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CORRESPONDENCE

Adherence to infectious disease screening and immunization guidelines when treating non-malignant immune-mediated hematologic disorders

To the Editor:

The use of immunosuppressive therapies in the management of non-malignant immune-mediated hematologic disorders leads to an increased risk of infections.[1] Preventive strategies, such as immunization and infectious disease screening, reduce the burden of infectious complications. However, lack of compliance to available national guidelines among healthcare providers represents a major concern. Currently, it is unclear what the adherence levels are in the United States (U.S.) as the limited available information and studies evaluating adherence comes from publications performed outside the U.S.[2,3]

We conducted a retrospective analysis of patients 18 years and older diagnosed and treated at the University of North Carolina hospitals and clinics, between January 2016 and July 2018 for the following non-malignant immune-mediated hematologic disorders: immune thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), autoimmune hemolytic anemia (AIHA), acquired coagulation factor deficiencies (ACFD), antiphospholipid syndrome (APS), atypical hemolytic uremic syndrome (aHUS), and paroxysmal nocturnal hemoglobinuria (PNH). To be included in the study, patients had to have received at least one of the following therapies: rituximab, eculizumab, or splenectomy. Patients were excluded if they had an immune-mediated hematologic disorder associated with a hematologic malignancy, or had had a splenectomy for a non-immune-mediated hematologic disorder. Patients were also excluded if they had "incomplete medical records", defined as absence or deficient proof of immunization records, or if infectious disease screening was documented as being negative but no laboratory report was found to corroborate this statement.

Adherence to existing immunization and infectious disease screening guidelines was evaluated based on available recommendations established by national entities and/or medical societies for the study period (Supporting Information, Table S1).[1] The vaccines that were considered for analysis included: pneumococcal vaccine (conjugated, and polysaccharide), meningococcal vaccine (quadrivalent meningococcal conjugate -MenACWY- and serogroup B -MenB), and *Haemophilus influenzae* type b vaccine. We also assessed the rate of influenza virus and herpes zoster immunization, the latter only in eligible patients (ie, 50 years or older).[4] We considered "appropriate use of an immunization recommendation by a healthcare provider" to be when, depending on the diagnosis and treatment employed, the patient received immunizations in accordance with the recommended schedule (Supporting Information, Table S1). To be assessed as an appropriately executed recommendation, all vaccines should have been given at least 2 weeks prior to immunotherapy (rituximab or eculizumab) and at least 4 weeks in patients undergoing splenectomy. Lastly, adherence to infectious disease screening in patients receiving rituximab was defined as patients who had been screened for both, hepatitis B surface antigen (HBsAg) and total hepatitis B core (anti-HBc) antibodies in serum.

A total of 435 patients were identified, with 269 eligible patients included in the analyses (Supporting Information, Figure S1). Clinical characteristics and adherence results are summarized in Table 1. Immunization rates are presented in Supporting Information, Figure S2. Overall, only 6% (16 out of 269) of patients received all their scheduled immunizations, as recommended for their therapy group, at the recommended time of at least 2 weeks prior to immunotherapy or 4 weeks prior to splenectomy. When evaluating possible predictors for the low rate of appropriate use of an immunization recommendation, there was not a statistical difference when looking at patient age (<50 years, n = 130 vs ≥50 years, n = 139, P = .31), sex (female, n = 156, vs male, n = 113, P = .6), type of disease (P = .46), type of therapy (P = .53), or the medical service where a patient received therapy (P = .26).

