Safety of Biologic and Nonbiologic Disease-modifying Antirheumatic Drug Therapy in Veterans with Rheumatoid Arthritis and Hepatitis C Virus Infection

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ABSTRACT. ***Objective.*** To examine the effect of disease-modifying antirheumatic drug (DMARD) therapy on hepatotoxicity among patients with rheumatoid arthritis (RA) and hepatitis C virus (HCV) infection.

Methods. We identified biologic and nonbiologic treatment episodes of patients with RA using the 1997–2011 national data from the US Veterans Health Administration. Eligible episodes had HCV infection (defined by detectable HCV RNA) and subsequently initiated a new biologic or nonbiologic DMARD. Cohort entry required a baseline alanine aminotransferase (ALT) < 66 IU/l and quantifiable HCV RNA within 90 days prior to starting biologic/DMARD therapy. The primary outcome of interest was hepatotoxicity, defined as ALT elevation ≥ 100 IU/l or increase in HCV RNA of 1 log or more, and was examined within the first year of biologic/DMARD use. Results were reported as the cumulative incidence of treatment episodes achieving predefined hepatotoxicity at 3, 6, and 12 months after biologic/DMARD initiation.

Results. RA patients with HCV (n = 748) were identified and contributed 1097 biologic/DMARD treatment episodes. Overall, ALT elevations were uncommon, with 37 (3.4%) hepatotoxicity events occurring within 12 months. Treatment episodes with biologic DMARD demonstrated more frequency of hepatotoxicity than did nonbiologic DMARD (4.8% vs 2.3%, p = 0.03). Among treatment episodes involving hepatotoxicity events, the majority occurred within 6 months of DMARD initiation (29/37, 78%).

Conclusion. In US veterans with HCV and RA receiving biologic and nonbiologic DMARD, the frequency of hepatotoxicity (ALT ≥ 100 IU/l) was low, with a higher frequency observed in treatment episodes with current biologic use. (J Rheumatol First Release March 1 2017; doi:10.3899/jrheum.160983)

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Chronic hepatitis C virus (HCV) infection is the most common cause of liver disease in the United States, affecting about 3.9 million persons[1]. Because rheumatoid arthritis (RA) affects 0.5%–1.0% of the US population, an estimated 40,000 persons are affected by both conditions[2].

Patients with RA and HCV pose a therapeutic challenge. Although use of disease-modifying antirheumatic drugs (DMARD) clearly reduces morbidity of RA, many RA medications have been associated with hepatotoxicity[3], as well as viral reactivation from immunosuppression[4]. Certain

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DMARD, such as methotrexate (MTX), may be less frequently prescribed in patients with RA with HCV because of concerns for hepatotoxicity[5]. Although several small studies suggest safety and tolerability of current RA treatments in RA patients with chronic HCV[6,7,8], there are reports of transaminase elevations[3,9] and increased liver fibrosis[10] in this setting. The 2015 American College of Rheumatology (ACR) guidelines for RA treatment recommend use of sulfasalazine (SSZ) and/or hydroxychloroquine (HCQ) over MTX, leflunomide (LEF), and tumor necrosis factor inhibitors (TNFi) in patients with RA and chronic HCV who have not received treatment for HCV[11]. These guidelines also conditionally recommend that in the setting of ongoing or successfully treated HCV, these patients should receive the same therapies as RA patients without HCV infection[11].

The US Department of Veterans Affairs (VA) Veterans Health Administration (VHA) is the nation's largest provider for HCV management, providing care annually to nearly 175,000 patients with chronic HCV[12]. Because the VA also provides care to an estimated 100,000 patients with RA[13], the medical records of this healthcare system provide an excellent opportunity to examine patients with both HCV and RA. Herein we evaluated the hepatotoxicity of current RA treatments in a national cohort of veterans with RA and chronic HCV infection.

