumatoid arthritis (RA). Arthritis has also been described in chronic viral hepatitis carriers[1]. The chances of identifying the cause of recent-onset polyarthritis may depend on the combination of clinical, imaging, and laboratory tests used. However, the diagnostic efficacy of the many possible test combinations has not been determined. Consequently, substantial variations exist among rheumatologists regarding the investigations used to evaluate recent-onset polyarthritis[2], leading to a mean cost of diagnostic investigations for undifferentiated arthritis of 406.5 € in France in 2000[3], even when the presentation is highly suggestive of RA. The appropriateness of testing for the hepatitis B (HBV) and C (HCV) viruses remains debated. A practice survey conducted recently in France showed that serological testing for HCV infection was deemed advisable by 19% of rheumatologists for patients with possible RA and 9% for patients with probable RA; corresponding figures for HBV were 18% and 8%[2]. The potential diagnostic usefulness of routine serological testing for HBV and HCV in patients with

recent-onset polyarthritis has not been evaluated, except in one study conducted in 2 tertiary referral centers and thus exposed to selection bias[4].

We sought to evaluate the diagnostic usefulness of serological testing for HBV and HCV in a cohort of 813 patients with recent-onset polyarthritis suggesting RA (the ESPOIR cohort)[5].

MATERIALS AND METHODS

Study population. The French Society for Rheumatology constituted a nationwide, longitudinal, prospective cohort, known as the ESPOIR cohort[5], to enable investigations of the diagnosis, outcome markers, epidemiology, pathogenesis, and medico-economics of early arthritis and RA. The cohort was constituted by prompting general practitioners and rheumatologists to refer patients with recent-onset arthritis to hospitals participating in the ESPOIR project. Patients were eligible for inclusion in the cohort if they had a definite or probable clinical diagnosis of RA or a diagnosis of undifferentiated arthritis with a potential for progressing to RA. The "definite clinical diagnosis of RA" was the 1987 ACR criteria, but there was no particular definition of "probable clinical diagnosis of RA" or "undifferentiated arthritis with a potential progressing to RA." The 2 last determinations depended on clinician diagnosis based on the clinician's experience.

Patients were included if they met the following criteria: age older than 18 years and younger than 70 years, swelling of at least 2 joints for 6 weeks, symptom duration of less than 6 months, and no prior treatment with disease modifying antirheumatic drugs or glucocorticoids; however, use of glucocorticoids for no longer than 2 weeks, with a mean dosage no greater than 20 mg/day and discontinuation at least 2 weeks earlier, did not prevent study inclusion. Patients who were included in the cohort were evaluated every 6 months for 2 years, then once a year.

The study was approved by the institutional review board of the Montpellier University Hospital, which was the coordinating center for this nationwide study. Prior to inclusion, all patients gave their written informed consent to participation in this prospective followup study.

Study design. The baseline assessment included a standardized interview; a general physical examination; laboratory tests (standard blood and urine variables; ELISA for IgM, IgG, and IgA rheumatoid factors (RF); tests for anticyclic citrullinated peptide and antinuclear antibodies; HLA-DR phenotype determination); and radiographs of the chest, pelvis, hands, and feet in the posteroanterior view; and feet in the oblique view. Each patient was asked to undergo an evaluation by an office-based rheumatologist every 6 months for 2 years and once a year thereafter. These evaluations were free of charge. Part of the blood sample collected at study inclusion was stored for further laboratory tests.

Serological tests. Tests for HBs antigen (HBsAg) and anti-HCV antibody were performed on 500 μl of the stored serum sample of each patient. All serological tests were done at the microbiology laboratory of the Brest Teaching Hospital, Brest, France, by a single microbiologist (VN).

HBsAg was detected using a chemiluminescent microparticle immunoassay (CMIA; ARCHITECT® HBsAg assay, Abbott, IL, USA). When the test was positive, a further sample of the stored blood was tested in the same way. If this second test was also positive, a neutralization test was performed to confirm the result. Patients with positive confirmation tests were classified as HBsAg-positive.

