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BRIEF REPORT

Safety of the Zoster Vaccine Recombinant Adjuvanted in Rheumatoid Arthritis and Other Systemic Rheumatic Disease Patients: A Single Center's Experience With 400 Patients

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Objective. Patients with rheumatoid arthritis (RA) and other systemic rheumatic diseases (SRDs) are at increased risk of developing herpes zoster (HZ). Zoster recombinant adjuvanted (ZRA) is a recombinant vaccine approved by the Food and Drug Administration in 2018. Concern has been raised that the ZRA may trigger disease flares in rheumatology patients who are immunocompromised. We investigated the impact of the ZRA vaccine in patients with RA and SRD and measured the incidence of flares and side effects.

Methods. A flare was defined as occurring within 12 weeks of vaccine administration by either 1) documentation of RA flare in office notes, telephone encounter, or patient portal communication or 2) new or increased dose of corticosteroids.

Results. We identified 403 patients (239 patients with RA and 164 patients with SRD) who received the ZRA vaccine from February 1, 2018, to February 1, 2019. We measured a 6.7% (n = 27) incidence of flare. Side effects occurred in 12.7% (n = 51) of patients. All flares and side effects were regarded as mild. Three cases of HZ were reported as occurring 2, 10, and 11 months after the vaccination.

Conclusion. In 403 patients who received the ZRA vaccine, the incidence of disease flares was 7% or less and that of side effects was 13% or less, both of which are less than the incidence rates observed in the pivotal trials.

INTRODUCTION

With an estimated one-million new cases of shingles within the United States annually, herpes zoster (HZ) is a prominent public health concern for patients taking immunosuppressive therapies 1,2. Vaccination preventing HZ is now recommended by the US Center for Disease Control for adults over the age of 50 2.

Immunosuppressant medications used to treat rheumatoid arthritis (RA) and other systemic rheumatic diseases (SRDs) (corticosteroids, methotrexate, biologic disease-modifying agents, and janus kinase inhibitors) can increase the incidence of HZ 3,4. The dermatomal rash seen in HZ may be more prolonged and severe in patients with RA or other SRDs 5,6. The risk of more severe neurologic complications, including myelitis, chronic encephalitis, meningoencephalitis, and cranial palsies, is heightened in this population 7. Furthermore, cutaneous dissemination is seen commonly in patients who are immunosuppressed 8.

A live attenuated vaccine was approved by the Food and Drug Administration (FDA) for HZ prevention in 2006 for adults age 60 or older 2. Although the efficacy of the vaccine differed throughout age groups, the overall efficacy was 51% and could not be given concomitantly in patients taking some background

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SIGNIFICANCE & INNOVATIONS

- This manuscript is the first to report on the experience with the zoster recombinant adjuvanted (ZRA) vaccine in patients with systemic rheumatic diseases, especially rheumatoid arthritis (RA), and examines the rate of disease flares, vaccination reactions, and occurrence of zoster.
- Pivotal trials of ZRA excluded patients who were known to be immunocompromised; this study supports the use of this vaccine among rheumatology patients exposed to immunosuppressive medications.
- Our findings of a disease flare rate of less than 7% and of side effects in less than 13% of immunocompromised rheumatology patients informs clinical decision-making in the real world; these rates are low, considering a 30% background incidence of RA disease flare observed in our RA registry at Brigham and Women's Hospital over a 6-month period.

immunosuppressive therapies, such as high dose corticosteroids 9. Approved by the FDA in 2018, the zoster recombinant adjuvanted (ZRA) vaccine is a novel recombinant vaccine that is more effective than the earlier vaccine. In clinical trials in patients older than 60 years of age, the vaccine was more than 90% effective 10. Patients known to be immunosuppressed were excluded in the original trials. Because of the potency of the adjuvant, there has been question as to whether the vaccine could induce a clinical flare of underlying rheumatic disease.