MATERIALS AND METHODS

Cohort eligibility criteria. We conducted a retrospective cohort study using electronic health record data from the VA Informatics and Computing Infrastructure, linked to administrative data from the VHA Decision Support System from 1997 to 2011. Eligible patients qualified to be in the cohort after they had at least 1 diagnosis of RA [International Classification of Diseases-9-Clinical Modification (ICD-9-CM) code: 714.X] from a rheumatology provider between October 1, 1997, and December 31, 2011, and a prescription for at least 1 biologic or nonbiologic DMARD between October 1, 2001, and September 30, 2011. VA prescription data was not available until fiscal year 2002. Nonbiologic DMARD included MTX, SSZ, LEF, and HCQ. Biologics included etanercept (ETN), infliximab (IFX), adalimumab (ADA), rituximab (RTX), and abatacept (ABA). For comparisons among biologics, we grouped ETN, IFX, and ADA as TNFi. Newer TNFi (e.g., certolizumab, golimumab) and other biologics [e.g., tocilizumab (TCZ)] were not used frequently enough to include in our study.

Patients were required to have a baseline alanine aminotransferase (ALT) < 66 IU/l and quantifiable HCV RNA within 90 days prior to starting biologic/DMARD therapy (defined as "index date") as well as ALT and/or HCV RNA measurement within 1 year after index date. National datasets using similar variables had > 95% specificity at excluding US males with significant preexisting liver disease using similar criteria[14].

In addition, biologic users were required to have baseline ALT and/or HCV RNA measurement within 30 days of index date. Patients diagnosed with human immunodeficiency virus infection or hematologic malignancy within 1 year prior to the index date were excluded from primary analysis of the cohort, because treatment for these conditions might affect the risk for hepatotoxicity in patients with concomitant HCV.

Exposure and outcome assessment. Each drug-specific index date defined a treatment episode. Patients could contribute > 1 treatment episode provided they initiated a new DMARD/biologic or reinitiated a previously prescribed DMARD/biologic with no exposure within 1 year of the index date. Current exposure was considered as-treated based on days' supply (pills or syringes dispensed) or usual dosing intervals (infused biologics). For RTX, exposure was assumed to extend 12 months after each infusion. Exposure was extended by 90 days after the end of days' supply or the usual dosing intervals for all other therapies.

The outcome of interest was hepatotoxicity, which was defined as an increase in serum ALT to > 100 IU/l or an increase in serum HCV RNA of > 1 log IU/ml. This degree of ALT elevation corresponds to about a 3-fold elevation of population normal levels for men[15], which has been previously used to identify clinically significant liver enzyme elevation in the setting of viral hepatitis reactivation as well as drug toxicity[16,17]. An increase in serum HCV RNA of > 1 log IU/ml was chosen because this has been previously used to identify HCV reactivation in similar clinical settings[18,19]. In addition, variations of serum levels of HCV RNA within an individual rarely exceed 1 log IU/ml[20].

Covariates were selected based on potential contribution to hepatotoxicity in patients with RA informed by review of the literature. These covariates included demographics, comorbidities (e.g., diabetes, solid cancer), other medications used for arthritis (e.g., oral glucocorticoids), antiviral therapy for HCV (interferon α, peginterferon α, ribavirin), and statin use (atorvastatin, fluvastatin, lovastatin, simvastatin, pitavastatin, pravastatin, rosuvastatin). The 12-month period preceding each index date defined the baseline period for assessment of most covariates, except for concomitant medication use (6 mos preceding the index date). Comorbid conditions were characterized using ICD-9 codes from provider diagnoses.

Laboratory evidence of prior hepatitis B virus (HBV) infection was defined as a positive result for any of the following serologic markers during the entire followup period: HBV surface antigen (HBsAg), HBV core antibody (HBcAb), HBV e antigen, and HBV DNA.