Anti-HCV antibodies were detected using a chemiluminescent microparticle immunoassay (CMIA; ARCHITECT® anti-HCV assay, Abbott, IL, USA). Positive samples were tested using a confirmation immunoblot test (RECOMBLOT HCV Ig G 2.0, MICROGEN, and INNO-LIA HCV). Patients with positive confirmation tests were classified as anti-HCV-positive.

Statistical analysis. Data were entered and analyzed using the Statistical Package for the Social Sciences (SPSS 15.0, Chicago, IL, USA). The chi-square test (or Fisher's exact test where appropriate) and the Mann-Whitney test were used. P values < 0.05 were considered significant.

RESULTS

The main characteristics of the 813 patients included in the ESPOIR cohort are listed in Table 1. Blood samples were missing for 5 patients, and 2 samples were received that could not be identified as coming from patients of the ESPOIR cohort. Thus, tests were done on 808 samples. After 24 month followup, 375 patients received treatment with methotrexate and/or biologics (anti-tumor necrosis factor or anti-interleukin 1).

Tests for antibody to hepatitis C virus (Figure 1). The CMIA for anti-HCV was positive in 16 (1.98%) of the 808 patients. The confirmation immunoblot test was positive in 7 [7/808, 0.86%; 95% confidence interval (95%CI) 0.38%–1.86%] patients; immunoblot results were negative in 7 patients and indeterminate in 2. These 2 patients underwent blood collection at their study centers for anti-HCV testing; the results were negative in both cases.

Table 2 lists the main characteristics of the 7 HCV-positive patients. A diagnosis of HCV-related arthritis had been given to 4 of these 7 patients (4/808, 0.50%; 95%CI, 0.16%–1.4%). HCV-positive patients had significantly higher serum transaminase levels (ALAT, 41.5 IU vs 23.2 IU, p = 0.02; and ASAT, 39.2 IU vs 21.83 IU, p = 0.001) versus the overall population (Table 3); however, only 2 HCV-positive patients had ASAT or ALAT levels > 40 IU (normal limit for aminotransferases < 40).

No other significant differences were found for any of the study variables, including the erythrocyte sedimentation rate, C-reactive protein level, or presence of anti-cyclic citrullinated peptide antibodies. The proportion of HCV-positive patients was significantly larger in the subgroup with a history of blood transfusions versus patients with no history of transfusion (3.7% vs 0.42%, p = 0.02). Of the 7 HCV-positive patients, 4 were known carriers of anti-HCV antibodies before study inclusion. Two of the 7 HCV positive patients were born in areas with higher prevalence of viral hepatitis (Togo, Vietnam).

Table 1. Mean baseline characteristics of the 813 patients in the ESPOIR cohort.

Characteristics	n = 813
Female/male	624/189
Mean age, yrs	48 ± 12.5
Disease duration, days	103 ± 52
Swollen joint count, mean ± SD	7.2 ± 5.4
Tender joint count, mean ± SD	8.4 ± 7
DAS28, mean ± SD	5.1 ± 1.3
ESR, mm/h	29.5 ± 24.5
Elevated CRP, n (%)	316 (38.9)
IgM RF, n (%)	359 (44.2)
Anti-CCP, n (%)	315 (38.7)
ACR criteria for RA, n (%)	578 (71.3)

DAS28: Disease Activity Score on 28 joints; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; IgM RF: immunoglobulin M rheumatoid factor; CCP: cyclic citrullinated peptides; ACR: American College of Rheumatology; RA: rheumatoid arthritis.

