Preventing Hepatitis B Reactivation During Anti-CD20 Antibody Treatment in the Veterans Health Administration

A. Jasmine Bullard,[1] Francesca E. Cunningham,[2] Bryan D. Volpp,[3] Elliott Lowy,[4] Lauren A. Beste,[5] Bernadette B. Heron,[6] Mark Geraci,[6] Julia M. Hammond,[7] Kourtney LaPlant,[8] Elise A. Stave,[9] Marsha J. Turner,[1] Meghan C. O'Leary,[1] Michael J. Kelley,[10,11] and Christine M. Hunt[1,12]

Hepatitis B virus (HBV) reactivation may occur with high risk immunosuppression, such as anti-cluster of differentiation (CD)20 antibodies (Abs). Appropriate HBV prophylaxis during anti-CD20 Ab therapy averts hepatitis, chemotherapy disruption, and death. Serologic evidence of prior HBV exposure is present in one in nine veterans in the Veterans Health Administration (VHA). In 2014, most (61%-73%) patients in the VHA who were receiving anti-CD20 Ab treatment underwent HBV testing, yet <20% of eligible patients received HBV antiviral prophylaxis. We aimed to prevent HBV reactivation by increasing HBV testing and antiviral treatment rates among anti-CD20 Ab recipients through prospective interventions. A multidisciplinary team of clinicians, pharmacists, and public health professionals developed comprehensive prevention systems, including national seminars/newsletters/websites; pharmacy criteria for HBV screening/treatment prior to anti-CD20 Ab use; changes to national formulary restrictions to expand HBV prophylaxis prescribing authority; Medication Use Evaluation Tracker to identify omissions; national e-mail alert to all VHA oncology providers detailing specific testing and HBV antiviral treatment needs; and a voluntary electronic medical record "order check" used at interested facilities (n = 11) to automatically assess pretreatment HBV testing and antiviral treatment and only generate a reminder to address deficiencies. Analysis of monthly data from June 2016 through September 2017 among anti-CD20 Ab recipients revealed pre-anti-CD20 Ab treatment HBV testing increased to 91%-96% and appropriate HBV antiviral prophylaxis to 76%-85% nationally following implementation of the intervention. Medical centers using the voluntary electronic medical record order check increased HBV testing rates to 93%-98% and HBV antiviral prophylaxis rates to 99%. *Conclusion:* Multimodal intervention systems to prevent HBV reactivation among VHA patients receiving anti-CD20 Ab therapies increased national rates of HBV testing to >90% and antiviral prophylaxis to >80%. (*Hepatology Communications* 2018;2:1136-1146)

Patients with chronic hepatitis B (HBV) infection or prior exposure are at risk for HBV reactivation if they receive immunosuppressive therapy, such as anti-cluster of differentiation (CD)20 antibody (Ab) treatment.[1,2] Anti-CD20 Abs, commercially available as rituximab, obinutuzumab, and ofatumumab, are a key component of treatment regimens for selected hematologic and rheumatologic

Abbreviations: Ab, antibody; ASCO, American Society of Clinical Oncology; CD, cluster of differentiation; EMR, electronic medical record; GI, gastrointestinal; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; ID, infectious disease; MUET, Medication Use Evaluation Tracker; VA, Department of Veterans Affairs; VAMC, Department of Veterans Affairs Medical Center; VHA, Veterans Health Administration.

Received February 28, 2018; accepted June 20, 2018.

Additional Supporting Information may be found at http://onlinelibrary.wiley.com/doi/10.1002/hep4.1238/full.

Supported in part by resources from the following organizations within the Department of Veterans Affairs: Center for Medication Safety, Northern California Healthcare System Clinical Informatics, Puget Sound Veterans Affairs Health Care System, Pharmacy Benefits Management Services, and the Cooperative Studies Program Epidemiology Center-Durham.

Previously presented at the Association of Veterans Affairs Hematology and Oncology Annual Meeting (September 2017) and the American Public Health Association Annual Meeting (November 2017).

The views expressed in this paper are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government.

conditions. In patients receiving anti-CD20 Ab treatment, HBV reactivation can result in hepatitis (33%-100%), liver failure (10%-13%), and death (3%-5%).[1,2] Between 17% and 55% of individuals with past or chronic HBV infection may experience reactivation unless they receive antiviral prophylaxis.[1] HBV reactivation is also associated with chemotherapy disruption and increased cancer mortality.[1,3]

HBV antiviral prophylaxis prevents reactivation in up to 98% of at-risk patients receiving anti-CD20 Ab therapy.[1] To identify and treat patients at risk for reactivation, HBV serologies must be obtained before starting anti-CD20 Ab therapy. In July 2015, the American Society of Clinical Oncology (ASCO) provided a Provisional Clinical Opinion Update[4] on HBV screening and antiviral prophylaxis, reporting earlier HBV testing rates of nearly 70% prior to initiating anti-CD20 Ab treatment among quality practices.[4] In this Update, ASCO recommends screening for hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb), followed by either initiation of HBV antiviral prophylaxis (in HBsAg-positive patients) or (in those positive for HBcAb alone) either HBV antiviral prophylaxis or monthly measurement of HBV DNA and alanine aminotransferase.[4] The reconstituted HBV-specific host-immune response may injure these HBV-laden liver cells up to 12 months after treatment; hence, HBV antiviral prophylaxis must be continued for 12 months posttreatment.[1]