Statistical analysis. Hepatotoxicity was examined in the first year after treatment initiation. The risk of hepatotoxicity for each drug treatment was reported as a cumulative incidence and quantified as the proportion of patients who met the primary outcome within 3, 6, and 12 months after the index date. Bivariate analysis was performed to examine the effect of baseline covariates on hepatotoxicity. Biologic treatment episodes were stratified into 3 categories for comparison of concomitant DMARD on hepatotoxicity: MTX/LEF without HCQ/SSZ, HCQ/SSZ without MTX/LEF, no MTX/LEF/HCQ/SSZ. Statistical comparisons were made using the chi-square or Fisher's exact tests where appropriate. Covariates with central tendency were presented as mean ± SD; those not showing central tendency were described using median and interquartile range.

For biologic treatment episodes, cohort entry also required an assessment of ALT or HCV RNA within 30 days of biologic exposure. The more stringent criteria were designed to rule out hepatotoxicity, which may not have been related to initiation of that particular biologic. To ensure that these more stringent criteria did not significantly reduce the number of hepatotoxicity episodes, the analysis was repeated, removing the more stringent criteria for biologic treatment episodes.

Analyses were performed using SAS 9.2 (SAS Institute).

Ethical approval. This study received approval from institutional review boards of the Birmingham VAMC (ID 1330) and the G.V. Sonny Montgomery VAMC (ID 0474). Informed consent was not required given the observational study design.

RESULTS

Cohort description. A cohort of 36,433 patients with RA was identified, from which a total of 748 unique patients with concomitant HCV contributed 1097 treatment episodes (Table 1). Mean age was 59.8 ± 9.4 years and 90.7% of the cohort was men. The most common comorbid diagnoses were hypertension (61.1%) and diabetes mellitus (24.0%).

A total of 640 nonbiologic DMARD treatment episodes and 457 biologic treatment episodes were identified (ABA

Table 1. Patient characteristics measured at the start of each medication treatment episode. Values are n (%) unless otherwise specified.

Characteristics	ABA, n = 22	ADA, n = 180	ETN, n = 179	IFX, n = 48	RTX, n = 28	LEF, n = 91	MTX, n = 156	SSZ-HCQ, n = 393	Total, n = 1097
Baseline covariates									
Unique patients, n	22	179	176	46	28	89	151	346	748
Age, yrs, mean (SD)	56.5 (8.6)	58.4 (8.5)	58.1 (8.2)	57.4 (7.1)	59.4 (7.9)	60.7 (9.8)	61.7 (10.6)	60.9 (9.9)	59.8 (9.4)
Male	17 (77.3)	160 (88.9)	170 (95.0)	42 (87.5)	23 (82.1)	78 (85.7)	141 (90.4)	364 (92.6)	995 (90.7)
Comorbid conditions[1]									
COPD	4 (18.2)	27 (15.0)	26 (14.5)	10 (20.8)	6 (21.4)	18 (19.8)	34 (21.8)	79 (20.1)	204 (18.6)
Hypertension	13 (59.1)	93 (51.7)	106 (59.2)	24 (50.0)	18 (64.3)	59 (64.8)	102 (65.4)	255 (64.9)	670 (61.1)
Diabetes mellitus	8 (36.4)	42 (23.3)	40 (22.4)	6 (12.5)	9 (32.1)	21 (23.1)	35 (22.4)	102 (26.0)	263 (24.0)
Solid cancer	0 (0.0)	7 (3.9)	6 (3.4)	4 (8.3)	1 (3.6)	6 (6.6)	17 (10.9)	27 (6.9)	68 (6.2)
Medication use 6 mos before start of treatment episode									
Oral glucocorticoids	8 (36.4)	66 (36.7)	73 (40.8)	17 (35.4)	16 (57.1)	42 (46.2)	60 (38.5)	131 (33.3)	413 (37.6)
Statins[2]	9 (40.9)	55 (30.6)	57 (31.8)	19 (39.6)	7 (25.0)	40 (44.0)	70 (44.9)	122 (31.0)	379 (34.5)
HCV antivirals[3]	0 (0.0)	9 (5.0)	9 (5.0)	3 (6.2)	0 (0)	1 (1.1)	4 (2.6)	24 (6.1)	50 (4.6)