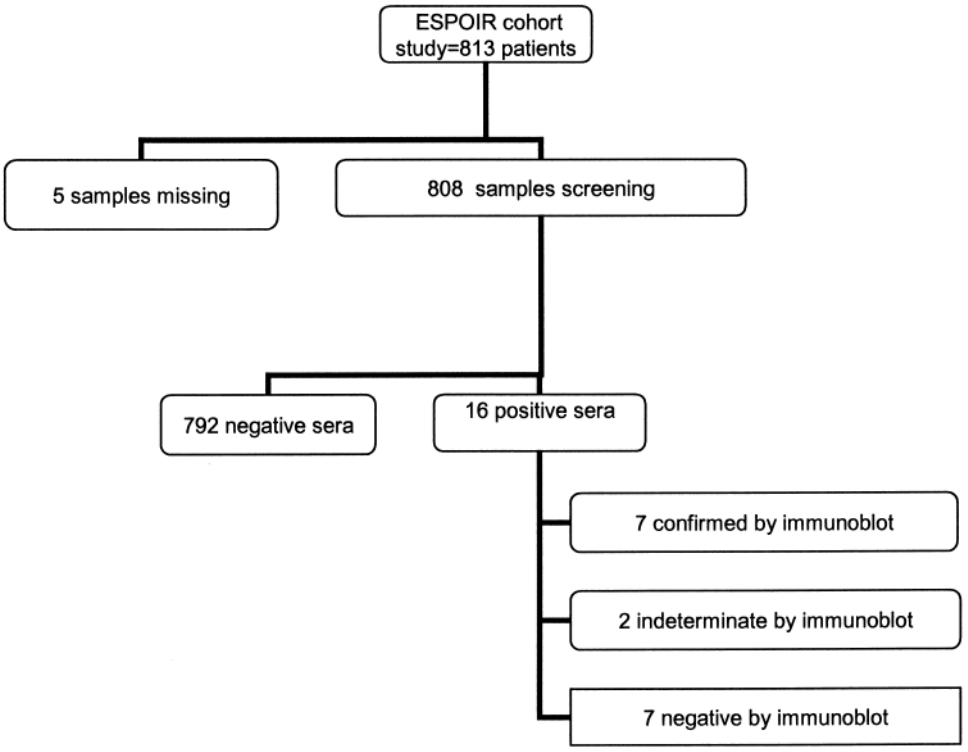

Figure 1. Screening for hepatitis C.

Tests for the hepatitis B virus antigen (Figure 2). Of the 808 patients, 7 (0.86%) had positive CMIA results for the HBsAg. Their main characteristics are reported in Table 4. The confirmation test was positive in 1 (1/808, 0.12%; 95%CI, 0.006%–0.8%) of the 7 patients. Confirmation testing was not done in 6 of our 7 patients with a positive initial test for the HBsAg, because the blood samples were inadequate. None of the 7 patients had been given a diagnosis of HBV-related

Table 2. Characteristics of the 7 patients who tested positive for antibodies to hepatitis C virus.

Patient	1	2	3	4	5	6	7
Sex	F	F	F	F	F	F	F
Age, yrs	53	47	54	59	62	53	60
Place of birth	France	France	France	Togo	France	Vietnam	Portugal
HCV infection known at inclusion	Yes	Yes	No	No	Yes	Yes	No
Transfusion	Yes	No	No	ND	Yes	No	Yes
Previous surgery	ND	ND	ND	ND	Yes	ND	Yes
Extraarticular symptoms	Neuropathic pain				Xerostomy		
Arthritis ≥ 3 joints	Yes	Yes	Yes	Yes	Yes	Yes	Yes
CRP ≤ 6 mg/l	0	0	0	66	18	0	30
ASAT ≤ 40 IU	41	35	29	20	83	32	39
ALAT ≤ 40 IU	34	32	35	7	117	35	31
GGT ≤ 40 IU	34	89	13	15	27	25	8
Positive IgM RF	Yes	No	No	Yes	Yes	No	Yes
Anti-CCP	0	0	0	982	0	0	0
X-ray erosions	Yes	No	No	No	No	No	No
Arthritis diagnosis	Unclassified	HCV-related + CG	HCV-related	RA	Unclassified	HCV-related	HCV-related

HCV: hepatitis C virus; CRP: C-reactive protein; ASAT: aspirate aminotransferase; ALAT: alanine aminotransferase; GGT: gamma-glutamyltransferase; RF: rheumatoid factor; CCP: cyclic citrullinated peptide; RA: rheumatoid arthritis; CG: cryoglobulinemia.

Table 3. Comparison of the 7 patients who tested positive versus those testing negative for anti-HCV antibodies.