In the rituximab group, 35% (n = 71/203) of patients had immunization recommendation written/discussed in the chart, but only 5% (n = 11/203) received all immunizations 2 weeks or more prior to therapy; 14% (n = 28/203) received all their scheduled immunizations less than 2 weeks prior to therapy, 10% (n = 20/203) received an incomplete immunization schedule, and 6% (n = 12/203) did not receive any immunization in spite of being recommended; 65% (n = 132/203) of patients did not have any immunization recommendation written/discussed in the chart and did not receive any vaccine. In the eculizumab group, although 100% of patients had immunization recommendation written/discussed in the chart, only 8% (n = 1/13) received all immunizations 2 weeks or more prior to therapy, 38% (n = 5/13) received all their scheduled immunizations less than 2 weeks prior to therapy, and 54% (n = 7/13) received an incomplete immunization schedule (either MenACWY or MenB). In the splenectomy group, 87% (n = 46/53) of patients had immunization recommendations written/discussed in the chart, but only 8% (n = 4/53) received all immunizations at least 4 weeks prior to splenectomy, 4% (n = 2/53) received all their scheduled immunizations less than

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TABLE 1 Clinical characteristics and adherence to immunization and infectious disease screening guidelines

Category	Rituximab n = 203	Eculizumab n = 13	Splenectomy n = 53	All Groups n = 269
Age, median years (range)	51 (34-90)	30 (27-74)	47 (31-80)	49 (27-90)
Gender, n (%)				
Female	117 (58)	6 (46)	32 (60)	155 (58)
Male	86 (42)	7 (54)	21 (40)	114 (42)
Diagnosis, n (%)				
ITP	96 (47)	-	46 (87)	142 (53)
TTP	37 (18)	-	1 (2)	38 (14)
AIHA	34 (17)	-	6 (11)	40 (15)
ACFD	22 (11)	-	-	22 (8)
APS	14 (7)	-	-	14 (5)
aHUS	-	10 (77)	-	10 (4)
PNH	-	3 (23)	-	3 (1)
Service location, n (%)				
Inpatient medicine	107 (53)	5 (38)	3 (6)	115 (43)
Outpatient hematology	94 (46)	8 (62)	7 (13)	109 (41)
Surgery	2 (1)	0	43 (81)	45 (17)
Time from diagnosis to treatment (median)	3 years	3 weeks	3 months	1.5 years
Time from starting immunization to treatment (median)	4 weeks	1 week	4 weeks	3 weeks
Immunization rate, n (%)				
Pneumococcal (conjugate or polysaccharide) vaccine	92 (45)	-	49 (92)	-
Haemophilus influenzae vaccine	46 (23)	-	46 (87)	-
Meningococcal (MenACWY or MenB) vaccine	48 (24)	47 (89)	12 (92)	-
Meningococcal (MenACWY and MenB) vaccine	N/A	5 (38)	8 (15)	-
Influenza virus vaccine	79 (39)	4 (31)	14 (26)	97 (36)
Herpes zoster vaccine (of eligible patients)[a]	15/120 (13)	1/5 (20)	1/25 (4)	17/150 (11)
Adherence to immunization recommendation[b], n (%)				
Received all scheduled immunizations at the recommended time	11 (5)	1 (8)	4 (8)	16 (6)
Received all scheduled immunizations outside the recommended time	28 (14)	5 (38)	2 (4)	35 (13)
Received an incomplete immunization schedule (within or outside the recommended time)	20 (10)	7 (54)	40 (75)	67 (25)
Did not receive immunization despite the recommendation by a health care provider	12 (6)	0	0	12 (4)
Did not receive immunization given lack of recommendation by a health care provider	132 (65)	0	7 (13)	139 (52)
Infectious disease screening[c], n (%)				
Screening was recommended	181 (89)	-	-	-
Screening was recommended and appropriately executed (HBsAg and anti-HBc)	139 (68)	-	-	-
Screening was recommended but not appropriately executed (only HBsAg or only anti-HBc obtained)	42 (21)	-	-	-
Screening was not obtained and/or not recommended	22 (11)	-	-	-

Abbreviations: ACFD, Acquired coagulation factor deficiency; aHUS, atypical hemolytic uremic syndrome; AIHA, Autoimmune hemolytic anemia; APS, Antiphospholipid syndrome; ITP, Immune thrombocytopenic purpura; N/A, Not applicable; PNH, paroxysmal nocturnal hemoglobinuria; TTP, Thrombotic thrombocytopenic purpura.