[1] Defined by ICD-9 codes and measured 12 months prior to the index date. [2] Statins: atorvastatin, fluvastatin, lovastatin, simvastatin, pitavastatin, pravastatin, rosuvastatin. [3] HCV antivirals were measured within 12 months of index date: interferon α, peginterferon α, ribavirin. ABA: abatacept; ADA: adalimumab; ETN: etanercept; IFX: infliximab; RTX: rituximab; LEF: leflunomide; MTX: methotrexate; SSZ-HCQ: sulfasalazine/hydroxychloroquine; COPD: chronic obstructive pulmonary disease; HCV: hepatitis C virus; ICD-9: International Classification of Diseases, 9th ed.

22, RTX 28, TNFi 407). The majority (88%) of TNFi use was ETN (179 episodes) and ADA (180 episodes). Among biologic and nonbiologic treatment episodes, the prevalence of baseline oral glucocorticoid use was 37.6% and about one-third (34.5%) were prescribed statins. Nearly half of biologic treatment episodes were prescribed concomitant MTX or LEF (48.1%). Prescription of concomitant MTX or LEF was more common among biologic treatment episodes than nonbiologic treatment episodes (48.1% vs 28.9%, p = 0.001). Fifty patients (4.6%) were prescribed HCV antiviral therapy within the 12 months prior to initiation of a biologic or nonbiologic DMARD and 1 patient initiated HCV antiviral treatment in the followup period.

Monitoring of ALT and assessment for hepatitis B infection. ALT was measured within 3 months after starting DMARD in 938 (85.5%) of treatment episodes, 844 (76.9%) between 3–6 months, and 993 (90.5%) between 6–12 months (Table 2). There was no significant difference in frequency of monitoring ALT between biologic and nonbiologic treatment episodes during the 0- to 3-month interval and 3- to 6-month interval (87.1% vs 84.4%, p = 0.22; 79.2% vs 75.3%, p = 0.15, respectively), but biologic treatment episodes were significantly more likely to have an ALT measured between 6–12 months than nonbiologic episodes (93.0% vs 88.8%, p = 0.02). HCV RNA was measured among 37 total treatment episodes during the 12-month followup period.

Of the 1097 DMARD treatment episodes, 388 (35.4%) were tested for HBsAg and 252 (23.0%) were tested for HBcAb. Of those tested, 5 (1.3%) had detectable HBsAg and 48 (19.1%) had detectable HBcAb.

Outcome. Among 1097 treatment episodes, 37 episodes (3.4%) of hepatotoxicity occurred (defined as ALT ≥ 100 IU/l or HCV RNA increase by 1 log; Table 2). All episodes of hepatotoxicity were identified by an increase in ALT ≥ 100 IU/l; no treatment episodes involved an increase of serum HCV RNA of > 1 log IU/l within 12 months of index date. Most hepatotoxicity events occurred within 0–6 months after DMARD initiation (29/37, 78%). In all treatment episodes that developed hepatotoxicity, subsequent laboratory monitoring documented an ALT of < 100 IU/l.

We observed a higher frequency of hepatotoxicity among biologic treatment episodes as compared with nonbiologic treatment episodes (4.8% vs 2.3%, p = 0.03). Among biologic treatment episodes, hepatotoxicity was similar among agents (TNFi 20/407, 4.9% vs non-TNFi 2/50, 4.0%, p = 1.00). There were no significant differences in hepatotoxicity among biologic treatment episodes with concomitant MTX/LEF (9/220, 4.1%), HCQ/SSZ (8/110, 7.3%), or no MTX/LEF/HCQ/SSZ (5/127, 3.9%, p = 0.38). Among nonbiologics, the number of treatment episodes with hepatotoxicity was not significantly different between SSZ-HCQ (7/386, 1.8%) and MTX (6/156, 3.9%, p = 0.2) or SSZ-HCQ and LEF (2/91, 2.2%, p = 0.70).

