ORIGINAL RESEARCH

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The Safety and Immunologic Effectiveness of the Live Varicella-Zoster Vaccine in Patients Receiving Tumor Necrosis Factor Inhibitor Therapy

A Randomized Controlled Trial

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Background: The safety and effectiveness of live virus vaccines, such as the varicella-zoster vaccine, are unknown in patients with inflammatory diseases receiving immunomodulatory therapy such as tumor necrosis factor inhibitors (TNFis).

Objective: To evaluate the safety and immunogenicity of the live attenuated zoster vaccine (ZVL) in patients receiving TNFis.

Design: Randomized, blinded, placebo-controlled trial. (ClinicalTrials.gov: NCT02538341)

Setting: Academic and community-based rheumatology, gastroenterology, and dermatology practices.

Patients: Adults aged 50 years or older receiving TNFis for any indication.

Intervention: Random assignment to ZVL versus placebo.

Measurements: Glycoprotein enzyme-linked immunosorbent assay (gpELISA) and enzyme-linked immunosorbent spot (ELISpot) from serum and peripheral blood mononuclear cells measured at baseline and 6 weeks after vaccination. Suspected varicella infection or herpes zoster was clinically assessed using digital photographs and polymerase chain reaction on vesicular fluid.

Results: Between March 2015 and December 2018, 617 participants were randomly assigned in a 1:1 ratio to receive ZVL (n = 310) or placebo (n = 307) at 33 centers. Mean age was 62.7 years (SD, 7.5); 66.1% of participants were female, 90% were White, 8.2% were Black, and 5.9% were Hispanic. The most common TNFi indications were rheumatoid arthritis (57.6%) and psoriatic arthritis (24.1%); TNFi medications were adalimumab (32.7%), infliximab (31.3%), etanercept (21.2%), golimumab (9.1%), and certolizumab (5.7%). Concomitant therapies included methotrexate (48.0%) and oral glucocorticoids (10.5%). Through week 6, no cases of confirmed varicella infection were found; cumulative incidence of varicella infection or shingles was 0.0% (95% CI, 0.0% to 1.2%). At 6 weeks, compared with baseline, the mean increases in geometric mean fold rise as measured by gpELISA and ELISpot were 1.33 percentage points (CI, 1.17 to 1.51 percentage points) and 1.39 percentage points (CI, 1.07 to 1.82 percentage points), respectively.

Limitation: Potentially limited generalizability to patients receiving other types of immunomodulators.

Conclusion: This trial informs safety concerns related to use of live virus vaccines in patients receiving biologics.

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Prescribing indications for biologics, as well as public health authorities such as the U.S. Centers for Disease Control and Prevention, recommend that patients receiving immunosuppressive treatments for autoimmune or inflammatory conditions avoid live virus vaccines (1), which carry a theoretical risk for primary infection in immunocompromised patients. Instead, these patients have been encouraged to receive inactivated or killed vaccines. However, not all vaccines are available in killed or inactivated formulations; at the start of this trial, only a live attenuated zoster vaccine (ZVL) was available to prevent herpes zoster (HZ) reactivation, also known as shingles. Other live attenuated vaccines include those for measles, mumps, and rubella; yellow fever; rotavirus; and primary varicella in children.

See also:

Web-Only
Supplement

The predilection of HZ to affect elderly and immunosuppressed persons makes it an important cause of illness, resulting in pain, depression, and long-term disability in the form of postherpetic neuralgia, encephalitis, ophthalmologic disease with permanent vision loss, and neurologic manifestations, including Ramsay Hunt syndrome (2). Furthermore, the ability of HZ to cause disseminated complications and death in immunosuppressed persons is well documented (3–5).

Targeted biologic therapies that inhibit tumor necrosis factor (TNF) are increasingly used in the United States and

worldwide but may result in immunosuppression. To treat a broad range of chronic autoimmune and inflammatory diseases, including rheumatoid arthritis, psoriasis and psoriatic arthritis, spondyloarthritis, and inflammatory bowel disease (Crohn disease and ulcerative colitis), TNF inhibitors (TNFis) are indicated. Compared with the general population, patients with these conditions are at higher risk for varicella-zoster virus (VZV) reactivation (shingles) (4) due to their underlying disease states and commonly used immunosuppressive treatments, such as glucocorticoids (3–5); thus, prevention of HZ in these populations is a high priority. Despite the demonstrated efficacy and safety of ZVL in healthy adults aged 50 years or older, no prospective data have examined the safety or the immunologic effectiveness of ZVL in patients receiving TNFis. Moreover, in the United States, uptake of ZVL in these patients has been minimal (6), likely due to the safety concerns described earlier, as well as specialty guidelines from the American College of Rheumatology, the European League Against Rheumatism, and other international groups that recommend avoidance of live virus vaccines in patients receiving biologics (7, 8).

