Hepatitis B Screening before Immunosuppressive Therapy: A statewide survey of current practice

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Abstract

Background: Reactivation of Hepatitis B virus (HBVr) in patients on immunosuppressive therapy (IST) can be prevented by screening for HBV and preemptive antiviral therapy in patients with prior exposure. Some internal medicine (IM) subspecialty guidelines recommend screening for HBV in all patients prior to starting IST while other guidelines do not and there is no consensus. Methods: We conducted a cross sectional survey to assess the current practice of IM sub-specialty physicians in Oklahoma regarding screening for HBV prior to starting IST. Results: There were seventy respondents from different clinical practice settings; 47.2% (33/70) free-standing specialty clinic, 18.6% (20/70) university hospital/VA hospital, 12.9% (9/70) community hospital and 21.4% (15/70) private hospital. Gastroenterologists accounted for 34.3% (24/70), rheumatologists 25.7% (18/70), hematology-oncologists 21.4% (15/70), and dermatologists 18.6% (13/70). Mean number of years of clinical practice was 27.7(SD 11.9 years). The majority of respondents 91.4% (64/70) were aware of an existing guideline within their respective specialty about screening for HBV prior to prescribing IST. There was a statistically significant difference in practice by subspecialty regarding the choice of serological tests for HBV screening and practice regarding care of screening positive patients ($P<0.05$). Conclusion: There was significant variation in clinical practice regarding HBV screening, choice of HBV serological tests and management of screening positive patients. The extent to which our results are influenced by divergent subspecialty guidelines is unclear. However, it highlights an unmet need for physician education at IM sub-specialty level and a need for consensus on guidelines for prevention of HBVr.

Background

Reactivation of Hepatitis B virus (HBVr) in patients on immunosuppressive therapy (IST) is an increasingly recognized problem that may lead to severe infection and mortality. Preemptive therapy with anti-Hepatitis B virus (HBV) medication in patients with prior exposure, who are identified by serology, prevents HBVr. Although some internal medicine (IM) sub-specialty guidelines recommend screening for HBV in all patients prior to receiving IST, other IM sub-specialty guidelines do not recommend screening, and unfortunately there is no consensus. The aim of this study was to assess the current practice of IM sub-specialty physicians in Oklahoma regarding screening for Hepatitis B infection prior to starting IST.

Methods

This study was waived for review by the Institutional Review Board at our institution. We formulated a 9-item pre-tested questionnaire, which was distributed with the help of the Oklahoma State Medical Board via e-mail to IM sub-specialty physicians in Hematology/Oncology, Dermatology, Gastroenterology and Rheumatology throughout the state. Data were analyzed for descriptive statistics and comparisons between IM sub-specialty groups were evaluated with Fisher's exact test; P-value < 0.05 was considered statistically significant.

Results

There were seventy respondents of which 55.7% (39/70) were males. Respondents were from different clinical practice settings; 47.2% (33/70) practiced at a free-standing specialty clinic, 18.6% (20/70) practiced at a university hospital/VA hospital, 12.9% (9/70) community hospital and 21.4% (15/70) practiced at a private hospital. Gastroenterologists accounted for 34.3% (24/70), rheumatologists 25.7% (18/70), Hematology-oncologists 21.4% (15/70), and Dermatologists 18.6% (13/70)(tab1).

The mean number of years of clinical practice was 27.7 SD 11.9 years (Fig 1).

Majority of respondents 91.4% (64/70) were aware of an existing guideline within their respective specialty about screening for HBV prior to prescribing IST. Clinical practice regarding the decision to screen for HBV varied by specific IST,47.1%(33/70) would screen prior to starting all forms of chemotherapy, 82.9%(58/70) would screen prior to starting tumor necrosis factor antagonists(anti-TNF), 70% (49/70) prior to starting B-cell depleting agents, 55.7%(39/70) prior to starting disease modifying anti-rheumatic drugs (DMARDs), 51.4% (36/70) prior to organ transplant or bone marrow transplant, and 7.1% (5/70) prior to starting corticosteroids(Table 2).There was no difference in practice regarding the decision to screen for HBV by years of clinical practice(Table 3).