We evaluated the incidence of disease flares and side effects of the ZRA in patients with RA and other SRDs.

PATIENTS AND METHODS

Setting. This study took place in the rheumatology outpatient center at Brigham and Women's Hospital, a large tertiary-care academic medical center. ZRA was prescribed to patients with RA and other SRDs.

Methods. We performed a retrospective chart review of all patients with RA and SRD who received at least one dose of ZRA from February 1, 2018 to February 1, 2019. ZRA is a two-dose series, with doses given two to six months apart. All patients were followed after their immunization for a minimum of three months or until a flare occurred. Patients enrolled earlier in the study period were followed through the duration of the study period. Documentation of flares and side effects occurring up to 12 weeks after each dose was abstracted from chart reviews (Figure 1). A flare was defined as occurring within 12 weeks of the ZRA administration by either 1) documentation of an RA or SRD flare in the rheumatologist's office notes, telephone encounter, or patient portal communication, or 2) a new corticosteroid prescription or an increase in the dose of a preexisting corticosteroid prescription. All potential flares were independently reviewed by three rheumatologists (EM, MEW, and SD), and discrepancies were resolved through discussion until consensus was reached.

Side effects were defined as muscle soreness at the injection site, redness, mild swelling, fatigue, fevers, myalgias, headaches, nausea, and abdominal pain. These were abstracted through chart review of the rheumatologist's office notes, telephone encounters, patient portal communications, or phone calls with the rheumatology nurse (FG). Given the lack of experience with ZRA in rheumatology patients, the first 110 rheumatology patients who were administered the vaccine were contacted by the rheumatology nurse (FG) 1 week after vaccination to specifically inquire as to the occurrence of disease flare and side effects.

An outbreak of HZ was defined as 1) documentation of HZ in the electronic medical record, including visits to the emergency department, office notes, telephone encounters, patient portal communications, or 2) a prescription for antiviral therapy (ie, valacyclovir). All possible HZ outbreaks were identified through chart review and validated by a rheumatologist (SD) to ensure that only true HZ outbreaks were reported.

RESULTS

A total of 403 patients with RA or another SRD received the new ZRA vaccine between February 1, 2018, and February 1, 2019 (Table 1). The mean age of patients was 67.2 years, 302 (75.0%) patients were women, and 345 (85.6%) patients identified as white. At baseline, 316 (78.4%) patients were treated with immunosuppressive medications: 143 (35.5%) patients were taking methotrexate (median disease duration was 20 mg/week; interquartile range [IQR] 15-25 mg/wk), 106 (26.3%) patients were taking prednisone (median dose of 5 mg/d; IQR 4-8 mg/d), 52 (12.9%) patients were taking tofacitinib, 105 (26.1%) patients were taking tumor necrosis factor inhibitors, 49 (12.2%) patients were taking other biologic response modifiers, and 49 (12.2%) patients were taking other immunosuppressants. Some patients (n = 150

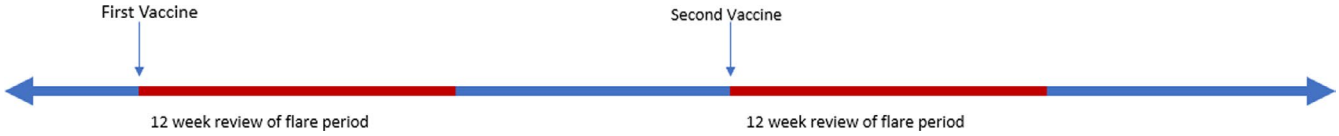

Figure 1. Depicts the study design timeline. The first dose of vaccine was administered and the second dose of vaccine, if given, was administered two to six months following the first dose. Flares were ascertained in the twelve weeks following the first dose of the vaccine and in the twelve weeks following the second dose of the vaccine.