When assessing the effect of covariates on hepatotoxicity (Table 3), we did not see a relationship between prescription of oral glucocorticoids (p = 0.08), statins (p = 0.11), or MTX/LEF (p = 0.61) and hepatotoxicity.

Our main analysis provided additional cohort entry criteria for biologics (assessment of ALT and/or HCV RNA within 30 days of index date). To ensure that this did not overly restrict treatment episodes and reduce the detection of hepatotoxicity, a separate analysis was performed that included biologic treatment episodes that had baseline laboratory assessment within 90 days of index date. The enlarged cohort provided 1214 treatment episodes, of which 40 (3.3%) met the definition of hepatotoxicity, which was not a significantly different rate of hepatotoxicity (vs 3.7%, p = 0.91).

Table 2. Surveillance for hepatotoxicity during followup period among treatment episodes[1]. Values are n (%) unless otherwise specified.

Drug	Treatment Episodes, n	Cumulative Events Within 12 Mos[2]	Episodes in Which Any ALT Testing Occurred During Followup Period			Event Rates for Hepatotoxicity		
			0–3 Mos[3]	3–6 Mos[3]	6–12 Mos[3]	0–3 Mos Events[4]	3–6 Mos Events[4]	6–12 Mos Events[4]
Biologic agents	457	22 (4.8)	398 (87.1)	362 (79.2)	425 (93.0)	8 (1.8)	10 (2.2)	4 (0.9)
ABA	22	1 (4.5)	19 (86.4)	19 (86.4)	21 (95.5)	0 (0)	1 (4.6)	0 (0)
ADA	180	8 (4.4)	151 (83.9)	146 (81.1)	168 (93.3)	3 (1.7)	4 (2.2)	1 (0.6)
ETN	179	10 (5.6)	156 (87.2)	138 (77.1)	167 (93.3)	4 (2.2)	3 (1.7)	3 (1.7)
IFX	48	2 (4.2)	45 (93.8)	37 (77.1)	44 (91.7)	0 (0)	2 (4.2)	0 (0)
RTX	28	1 (3.6)	27 (96.4)	22 (78.6)	25 (89.3)	1 (3.6)	0 (0)	0 (0)
Nonbiologic agents	640	15 (2.3)	540 (84.4)	482 (75.3)	568 (88.8)	6 (0.9)	5 (0.8)	4 (0.6)
LEF	91	2 (2.2)	80 (87.9)	79 (86.8)	80 (87.9)	1 (1.1)	1 (1.1)	0 (0)
MTX	156	6 (3.8)	140 (89.7)	120 (76.9)	138 (88.5)	0 (0)	4 (2.6)	2 (1.3)
SSZ-HCQ	393	7 (1.8)	320 (81.4)	283 (72.0)	350 (89.1)	5 (1.3)	0 (0)	2 (0.5)
Total	1097	37 (3.4)	938 (85.5)	844 (76.9)	993 (90.5)	14 (1.5)	15 (1.8)	8 (0.8)

[1] No episodes met the HCV RNA definition for hepatotoxicity within the 12-month followup period. [2] Hepatotoxic events in time period divided by treatment episodes for drug listed in row. [3] Represents episodes that had at least 1 ALT test performed in given followup time period. Summation of 3 columns will exceed the total episodes because an ALT could be performed in all 3 followup periods, unless censoring occurred (failure or end of followup period). [4] Event rate % equals the number of hepatotoxicity events in time period divided by the number of ALT tests performed in same time period for drug row. ALT: alanine aminotransferase; ABA: abatacept; ADA: adalimumab; ETN: etanercept; IFX: infliximab; RTX: rituximab; LEF: leflunomide; MTX: methotrexate; SSZ-HCQ: sulfasalazine/hydroxychloroquine; COPD: chronic obstructive pulmonary disease; HCV: hepatitis C virus.

Table 3. Effect of baseline covariates on hepatotoxicity in cohort. Values are n (%) unless otherwise specified.