Among patients in the Veterans Health Administration (VHA) initiating anti-CD20 Ab treatment, approximately 11% have evidence of chronic or prior hepatitis B infection, putting them at risk for reactivation.[5] Most patients are unaware of their HBV status, and even those with chronic HBV frequently do not receive antiviral treatment.[6] In an earlier analysis of all VHA patients initiating anti-CD20 Ab treatment at a total of 112 facilities, 61%-73% had pretreatment HBV testing (with 43% tested within 6 months of initiation) in 2014.[5] A median of 17% meeting criteria for HBV antiviral treatment received prophylaxis (2012-2014).[5] Non-VHA hospitals have reported rates of HBV testing of up to 61%-90%,[7–9] yet generally low (17%-45%) rates of appropriate HBV antiviral prophylaxis[7,9,10] despite the use of a computer-assisted reminder system. This may relate to the generally limited use of HBV antiviral treatment among oncologists requiring a change in prescribing practice. However, in two hospital systems, HBV antiviral prophylaxis rates varied from 46% to 92% in at-risk patients receiving rituximab or cancer chemotherapy.[7,8]

View this article online at wileyonlinelibrary.com.
DOI 10.1002/hep4.1238

Potential conflict of interest: Dr. Hunt has received consultancy fees from Otsuka and Indivior. The other authors have nothing to report.

ARTICLE INFORMATION:

From the [1]Cooperative Studies Program Epidemiology Center-Durham, Durham Veterans Affairs Health Care System, Durham, NC; [2]Center for Medication Safety, Veterans Affairs Pharmacy Benefits Management Services, Hines, IL; [3]Veterans Affairs Northern California Healthcare System, Martinez, CA; [4]Veterans Affairs Puget Sound Health Care System, Health Services Research and Development, University of Washington School of Public Health, Seattle, WA; [5]Veterans Affairs Puget Sound Health Care System, Health Services Research and Development, Department of Medicine, University of Washington, Seattle, WA; [6]Veterans Affairs Pharmacy Benefits Management Services, Hines, IL; [7]Pharmacy Department, Durham Veterans Affairs Health Care System, Durham, NC; [8]Malcom Randall Veterans Affairs Medical Center, Veterans Health System, North Florida, South Georgia, Gainesville, FL; [9]Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY; [10]Office of Patient Care Services, Department of Veterans Affairs, Washington, DC; [11]Hematology-Oncology Service, Durham Veterans Affairs Health Care System, Durham, NC; [12]Department of Medicine, Duke University Medical Center, Durham, NC.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

A. Jasmine Bullard, MHA
Cooperative Studies Program Epidemiology Center-Durham
Durham Veterans Affairs Health Care System
508 Fulton St. (152)
Durham, NC

E-mail: Alyssa.Bullard@va.gov
Tel: +1- 919-286-0411, ext. 4056

Preventing HBV reactivation is both cost effective and critical to patient safety, averting death in 1 in 1,000 patients screened.[5] While evidence-based guidelines are increasingly available to guide clinical practice, implementation science offers limited recommendations on how to successfully integrate these guidelines into practice.[11–15] A VHA cross-sectional study was completed to study the effect of audit and feedback in six facilities implementing clinical guidelines[13]; the greatest success in guideline adherence was seen at sites receiving timely, personalized, and nonpunitive provider feedback. However, in a Cochrane review, audit and feedback resulted in only a median 4% absolute improvement across 140 studies.[16]

To change clinical practice, the National Institute for Health and Care Excellence has reported evidence supporting the value of talking to key individuals, assessing barriers to change, combining education with other methods, and using interactive workshops, patient-friendly education, and reminders at the point of decision making.[15] Endorsement of an initiative by opinion leaders and respected peers is also an effective impetus for clinical practice change.[15] Among these interventions, meta-analyses assessing ways to optimally influence physician behavior suggest that education alone is of limited value but computerized recommendations and follow-up treatment algorithms can be 68%-100% effective.[14] In a single Spanish hospital (2012-2013), the use of a computerized physician-ordering system increased HBsAg testing from <50% to 94%, increased HBcAb testing from 29% to 85%, and completely prevented HBV reactivation events.[11]

We sought to increase HBV testing and antiviral prophylaxis with anti-CD20 Ab treatment initiation in the VHA. Our goal was to maximize rates of HBV testing and appropriate HBV antiviral prophylaxis with anti-CD20 Ab treatment. We hypothesized that professional development and informational campaigns, expansion of HBV antiviral prescribing authority to all providers, and patient education would increase the overall testing/treatment rates by 10%-20%. We predicted that an electronic medical record (EMR) order check and Medication Use Evaluation Tracker (MUET) for tracking HBV testing and antiviral treatment omissions would increase rates to 70% or greater.[14]

Materials and Methods

STUDY DESIGN AND DATA SOURCE

We performed a retrospective cohort study (January 2015 to November 2016) of all patients initiating anti-CD20 Ab treatment (rituximab, ofatumumab, or obinutuzumab), using described methods.[5] All analyses were performed using the VHA EMR data repository: the Corporate Data Warehouse. Starting in September 2016, we used a voluntary anti-CD20 Ab MUET to identify patients at risk for HBV reactivation. MUET is a risk-reduction tool that uses medication and laboratory data to identify at-risk patients receiving specific medications that pose potential safety risks.[17] The MUET provided national monthly data on our two primary analyses: 1) HBV testing within 12 months of starting anti-CD20 Ab treatment and 2) HBV antiviral medication in patients with chronic or prior HBV, within 1 month of starting anti-CD20 Ab treatment.