	HCV – Patients, no. (%) N = 801	HCV + Patients no. (%) N = 7	p
Male/female	189/612	0	
Hx of blood transfusion	78 (9.7)	3 (42.8)	0.02
Diabetes	31 (3.8)	0 (0)	0.59
Morning stiffness > 30 min	683 (85.2)	6 (85.7)	0.96
Swollen joints, ≥ 3	642 (80.1)	7 (100)	0.19
Hand synovitis	744 (92.8)	7 (100)	0.47
Symmetric synovitis	611 (76.2)	6 (85.7)	0.57
Nodes	17 (2.1)	0 (0)	0.69
Normal radiographs	690 (86.14)	6 (85.7)	0.95
Positive IgM RF	334 (41.6)	4 (57.1)	0.41
ALAT > 40	83 (10.3)	1 (14.2)	0.73
ASAT > 40	42 (5.2)	2 (28.5)	0.007

HCV: hepatitis C virus; RF: rheumatoid factor; ASAT: aspirate aminotransferase; Hx: history; ALAT: alanine aminotransferase; normal limit for aminotransferases < 40.

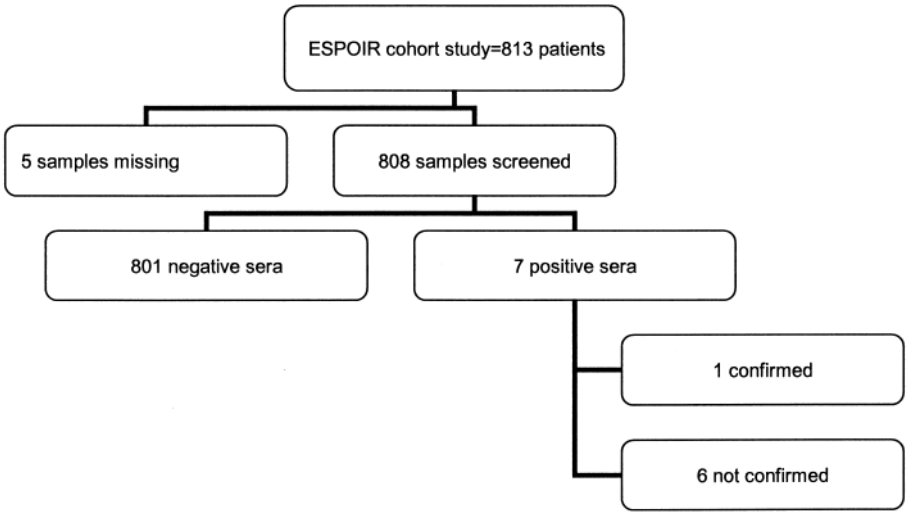

Figure 2. Screening for hepatitis B.

arthritis. The patient with a positive confirmation test was known to be HBsAg-positive at study inclusion.

DISCUSSION

The seroprevalences of HCV and HBV infection in the ESPOIR cohort were 0.86% and 0.12%, respectively. These values are similar to those reported in the general population[6-11] and in a population of 309 RA patients[4,12] in France (Table 5). In the study of RA patients, who were included between 1999 and 2001, anti-HCV antibodies were found in only 2 patients (0.65%; 95%CI, 0.08%–2.3%), who had typical RF-positive RA with erosions. Serum aminotransaminase and alkaline phosphatase levels were normal in both patients. Serum gammaglutamyl transferase levels were normal in 1 patient and elevated to twice the upper limit of normal in the other. Reverse-transcriptase polymerase-chain-reaction (RT-PCR) for HCV RNA was positive in one patient and negative in the other.

The potential diagnostic usefulness of HCV screening was evaluated in 322 patients who had inflammatory polyarthralgia, monoarthritis, oligoarthritis, or polyarthritis of less than 1 year duration[4]. The patients were recruited at 2 tertiary referral centers in France. Serum transaminase levels were high in 34 (10.6%) patients, but only 6 (2.7%) patients had positive tests for anti-HCV antibodies. Of these 6 patients, 2 had previously diagnosed HCV infection, 2 were negative by RT-PCR, and 2 were positive by RT-PCR. Thus, there were 2 new diagnoses of HCV infection (0.6%; 95%CI, 0.07%-2.2%). In one of these 2 patients, the arthritis was considered unrelated to the HCV infection. Tests for HBV infection were done in 80 patients and were consistently negative. The authors concluded that serum transaminase levels were not useful for

Table 4. Characteristics of the 7 patients with positive screening test for hepatitis B antigen. Only one patient had a positive confirmation test (Patient 5).