There was a statistically significant difference in practice by subspecialty regarding the choice of serological tests for screening; 25.4% (17/67) chose acute HBV panel, 35.8% (24/67) chose chronic HBV panel and 38.8% (26/67) chose both (acute and chronic HBV panel; $P < 0.05$)(Table 4).There was a statistically significant difference in practice by subspecialty regarding care of screening positive patients (patients who test positive for hepatitis B surface antigen); Majority of gastroenterologists and hematology-oncologists would refer to a gastroenterologist (75% and 66.7% respectively), majority of dermatologists(53.9%) would refer to an infectious disease physician while majority of rheumatologists(44.4%)would treat with antivirals and delay immunotherapy ($P<0.05$, table 5).

Discussion

Patients with prior exposure HBV or chronic carriers of HBV are at a risk of re-activation if treated with immunosuppressive agents. This incidence of HBVr has been reported to be as high as 38% to 41% in patients undergoing chemotherapy for solid tumorsand breast cancerrespectively[1,2]. HBVr can be reduced by screening patients for HBV infection prior to starting IST and initiation of prophylactic antiviral therapy, at least in moderate and high-risk patients.

In this survey, we confirmed that there was great variation amongst sub-specialty physicians in Oklahoma regarding screening and prophylaxis of patients at risk of HBVr. The majority of physicians were aware of specific evidence-based guidelines regarding screening for HBV in their area of expertise. However, the awareness of sub-specialty guidelines did not appear to consistently influence their practice regarding which patients require screening for HBV, choice of appropriate screening tests and management of screening positive patients. According to the American Gastroenterological Association(AGA) guidelines(2014) the use of anti-viral therapy is strongly recommended in patients with prior HBV

exposure before initiation of IST.[3] This recommendation was emphasized more in patients being treated with B-cell-depleting agents (e.g. rituximab, ofatumumab) because they were considered to be at high risk (>10%) for HBVr [3].A recent systematic review also recommended anti-viral therapy in patients with hematological malignancies regardless of their baseline anti-HBs and serum HBV DNA status[4]. They further recommended continuation of anti-viral therapy up to 12 months after the discontinuation of immunosuppression, as HBVr often develops after the completion of IST [4]. This contrasts with another study where researchers mandated screening for active or resolved HBV infection prior to immunosuppressive treatment of hematological malignancies, but strongly recommended prophylactic antiviral therapy only in those patients with positive HBsAg[5]. In patients with resolved infection, they offered a choice between two approaches of pre-emptive monitoring with HBV DNA or anti-viral therapy[5]. A retrospective analysis of patients with serological markers of previous HBV infection, compared outcomes of those receiving anti-viral therapy with a control group that did not receive antivirals[6]. HBVr was observed in all patients in the control group thus supporting the practice of screening and prophylaxis before chemotherapy[6].

However, there are contrary recommendations from experts in rheumatology. A multi-center study concluded that combination of rituximab and DMARDs in patients with Rheumatoid arthritis (RA) had a negligible risk of HBVr. They therefore recommended serum monitoring but not prophylaxis in these patients [7]. Thus, the decision of using anti-viral prophylaxis to prevent reactivation of HBV infection remains controversial, although strong evidence exists in the favor of prophylaxis.

Decisions can also be made on an individual case basis(selective screening and treatment) with the two most important predictive factors for HBVr being rituximab-based regimen (hazard ratio: 11.74) and anti-HBs-positive status (hazard ratio: 0.17) [8]. Patients with non-hematological diseases or rituximab-free regimens have a low risk of HBVr and may not require anti-HBV prophylaxis if they have undetectable HBV DNA and positive anti-HBs[4]. Some studies have even proposed algorithms to help physicians cluster patients based on the risk for HBVr[9]. The concept of selective screening hinges on appropriate risk stratification or physician discretion to identify patients at risk of HBV infection and reactivation prior to chemotherapy or IST. Recent studies suggest that recognition of risk factors for HBV by physicians (hematologists, rheumatologists and medical oncologists) prescribing IST is suboptimal[10]. In another study, missed opportunities for HBV-screening were attributed to physicians underestimating country of origin as a risk-factor.[11] Taken together, the reported low awareness of HBV risk and low screening rates suggest that physicians prescribing IST are unlikely to correctly identify and screen all high-risk patients for HBV[10,11]. This is a trend that has been reported in other studies[11,12]. Pre-emptive antiviral prophylaxis is highly effective in all patients with serological evidence of past HBV infection, and delayed treatment until HBVr, results in decreased cure rates[6]. Studies have shown that lamivudine can reduce the risk for HBVr and HBV-associated morbidity and mortality in patients who test positive for HBs Ag and are undergoing chemotherapy[13]. However, recent literature supports use of entecavir and tenofovir, given their safety profiles, potency and low risk of resistance [9].