Using 2015 national VHA data, we determined a mean pretreatment HBV testing rate of 63% overall of anti-CD20 Ab treatment initiation and mean HBV antiviral treatment rates of 44% in at-risk patients (either positive HBsAg or HBcAb pretreatment).[5]

PATIENT POPULATION

The VHA provides care across 170 Department of Veterans Affairs (VA) medical centers (VAMCs) to more than 9 million veterans annually[18]; 112 of these medical centers provide anti-CD20 Ab therapy. For decades, the VHA has used a national EMR, which also allows for site variation in computerized recommendations/treatment algorithms, pharmacy prescribing software, and laboratory terminology.

ANTI-CD20 AB MUET

The VA Center for Medication Safety developed the anti-CD20 Ab MUET. Baseline data for the MUET were derived from all identified patients receiving anti-CD20 Ab treatment from May to August 2016. The MUET was launched in September 2016 using all monthly MUET data extractions of patients

initiating anti-CD20 Ab therapy between September 2016 and September 2017.

Patients receiving anti-CD20 Ab therapy were considered at risk for HBV reactivation if either their HBV status had not been recently confirmed or they were HBV positive and not receiving prophylaxis. For the MUET, "recent" confirmation was defined relative to anti-CD20 Ab treatment initiation as: 1a) within 12 months prior, for patients with no earlier testing; 1b) within 6 months prior, for patients testing negative between 1 and 5 years prior; 1c) ever, for patients testing positive during the prior 5 years. We required HBV testing within 12 months of initiating anti-CD20 Ab treatment in order to identify patients with prior or newly acquired HBV. For the MUET, "prophylaxis" was defined as HBV antiviral treatment between the time of positive HBV test determination and 1 month after anti-CD20 Ab treatment initiation.

Lists of at-risk patients were accessible to providers through a secure website, but MUET participation was voluntary. At participating VAMCs, HBV testing and antiviral treatment interventions were documented for each at-risk patient.[17]

The MUET data provided the percentage of patients treated with anti-CD20 who had recent HBV testing. In this analysis, the HBV-positive population was estimated by multiplying the number of patients treated with anti-CD20 Ab by 11% (the prevalence of patients exhibiting HBsAg and/or HBcAb according to prior VHA reports).[5] To align with our earlier national VHA analyses, the MUET was limited to patients newly initiating anti-CD20 Ab therapy from October 2016 onward.

EMR ANTI-CD20 AB ORDER CHECK

We created a voluntary anti-CD20 Ab treatment EMR order check to assess pretreatment HBV testing and antiviral prophylaxis. When anti-CD20 antibody is ordered, the electronic medical record searches for HBsAg and HBcAb testing and generates an order check only if no serology is done or the serology is positive for HBsAg or HBcAb. If HBV serology is absent, the provider is reminded to obtain HBsAg and HBcAb. If HBsAg or HBcAb is positive and the patient is not receiving HBV antiviral treatment, the provider is prompted to initiate HBV antiviral prophylaxis throughout the anti-CD20 antibody treatment and 12 month follow-up, record the patient's HBV antiviral treatment outside the VA, obtain an infectious disease (ID) or gastrointestinal (GI) consult for treatment and follow-up, or record the patient's declining HBV antiviral treatment.

This order check was piloted at three sites with slight modifications (e.g., assuring order check capture of both local and VHA reference laboratory tests). When tested over a 3-month period, the order check accurately determined patients with or without prior HBV testing and antiviral prophylaxis and provided required reminders. On expanding the voluntary anti-CD20 Ab treatment EMR order check to the many additional sites requesting its use, select sites performed detailed order check testing and cross-checking with the MUET, affirming the order check was operating correctly. Although the number of sites instituting the voluntary anti-CD20 Ab treatment EMR order check increased monthly, we analyzed pretreatment HBV testing and antiviral prophylaxis rates only in the 11 sites with 6 or more months of data to examine the order check's effectiveness.

INSTITUTIONAL REVIEW BOARD REVIEW

This prospective interventional analysis was waived by the Durham VAMC Institutional Review Board as it was completed for VHA quality improvement rather than research. Because the analysis solely used de-identified patient information, informed consent was not required.

STATISTICAL ANALYSIS

To assess the effect of our interventions, we evaluated significant changes over time using run charts.[19] In comparison to pre-intervention baseline rates, changes over time were plotted graphically for the following two national monthly measures: rates of timely pretreatment HBV testing and rates of HBV antiviral prophylaxis in HBV-positive patients (with chronic or prior HBV infection).

We interpreted run charts through inspection for multiple probability-based patterns that indicated a significant change from the plotted pre-intervention mean rates, defined by the following characteristics: shift, trend, and runs.[19] Shift is defined by "six or more consecutive points either all above or all below" the pre-intervention mean rates. Trend is seen by "five or more consecutive points" that are in a consistent ascension or descent. For trending, neighboring equivalent values only contribute a single point to the count. A run is defined as "a series of points in a row on one

side" of the mean. Runs are evaluated by determining how many times a line through the points would cross the mean pre-intervention rates and are compared to a set of expected values.

Results

BASELINE DATA

Our earlier analysis of the VHA Corporate Data Warehouse provided 2014 data on hepatitis B testing and antiviral prophylaxis.[5] Examining this database in 2015, 2,655 identified VHA patients initiated anti-CD20 antibody treatment. Pretreatment HBsAg testing was performed in 78% and HBcAb testing in 63% (Fig. 1). Among them, 318 patients had chronic or prior HBV requiring HBV antiviral prophylaxis. A total of 141 (44%) patients received HBV antiviral prophylaxis. During January through November 2016, a total of 2,238 patients initiated anti-CD20 antibody treatment, with 78% and 64% HBsAg and HBcAb testing rates, respectively.