	1	2	3	4	5*	6	7
Sex	F	M	F	F	M	F	F
Age	56	69	44	47	35	56	36
Place of birth	France	France	France	France	Senegal	France	Cape Verde
HBV infection at inclusion	No	No	No	No	Yes	No	No
Transfusion	No	Yes	ND	No	No	No	No
Extraarticular symptoms (including purpura)				Xerostomy		Xerostomy	
Arthritis ≥ 3 joints	No	Yes	Yes	No	Yes	Yes	No
CRP	6	47	0	8	11	5	3
ASAT	18	18	15	13	20	22	21
ALAT	14	20	16	29	15	22	1
GGT	7	124	15	100	19	21	24
Positive IgM RF	Yes	No	No	No	No	No	No
Anti-CCP unit	0	0	4354	191	0	899	142
X-ray erosions	No	No	No	No	No	No	No
Diagnosis	RA	RA	RA	RA	RA	RA	RA

* Confirmed positive. HCV: hepatitis C virus; CRP: C-reactive protein; ASAT: aspirate aminotransferase; ALAT: alanine aminotransferase; GGT: gamma-glutamyltransferase; RF: rheumatoid factor; CCP: cyclic citrullinated peptide; RA: rheumatoid arthritis. Normal limit for aminotransferases < 40.

Table 5. Previous studies of hepatitis C virus (HCV) in patients with rheumatic diseases.

Study, Ref.	Country	Inclusion Period	Disease, no.	HCV Seroprevalence, %	Prevalence HCV/General Population, %	Patient Age, mean, yrs	Female/Male, %
ESPOIR cohort	France	2003–2005	Recent-onset polyarthritis, 813	0.86	1	48.07	76.7:23.3
Maillefert, 4, 12	France	1999–2001	RA, 309	0.65	1	54.1	75:25
Rivera, 13	Spain	1995–1996	RA, 303	7.6	0.95	58.3	77:23
Hsu, 14	USA	1988–1994	Probable RA, 196	1	1.3	71	51:49
Barbosa, 15	Brazil	2000	Inflammatory rheumatic diseases, 367	1.9	0.9 to 2	38.3	85:15

determining which patients should be screened for HCV and HBV infection.

Of 303 consecutive RA patients seen at a rheumatology clinic of a teaching hospital in Spain[13], 23 (7.6%) had HCV antibodies, compared to only 3 (0.95%) of 315 first-time blood donors ($p < 0.001$; 95%CI, 0.03%-0.10%)[12]. However, only 13 (13/303, 4.3%) of these 23 patients had a positive confirmation RIBA. Moreover, the blood donors were younger than the RA patients (mean age, 33.4 years vs 58.3 yrs). A population-based survey was conducted in the US from 1988 to 1994 to look for an association between RA and HCV infection[14]. Using data from the National Health and Nutrition Examination Survey III, HCV and RA status were determined for 4769 patients aged 60 years or over. There were 196 (4.1%) patients with RA, 63 (1.3%) patients with anti-HCV antibodies, and 35 patients with HCV RNA by RT-PCR (0.7 %). Only 2 patients had both anti-HCV antibodies and RA and a single patient had HCV RNA and RA. Anti-HCV antibodies were not significantly associated with RA [odds ratio (OR) 0.44; 95%CI, 0.07-2.80]; neither was HCV RNA (OR, 0.77; 95%CI, 0.10-6.19). Of the 63 anti-HCV-positive patients, 21 (33.3%) were RF-positive, compared to only 307 (6.5%) of the 4706 anti-HCV-negative patients ($p < 0.0001$).

