BRIEF REPORT

Tolerability of Coronavirus Disease 2019 Vaccines, BNT162b2 and mRNA-1273, in Patients With Thymic Epithelial Tumors

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ABSTRACT

Introduction: Defects in immunologic self-tolerance result in an increased risk for development of paraneoplastic autoimmune diseases (ADs) and immune-mediated toxicity in response to immune stimulation in individuals with thymic epithelial tumors (TETs). We conducted a survey to evaluate the tolerability of coronavirus disease 2019 (COVID-19) mRNA vaccines in patients with TETs, including individuals with preexisting AD.

Methods: After reviewing published data on adverse events associated with the BNT162b2 (Pfizer, Inc., and BioNTech) and mRNA-1273 (ModernaTX, Inc.) mRNA vaccines, we designed and administered a questionnaire to participants at the following three time points: after each dose of vaccination and 1 month after the final dose. Questions related to AD and use of immunosuppressive drugs were included. Descriptive statistics were used to analyze data, and results were compared with previously described results related to the BNT162b2 and mRNA-1273 vaccines.

Results: From February 26 to June 1, 2021, we administered the survey to 54 participants (median age = 58 y, thymoma = 33, preexisting AD = 19). Common adverse events included injection site pain, fatigue, and headaches. There were no vaccination-related hospitalizations or deaths. Autoimmune flares occurred in three patients (16%) after the first dose and three patients (17%) after the second dose. Most AD flares were mild and self-limited. One patient (2%) was diagnosed with having a new AD after vaccination.

Conclusions: Tolerability of COVID-19 mRNA vaccines in patients with TETs is comparable to the general population. Most patients with preexisting AD did not experience disease flares, and the development of new AD was rare. Patients with TETs should be encouraged to get vaccinated against COVID-19 owing to the documented benefits of vaccination and manageable risk profile.

Keywords: Thymoma; Thymic carcinoma; Autoimmunity; COVID-19; Vaccination

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Introduction

Thymomas and thymic carcinomas, collectively referred to as thymic epithelial tumors (TETs), are rare thoracic cancers with an incidence of 1.5 cases per million.[1,2]

TETs, particularly thymomas, are often associated with paraneoplastic autoimmune diseases (ADs) owing to impaired immunologic self-tolerance resulting from the persistence of autoreactive T cells.[1,3–6]

Owing to these underlying defects in immunologic tolerance, patients with TETs display increased sensitivity to immune stimulation.[2] Treatment with immune checkpoint inhibitors or cancer vaccines intended to stimulate the immune system can cause severe immune-related adverse events (AEs) in 3% to 57% of patients.[2,7,8] This reactivity raises questions on the tolerability of other forms of immune stimulation, such as vaccination against coronavirus disease 2019 (COVID-19), in patients with TETs.

At the time of study design, two mRNA vaccines had received emergency use authorization from the U.S. Food and Drug Administration for vaccination against COVID-19: BNT162b2 manufactured by Pfizer, Inc., and BioNTech and mRNA-1273 produced by ModernaTX, Inc. Phase 2 and phase 3 clinical trials have shown that both vaccines are safe and highly effective at preventing severe COVID-19 infection, hospitalization, and death.[9,10] Despite inclusion of a small number of participants with a history of AD in clinical trials evaluating the BNT162b2 vaccine, no specific safety concerns were observed after subgroup analysis by medical comorbidities.[9] Development of AD was not observed after vaccination with mRNA-1273 either, except for one case of rheumatoid arthritis after the second dose of the vaccine, which was considered not related to vaccination.[10] Taken together, these data do not indicate an increased risk of developing new AD or a flare of a previously existing AD after vaccination with the BNT162b2 or mRNA-1273 vaccine.

In view of the unique immune biology of TETs and absence of data regarding tolerability of COVID-19 vaccines in this population, we conducted this study to find the tolerability of vaccination in adults with TETs.