HEPATITIS B PREVENTION TEAM

Despite a broad VHA educational campaign, continued low rates of HBV antiviral prophylaxis were observed among at-risk patients initiating anti-CD20 Ab treatment.[1,20] We assembled a national team to prevent HBV reactivation. The team was comprised of oncologists, oncology and viral hepatitis pharmacists, primary care, infectious disease and rheumatology physicians, public health and quality experts, drug safety and medical informatics experts, and hepatologists. All clinicians in the group were involved in anti-CD20 Ab treatment or HBV reactivation.

We started by identifying potential barriers to HBV testing and treatment in each clinical area as well as professional development needs to increase awareness of HBV reactivation among providers and patients (Table 1). One barrier was that only GI or ID physicians and not oncologists or rheumatologists were allowed to prescribe HBV antiviral prophylaxis on the VHA formulary. Our pharmacist team members worked with the VHA formulary committee to enable HBV antiviral prescribing by all licensed providers. National pharmacy criteria for use of anti-CD20 Ab treatment were amended to include the need for HBV testing and appropriate HBV antiviral prophylaxis.

Although the VHA uses a national EMR, the process in which a provider orders infusion biologics can vary by site. We surveyed oncology pharmacists nationally by e-mail. We found that most used the VHA Computerized Patient Record System, while 32 sites employed a proprietary ordering system, VistA Chemotherapy Manager, which has not yet enabled use of the requested anti-CD20 Ab treatment EMR order check.

We found that both GI and ID providers were frequently consulted for HBV management when at-risk patients were identified prior to anti-CD20 Ab therapy. In response, we developed a GI consult template with HBV testing and antiviral prophylaxis algorithms (Supporting Material S1) that was shared with the national VHA GI Field Advisory Committee. As GI and ID subspecialists may not be on site at some facilities, we sought to create a system to enable HBV antiviral prescribing by any provider.

In addition to identifying barriers, we launched a broad informational campaign, with interactive national seminars and webinars for GI/hepatology, public health/ID, and oncology providers (Table 1). We highlighted information on HBV reactivation in

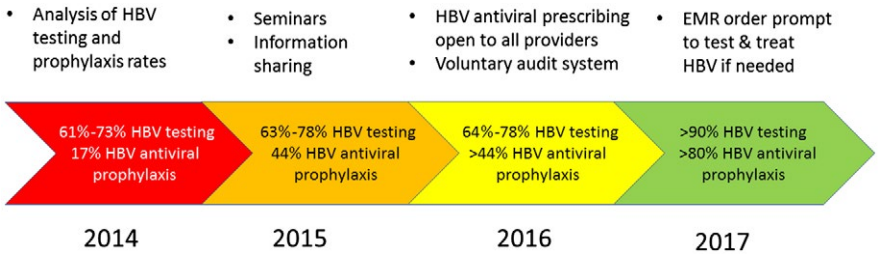

FIG. 1. Increases in VHA national hepatitis B testing and antiviral prophylaxis rates with initiation of anti-CD20 antibody treatment are profiled in the chevron figure over time (2014-2017). Derived from the VHA Corporate Data Warehouse, the 2014 data is from an earlier analysis (5) while the 2015-2016 data were analyzed within this study. Data from September 2016 to September 2017 were derived from the national anti-CD20 antibody Medication Use Evaluation Tracker. Key interventions are outlined above the figure.

TABLE 1. VHA SYSTEMS TO PREVENT HBV REACTIVATION WITH ANTI-CD20 AB INITIATION

Date	Activity	Professional Development	Address Barriers	Patient Information	Clinical Audit	Opinion Leader	EMR order check
11/15	Multisite hepatology SCAN seminar	X					
11/15	National public health seminar	X					
3/16	GI consult template created for HBV reactivation treatment algorithms		X				
5/16	HBV antiviral prescribing open to all		X				
6/16	Anti-CD20 Ab criteria for use include HBV testing & HBV antiviral treatment	X					
6/16	National oncology seminar	X					
7/16	Oncology HBV reactivation website launches with information, references	X					
7/16	Patient education slides & pamphlet posted to VHA external website			X			
8/16	National pharmacy newsletter	X					
8/16	Pharmacist survey on anti-CD20 Ab ordering process		X				
9/16	Medication Use Evaluation Tracker launched				X		
9/16	Association of VA hematology/ oncology newsletter	X					
10/16	National Oncology Director emails all oncologists to test and treat HBV with anti-CD20 Ab initiation					X	
11/16	Anti-CD20 Ab EMR order check pilot tested in CPRS						X
11/16	Provider workroom posters/ flyers on HBV reactivation on Sharepoint	X					
3/17	Oncology pharmacists invited to use anti-CD20 Ab EMR order check		X				X
4/17	15 sites incorporate anti-CD20 Ab EMR order check						X
6/17	HBV antiviral patient medication information developed for website			X			
9/17	Association of VA hematology/ oncology poster to increase order check use	X					
11/17	American Public Health Association poster to discuss possible improvements	X					

Abbreviations: CPRS, computerized patient record system; SCAN, Specialty Care Access Network.

our VHA pharmacy newsletter (Supporting Material S2).

In parallel with professional development activities, we developed brief patient educational information (at a fifth-grade reading level) on HBV infection, reactivation, and preventive treatment as slides posted to the public VHA patient website[21] as well as a pamphlet (Supporting Material S3). Using a one-page format selected by patients,[22] we created HBV antiviral patient medication information at a sixth-grade reading level (Supporting Material S4). For easy provider access, we created a VHA Oncology SharePoint for HBV reactivation and posted frequently asked questions on HBV reactivation (Supporting Material S5), provider and patient educational material, our published VHA national analysis of HBV testing and treatment with anti-CD20 Ab, and ASCO and American Gastroenterological Association clinical guidance documents.