Conclusions

This study showed significant variation in clinical practice regarding HBV screening, choice of HBV serological tests and management of screening positive patients. The extent to which the results of our study are influenced by divergent subspecialty guidelines is unclear. However, it highlights an unmet need for patient care and physician education which must be addressed at IM sub-specialty level. There is need for consensus on guidelines for prevention of HBVr.

Abbreviations

Reactivation of Hepatitis B virus (HBVr)

immunosuppressive therapy (IST)

internal medicine (IM)

Standard deviation (SD)

tumor necrosis factor antagonists(anti-TNF)

disease modifying anti-rheumatic drugs (DMARDs)

American Gastroenterological Association(AGA)

Rheumatoid arthritis (RA)

References

1.Yeo W, Zee B, Zhong S, et al. Comprehensive analysis of risk factors associating with Hepatitis B virus (HBV) reactivation in cancer patients undergoing cytotoxic chemotherapy. British Journal of Cancer 2004;90:1306–1311.

2.Yeo W, Chan PK, Zhong S, et al. Frequency of hepatitis B virus reactivation in cancer patients undergoing cytotoxic chemotherapy: a prospective study of 626 patients with identification of risk factors. J Med Virol 2000;62:299–307.

3.Reddy KR, Beavers KL, Hammond SP, et al. American Gastroenterological Association Institute Guideline on the Prevention and Treatment of Hepatitis B Virus Reactivation During Immunosuppressive Drug Therapy. Gastroenterology 2015;148:215–219.

4.Cholongitas E, Haidich A-B, Apostolidou-Kiouti F, et al. Hepatitis B virus reactivation in HBsAg-negative, anti-HBc-positive patients receiving immunosuppressive therapy: a systematic review. Annals of Gastroenterology 2018;31:480–490.

5.Law MF, Ho R, Cheung CKM, et al. Prevention and management of hepatitis B virus reactivation in patients with hematological malignancies treated with anticancer therapy. World Journal of Gastroenterology 2016;22:6484–6500.

6.Papadopoulos N, Deutsch M, Manolakopoulos S, et al. Efficacy of prophylactic antiviral therapy and outcomes in HBsAg-negative, anti-HBc-positive patients receiving chemotherapy: a real-life experience. Eur J Gastroenterol Hepatol 2017;29:56–60.

7.Varisco V, Vigano M, Batticciotto A, et al. Low Risk of Hepatitis B Virus Reactivation in HBsAg-negative/Anti-HBc-positive Carriers Receiving Rituximab for Rheumatoid Arthritis: A Retrospective Multicenter Italian Study. J Rheumatol 2016;43:869–74.

8.Su YC, Lin PC, Yu HC, et al. Hepatitis B virus reactivation in patients with resolved hepatitis B virus infection receiving chemotherapy or immunosuppressive therapy. Eur J Gastroenterol Hepatol 2018;30:925–929.

9.Hwang JP, Lok ASF. Management of patients with hepatitis B who require immunosuppressive therapy. Nature reviews. Gastroenterology & hepatology 2014;11:209–219.

10. Bottero J, Boyd A, Lemoine M et al. Current state of and needs for hepatitis B screening:

results of a large screening study in a low-prevalent, metropolitan region. PLoS One. 2014

Mar 24;9(3):e92266.

11. Lee R, Bell C, Singh J, Hicks L. Hepatitis B screening before chemotherapy: a survey of

practitioners' knowledge, beliefs, and screening practices. J Oncol Pract, 2012. 8(6): 325–8

12. Khokhar O, Farhadi A, McGrail L, Lewis J. Oncologists and hepatitis B: a survey to

determine current level of awareness and practice of antiviral prophylaxis to prevent

reactivation. Chemotherapy, 2009. 55(2): p. 69–75.

13. Loomba R, Rowley A, Wesley R, et al. Systematic Review: The Effect of Preventive Lamivudine on Hepatitis B Reactivation during Chemotherapy. Annals of internal medicine 2008;148:519–528.