Table 1. Baseline characteristics of 403 study subjects at a single center investigation of the safety of the zoster vaccine recombinant

Baseline Patient Characteristics	Results
Age, mean (SD), y	67.3 (10.6)
Females, n (%)	302 (74.9)
White, n (%)	345 (85.6)
Received second vaccine, n (%)	222 (55.1)
Time between first and second vaccine, mean (SD), wk	18.3 (8.5)
Patients with RA, n (%)	239 (59.3)
Patients with SRD,a n (%)	164 (40.7)
Medications	
On any immunosuppressant medication, n (%)	316 (78.4)
MTX, n (%)	143 (35.5)
Mean MTX dose, mg/wk	17.1
MTX dose, median (IQR), mg/wk	20 (15-25)
Prednisone, n (%)	106 (26.3)
Mean prednisone dose, mg/d	4.7
Prednisone dose, median (IQR), mg/d	5 (4–8)
Tofacitinib, n (%)	52 (12.9)
TNF inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab), n (%)	105 (26.1)
Other biologic therapy (abatacept, belimumab, tocilizumab, rituximab, sarilumab), n (%)	49 (12.2)
Other immunosuppressants (azathioprine, cyclophosphamide, mycophenolic acid, leflunomide), n (%)	49 (12.2)

Abbreviation: GCA, Giant-cell arteritis; IQR, interquartile range; MTX, methotrexate; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SRD, systemic rheumatic disease; TNF, tumor necrosis factor.
aSRDs include psoriatic arthritis (n = 28), SLE (n = 16), spondylitis (n = 12), Sjogren syndrome (n = 12), GCA (n = 8), and other diseases (n = 88).

[37.2%]) reported taking multiple immunosuppressive medications. Immunosuppressants were not held prior to or after vaccination. More than half of patients (n = 222 [55.1%]) received the second vaccine within the study window. The length of time between doses ranged from 7 to 45 weeks, with an average of 18 weeks. Mean follow-up with a rheumatologic care provider was 13.2 weeks after vaccination, ranging from 1 to 50 weeks. Additional patient characteristics are shown in Table 1.

Flares were identified in 27 (6.7%) individual patients (an incidence rate of 6.7 cases per 100 patient-years), with 23 (5.7%) flares occurring after the first dose and 5 (2.3%) flares occurring after the second. One patient experienced a flare following both doses. Nineteen (5.0%) flares were identified in patients with RA, and nine (3.6%) flares were identified in patients with an SRD. The incidence rate of flares in patients with systemic lupus erythematosus was 7.1% versus 8.0% ($P < 0.05$) in patients with RA. Three (2.7%) flares were identified in the first 110 patients called by the rheumatology nurse, compared with 25 (5.3%) flares found through chart review or prednisone prescription. Flares were commonly treated with a prednisone taper. All flares were mild and self-limited, responded to treatment with glucocorticoids, and did not warrant a change in immunosuppressive therapy. Additional characteristics of disease flares are shown in Table 2.

Side effects were noted in 51 (12.7%) patients: 43 (10.7%) patients after the first dose and 12 (5.4%) patients after the second. Four patients experienced side effects following both doses. The most common side effects were soreness at the injection site, rash, fever, stomach ache, nausea, and flu-like symptoms. All side effects were regarded as mild, reported in previous studies, and not unexpected.

Three cases of HZ were reported. One patient had RA and was taking tofacitinib and methotrexate, a second patient with RA was taking tofacitinib alone, and a third patient with lupus was taking mycophenolate mofetil and belimumab. All cases were self-limited, occurred in a single dermatome, and were successfully treated with antiviral therapy (Table 3).

DISCUSSION

In our experience of 403 rheumatology patients (239 patients with RA and 164 patients with an SRD) who received the ZRA vaccine, the incidence of flares among all patients was less than 7%. The observed flare rate of 5.0% in patients with RA over 12 weeks is lower than the 30% background incidence of RA disease flare observed in our RA registry at Brigham and Women's Hospital over a 6-month period 11.

