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Postvaccination Symptoms After a Third Dose of mRNA SARS-CoV-2 Vaccination in Patients With Inflammatory Bowel Disease: Results From CORALE-IBD

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Background: The safety of a third dose of SARS-CoV-2 mRNA vaccination in patients with inflammatory bowel disease is unknown.

Methods: We compared symptoms following a third SARS-CoV-2 mRNA vaccine dose with symptoms after the second dose in IBD.

Results: The study group included 594 patients (70% female, 58% BNT162b2). Overall, 41% reported symptoms after a third dose. Symptom frequency and severity were lower after the third dose relative to the second dose for every organ system, except for gastrointestinal symptoms which were marginally worse.

Conclusion: The frequency and severity of symptoms after a third mRNA vaccine dose are generally similar or milder than after a second dose for most organ systems.

Lay Summary

The postvaccination symptom profile in patients with IBD is unknown after a third mRNA COVID vaccine dose. In a cohort of 594 subjects with IBD, we demonstrated that 41% experienced any symptoms after a third dose, the vast majority of which were mild and lasted less than 2 days. Symptoms after third dose were less frequently reported than after the second dose.

Introduction

Vaccine safety concerns are a major contributor to vaccine hesitancy.[1] Symptoms after SARS-CoV-2 primary vaccination among patients with inflammatory bowel disease (IBD) are generally of similar frequency, severity, and duration to those reported in the general population.[2–5] In the general population, the frequency of reactions after a third dose of mRNA vaccination in the general population was similar to the second dose.[6] However, the symptom profile after a third mRNA vaccine dose in the predominantly immune-compromised IBD population is unknown. We aimed to assess symptomology after a third or booster dose of mRNA vaccination in adults with IBD.

Methods

Participants included those with IBD ages 13 and older enrolled in the prospective Coronavirus Risk Associations and Longitudinal Evaluation in IBD (CORALE-IBD) vaccine registry[7] who received a third mRNA vaccine dose. Subjects were initially recruited for enrollment at the time of initial vaccination at Cedars-Sinai Medical Center, through referrals from 26 IBD practices/clinics in the United States and through a social media campaign. Subjects were queried regarding postvaccination symptoms 1 week after each vaccine dose. Symptoms were assessed across 11 organ systems, including injection site symptoms (eg, pain, erythema, swelling); fatigue or malaise; headache, dizziness or lightheadedness; fever or chills; rheumatologic (eg, muscle, joint, or nerve) symptoms; gastrointestinal (eg, nausea, vomiting, abdominal pain, diarrhea, or other) symptoms; sleep changes; swollen lymph nodes; skin/nail or facial changes; eye, ear, mouth, or throat changes; cough, chest, or breathing symptoms; and memory or mood changes. Symptoms were graded by severity as mild, moderate, or severe impact on activities of daily living or requiring hospitalization.[2] The category of "severe+" included those with severe symptoms or hospitalization. We stratified patients by age as younger than 55 years or 55 years and older due to the known influence of age on adverse events. Categorical and continuous variables were summarized and compared across age strata (<55 and >55 years) using χ^2 and Student t test, respectively. Pairwise χ^2 (McNemar test) and t test were used when appropriate.

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Key Messages

• What is already known?
Post-mRNA-vaccination symptoms are worse after a second dose relative to after a first dose in patients with IBD.
• What is new here?
Symptoms after a third mRNA vaccine dose in patients with IBD are less frequent and generally milder than after a second dose and less frequent than symptoms reported in the general population.
• How can this study help patient care?
Patients with IBD and their providers can be reassured that postvaccination symptoms after a third mRNA vaccine dose are generally mild and less frequent than after a second dose.

We also compared the frequency and severity of symptoms after dose 3 relative to those reported after dose 2, given that symptoms after the second dose of the primary series were more frequent and severe than after the first dose (R version 3.5.1). We additionally assessed severity after each vaccine dose (none or mild, moderate, and severe+) to clarify the frequency of severe symptoms after dose 3 relative to the severity of symptoms experienced after dose 2. The study protocol was approved by the Cedars-Sinai institutional review board. All study participants provided informed consent.

Results

The cohort included 524 participants (70% female, mean age 45 years) reporting a third dose of mRNA vaccination through October 11, 2021. The majority had Crohn's disease (71%), with the remainder having ulcerative colitis or IBD-unclassified, and 89% were receiving biologic therapies. The majority of participants (58%) received primary vaccination with BNT562b2 (Pfizer), with the remainder receiving mRNA-1273 (Moderna), and only 3.5% of the overall cohort reported a previous COVID infection at the time of initial vaccination. Overall, 97% of subjects received a third dose with the same mRNA vaccine as in their initial series, with the remainder receiving the other mRNA vaccine type.

In total, 41% of patients reported symptoms after a third dose, with symptoms generally more frequent and more severe among participants younger than 55 years (Table 1). The

Table 1. Frequency and severity of postvaccination symptoms by age.