As these efforts progressed in 2016 (Table 1), we sought to determine how these activities affected rates of HBV testing and antiviral prophylaxis with anti-CD20 Ab therapy. The VA Center for Medication Safety developed an anti-CD20 Ab MUET to identify omissions of HBV testing and antiviral prophylaxis.

ANTI-CD20 AB MUET

The anti-CD20 Ab MUET tracked HBV testing and antiviral prophylaxis omissions monthly across the VHA nationally (Fig. 2A) and provided feedback to the majority of sites that volunteered to participate.[17] We observed that 40%-50% of all identified patients receiving anti-CD20 Ab treatment in June to August 2016 did not have pretreatment HBV testing completed. Among patients with chronic or prior HBV requiring HBV antiviral prophylaxis, up to 40% of patients did not receive antiviral prophylaxis within 1 month of initiating anti-CD20 Ab therapy. At the MUET's national launch in September 2016, we highlighted its availability for use with informational updates in a national VHA hematology/oncology newsletter (Supporting Material S6). In October 2016, the national VHA oncology director sent a brief informative e-mail encouraging all providers to test and treat HBV prior to initiating anti-CD20 Ab therapy (Supporting Material S7). Immediately following these efforts, we observed the highest rates of HBV testing (>90%) and HBV antiviral prophylaxis

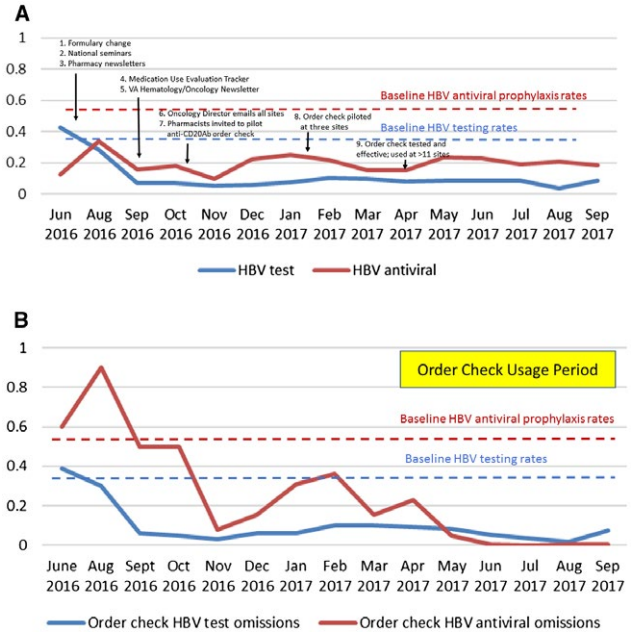

FIG. 2. (A) Omissions in VHA national hepatitis B testing and antiviral prophylaxis are plotted in all identified patients initiating anti-CD20 antibody treatment in a medication use evaluation tracker. The medication use evaluation tracker obtained baseline data in June to August 2016, and provided a voluntary audit notification to sites of HBV testing or antiviral prophylaxis omissions to sites from September 2016 onward. (B) Eleven urban VA medical centers installed the voluntary VHA anti-CD20 antibody order check at their center from April to September 2017. The electronic medical record searches for HBsAg and HBcAb testing and generates an order check only if 1) no serology is done or 2) the serology is positive HBsAg or positive HBcAb. The order check provides explicit suggestions for HBV serology testing. The electronic medical record then searches for HBsAg and HBcAb testing and generates an order check only if positive HBsAg or positive HBcAb, providing suggested HBV antiviral prophylaxis dosing and treatment duration.

(>80%) seen to date (Fig. 1). Even at the lowest performing sites, most patients received pretreatment HBV testing and HBV antiviral prophylaxis.

EMR ANTI-CD20 AB ORDER CHECK

After piloting and testing our voluntary anti-CD20 Ab treatment EMR order check (Fig. 3), we partnered with national oncology pharmacists to identify sites volunteering for its use. In March 2017, we installed the order check at all interested sites to augment pretreatment HBV testing and reactivation prophylaxis,

providing an explicit reminder only when deficiencies were detected. We then analyzed the order check effectiveness at 11 urban medical centers using it for 6 months or more and found significantly improved HBV testing and prophylaxis rates compared to the national rates of pretreatment HBV testing, which exceeded 90% and showed HBV antiviral prophylaxis increasing up to 85% (Fig. 2A,B). With use of the voluntary EMR order check, these sites markedly improved from 70%-79% pretreatment HBV testing rates and 10%-30% antiviral prophylaxis rates (June to August 2016) to 93%-98% pretreatment HBV testing rates and 99% HBV antiviral prophylaxis rates (April to September 2017). Based on favorable site feedback, the numbers of sites incorporating the voluntary EMR order check was continuing to increase monthly. However, fewer than 20% of sites nationally had employed this tool by September 2017 (and nearly 30% of sites with VCM ordering systems are currently precluded from using the order check).