Materials and Methods

Individuals 18 years or older with active or previously treated thymoma or thymic carcinoma with or without paraneoplastic AD who had received vaccination against COVID-19 were invited to participate in this survey. The participants had either received care at the National Institutes of Health (NIH) Clinical Center or were in the process of screening for ongoing NIH institutional review board–approved clinical trials. Consenting patients were interviewed in person during scheduled clinic visits or by means of a phone call.

The study questionnaire was designed on the basis of solicited local and systemic AEs reported within seven days of BNT162b2 and mRNA-1273 vaccination in participants aged 18 years and older (details in Supplementary Appendix). All efforts were made to conduct interviews within 1 week after each dose of the vaccine and within 1 month after the second dose to correspond to the BNT162b2 and mRNA-1273 data collection time points. Information was collected on TET histology, patient age, presence or absence of thymoma-related AD, and use of concomitant medications, including immunosuppressive drugs. Data were deidentified and secured per institutional guidelines. The study was reviewed by the NIH institutional review board and determined to meet the criteria for category 2 of exempt human subject research.

Statistical Analysis

Statistical analysis was conducted using descriptive statistics. A two-sided Fisher's exact test was used for appropriate paired comparison to evaluate differences in tolerability of BNT162b2 and mRNA-1273 vaccines in patients with TETs and individuals without TETs as reported from published vaccine clinical trial results. The frequency and relative risk of developing AEs were calculated for each group. Because this is an initial effort to evaluate the tolerability of COVID-19 mRNA vaccines in patients with TETs, power calculations were not performed for a study of this nature. Nevertheless, with a minimum of 50 participants, the study was expected to provide indications on differences in tolerability of vaccination among individuals with and without TETs.

Results

Between February 26, 2021, and June 1, 2021, responses were collected from 54 individuals. As of data cutoff on June 1, 2021, a total of 50 individuals had completed all three questionnaires, 52 had completed two questionnaires, and 54 had completed one questionnaire. Baseline characteristics are included in Table 1. Of the 54 patients, 33 (61.1%) had thymoma and 20 (37.0%) had thymic carcinoma. Furthermore, 19 (35.2%) had preexisting AD, and 12 patients (22.2%) were using immunosuppressive drugs. All patients were vaccinated against COVID-19 with either the BNT162b2 or mRNA-1273 vaccine.

AEs experienced by patients with TETs and reported in the participants of the BNT162b2 and mRNA-1273 clinical trials stratified by dose number and vaccine type are illustrated in Table 2 and Figure 1. AEs

Table 1. Patient Characteristics

Characteristics	n[a] (%)
Age, median (range, y)	58 (32-81)
Sex	
Female	26 (48.1)
Male	28 (51.9)
Histology (WHO subtype)	
B1 thymoma	2 (3.7)
B2 thymoma	21 (38.9)
B2/3 thymoma	3 (5.6)
B3 thymoma	7 (13.0)
Thymic carcinoma	20 (37.0)
Unknown	1 (1.9)
Vaccine	
BNT162b2	25 (46.3)
mRNA-1273	29 (53.7)
Paraneoplastic autoimmune disease[b]	19 (35.2)
Immunosuppressant use[c]	12 (22.2)
Corticosteroids	2 (3.7)
Noncorticosteroids[d]	4 (7.4)
Both types	7 (13.0)
NSAID/acetaminophen routine use	11 (20.4)
NSAID/acetaminophen prophylactic use[e]	3 (5.6)

[a]Includes individuals who received at least one dose of the vaccine and completed the questionnaire at the first time point.
[b]Paraneoplastic autoimmune diseases include eight participants with myasthenia gravis, five with inflammatory arthritis, two with myositis, two with Sjogren's syndrome, two with systemic lupus erythematosus, and one each with Isaac syndrome, Hashimoto disease, lichen planus, minimal change nephrotic syndrome, pure red cell aplasia, and ulcerative colitis.
[c]Two patients were taking immunosuppressive agents at the time of dose 1, but not when they received dose 2. In one case, a patient was on a taper of prednisone and mycophenolate, which stopped around the time of dose 1. In the second case, a patient received dexamethasone on the day of vaccination as premedication for chemotherapy; this did not occur again during dose 2.
[d]Nonsteroidal immunosuppressant drugs include intravenous immunoglobulin, rituximab, mycophenolate mofetil, methotrexate, and azathioprine.
[e]Two of three patients who took an NSAID or acetaminophen prophylactically did so only before dose 1.
NSAID, nonsteroidal anti-inflammatory drug.