Tables

Table 1: Demographic characteristics of respondents

Variable	Frequency	Percentage
Gender		
Female	31	44.3
Male	39	55.7
IM Sub-Specialty		
Rheumatology	18	25.7
Gastroenterology	24	34.3
Hematology/oncology	15	21.4
Dermatology	13	18.6
Practice Setting		
University Hospital	5	7.2
Veterans Affairs Hospital	8	11.4
Community Hospital	9	12.9
Private Hospital	15	21.4
Free Standing Clinic	33	47.2

Table 2: Decisions on HBV screening by subspecialty and type of IST

Table 3: Decisions on HBV screening by subspecialty and number of years of subspecialty practice

Immunosuppressive therapy	Frequency (%)				Total	P-value*
	Rheum	Hem/Onc	Derm	Gastro		
Chemotherapy						
No	7(38.9)	3(20.0)	10(76.9)	17(70.8)	**37**	**0.003**
Yes	11(61.1)	12(80.0)	3(23.1)	7(29.1)	33	
Total	18	15	13	24	70	
Tumor Necrosis Factor Inhibitors(Anti-TNF)						
No	0 (0.0)	2(13.3)	7(53.9)	2(8.3)	11	**0.0004**
Yes	18(100.0)	13(86.7)	6(46.2)	22(91.7)	**59**	
Total	18	15	13	24	70	
Corticosteroids						
No	13(72.2)	12(80.0)	13(100.0)	21(87.5)	**59**	0.1850
Yes	5(27.8)	3(20.0)	0(0.0)	3(12.5)	11	
Total	18	15	13	24	70	
Disease Modifying Anti- Rheumatic Drugs (DMARDS)						
No	8(44.4)	2(13.3)	8(61.5)	12(50.0)	30	**0.0466**
Yes	10(55.6)	13(86.7)	5(38.5)	12(50.0)	40	
Total	18	15	13	24	70	
CD20 inhibitors(Anti-CD 20 e.g. Rituximab)						
No	7(38.9)	6(40.0)	2(15.4)	19(79.2)	34	**0.0010**
Yes	11(61.1)	9(60.0)	11(84.6)	5(20.8)	36	
Total	18	15	13	24	70	
Organ/Bone marrow transplant (Anti-rejection)						
No	10(55.6)	2(13.3)	1(7.7)	9(37.5)	22	**0.0126**
Yes	**8(44.4)**	**13(86.7)**	12(92.3)	15(62.5)	48	
Total	18	15	13	24	70	

Covariate	Statistics	Level	<10 N=23	>10 N=47	P-value*	P-value**
Chemo	N (%)	0	12 (52.17)	25 (53.19)	0.936	1.000
	N (%)	1	11 (47.83)	22 (46.81)		
Anti-TNF	N (%)	0	4 (17.39)	7 (14.89)	0.787	1.000
	N (%)	1	19 (82.61)	40 (85.11)		
Steroids	N (%)	0	18 (78.26)	41 (87.23)	0.333	0.485
	N (%)	1	5 (21.74)	6 (12.77)		
DMARDS	N (%)	0	10 (43.48)	20 (42.55)	0.941	1.000
	N (%)	1	13 (56.52)	27 (57.45)		
Anti-CD20	N (%)	0	8 (34.78)	14 (29.79)	0.672	0.785
	N (%)	1	15 (65.22)	33 (70.21)		
Organ/BM transplant	N (%)	0	10 (43.48)	24 (51.06)	0.551	0.616
	N (%)	1	13 (56.52)	23 (48.94)		

Level: 0= No, 1= Yes

<10= less than 10 years of practice within their respective subspecialty.

>10= greater than 10 years of practice within their respective subspecialty.

* The parametric p-value is calculated by chi-square test.

** The non-parametric p-value is calculated by Fisher's exact test.

Table 4: Choice of serological tests for HBV screening by subspecialty

HBV serology	Rheum	Hem/Onc	Derm	Gastro	Total
Acute panel*	4(22.2)	2(13.3)	5(41.7)	6(27.3)	17
Chronic panel**	8(44.4)	11(73.3)	3(25.0)	2(9.1)	24
Both	6(33.3)	2(13.3)	4(33.3)	14(63.6)	26
Total	18	15	12	22	67
* Acute panel: Hepatitis B core antibody (IgM), Hepatitis B surface antigen **Chronic panel: Hepatitis B surface antibody, Hepatitis B core antibody (IgG) Fischer's exact test P=0.0029					

Table 5: Clinical practice regarding care of screening positive patients

Clinical decision	Rheum	Hem/Onc	Derm	Gastro	Total
Refer to gastroenterology	5(27.8)	10(66.7)	5(38.5)	18(75.0)	**38**
Refer to infectious disease	2(11.1)	4(26.6)	7(53.9)	6(25)	19
Start anti-HBV therapy, delay IST	8(44.4)	1(6.7)	1(7.7)	0(0)	10
None of the above	3(16.7)	0(0.0)	0(0.0)	0(0.0)	3
Total	18	15	13	24	70
Fischer's exact test P=0.0001					