In Brazil, 367 patients seen at a teaching hospital rheumatology clinic for diffuse connective tissue diseases were interviewed and tested for HCV antibodies using ELISA[15]. Positive samples were tested for antibodies using a line immunoassay and for HCV RNA using RT-PCR. Diagnoses were systemic lupus erythematosus (n = 175, 47.7%), RA (n = 89, 24.2%), spondyloarthropathy (n = 42), mixed connective tissue disease (n = 17), vasculitis (n = 10), systemic sclerosis (n = 8), juvenile RA (n = 8), dermatomyositis/polymyositis (n = 7), sicca syndrome (n = 5), rheumatic fever (n = 4), and primary antiphospholipid syndrome (n = 2). Seven (1.9%) patients were anti-HCV positive, including 4 with systemic lupus erythematosus (4/175, 2.3%) and 3 with RA (3/89, 3.4%). All 7 anti-HCV-positive samples were positive for HCV RNA. The HCV seroprevalence in the overall population was not significantly different from that reported previously in blood donors from the same geographical area (1.4 %)[6-11]. However, HCV seroprevalence was elevated in the subgroups with lupus or RA, compared to the blood donors.

The authors suggest including a test for anti-HCV antibodies in routine investigations for rheumatic disease.

Our study has a number of limitations. First, patient inclusion criteria may have led to a lower prevalence of HBV and HCV infection, compared to that in the overall population of patients with recent-onset polyarthritis. Patients who had undifferentiated arthritis with no potential for developing RA and those with other well-defined rheumatic diseases (i.e., viral arthritis) were not included. Second, we did not screen our patients for anti-HBs and anti-HBc antibodies. Therefore, we cannot rule out that some of our patients had HBV infection with HBsAg levels below the detection threshold. Third, false-positive results with an HCV ELISA were reported in patients with hypergammaglobulinemia related to Sjögren's syndrome[16]. Conceivably, some of our patients may have had hypergammaglobulinemia related to their rheumatic disease. Fourth, confirmation testing was not done in 6 of our 7 patients with a positive initial test for the HBsAg, because the blood samples were inadequate. Although this limits the interest of our study, even if the 7 patients with positive CMIA results for the HBsAg had been confirmed, the prevalence of 0.86% in the ESPOIR cohort wouldn't be higher than in the general population. All 7 patients had a diagnosis of RA. Only one had documented HBV infection and he was born in Senegal.

In conclusion, HBV and HCV seroprevalences, in our population of patients with recent-onset polyarthritis suggestive of RA, were not higher than in the general population. Routine HBV and HCV testing did not contribute noticeably to the diagnosis. In a recent survey, 19% of rheumatologists in France recommended HCV testing in patients with recent-onset polyarthritis suggestive of RA and 9% in patients with probable RA[1]. Corresponding figures for HBV testing were 18% and 8%. Our data suggest that such recommendations may be unwarranted. Two factors were significantly associated with HBV or HCV infection in our study, namely, transaminase elevation and a history of blood transfusion. If HBV and HCV testing is reserved for patients with risk factors or high enzyme levels, we will not detect all patients with viral hepatitis, but our study does not demonstrate the usefulness of these tests compared with the general population, except when treatment with liver toxicity is prescribed. So, HBV and HCV tests may be best reserved for patients with risk factors for viral hepatitis, suggestive symptoms, high liver enzyme levels, history of hepatitis; and for patients who come from areas with a stronger prevalence for viral hepatitis. The tests must also be performed routinely before initiating methotrexate therapy[17-22], and are recommended before initiating biologic therapies[23-28]: in the context of early arthritis, 375 of 808 patients in our study received methotrexate and biologics after a 24 month followup. Finally, a large proportion of these patients should have these tests during their followup, but not necessarily in all patients at inclusion; rather in some cases at inclusion and in others prior to starting treatment.

In the above-mentioned survey[1], 13% of rheumatologists recommended Lyme disease serology, 11% HIV serology, and 8% parvovirus B19 serology. Determining the prevalences of these diseases among patients with recent-onset polyarthritis may help to rationalize the use of these tests.

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