To address this evidence gap, and in light of observational studies suggesting that ZVL might be safe and effective in TNFi-treated patients (6), we conducted a large, pragmatic, randomized, controlled trial to evaluate the safety and immunologic effectiveness of ZVL in patients aged 50 years or older receiving TNFis.

METHODS

Study Design

The VaricElla zosteR VaccinE (VERVE) trial is a 2-group, randomized, blinded, placebo-controlled, multicenter, pragmatic trial of ZVL compared with placebo. Participants were randomly assigned in a 1:1 ratio to ZVL or placebo. All participants were followed in a blinded manner until month 6, when clinical sites and participants were unblinded. Participants randomly assigned to the active ZVL group were followed in an unblinded manner until year 1.

Participants

In keeping with the design of a large pragmatic trial intended to yield highly generalizable results, participants were required to be aged 50 years or older and to be receiving any TNFi (adalimumab, certolizumab, etanercept, golimumab, or infliximab) at least 30 days before and at the time of randomization. No specific disease indications were required for eligibility. The intent of the study was to enroll patients with stable therapy regimens, not new initiators. Patients with active cancer requiring treatment were prohibited from participating, as were patients with any additional known immunosuppressive condition (for example, HIV or organ transplantation). Premenopausal women (within 1 year of the most recent menstrual period), those who had received ZVL previously, or those receiving antiviral therapy (for example, acyclovir for herpes simplex) were also excluded.

Because of safety concerns, the U.S. Food and Drug Administration requested that the first 100 randomly assigned participants have a positive test result for VZV IgG and be prohibited from taking concurrent systemic glucocorticoids within 30 days before vaccination. After the first 100 randomizations, the requirement was removed if participants had a self-reported history of varicella infection (for example, chickenpox) or long-term residence in the continental United States (>30 years). Low-dose glucocorticoids were also permitted (prednisone or equivalent, ≤10 mg/d). All patients provided written or electronic informed consent.

Randomization and Study Procedures

The trial began in March 2015 and enrolled patients through December 2018 in 33 community and major research centers in the United States (**Appendix Figure**, available at Annals.org) under the oversight of a National Institutes of Health–appointed data and safety monitoring board (DSMB) and the U.S. Food and Drug Administration (IND 015202). Informed consent was obtained before any screening procedures or enrollment. The protocol (**Supplement**, available at Annals.org) and all 8 amendments were approved by the applicable central or institutional review boards and the National Institutes of Health–appointed DSMB before site initiation and participant recruitment.

Participants reviewed the trial's procedures (**Figure**) on a tablet device that administered screening questions and provided electronic informed consent (eConsent). Eligible participants were randomly assigned via a computerized data-entry system that masked treatment group allocation. An unblinded study nurse or pharmacist at each site, who masked the visual appearance of the injection to maintain allocation concealment, administered the intervention (ZVL, a lyophilized preparation of live attenuated VZV [Oka/Merck] reconstituted with sterile diluent following the manufacturer's administration instructions or saline) and was not responsible for any end point–related data collection or analysis. Within sites, participants were randomly assigned using a permuted block design with block sizes of 4 and 8, stratified by baseline glucocorticoid use. The study vaccine product was administered subcutaneously as a single 0.65-mL dose in the deltoid region of the upper arm.