Declarations

Declarations

Ethics approval and consent to participate

Not Applicable

Consent for Publication

Not Applicable

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

IA and AA were involved in idea development. IA was involved in distribution of survey. DZ AC were involved in analyzing data. IA, JF, MH, RK and AA were involved in manuscript writing. All authors read and approved the final manuscript

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Figures

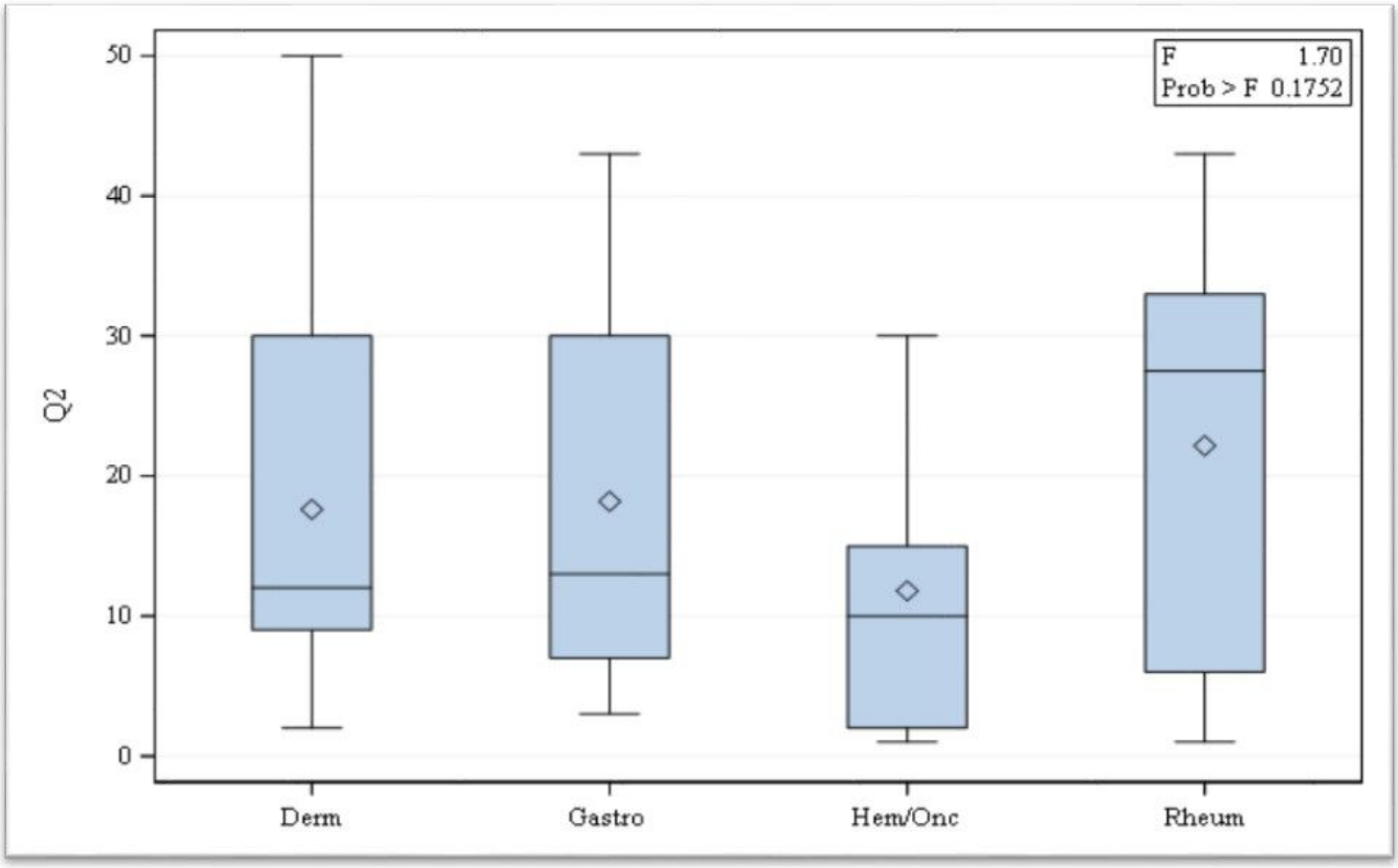

Figure 1

Distribution of respondents by mean number of years of subspecialty practice