RUN CHART ANALYSIS

We examined the effects of our VHA quality improvement interventions using a run chart (Fig. 2A,B), which depicts omissions of HBV testing or HBV antiviral prophylaxis with anti-CD20 Ab treatment compared to pre-intervention baseline rates. The baseline rates of 64%-78% HBV testing (64% for HBcAb and 78% for HBsAg) are conservatively portrayed as 36% of patients missing or not receiving HBV testing, while the baseline rates of 44% HBV antiviral prophylaxis with anti-CD20 Ab treatment initiation appear as 56% of patients missing or not receiving HBV antiviral prophylaxis. After obtaining baseline MUET data for June through August 2016 on all identified patients receiving anti-CD20 Ab therapy, the run chart revealed general improvements (or fewer omissions over time) as sequential interventions occurred. Enabling HBV antiviral prescribing by all providers, increasing awareness of HBV reactivation through professional

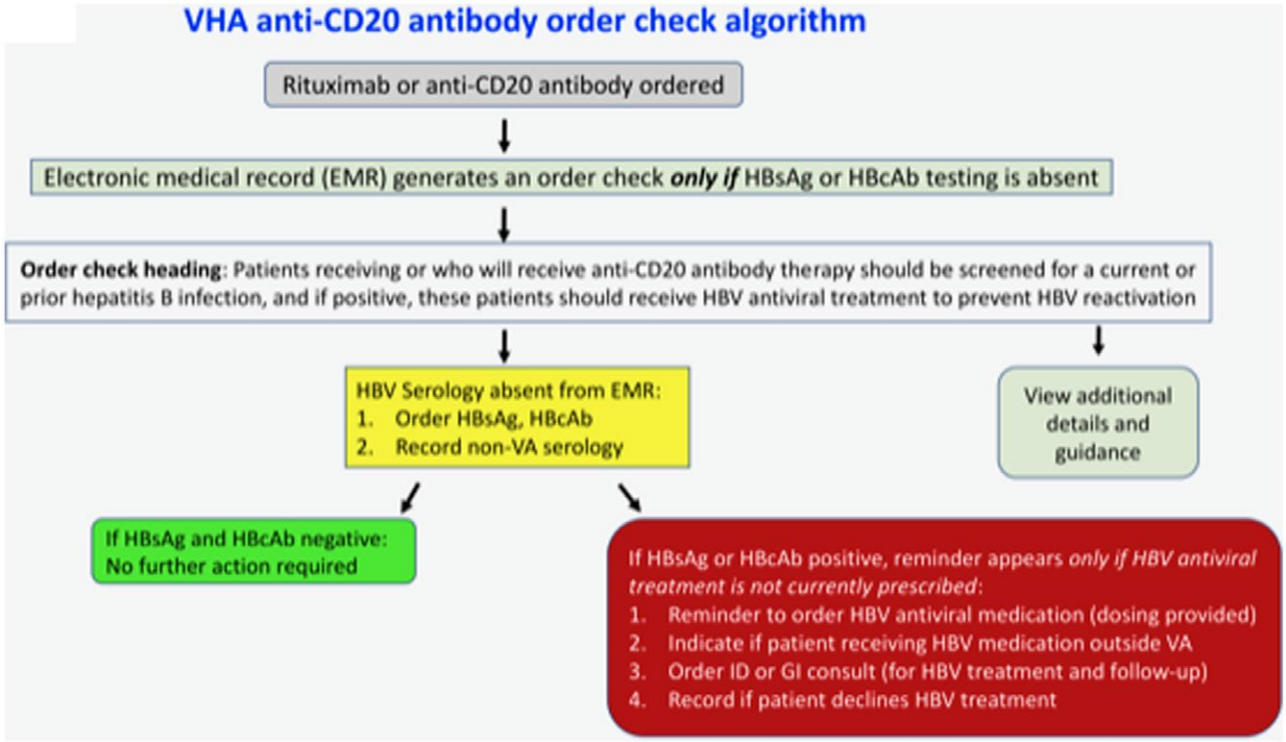

FIG. 3. The VHA electronic medical record algorithm for the voluntary anti-CD20 antibody order check is depicted. When anti-CD20 antibody is ordered, the electronic medical record searches for HBsAg and HBcAb testing and generates an order check only if 1) no serology is done or 2) the serology is positive HBsAg or positive HBcAb. If HBV serology is absent, the provider is reminded to obtain HBsAg and HBcAb. If HBsAg or HBcAb is positive, and the patient is not receiving HBV antiviral treatment, the provider is prompted to initiate HBV antiviral prophylaxis throughout anti-CD20 antibody treatment and 12 month follow-up, record the patient's HBV antiviral treatment outside the VA, obtain an Infectious Disease (ID) or Gastroenterology (GI) consult for treatment and follow-up, or record the patient's declining HBV antiviral treatment.

development, and institution of the anti-CD20Ab MUET yielded significantly improved national rates of both HBV testing and HBV antiviral prophylaxis from September 2016 to September 2017. The use of the voluntary EMR order check further improved these rates.

Discussion

To enhance prevention of HBV reactivation with anti-CD20 Ab treatment in the VHA, we launched a national quality improvement effort comprised of six interrelated interventions that was associated with higher than 90% national HBV testing and 80% antiviral prophylaxis rates in identified anti-CD20 Ab recipients. To effect this change, we assembled a multidisciplinary team of providers, published and widely shared VHA results demonstrating the need to increase HBV testing and treatment, expanded HBV antiviral prescribing authority to all VHA providers, provided interactive and online information to providers and patients, and emphasized the importance of HBV testing and antiviral prophylaxis through a national communication by the VHA Director of Oncology. To assess progress, we developed a voluntary anti-CD20 Ab MUET to alert pharmacists and other providers to omissions in HBV testing and antiviral prophylaxis. In parallel, we created and tested an anti-CD20 Ab treatment EMR order check to automatically assess pretreatment HBV testing and antiviral prophylaxis and to prompt providers when deficiencies were detected. Through the voluntary use of the anti-CD20 Ab MUET and EMR order check, we observed high and stable national rates of HBV testing and HBV antiviral prophylaxis. The minority of VHA medical centers using the voluntary EMR order check exhibited the highest rates of HBV testing (93%-98%) and antiviral prophylaxis (99%) among identified patients starting anti-CD20 Ab treatment.