experienced by greater than 10% of patients with TETs are described in the Supplementary Appendix. Patients with TETs were significantly more likely to experience local redness (20.7%; $p = 0.03$) after the second dose of the mRNA-1273 vaccine, whereas the incidence of myalgia was significantly less after the second dose of the BNT162b2 (8.7%; $p = 0.01$) and mRNA-1273 vaccines (24.1%; $p = 0.0005$) (Table 2 and Fig. 1).

Of the 19 patients with a previously diagnosed AD, all completed the first questionnaire and 18 completed the second. Of these patients, three experienced symptomatic flares after dose 1 and three experienced flares after dose 2 (Supplementary Table 1). Patients who experienced an autoimmune flare after the first dose had been diagnosed with having myasthenia gravis (MG), MG and polymyositis, and Isaac syndrome, MG, systemic lupus erythematosus, and arthritis, respectively. These autoimmune flares were mild and self-limited, with the exception of the last patient, who experienced intermittent burning of hands and feet, difficulty in swallowing, fasciculations, and a rash that was treated with a topical steroid. This patient experienced similar symptoms after receiving the second dose of vaccination. Other patients who experienced mild and self-limited flares after the second dose included an individual with MG and another with inflammatory arthritis.

Two patients were diagnosed with having new AD after receiving the first dose of the mRNA-1273 vaccine: one patient with autoimmune alopecia who had been symptomatic for several months but had sought medical attention after vaccination and another patient with chronic idiopathic urticaria presenting as a full-body rash that responded temporarily to oral corticosteroids but recurred after discontinuation of steroids and has not resolved at the time of data cutoff.

Discussion

To our knowledge, this survey represents the first attempt to systematically evaluate the tolerability of COVID-19 vaccines in patients with TETs. Our results indicate that most patients with TETs tolerate the mRNA vaccines, BNT162b2 and mRNA-1273, without complications. Common AEs such as local pain and swelling, fatigue, and headaches are self-limited and manageable. The use of immunosuppressive drugs to treat AD or nonsteroidal anti-inflammatory drugs and acetaminophen to manage pain could abrogate constitutional symptoms, such as headaches, myalgia, and arthralgia. Nevertheless, the use of these concomitant medications was comparable between patients with TET who did and did not experience these AEs. Of note, patients with TETs were significantly less likely to experience myalgia after the second dose of both BNT162b2 ($p = 0.01$) and mRNA-1273 ($p = 0.0005$) vaccines. This observation is of particular interest because patients with TETs, especially thymoma, are at increased risk of muscle inflammation when exposed to immune stimulation, such as with immune checkpoint inhibitors.[11,12] Notwithstanding the decreased incidence of myalgia, it is advisable to initiate workup for myositis if patients with TETs experience persistent or severe myalgia after receiving the BNT162b2 and mRNA-1273 vaccines.

Despite underlying defects in immune tolerance and a predisposition to paraneoplastic autoimmunity, very few patients with TETs developed new AD after vaccination and most of those with preexisting AD did not experience a disease flare, even though a large fraction of patients (61%) had WHO subtype B thymomas, the histologic subtype most associated with paraneoplastic

Table 2. Adverse Events After Vaccination in Patients With TETs and Published Results From Phase 2 and Phase 3 Clinical Trials Evaluating the BNT162b2 and mRNA-1273 Vaccines