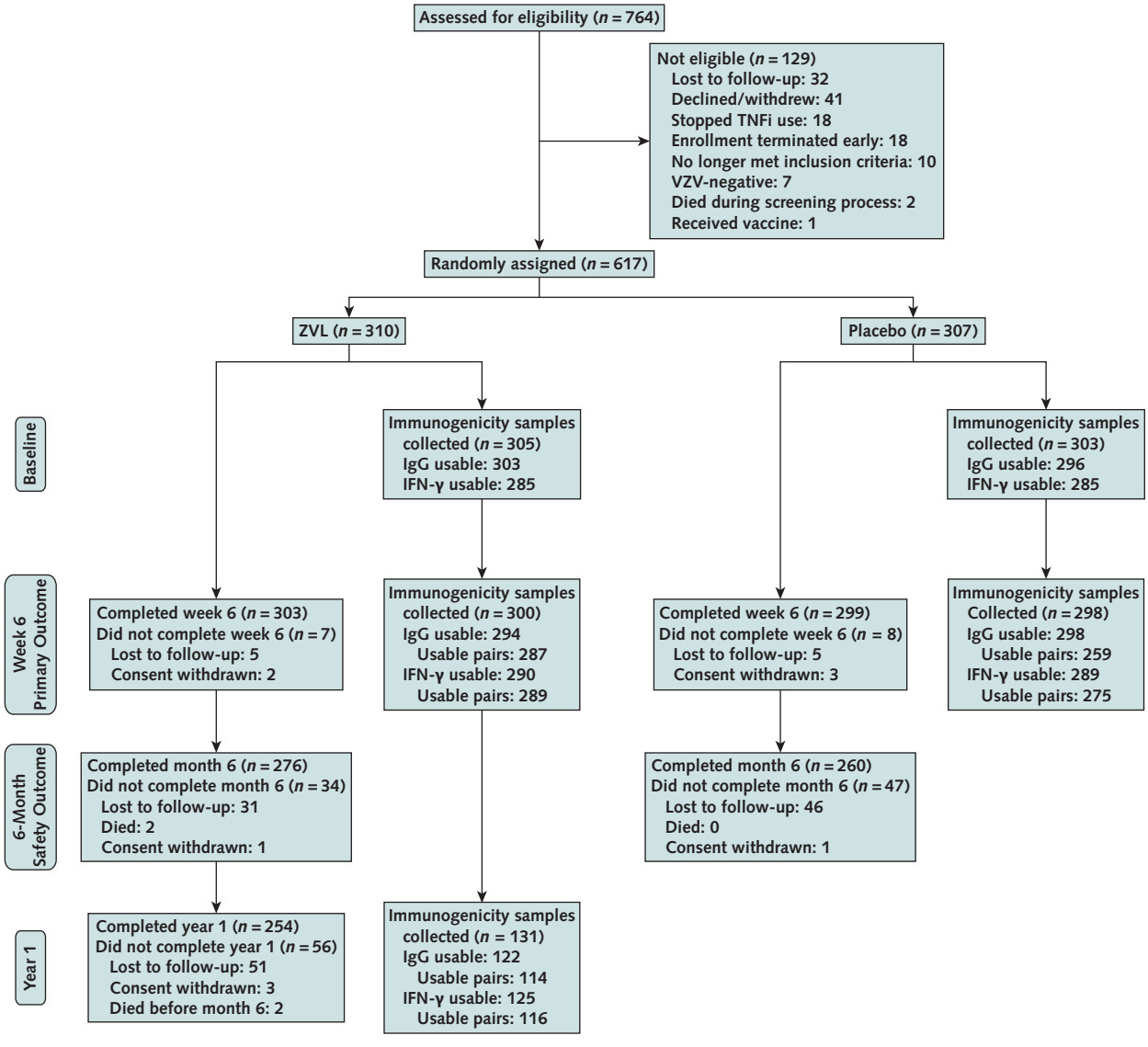
After randomization, at day 3 and at weeks 1 through 5, trial staff contacted participants by telephone to ask about any rash, side effects, and adverse or serious adverse events (SAEs) they might have experienced. All participants returned for an in-person visit at 6 weeks—the primary assessment time point of the study—and also received a follow-up telephone call at 6 months. Trial staff collected blood samples from all participants at baseline and at week 6 and, as an exploratory outcome to assess the immunologic persistence of ZVL among those vaccinated, invited participants at selected centers to provide a year 1 blood sample for the same laboratory assessments.

Primary Outcome: Immunogenicity

Assessment of the Humoral Immune Response: Glycoprotein Enzyme-Linked Immunosorbent Assay

High-binding plates were coated with 3 μg/mL VZV–Ellen viral lysate (ZeptoMetrix) overnight at 4 °C. Plates were then blocked using 0.1% Tween–phosphate-

Figure. Study disposition of participants.



IFN-γ = interferon-γ; TNFi = tumor necrosis factor inhibitor; VZV = varicella-zoster virus; ZVL = live attenuated zoster vaccine.

buffered saline (PBS) with 5% weight/volume nonfat dry milk for 1 hour followed by 3 washes with 0.05% Tween-PBS. Plasma samples were added at a 1/30 dilution in duplicates, followed by 3-fold dilutions, and incubated for an additional 1.5 hours. After washing 3 times with 0.05% Tween-PBS, plates were developed using horseradish peroxidase–conjugated mouse antihuman monoclonal IgG (BD Biosciences) for 1.5 hours, followed by addition of chromogen *o*-phenylenediamine dihydrochloride substrate (Sigma) to allow detection and quantitation of bound antibody molecules. The reaction was stopped with the addition of 1 M hydrochloric acid. The optical density was measured at 490 nm using a Victor3 plate reader (PerkinElmer). End-point IgG titers were calculated using log–log transformation of the linear portion of the curve, with 0.1 optical density unit used as the cutoff. For each plate, a positive control sample was used to normalize enzyme-linked immunosorbent assay (ELISA) titers among assays, and a negative control sample (pooled plasma from seronegative infants) was used to ensure specificity of the assay.