The incidence of side effects was 13% or less, and these were similar to those reported in the nonimmunosuppressed patients studied in the pivotal trials of ZRA 10. In two large randomized double-blind, placebo-controlled studies of nonimmunosuppressed patients, the rates of side effects were age dependent. Side effects were reported more frequently among younger patients 9. In the clinical trials of ZRA, the most common side effects included pain, ranging from 68.7% to 79.1%; myalgia, ranging from 31.2% to 46.3%; and fatigue, ranging from 32.9% to 45.9% 10. The lower-than-expected incidence of side effects in our population may be related to the effects of the concomitant immunosuppressive therapy 12. Because of the national shortage of ZRA in the United States during the study period, just over half of the patients (222 [55.1%]) received the second vaccine, and not all patients received the vaccine within the recommended 2- to 6-month time frame. A similar study researching ZRA in inflammatory bowel disease found that there was a low (1.5%) flare rate after ZRA administration 15.

Table 2. Flare rate of 403 study subjects at a single-center investigation of the safety of the zoster vaccine recombinant

Patients Who Experienced Flares	Flare Rate
After first dose, n (%)	23 (5.7)
After second dose, n (%)	5 (2.3)
After both, n (%)	1 (0.2)
Patients with RA, n (%)	19 (5.0)
Patients with SRD, n (%)	9 (3.6)
First 110 patients called by nurse, n (%)	3 (2.7)

Abbreviation: RA, rheumatoid arthritis; SRD, systemic rheumatic disease.

Table 3. Description of three herpes zoster cases

Patient	Age, y	Dx	Medications Prescribed	Length of Time Between Vaccine and Herpes Zoster Infection, mo	Doses Received
A	42	SLE	Mycophenolate mofetil and belimumab	2	1
B	79	RA	Tofacitinib and methotrexate	11	2
C	54	RA	Tofacitinib	10	2

Abbreviation: Dx, diagnosis; RA, rheumatoid arthritis; SLE, systemic lupus erythematous.

In clinical trials of ZRA, the clinical efficacy was defined as a reduced incidence in the occurrence of zoster in more than 90% of people. The incidence rate of HZ in our population was 0.7%, which is not higher than that observed in the clinical studies 10,13. Three (0.7%) cases of HZ were reported, and these occurred 2, 10, and 11 months following vaccine administration. One patient was taking mycophenolate mofetil, and two of the patients were taking tofacitinib, which has been associated with an increased risk of zoster (Table 3) 13. Both tofacitinib and tocilizumab have been shown be associated with an increased incidence of HZ 14. In a study comprised of 2500 subjects initiating tofacitinib compared with 67 200 subjects initiating other biologics, the rate of HZ was twice as high in patients taking tofacitinib than in patients taking other biologic medicines 13.

This study's strengths include the continuity of rheumatology care at a single center and the large number of patients reported. Limitations include the retrospective study design, possible underreporting of flare rate and side effects in the electronic medical record, and lack of a control group. Cases of HZ in patients seen outside of our health care network may not have been fully captured in the retrospective electronic medical record review. We also did not evaluate the immune response to the vaccine following administration. Previous studies report that immunosuppressive therapies commonly used to treat patients with RA and SRD may reduce the vaccine response 12. Further studies are needed to examine the effectiveness and durability of the HZ vaccine in rheumatology patients who are immunocompromised.

In 403 rheumatology patients who received the new ZRA vaccine, the incidence of disease flares was 7% or less and the incidence of side effects was 13% or less. Both flares and side effects were mild and self-limited, and did not require a change in disease-modifying antirheumatic drug therapy. Three cases of HZ were reported. Larger studies of patients vaccinated with ZRA are required to confirm this observation in addition to confirming its efficacy and safety in this population. Based on our results, we encourage the use of the ZRA vaccine in patients with RA and other SRDs treated with immunosuppressive therapies.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Ms. Stevens had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Stevens, Weinblatt, Massarotti, Griffin, Emani, Desai.

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