BNT162b2	Dose 1				Dose 2			
Symptoms	TET AE, n (%)	Trial AE, n (%)	Relative Risk (95% CI)	*p* Value	TET AE, n (%)	Trial AE, n (%)	Relative Risk	*p* Value
Local pain	16 (64.00)	3186 (77.84)	0.82 (0.61-1.10)	0.14	13 (56.52)	2730 (72.65)	0.78 (0.54-1.11)	0.10
Local redness	1 (4.00)	189 (4.62)	0.87 (0.13-5.94)	1.00	1 (4.35)	243 (6.47)	0.67 (0.10-4.59)	1.00
Local swelling	2 (8.00)	250 (6.11)	1.31 (0.34-4.98)	0.66	3 (13.04)	256 (6.81)	1.91 (0.66-5.54)	0.21
Fatigue	7 (28.00)	1700 (41.53)	0.67 (0.36-1.27)	0.22	15 (65.22)	2086 (55.51)	1.17 (0.87-1.59)	0.40
Headache	4 (16.00)	1413 (34.52)	0.46 (0.19-1.14)	0.06	6 (26.09)	1732 (46.09)	0.57 (0.28-1.13)	0.06
Myalgia	1 (4.00)	738 (18.03)	0.22 (0.03-1.52)	0.07	2 (8.70)	1260 (33.53)	0.26 (0.07-0.98)	0.01
Arthralgia	2 (8.00)	406 (9.92)	0.81 (0.21-3.06)	1.00	2 (8.70)	772 (20.54)	0.42 (0.11-1.59)	0.20
Chills	2 (8.00)	434 (10.60)	0.75 (0.20-2.86)	1.00	3 (13.04)	1114 (29.64)	0.44 (0.15-1.27)	0.11
Fever	1 (4.00)	111 (2.71)	1.48 (0.21-10.2)	0.50	4 (17.39)	512 (13.62)	1.28 (0.52-3.12)	0.54
Vomiting	0	37 (0.90)	—	1.00	0	51 (1.36)	—	1.00
Diarrhea	0	402 (9.82)	—	0.17	1 (4.35)	356 (9.47)	0.46 (0.07-3.13)	0.72
mRNA-1273	**Dose 1**				**Dose 2**			
Symptoms	TET AE, n (%)	Trial AE, n (%)	Relative Risk (95% CI)	*p* Value	TET AE, n (%)	Trial AE, n (%)	Relative Risk (95% CI)	*p* Value
Local pain	26 (89.66)	12,690 (83.69)	1.07 (0.95-1.21)	0.61	25 (86.21)	12,325 (88.39)	0.98 (0.84-1.13)	0.77
Local redness	1 (3.45)	431 (2.84)	1.21 (0.18-8.34)	0.57	6 (20.69)	1193 (8.56)	2.42 (1.18-4.94)	0.03
Local swelling	3 (10.34)	934 (6.16)	1.68 (0.57-4.91)	0.42	5 (17.24)	1695 (12.16)	1.42 (0.64-3.15)	0.39
Axillary swelling	0	1553 (10.24)	—	0.07	1 (3.45)	1956 (14.03)	0.24 (0.04-1.69)	0.11
Fatigue	6 (20.69)	5635 (37.17)	0.56 (0.27-1.14)	0.08	17 (58.62)	9096 (65.23)	0.90 (0.66-1.22)	0.44
Headache	6 (20.69)	4952 (32.66)	0.63 (0.31-1.29)	0.23	5 (17.24)	8165 (58.56)	0.29 (0.13-0.65)	<0.0001
Myalgia	3 (10.34)	3441 (22.70)	0.46 (0.16-1.33)	0.12	7 (24.14)	8036 (57.63)	0.42 (0.22-0.80)	0.0005
Arthralgia	2 (6.90)	2510 (16.55)	0.42 (0.11-1.59)	0.21	5 (17.24)	5937 (42.58)	0.40 (0.18-0.90)	0.0073
Chills	2 (6.90)	1253 (8.26)	0.83 (0.22-3.18)	1.00	7 (24.14)	6100 (43.75)	0.55 (0.29-1.05)	0.04
Fever	0	115 (0.76)	—	1.00	4 (13.79)	2172 (15.58)	0.89 (0.36-2.20)	1.00
Nausea/ vomiting	0	1263 (8.33)	—	0.17	6 (20.69)	2634 (18.89)	1.10 (0.54-2.24)	0.81

AE, adverse event; CI, confidence interval; TET, thymic epithelial tumor; TET AE, AEs observed in patients with TETs; Trial AE, AEs reported in clinical trials evaluating the BNT162b2 and mRNA-1273 vaccines.