Assessment of Cell-Mediated Immunity (T-Cell Response): Enzyme-Linked Immunosorbent Spot

A total of 200 000 peripheral blood mononuclear cells per well from each subject were added to 12 wells in precoated antihuman interferon-γ (IFN-γ) monoclonal antibody ELISpot^{PLUS} plates (Mabtech) conditioned with RPMI supplemented with 10% fetal bovine serum for 30 minutes at room temperature. Peripheral blood mononuclear cells were then stimulated with VZV–Ellen lysate at a concentration of 1 μg per well or anti-CD3

monoclonal antibody (included in kit), or they were left unstimulated in triplicates. After incubation for 18 hours at 37 °C, the plates were washed with PBS. Biotinylated antihuman IFN-γ monoclonal antibody at a concentration of 1 μg/mL was added, and plates were incubated for an additional 2 hours at room temperature. After washing with PBS, streptavidin–alkaline phosphatase was added to all wells and the plates were incubated for 1 hour at room temperature. Following washing with PBS, BCIP/NBT-plus substrate was added, and the plates were allowed to develop in the dark for 5 to 15 minutes until spots appeared. Color development was stopped by washing with tap water. After drying, the number of VZV-specific IFN-γ–secreting spot-forming cells was counted in an AID EliSpot reader (Autoimmun Diagnostika) using AID EliSpot 7.0 software.

Secondary Outcomes: Safety, Vaccine Tolerability, and Disease Worsening

Within 6 weeks of vaccination, the active and placebo groups were compared to determine the composite outcome of all SAEs and of nonserious vaccine-strain VZV events and tolerability (for example, injection-site reactions). In addition, for patients with rheumatoid arthritis, tolerability, including worsening of disease activity, was assessed at 6 weeks using the Clinical Disease Activity Index (CDAI) (9) and Routine Assessment of Patient Index Data 3 (RAPID3) (10).

Statistical Analysis

Descriptive analyses (means, medians, SDs, frequency distributions) were conducted to assess and describe the cohort. Baseline comparability and early terminations were assessed by parametric and nonparametric 1-factor (treatment group) analysis of variance or χ^2 analyses, as applicable. Median change from baseline to week 6 in CDAI and RAPID3 scores was compared with the Kruskal–Wallis test. Probability values less than 0.05 were considered meaningful for the primary analysis. Analyses were performed using JMP Pro, version 14/15, and SAS, version 9.4 (SAS Institute).

Immunogenicity

For vaccine and placebo recipients, geometric means, 95% CIs, and percentage increases in geometric mean fold rise (GMFR) were calculated 6 weeks after vaccination. For year 1, only those receiving active vaccine were included in the analysis of the GMFR increase over baseline. The primary outcomes are presented as observed differences (week 6 minus baseline) as well as the GMF ratio of active vaccine to placebo at week 6. A generalized linear model on the rank order of the change in scores within treatment group, using a normal distribution with reciprocal link, was used for statistical comparison of active versus placebo vaccine at week 6. For immunogenicity values below the level of sensitivity, a value of 0.6 was used for analysis. In addition, generalized linear models adjusted for age and other covariates were run, with the rank order of change in VZV-specific response as the response variable and treatment or subgroup as independent variables. In addition to age, other covariates considered included sex, background methotrexate use, immune response at baseline, and specific TNFi construct (monoclonal [infliximab, adalimumab, golimumab] or fusion protein [etanercept, certolizumab]).

Safety

Per the safety hypothesis, the cumulative incidence of SAEs and vaccine-strain VZVs occurring in the first 6 weeks in the vaccinated group would be noninferior to (that is, no higher than) the prespecified noninferiority margin of 1.25 percentage points compared with the control group. This margin was based on clinical input from the expert panel of virologists, immunologists, and rheumatologists that created the VERVE study protocol. The 95% CIs for incidence rates in each group (vaccinated vs. unvaccinated) were calculated using exact methods.

Power and Sample Size Determination

The trial was powered based on a hypothesized 30% reduction in immunogenicity compared with findings from Levin and colleagues (11) to account for a cohort with autoimmune and inflammatory diseases. Assuming 10% attrition and an α of 0.05, 1000 participants (500 per group) would achieve at least 80% power to detect a GMFR of 1.68 with an SD of 2.25. Power was estimated using PASS 13 (NCSS), assuming a log-normal distribution for a 2-group *t* test.

Analysis Populations

An intention-to-treat cohort, defined as all participants who were recruited and randomly assigned into the study with usable immunogenicity samples, was used for the primary analyses. The safety population was defined as all participants who received at least 1 dose of study vaccine and had at least 1 postbaseline assessment of the safety variable being analyzed.

Missing Values and Imputation

For the primary outcome analysis, participants had to have at least 1 postvaccine immunogenicity measure to determine the GMFR. For both glycoprotein ELISA (gpELISA) and enzyme-linked immunosorbent spot (ELISpot), results were imputed for responses assessed to be below the limit of detection. No other missing values were imputed for the immunogenicity outcomes.