Covariate	Covariate Present		Covariate Absent		p[1]
	Treatment Episodes, n	Hepatotoxic Episodes	Treatment Episodes, n	Hepatotoxic Episodes	
Hepatitis B surface antigen detected[2]	5	0 (0)	1092	37 (3.4)	1.0
Hepatitis B core antibody detected[2]	48	3 (6.3)	1049	34 (3.3)	0.22
Concomitant MTX/LEF[3]	405	12 (2.9)	692	25 (3.6)	0.61
HCV antiviral prescription[3]	50	3 (6.0)	1047	34 (3.3)	0.23
Oral glucocorticoid prescription[4]	413	19 (4.6)	684	18 (2.6)	0.08
Statin prescription[4]	379	8 (2.1)	718	29 (4.0)	0.11
Diabetes mellitus[5]	263	6 (2.2)	834	31 (3.7)	0.33

[1] Chi-square or Fisher's exact test. [2] Detected at any point during the observation period. [3] Defined within 12 months of index date; HCV antivirals: interferon α, peginterferon α, ribavirin. [4] Prescription within 6 months of index date. [5] Defined by ICD-9 codes and measured 12 months prior to the index date. MTX: methotrexate; LEF: leflunomide; HCV: hepatitis C virus; ICD-9: International Classification of Diseases, 9th ed.

DISCUSSION

Our study analyzed hepatotoxicity in a real-world cohort of RA patients with chronic HCV infection and is among the largest studies to date of RA patients with HCV. Our results demonstrate a low rate of hepatotoxicity with conventional therapies for RA in patients with chronic HCV infection, the majority of whom were not receiving treatment for viral hepatitis. We observed a greater number of hepatotoxicity events during the first 6 months after DMARD initiation as compared to the final 6 months of the 12-month observation period. Hepatotoxicity was more frequently observed among biologic treatment episodes than among nonbiologic treatment episodes, although a majority of biologic users were receiving combination therapy with nonbiologic DMARD. Among biologics, hepatotoxicity was similar between TNFi and the non-TNFi we studied (ABA and RTX, excluding TCZ).

To date, most studies examining DMARD safety in RA patients with chronic HCV were small clinical trials, retrospective case series, or sporadic case reports. A systematic review of RA patients with HCV treated with TNFi reported that out of 91 cases, increased transaminases were reported in 1 patient and increased HCV viral load in 7 patients[6]. A clinical trial examining ETN as adjuvant therapy to pegylated interferon and ribavirin for HCV treatment determined the ETN had no adverse effect on HCV-related liver disease in

patients without RA[8]. An open-label clinical study that randomized 29 RA patients with chronic HCV to receive MTX alone, ETN alone, and ETN + MTX found no difference in hepatotoxicity between the 3 arms[21].

After consideration of the limited amount of high-quality data regarding DMARD safety in RA patients with chronic HCV, the ACR 2015 guidelines recommend the use of SSZ and/or HCQ over MTX and TNFi in RA patients with untreated chronic HCV. In our study, SSZ/HCQ had the lowest numeric frequency of hepatotoxicity events, but this was not significantly different from the frequencies of hepatotoxicity seen with MTX or LEF. Although MTX and LEF are considered hepatotoxic medications, studies suggest relatively low frequencies of liver toxicity with these DMARD[22]. In a study of 16 patients with RA and mild liver disease from HCV who received MTX alone or in combination with TNFi, 1 patient (6.3%) discontinued MTX because of elevated liver enzymes[21]. MTX and LEF are often prescribed as anchor drugs for biologics. In our study, nearly half of biologic treatment episodes were prescribed concomitant MTX or LEF, but we did not observe a significant difference in hepatotoxicity events among biologic treatment episodes with concomitant MTX/LEF as compared with those with HCQ/SSZ or without MTX/LEF/HCQ/SSZ. In addition, covariate analysis did not demonstrate a relationship between MTX/LEF use and hepatotoxicity.