Variable	Total	Age < 55	Age>=55	*P*
	N (%)	N (%)	N (%)	
N	524(100)	387(100)	137(100)	
Age	45.3(14.44)	38.07(8.24)	65.72(6.33)	2.09E-267
Female	370(70.75)	293(75.91)	77(56.2)	7.17E-05
Crohn's disease	370(70.61)	274(70.8)	96(70.07)	0.872
White	491(93.88)	360(93.26)	131(95.62)	0.422
Primary vaccine: BNT162b2 (Pfizer/BioNtech)	306(58.4)	231(59.69)	75(54.74)	0.313
Prior COVID	18(3.45)	15(3.9)	3(2.19)	0.347
On biologic therapy at time of vaccination	467(89.12)	347(89.66)	120(87.59)	0.503
Duration between doses 2 and 3 (days, SD))	166.00(32.36)	164.19(34.11)	170.80(26.76)	0.456
Adverse Events				
Local pain	206(39.3)	167(43.15)	39(28.46)	2.49E-03
Local redness	58(11.07)	47(12.14)	11(8.03)	0.187
Local swelling	58(11.07)	49(12.66)	9(6.57)	0.051
Fever or chills	87(16.6)	72(18.6)	15(10.95)	0.038
Fatigue or malaise	176(33.59)	142(36.69)	34(24.82)	0.011
Headache	119(22.71)	97(25.06)	22(16.06)	0.031
Eye, ear, mouth or throat symptoms	11(2.1)	11(2.84)	0(0.00)	0.046
Lymph node, skin or facial symptoms	36(6.87)	31(8.01)	5(3.65)	0.083
Cough, chest or breathing symptoms	9(1.72)	7(1.81)	2(1.46)	0.787
Digestive symptoms	46(8.78)	40(10.34)	6(4.38)	0.034
Urinary or genital	0(0.00)	0(0.00)	0(0.00)	1.000
Muscle, bone or joint	66(12.6)	54(13.95)	12(8.76)	0.115
Memory or mood	7(1.34)	6(1.55)	1(0.73)	0.472
Sleep symptoms	31(5.92)	28(7.24)	3(2.19)	0.031
Overall Severity				
None	307(58.59)	213(55.04)	94(68.61)	0.026
Mild	30(5.73)	25(6.46)	5(3.65)	
Moderate	121(23.09)	93(24.03)	28(20.44)	
Severe+	66(12.6)	56(14.47)	10(7.3)	

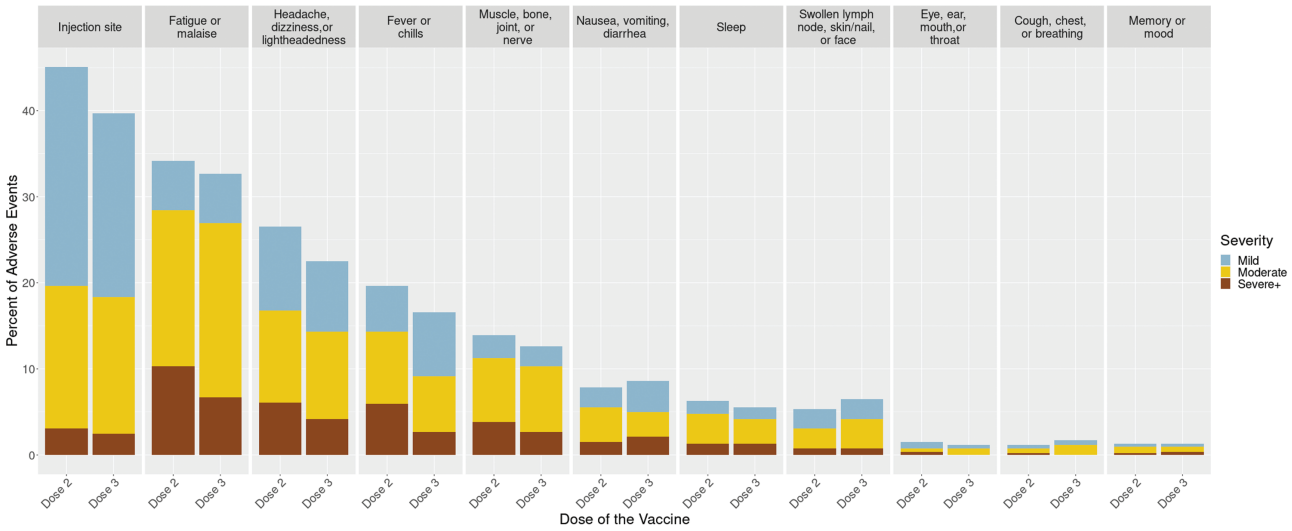

Figure 1. Severity of symptoms by system for dose 3 relative to dose 2.

most frequent postvaccination symptom was injection site pain (39%). Commonly reported systemic symptoms were fatigue or malaise (34%), headache (23%), and muscle, bone, and joint symptoms (13%). These symptoms were all less frequently reported after dose 3 than after dose 2 (Figure 1). Gastrointestinal symptoms were reported by 8.8%, which was slightly more frequent than after dose 2 (7.8%). Among those with postvaccination symptoms, the proportion with severe+ symptoms after dose 3 was lower than dose 2 for fatigue/malaise, headache, dizziness and lightheadedness, fever or chills, and rheumatologic symptoms—but was slightly higher than dose 2 for gastrointestinal symptoms (Figure 1).