Role of the Funding Source

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) had no role in the writing of the manuscript or the decision to publish it. None of the authors was paid to write this article by a third party. Design, analysis, and the decision to publish results were the responsibility of the study investigators and the DSMB; the lead author had full access to all of the data in the study and had final responsibility for the decision to submit the manuscript for publication. The Clinical Coordinating Center was located at the School of Medicine, and the Statistical and Data Management Center was located at the Department of Biostatistics, School of Public Health, both at the University of Alabama at Birmingham.

Table 1. Baseline Characteristics of the Intention-to-Treat Population, by Treatment Group

Characteristic	Overall (*n* = 617)	ZVL (*n* = 310)	Placebo (*n* = 307)
Mean age (SD), *y*	62.7 (7.5)	62.7 (7.6)	63.1 (7.4)
Sex, *n (%)*			
Female	408 (66.1)	207 (66.8)	201 (65.5)
Male	209 (33.9)	103 (33.2)	106 (34.5)
Race/ethnicity, *n (%)**			
Non-Hispanic White	397 (90.0)	202 (88.2)	195 (92.0)
Non-Hispanic Black	36 (8.2)	24 (10.5)	12 (5.7)
Other/multiple	8 (1.8)	3 (1.3)	5 (2.4)
Hispanic/Latino	26 (5.9)	14 (6.1)	12 (5.6)
Specific TNFi used, *n (%)*†			
Adalimumab	202 (32.7)	118 (38.1)	84 (27.4)
Certolizumab	35 (5.7)	14 (4.5)	21 (6.8)
Etanercept	131 (21.2)	59 (19.0)	72 (23.5)
Golimumab	56 (9.1)	31 (10.0)	25 (8.1)
Infliximab	193 (31.3)	88 (28.4)	105 (34.2)
Concurrent medication use, *n (%)*			
Methotrexate	294 (47.7)	153 (49.4)	141 (45.9)
Glucocorticoid	65 (10.5)	30 (9.7)	35 (11.4)
TNFi indication, *n (%)*†			
Arthritis-related			
Ankylosing spondylitis	50 (7.8)	23 (7.2)	27 (8.5)
Inflammatory bowel disease–related arthritis	23 (3.6)	13 (4.1)	10 (3.1)
Other inflammatory arthritis	39 (6.1)	14 (4.4)	25 (7.9)
Psoriatic arthritis	154 (24.1)	78 (24.3)	76 (23.9)
Reactive arthritis	3 (0.5)	2 (0.6)	1 (0.3)
Rheumatoid arthritis	368 (57.6)	190 (59.2)	178 (56.0)
Undifferentiated arthritis	2 (0.3)	1 (0.3)	1 (0.3)
Non–arthritis-related			
Crohn disease	32 (38.5)	14 (33.3)	18 (43.9)
Ulcerative colitis	15 (18.1)	9 (21.4)	6 (14.6)
Sarcoidosis	10 (12.1)	7 (16.7)	3 (7.3)
Psoriasis	17 (20.5)	7 (16.7)	10 (24.4)
Other	9 (10.8)	5 (11.9)	4 (9.8)
Median Clinical Disease Activity Index score (range)‡	6 (0–57.5)	6 (0–57.5)	6 (0–45)

TNFi = tumor necrosis factor inhibitor; ZVL = live attenuated zoster vaccine.
* In the ZVL group, data on race and ethnicity were available for 229 participants. In the placebo group, data on race and ethnicity were available for 212 and 213 participants, respectively.
† Indications are not mutually exclusive.
‡ The Clinical Disease Activity Index is a measure of rheumatoid arthritis disease activity and is scored on a scale ranging from 0 to 76, with lower numbers indicating better control of the disease. Scores were available for 368 participants (190 in the ZVL group and 178 in the placebo group). Values ≤10 are consistent with low disease activity or remission.

RESULTS

From 20 March 2015 to 12 December 2018, 764 persons were screened for the trial; 635 were enrolled, and 617 were randomly assigned (**Figure**). At the primary 6-week assessment time point, 601 participants (97.4%) had completed the trial; completion rates did not differ between the ZVL (2.3%) and placebo (2.6%) groups ($P = 0.78$). Similarly, at month 6, early termination did not differ between the ZVL (11.0%) and placebo (15.3%) groups ($P = 0.110$) (see the **Appendix Table**, available at Annals.org, for the early termination sensitivity analysis at month 6).