We believe this to be the first successful national effort in HBV reactivation prevention in a large integrated health system. We deliberately used evidence-supported methods,[15] including broad discussions to understand beliefs and obstacles, enhancement of disease awareness, addressing barriers, surveying key providers, developing patient and provider educational materials, engaging opinion leaders, creating automated EMR order checks, and compiling monthly metrics to assess transient and sustained change. Although the literature in implementation science generally finds modest effects from education or audit and feedback alone, we found notable effects when combined with expanded prescribing authority for HBV antiviral prophylaxis. These improvements further increased with opinion leader input and were sustained with initiation of an EMR order check. As we rapidly instituted system changes (initiating some measures simultaneously), it is difficult to ascertain the relative effectiveness of each measure. Nevertheless, the following interventions yielded significant and sustained improvements: expanding prescribing authority for HBV antiviral prophylaxis to all providers, initiating the national anti-CD20 Ab MUET audit, and National Oncology Director input. Sites employing the order check even further improved and sustained high rates of HBV testing and antiviral prophylaxis. Our comprehensive and wholly voluntary VHA system has yielded high rates of HBV testing and antiviral prophylaxis, sustained over 12 months. Our VHA interventional systems approach yielded notably higher rates of HBV testing and antiviral prophylaxis than was seen in a recent observational study of a northern California university hospital system (61% HBV testing and 66% HBV antiviral prophylaxis among 926 patients initiating rituximab).[8] This suggests the value of a systems approach to quality improvement.

Our initiative also compares favorably with single-site studies[7,8,11] reporting 90% or higher rates of HBV antiviral prophylaxis and/or HBV reactivation prevention, generally with use of a computerized physician-ordering system.[7,11] Our slightly lower national HBV antiviral prophylaxis rates may be related to the voluntary use of the anti-CD20 Ab treatment EMR order check and MUET. Further VHA improvements in HBV testing and antiviral prophylaxis may be possible with additional interventions (e.g., broader or mandatory use of the EMR order check and MUET).

The strengths of our project include its national scope, the availability of national pharmacy data, our ability to intervene to address barriers, the relatively high rate of HBV testing at baseline (potentially suggesting providers' guideline awareness), the concentration of relevant providers in a single subspecialty (hematology/oncology), the nationally representative adoption of our suggested tools (order check and MUET), and the collaborative VHA infrastructure that enabled us to easily share information with providers and patients. The low baseline HBV antiviral treatment prescribing rates may have been related to the limited use or familiarity with these antivirals among oncologists. When the MUET audits were first launched, we noted variable HBV testing and antiviral treatment across some sites. Sharing HBV antiviral prescribing information while enabling

prescribing access by all providers was associated with increased treatment rates. Despite low baseline HBV antiviral treatment rates, most VHA patients now receive pretreatment HBV testing and HBV antiviral prophylaxis, even in sites with the lowest rates. For example, the 11 sites using the voluntary order check had lower average baseline pretreatment HBV testing and antiviral prophylaxis rates than the national average, yet exceeded the high national rates with order check use.

This analysis is limited by use of observational data, which do not prove causality. Earlier demonstrated to enhance laboratory testing and safe VHA medication use,[17] the MUET currently identifies omissions of HBV testing and antiviral prophylaxis among all those identified as initiating anti-CD20 Ab therapy and provides voluntary feedback to sites. As pretreatment HBV testing remains incomplete, our analyses required use of an estimation of 11% of patients with chronic or prior HBV (as observed in an earlier national VHA analysis[5]) to determine rates of HBV antiviral prophylaxis; the true numbers may differ slightly. The disparate subspecialty treatment recommendations for HBV reactivation with anti-CD20 Ab treatment[4,20] made it more challenging to align with guidelines across disciplines.

Lessons learned from this quality improvement initiative can be directly applied to other areas within and outside the VHA. Although we targeted anti-CD20 Ab therapy, HBV antiviral prophylaxis is recommended for patients receiving other high- and moderate-risk immunosuppressive therapies, such as doxorubicin, epirubicin, and prolonged corticosteroids.[20] A parallel VHA initiative is underway to encourage appropriate HBV antiviral prophylaxis in patients receiving direct-acting antivirals for hepatitis C treatment. Additionally, most VHA patients with chronic HBV with alanine aminotransferase or HBV DNA elevations are not yet receiving treatment.[6] Aligning with evidence-based treatment guidelines,[23] a similar VHA change initiative could help increase treatment rates. At the VHA's incidence of hepatitis B infection,[5] it is cost effective to obtain pretreatment HBV screening and appropriately initiate HBV antiviral prophylaxis in those positive for HBsAg or HBcAb during anti-CD20 Ab treatment and 12-month follow-up.

In conclusion, our multidisciplinary team increased awareness of HBV reactivation with anti-CD20 Ab therapy through a broad informational campaign for providers and patients, removed restrictions from the VHA formulary to enable HBV antiviral prescribing by all providers, used an anti-CD20 Ab MUET to identify HBV testing or treatment omissions, and employed a highly effective anti-CD20 Ab treatment EMR order check. Although entirely voluntary, these national collaborative efforts increased baseline rates of HBV testing from 61% to >90% and appropriate HBV antiviral prophylaxis from 17% to >80%. These clinically important improvements are anticipated to decrease hepatitis, chemotherapy disruption, and mortality due to HBV reactivation in the VHA.