The ACR conditionally recommends that RA patients with chronic HCV who have received or are receiving effective antiviral therapy for HCV could be prescribed the same therapies as patients with RA who are not infected with HCV[11]. The support for the latter recommendation stems from several case reports of interferon-based HCV treatment coinciding with the use of biologic agents for patients with autoimmune disease, including RA[23,24,25,26]. A total of 50 episodes in our sample had received a prescription for HCV medications (interferon α, peginterferon α, ribavirin) within 12 months of DMARD initiation. We did not observe a relationship between HCV antiviral prescription and hepatotoxicity, but it is difficult to draw conclusions given that so few were receiving HCV treatment. Since the advent of direct-acting antivirals for HCV, the VA and other healthcare systems have seen markedly increased uptake in HCV treatment. In practice, RA providers will be more likely to encounter patients with RA receiving these HCV treatments[12]. While we surmise this will likely decrease the frequency of hepatotoxicity, the effects of direct-acting antivirals in patients with RA and chronic HCV merits further study.

When analyzing other covariates associated with hepatotoxicity, glucocorticoid prescription within 6 months of starting a DMARD was not significantly associated with a higher frequency of hepatotoxicity. Although the immune effects of glucocorticoids could predispose to viral hepatitis reactivation, a small case series (n = 28) of HCV-infected patients receiving daily prednisone illustrated no adverse effects during an average followup of 76 months[27]. Statin therapy has been associated with a reduced risk of hepatic decompensation in retrospective studies of patients with HCV-related cirrhosis[28]. Our analysis did not find a significant association between statin prescription and hepatotoxicity.

The ACR 2015 treatment guidelines for RA recommend monitoring of aminotransferases every 2–4 weeks for the first 3 months after starting MTX, LEF, and SSZ, and then every 8–12 weeks for months 3–6 and every 12 weeks thereafter[11]. Testing for HBV prior to conventional and biologic DMARD initiation is also recommended. Monitoring of ALT at the recommended intervals was frequently observed in our cohort; however, we found infrequent screening for HBV infection among these treatment episodes, a finding reported in another analysis of VA patients with RA[29]. Given the potential serious consequences of HBV reactivation and the availability of well-tolerated HBV antivirals that may prevent HBV reactivation, increased attention to screening and monitoring for HBV in patients with RA receiving immunosuppressive therapy is warranted.

Our study has several limitations. To reduce confounding from preexisting liver disease, cohort entry required a baseline ALT < 66 IU/l. This criterion may have led to underestimation of hepatotoxicity by eliminating patients who were more susceptible to this outcome. Our observation period was limited to 12 months after DMARD initiation. Although we observed a lower rate of hepatotoxicity in the latter 6 months of the observation period, it is possible that longer durations of DMARD use could result in increased frequency of hepatotoxicity. A retrospective evaluation of 9 autoimmune disease patients with chronic HCV who received TNFi for a minimum of 36 months reported 1 episode of HCV reactivation and a separate case of accelerated liver disease progression[10]. We did not assess the effect of alcohol use or obesity, 2 comorbid conditions that could result in hepatotoxicity. We did not have access to imaging results or liver biopsy reports, which could more clearly delineate the etiology of liver enzyme elevation. We also did not assess for additional concomitant medications that have been demonstrated to result in hepatotoxicity, including nonsteroidal inflammatory drugs and antibiotics[30,31]. Because of the limited testing for HBV markers in this cohort, unrecognized HBV infection could also have influenced the results.

We could only review the records of care within the VHA healthcare system. We cannot exclude the possibility that some patients may have had monitoring performed, hepatotoxicity detected, and received treatment for HCV from outside providers. Last, our cohort largely consisted of older American men with RA and may not be generalizable to other RA populations.

We observed a low rate of hepatotoxicity (ALT > 100 IU/l) among a large cohort of veterans with RA and chronic HCV infection who were prescribed conventional DMARD. An

increased frequency of hepatotoxicity was seen among treatment episodes with biologic DMARD. The majority of events occurred within the first 6 months of DMARD initiation.

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