AD and immune-mediated toxicity on immune stimulation.[4,11,12] The episodes that did occur were generally self-limited and did not require medical intervention. Nevertheless, given the potential risk for AD flare or development, patient education and close monitoring are highly recommended after vaccination in this population.

Limitations of this study include a small sample size owing to the rarity of TETs and self-reporting by participants, which can potentially add an element of subjectivity in assessment. Despite these limitations, we feel that the results of this study are clinically meaningful and provide guidance to patients with TETs considering vaccination against COVID-19.

Physician awareness of the tolerability of vaccination against COVID-19 among patients with TET and the relatively low frequency of autoimmune flares, most of which are mild and self-limited, are keys to promoting vaccination within this population. Two surveys conducted among individuals with AD regarding vaccination against COVID-19 found that the percentage of those willing to get vaccinated ranged from 54% to 61%.[13,14] Key concerns among these patients regarding vaccination were the potential for inducing an autoimmune flare or experiencing other AEs. Notably, both surveys found that recommendations from their physicians regarding vaccination increased the percentage of patients willing to get vaccinated. This observation is particularly relevant to physicians treating patients with TETs to allay patient concerns.

The need for an additional (booster) dose of COVID-19 vaccines to maintain immunogenicity is under review. The U.S. Centers for Disease Control and Prevention has recently recommended an additional dose of an mRNA COVID-19 vaccine for individuals with moderately to severely compromised immune systems, including patients on active or recent treatment for solid tumor and hematological malignancies, at least 28