Acknowledgment: We thank Muriel Burk, Von R. Moore, Anna SF Lok, Byungjoo Han, Rachel Britt, Colleen Boatright, Sidney Keisner, Julia Close, Kim Huffman, Ayako Suzuki, Cynthia A. Moylan, Hans L. Tillmann, Joseph Lim, and David Ross for their valuable input and support of this work.

REFERENCES

1) Perrillo RP, Gish R, Falck-Ytter YT. American Gastroenterological Association Institute technical review on prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology 2015;148:221-244.e223.
2) Loomba R, Rowley A, Wesley R, Liang TJ, Hoofnagle JH, Pucino F, et al. Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy. Ann Intern Med 2008;148:519-528.
3) Saab S, Dong MH, Joseph TA, Tong MJ. Hepatitis B prophylaxis in patients undergoing chemotherapy for lymphoma: a decision analysis model. Hepatology 2007;46:1049-1056.
4) Hwang JP, Somerfield MR, Alston-Johnson DE, Cryer DR, Feld JJ, Kramer BS, et al. Hepatitis B virus screening for patients with cancer before therapy: American Society of Clinical Oncology provisional clinical opinion update. J Clin Oncol 2015;33:2212-2220.
5) Hunt CM, Beste LA, Lowy E, Suzuki A, Moylan CA, Tillmann HL, et al. Veterans health administration hepatitis B testing and treatment with anti-CD20 antibody administration. World J Gastroenterol 2016;22:4732-4740.
6) Serper M, Choi G, Forde KA, Kaplan DE. Care delivery and outcomes among US veterans with hepatitis B: a national cohort study. Hepatology 2016;63:1774-1782.
7) Sun W-C, Hsu P-I, Yu H-C, Lin K-H, Tsay F-W, Wang H-M, et al. The compliance of doctors with viral hepatitis B screening and antiviral prophylaxis in cancer patients receiving cytotoxic chemotherapy using a hospital-based screening reminder system. PLoS One 2015;10:e0116978.
8) Schmajuk G, Tonner C, Trupin L, Li J, Sarkar U, Ludwig D, et al. Using health-system-wide data to understand hepatitis B virus prophylaxis and reactivation outcomes in patients receiving rituximab. Medicine (Baltimore) 2017;96.e6528.
9) Junus K, Aguilar M, Patel P, Irwin D, Yee S, Liu B, et al. Improvements in hepatitis B virus screening before rituximab therapy: a community-based, safety-net hospital experience. Cancer 2017;123:650-656.
10) Hwang JP, Barbo AG, Perrillo RP. Hepatitis B reactivation during cancer chemotherapy: an international survey of the

membership of the American Association for the Study of Liver Diseases. J Viral Hepat 2015;22:346-352.
11) Sampedro B, Hernandez-Lopez C, Ferrandiz JR, Illaro A, Fabrega E, Cuadrado A, et al. Computerized physician order entry-based system to prevent HBV reactivation in patients treated with biologic agents: the PRESCRIB project. Hepatology 2014;60:106-113.
12) Brehaut JC, Colquhoun HL, Eva KW, Carroll K, Sales A, Michie S, et al. Practice feedback interventions: 15 suggestions for optimizing effectiveness. Ann Intern Med 2016;164:435-441.
13) Hysong SJ, Best RG, Pugh JA. Audit and feedback and clinical practice guideline adherence: making feedback actionable. Implement Sci 2006;1:9.
14) Kawamoto K, Houlihan CA, Balas EA, Lobach DF. Improving clinical practice using clinical decision support systems: a systematic review of trials to identify features critical to success. BMJ 2005;330:765.
15) National Institute for Health and Clinical Excellence. How to change practice. https://www.nice.org.uk/media/default/about/what-we-do/into-practice/support-for-service-improvement-and-audit/how-to-change-practice-barriers-to-change.pdf. Published December 2007. Accessed July 2017.
16) Ivers N, Jamtvedt G, Flottorp S, Young JM, Odgaard-Jensen J, French SD, et al. Audit and feedback: effects on professional practice and healthcare outcomes. Cochrane Database Syst Rev 2012;6:CD000259.
17) Burk M, Moore V, Glassman P, Good CB, Emmendorfer T, Leadholm TC, et al. Medication-use evaluation with a Web application. Am J Health Syst Pharm 2013;70:2226-2234.
18) Veterans Health Administration. About VHA. https://www.va.gov/health/aboutVHA.asp. Accessed July 20, 2017.
19) Perla RJ, Provost LP, Murray SK. The run chart: a simple analytical tool for learning from variation in healthcare processes. BMJ Qual Saf 2011;20:46-51.
20) Reddy KR, Beavers KL, Hammond SP, Lim JK. Falck-Ytter YT; American Gastroenterological Association Institute. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology 2015;148:215-219.
21) VHA Hepatitis B patient education slides. What is hepatitis B? https://www.hepatitis.va.gov/pdf/HBV-patient-education.pdf. Published June 2016. Accessed July 2017.
22) Aker J, Beck M, Papay JI, Cantu T, Ellis M, Keravich D, et al. Consumers better understand and prefer simplified written drug information: an evaluation of 2 novel formats versus the current CMI. Ther Innov Regul Sci 2013;47:125-132.
23) Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH. American Association for the Study of Liver Diseases. AASLD guidelines for treatment of chronic hepatitis B. Hepatology 2016;63:261-283.

Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep4.1238/full.