Characteristics of the 617 trial participants randomly assigned to ZVL ($n = 310$) or placebo ($n = 307$) are shown in **Table 1**. Adalimumab, infliximab, and etanercept were the most common TNFis used. Participants taking adalimumab were more likely to be randomly assigned to ZVL (38.1% vs. 27.4%; $P = 0.032$). However, when monoclonal antibody use versus etanercept was considered, no difference by TNFi use was shown ($P = 0.180$). Among the randomly assigned participants, 10.5% were receiving systemic glucocorticoids; as expected, this did not differ by treatment group ($P = 0.49$). The most common disease indications for TNFis were rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis; these also did not differ by treatment group (all $P > 0.40$). Randomization balanced all demographic and clinical characteristics, except as noted throughout this section (all $P > 0.05$).

Between the ZVL and placebo groups, a statistically significant difference was shown in the GMFR from baseline to week 6 in the VZV-specific gpELISA (IgG) values (1.33 vs. 1.02; GMFR, 1.30; $P = 0.015$ from the generalized linear model) (**Tables 2** and **3**). For the ELISpot (IFN-γ) outcome, the ZVL group had a significant increase in GMFR (1.39 [95% CI, 1.07 to 1.82]), and the placebo group did

not (1.15 [CI, 0.58 to 1.50]), although the ratio of the two did not achieve statistical significance (1.22 [CI, 0.83 to 1.78]; $P = 0.150$ from the generalized linear model). For IgG, treatment differences persisted in individual generalized linear models when adjusted for sex ($P = 0.37$), age group ($P = 0.40$), smoking status ($P = 0.32$), use of methotrexate ($P = 0.31$), and TNFi class ($P = 0.51$). Use of glucocorticoids at randomization was related to IgG response at week 6 ($P = 0.016$), with those taking steroids at baseline having an elevated response. However, the results are based on 58 participants taking glucocorticoids at baseline: only 26 received active vaccine, and 32 received placebo. At year 1, in the active group, gpELISA maintained the significant increase from baseline (1.42 [CI, 1.07 to 1.88]; $n = 114$), whereas the ELISpot was no longer significantly different from baseline (0.76 [CI, 0.51 to 1.15]; $n = 116$).

By year 1 of follow-up, mean IFN-γ had returned to baseline levels, with 75.0% of participants at or below their baseline levels (Table 4). The mean IgG was still elevated at year 1, with 58.8% of participants exceeding 20% higher response levels compared with baseline. Twelve participants were suspected of having VZV (7 in the ZVL group and 5 in the placebo group); of those, 8 were tested, and all results were confirmed to be negative for VZV (Table 4). Four participants were not tested: 1 did not have any visibly affected skin for testing; 2 had likely allergic reactions, not shingles, per their physicians; and 1 was evaluated by a local physician and did not contact the VERVE coordinating center for testing. No difference was shown in the proportion of participants suspected of having VZV by treatment group (active [2.3%] vs. placebo [1.6%]; $P = 0.72$). Based on zero cases, the risk for VZV infection was 0.0% (CI, 0.0% to 1.2%) in both groups.

Through month 6, no difference was seen in the proportion of participants completing the safety assessment ($P = 0.110$) or those experiencing an SAE (ZVL, 3.2% [CI, 1.7% to 5.8%]; placebo, 2.6% [CI, 1.3% to 5.1%]; difference, 0.6 percentage point [CI, −0.22 to 3.4 percentage points]), with the difference in event rates falling below the noninferiority margin of 1.25 percentage points. A statistically significantly higher proportion of injection-site reactions was seen in the ZVL group (19.4%) compared with the placebo group (4.2%). No difference was shown in the proportion of participants reporting non–injection-site reaction adverse events through week 6 (31.9% in the ZVL group vs. 31.3% in the placebo group) or between week 6 and month 6 (ZVL, 5.5%; placebo, 5.5%). In the subgroup of participants with rheumatoid arthritis ($n = 368$), disease activity did not worsen at 6 weeks (median change in CDAI score = 0 in both groups [$P = 0.73$]; median change in RAPID3 score = 0 in both groups [$P = 0.99$]) (9, 10).

In November 2018, the VERVE DSMB requested a protocol-defined interim analysis of the immunogenicity outcomes only. The DSMB recommended halting the VERVE trial early based on the superiority of the VZV-specific gpELISA results, the futility of the gpELISA outcome, and no participants having vaccine-associated VZV infection. At the recommendation of the DSMB, randomization stopped in December 2018, with continued follow-up for the week 6 immunogenicity sample collection for all participants, through month 6 for the final safety assessment for the placebo groups, and as