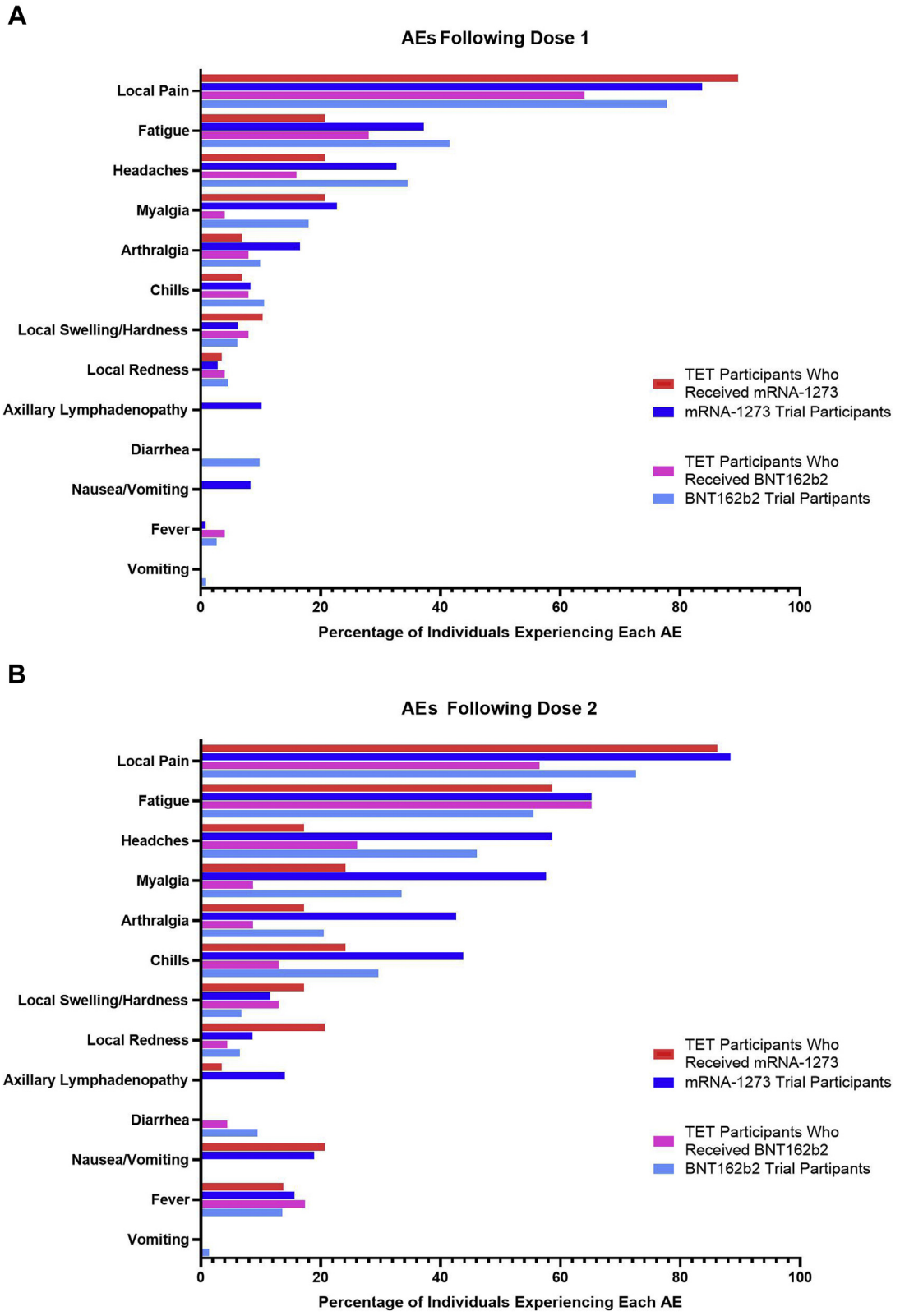

Figure 1. AEs after administration of BNT162b2 and mRNA-1273 vaccines in patients with TETs. The frequency of selected AEs observed in patients with TETs is compared with the frequency of solicited AEs reported from phase 2 and phase 3 trials evaluating the BNT162b2[9] and mRNA-1273[10] vaccines after (*A*) dose 1 and (*B*) dose 2. AE, adverse event; TET, thymic epithelial tumor.

days after a second dose of the BNT162b2 or mRNA-1273 vaccine.[15] Previous observations of high rates of mortality among patients with cancer hospitalized with COVID-19 and lower antibody titers in patients with cancer after two doses of BNT162b2 vaccination support the recommendation for a booster dose to achieve adequate protection.[16,17] Studies of a booster dose of the BNT162b2 or mRNA-1273 vaccine in solid-organ transplant recipients have revealed them to be safe and result in substantially improved immunogenicity.[18,19] In view of these data, and the ability of most patients with TETs to tolerate two doses of COVID-19 mRNA vaccines without complications, a booster dose should be considered to improve immunogenicity, especially in individuals receiving myelosuppressive chemotherapy or other immunosuppressive medicines.

In conclusion, patients with TETs seem to tolerate vaccination against COVID-19 with the mRNA vaccines, BNT162b2 and mRNA-1273, and those without TETs. AEs, including flares of preexisting AD, are usually mild and self-limited, and the likelihood of inducing paraneoplastic autoimmunity is low. Given the risks associated with severe COVID-19 infection and the tolerability of vaccination, the overall benefit seems to outweigh risks, and patients with TETs should be encouraged to undergo vaccination after discussion with their physicians. Close monitoring for new or worsening AD is essential. Further research in patients with TETs experiencing autoimmune flares can potentially yield insights into the immune changes induced by vaccination in these individuals.

CRediT Authorship Contribution Statement

Madison Ballman: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing - original draft, Writing - review & editing.

Shannon Swift, Cristina Mullenix, Yvonne Mallory: Methodology, Investigation, Data curation, Writing - review & editing.

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Susan Sansone, Meredith J. McAdams: Writing - review & editing.

Seth M. Steinberg: Methodology, Formal analysis, Software, Resources, Writing - review & editing.

Arun Rajan: Conceptualization, Methodology, Visualization, Formal analysis, Project administration, Resources, Supervision, Writing - review & editing.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2021.100229.

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