[a]Eligible patients for herpes zoster vaccination are all individuals 50 years or older.

[b]Immunization in rituximab-treated patients include at least one pneumococcal (conjugated, or polysaccharide vaccines), one meningococcal (quadrivalent meningococcal conjugate -MenACWY- or serogroup B -MenB), and *H. influenzae type b* vaccine; immunizations in splenectomy-treated patients are the same as in the rituximab group with the caveat of including both pneumococcal (conjugated and polysaccharide) and both meningococcal vaccines (MenACWY and MenB); immunization in eculizumab-treated patients include both meningococcal vaccines (MenACWY and MenB). The recommended time for immunization is at least 2 weeks prior to initiating immunotherapy (rituximab and eculizumab) or 4 weeks prior to scheduled splenectomy.

[c]Appropriate infectious disease screening in patients treated with rituximab are the serological evaluation of both hepatitis B surface antigen (HBsAg) and total hepatitis B anti-core antibodies (anti-HBc).

4 weeks prior to splenectomy, and 75% (n = 40/53) received an incomplete immunization schedule, the latter, mainly related to inappropriate meningococcal immunization (ie, 74% of patients received either MenACWY or MenB vaccines compared to 1% who received both); 13% (n = 7/53) of patients did not have any immunization recommendation written/discussed in the chart and did not receive any vaccine.

Annual influenza virus vaccine was received by 36% (n = 97/269) of patients (39%; 31%; and 26% for rituximab, eculizumab, and splenectomy groups, respectively). Eleven percent (17 of 150 eligible patients) received herpes zoster vaccine (Table 1 and Supporting Information, Figure S2).

In respect to our second outcome, infectious disease screening (hepatitis B serology) was ordered in 89% (181 out of 203) of all patients treated with rituximab. However, only 68% (139/203) of patients had an appropriate infectious disease screening completed by having had both HBsAg and anti-HBc antibodies serology testing performed; 21% (42/203) had either HBsAg or anti-HBc performed but not both, and 11% (22/203) did not have any hepatitis B serology performed, and no documentation of this recommendation by a healthcare provider (Table 1). Additionally, among the patients who had hepatitis B serology performed, 32% (26/181) had it done several days after having received the first rituximab infusion.

Immunization and infectious disease screening are important tools in preventing infectious complications when using immunosuppressive agents. Our study found that only 6% of all evaluable patients were appropriately immunized as recommended by national guidelines. Low adherence was mainly related to: possible lack of recognition by a health care provider of the need for immunization (52%, n = 139/269), incomplete administration of an immunization schedule (25% non-adherence), and lack of administration of immunizations at the recommended time of at least 2 weeks prior to immunotherapy and 4 weeks prior to splenectomy (13% non-adherence). Furthermore, only two thirds of patients receiving rituximab had pretreatment screening for hepatitis B infection, at odds with national recommendations. Lastly, low immunization rates against influenza virus and herpes zoster were found.

Acknowledging the limitations of a single-center retrospective study, we believe that a particular focus of education directed to health care providers needs to be on: (a) raising awareness of current medical societal and CDC immunization and infectious disease prevention guidelines, (b) the appropriate use of immunization against meningococcal infection in patients receiving eculizumab or undergoing splenectomy (ie, administration of the two meningococcal vaccines, MenACWY and MenB, instead of only one), and (c) improving recognition that splenectomy may eventually have to be a treatment modality in cases of rituximab failure and that impaired response to vaccination for several months has been demonstrated in patients treated with rituximab; hence, vaccination against encapsulated organism is recommended prior to rituximab.[3,5] In conclusion, there is an urgent need for the development of strategies to improve physician awareness of and adherence to immunization and infectious disease screening recommendations.

CONFLICT OF INTEREST

The authors declare no competing financial interests.

AUTHOR CONTRIBUTION

L.M., A.D., S.C., and S.M. designed the research; and L.M., S.P., A.Z., A.D., S.C., and S.M. extracted data, analyzed results and/or wrote the paper.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.