Table 2. GMFR in VZV-Specific Levels From Baseline at 6 Weeks

Variable	gpELISA: IgG		ELISpot: IFN-γ	
	ZVL ($n = 287$)	Placebo ($n = 289$)	ZVL ($n = 259$)	Placebo ($n = 275$)
Raw values				
Baseline				
Mean (SD)	7298.0 (11 308.4)	7746.3 (13 281.9)	8.0 (21.1)	14.1 (40.7)
Median (IQR)	3517.9 (1417.0 to 9311.7)	3854.1 (1624.1 to 7766.8)	0.6 (0.6 to 4.7)	0.6 (0.6 to 5.0)
Week 6				
Mean (SD)	9702.2 (26 514.4)	8987.0 (32 900.1)	16.4 (36.3)	11.5 (30.1)
Median (IQR)	4636.7 (1988.9 to 9439.2)	3684.7 (1682.1 to 8277.7)	0.6 (0.6 to 11.0)	0.6 (0.6 to 8.3)
Week 6				
Baseline (SD) (95% CI)	2441.42 (23 395.8) (−276.8 to 5159.7)	1413.4 (28 680.0) (−1889.2 to 4751.9)	7.6 (40.1) (2.8 to 12.5)	−1.5 (47.4) (−7.1 to 4.0)
Change (IgG − placebo) (95% CI)	1010.1 (−3275.1 to 5295.2)	–	9.1 (1.7 to 16.5)	–
GMF				
Week 6/baseline (95% CI)*	1.33 (1.17 to 1.51)	1.02 (0.91 to 1.14)	1.39 (1.07 to 1.82)	1.15 (0.88 to 1.5)
Ratio (ZVL to placebo) (95% CI)	1.30 (1.11 to 1.54)	–	1.22 (0.83 to 1.78)	–
P value†	0.002		0.31	

ELISpot = enzyme-linked immunosorbent spot; GMF = geometric mean fold; GMFR = geometric mean fold rise; gpELISA = glycoprotein enzyme-linked immunosorbent assay; IFN-γ = interferon-γ; IQR = interquartile range; VZV = varicella-zoster virus; ZVL = live attenuated zoster vaccine.
* From a priori analysis.
† *P* values are from a generalized linear model on the rank order of the change at week 6 from baseline using normal distribution and reciprocal link.

Table 3. GMFR in VZV-Specific Levels From Baseline at 1 Year: ZVL Group Only

Variable	gpELISA: IgG (*n* = 114)	ELISpot: IFN-γ (*n* = 116)
Median raw value at year 1 (IQR)	4174.5 (1629.6–8174.8)	0.6 (0.6–1)
Percentage change from baseline at year 1, *n (%)*		
Baseline or lower	41 (36.0)	87 (75.0)
≤20%	6 (5.3)	2 (1.7)
>20%	67 (58.8)	27 (23.3)

ELISpot = enzyme-linked immunosorbent spot; GMFR = geometric mean fold rise; gpELISA = glycoprotein enzyme-linked immunosorbent assay; IFN-γ = interferon-γ; IQR = interquartile range; VZV = varicella-zoster virus; ZVL = live attenuated zoster vaccine.

consented through year 1 for safety and immunogenicity for the ZVL group.

Discussion

We evaluated the safety and immunogenicity of ZVL in patients with immune-mediated inflammatory disease using TNFis and/or background methotrexate and low-dose corticosteroids. We observed no cases of vaccine-associated shingles in our study, and the vaccine was well tolerated in this population. Although vaccine-induced IgG responses were robust, we found cell-mediated responses to be more variable and not sustained at 1 year after vaccination. Our data suggest that this vaccine, although historically contraindicated in those using TNFis, can be safely used in this setting; however, its long-term efficacy in such patients is unknown. In addition, our immunogenicity data indicate that these patients may need to be evaluated for a booster vaccination.

The contraindication of this vaccine in many immunosuppressed populations was largely supported by expert opinion and theoretical concerns. Case reports of disseminated and local vaccine-strain shingles are well documented in the literature but have primarily occurred in the setting of advanced immunosuppression (12). To our knowledge, no prospective trials have been conducted evaluating the safety of this vaccine in persons using biologic immunosuppressive therapies. Given the high unmet need among patients with immune-mediated inflammatory diseases for shingles prevention and the common use of TNFis, directly evaluating this question in such patients is important.

The live attenuated zoster vaccine has undergone similar evaluation in other settings of immunocompromised patients. A large randomized controlled trial in 295 patients with HIV who had $CD4^+$ T-cell counts above 0.200×10^9 cells/L found no vaccine-associated varicella events (13). Other studies evaluating the safety of this vaccine in immunocompromised persons have been observational in nature (6, 14). Formative data supporting the VERVE trial were in part motivated by a population-based analysis evaluating the safety and effectiveness of vaccination among more than 460 000 Medicare beneficiaries (6); 633 patients were identified who received the vaccine while prescribed TNFi therapy, and in the 42 days after vaccination, none were diagnosed with shingles. This study, though observational, indicated that vaccination in TNFi users might be safe and helped motivate the trial.