We evaluated the severity of symptoms after dose 3 by the severity of symptoms after dose 2 (Supplemental Table 1). Overall, the majority (75%) experienced none or mild symptom severity for both doses. Severe+ symptoms were comparable at dose 2 and 3 (17% and 14%, respectively). Of those with severe+ symptoms after dose 2, 34% experienced severe+ symptoms after dose 3 (odds ratio [OR], 5.15; $P < .001$). In comparison, about 22% experienced severe+ symptoms after dose 3 but did not report severe+ symptoms after dose 2.

Discussion

We demonstrate several key findings with respect to symptoms after a third mRNA vaccine among patients with IBD. First, postvaccination symptom frequency and severity are significantly greater among those younger than 55 years, similar to findings after a second vaccine dose and similar to findings reported in the pivotal BNT162b2 vaccine trials.[3] Second, symptoms after dose 3 were generally less frequent and less severe for most organ systems, with the notable exception of gastrointestinal symptoms which were slightly more common and severe after dose 3 relative to dose 2. Third, the frequency of severe+ symptoms were comparable after dose 2 and dose 3. However, because about 1 in 5 experience severe+ symptoms after dose 3 even without previous severe+ symptoms, patients should consider vaccination with a third dose at a time when short-lived severe symptoms can be best tolerated and addressed. We found that the frequency of adverse events after a third mRNA vaccine dose in the IBD population was generally lower than rates reported in the general population, where approximately 75% reported a local or systemic reaction within 7 days of vaccination.[6] Our results are consistent with the lower frequencies of postvaccination reactions reported in various immune-compromising conditions.[8] Our finding that gastrointestinal symptoms after a third dose were slightly higher than after a second dose raises the question about whether these represented postvaccination reactions or coincidental exacerbation of IBD. Previous publications are reassuring that IBD disease exacerbation does not occur more frequently after COVID vaccination.[5,9]

Limitations of this study include recall bias and a lack of racial and ethnic diversity. To minimize recall bias, we sent our survey at 1 week after vaccination, similar to the period of solicitation of adverse events in the pivotal BNT162b and mRNA-1273 clinical trials.[3] However, symptoms manifesting after 1 week, such as menstrual irregularities, might therefore not have been captured. A further limitation is our female predominance of study participants which is skewed relative to the 1:1 female:male ratio in the IBD population.

Our findings can reassure the IBD patients and providers that the likelihood and distribution of symptoms after a third mRNA vaccine dose are generally similar to those after a second dose and that fewer people experienced postvaccination symptoms after dose 3 than after dose 2 for most organ systems. Postvaccination symptoms appear to occur less frequently in IBD than in the general population, although further evaluation of postvaccination gastrointestinal symptoms among those with IBD is warranted.

Supplementary Data

Supplementary data is available at *Inflammatory Bowel Diseases* online.

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Conflicts of Interest

G.Y.M. has consulted for AbbVie, Arena Pharmaceuticals, Boehringer-Ingelheim, Bristol-Myers Squibb/Celgene, Entasis, Janssen, Medtronic, Pfizer, Samsung Bioepis, Shionogi, Takeda, and Techlab and has received research funding from Pfizer for an unrelated investigator-initiated study. J.B. has received research funding from Janssen. J.C.P., J.L.S., and E.C.F. work for Abbott Diagnostics, a company that performed the serological assays on the biospecimens that were collected for this study. D.P.B.M.: Bridge Biotherapeutics, Gilead, Palatin, Pfizer, Promteheus Biosciences, Prometheus Laboratories, Takeda. M.C.: Abbvie, Arena, Bristol-Meyers Squibb, Janssen, Medtronic, Pfizer, and Takeda. E.C.: Abbvie and Pfizer. D.F.: Pfizer. C.H.: Abbvie, Janssen and Pfizer. D.L.: Abbvie, Janssen and Takeda. R.M.: Abbvie, Bristol Myers Squibb, Pfizer, and Prometheus Bioscience. N.P.: Pfizer. DW: Abbvie, Arena, Bristol Meyers Squibb, Corevitas, Janssen, Lilly, Pfizer, and Takeda. B.M.: Abbvie, Bristol Myers Squibb, Janssen, Pfizer and Takeda. S.G.: Abbvie, Janssen, and Takeda. C.H.: Abbvie, Bristol Meyers Squibb, Genentech, InbDex Pharmaceuticals, Janssen, Lilly, and Pfizer. G.S.: research funding for unrelated investigator study from Pfizer. S.T.: Prometheus Bioscience.

The remaining authors have no competing interests.

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