Based on the findings of the VERVE trial, the efficacy of ZVL among immunosuppressed populations is likely reduced compared with its efficacy in healthy persons. We found gpELISA and cell-mediated immunity vaccine responses (33% and 39% increases above baseline, respectively) of lower magnitude than those identified in the larger Shingles Prevention Study (120% and 78%, respectively), which recruited healthy persons (11). Notably, the subset of persons we evaluated at 1 year after vaccination showed a significant increase in gpELISA but not cell-mediated immunity compared with baseline. The healthy populations from the Shingles Prevention Study had an elevated GMFR for both gpELISA and cell-mediated immunity measures relative to placebo observed at 1, 2, and even 3 years after vaccination (15). Furthermore, the aforementioned trial conducted in persons with HIV (13) also produced relatively greater and longer-lived vaccine responses than in our study. However, in that trial, unlike our study and the Shingles Prevention Study, patients with HIV were administered a second vaccine dose 6 weeks after the first dose. This second dose was associated with maintenance of gpELISA responses observed with the first dose and an almost doubling of cell-mediated responses compared with those seen at week 6 after the first vaccination. Even after the first vaccination alone, gpELISA responses were 78% higher than baseline, substantially greater than those observed in our study.

Table 4. Participants With Suspected VZV and SAEs

Variable	All (*n* = 617)	ZVL (*n* = 310)	Placebo (*n* = 307)	Difference
Participants with SAEs reported up to year 1, *n (% of total participants [95% CI])*	18 (2.9 [1.7 to 4.6])	10 (3.2 [1.6 to 5.9])	8 (2.6 [1.1 to 5.1])	0.6* (−0.22 to 3.4)
Reported SAEs, *n (% of total SAEs reported)*	20 (100)	10 (50.0)	10 (50.0)	–
Participants with an event before month 6, *n (%)*	15 (83.3)	8 (80.0)	7 (87.5)	–
Participants with suspected varicella, *n (% of total participants [95% CI])*	12 (1.9 [0.1 to 3.4])	7 (2.3 [0.9 to 4.6])	5 (1.6 [0.5 to 3.8])	–
Samples collected and tested, *n (% of samples collected)*	8 (66.7)	4 (57.1)	4 (80.0)	–
Participants with confirmed varicella, *n (95% CI)*	0 (0.0 to 0.6)	0 (0.0 to 1.2)	0 (0.0 to 1.2)	–

SAE = serious adverse event; VZV = varicella-zoster virus; ZVL = live attenuated zoster vaccine.
* Below the noninferiority margin of 1.25 percentage points.

How these immune responses translate to efficacy in immunosuppressed populations is unknown. In the Shingles Prevention Study, overall efficacy was 67% with regard to prevention of a combined outcome of shingles plus postherpetic neuralgia (16). In the observational study mentioned earlier (6), among Medicare patients with immune-mediated inflammatory disease, the incidence rate of shingles was reduced among those who were vaccinated compared with unvaccinated patients (adjusted hazard ratio, 0.61 [CI, 0.52 to 0.71], a 39% relative risk reduction). The immunogenicity results from our study are consistent with the hypothesis that clinical efficacy is likely reduced in persons with autoimmune and inflammatory diseases receiving TNFis, which also may be given concomitantly with other immunomodulatory therapies (such as methotrexate or prednisone). Indeed, reduced immunogenicity of vaccines has been repeatedly observed in other vaccine trials (for example, influenza) conducted in patients receiving these immunomodulatory therapies (17, 18). The experience in the population of persons with HIV discussed herein would suggest that a booster strategy might be more successful at producing more robust and longer-lasting responses. Although our data suggest that ZVL can be used safely in this population, the duration of protection is likely limited after 1 dose of the vaccine, and booster approaches would probably need to be pursued.

Alternatively, the HZ subunit vaccine has shown a greater magnitude of protection than the live vaccine in healthy populations, and immunogenicity data suggest longer-term memory response associated with the vaccine (19). In persons with autoimmune disease, the vaccine has received scant evaluation and has been limited to single-center experiences (20, 21). Its performance in healthy populations raises the possibility that it will be more efficacious than ZVL in patients with immune-mediated inflammatory disease. How TNFis and other biologics or targeted therapies (for example, Janus kinase inhibitors) might affect vaccine responses is unclear, and when and how to give the vaccine to patients using these therapies should be studied. Moreover, the HZ subunit vaccine is not available in many countries; in those areas, ZVL will continue to remain relevant from a public health perspective.

Despite the pragmatic nature of this trial with broad inclusion criteria, its limitations are largely related to generalizability. Patients were required to be aged 50 years or older, and immune responses in younger persons may be superior to those in older patients. Tumor necrosis factor inhibitors remain among the most commonly used targeted therapies, but we would not extrapolate our findings to other classes of immunomodulators, such as Janus kinase inhibitors, particularly due to the safety outcomes.

In conclusion, results from this study suggest that ZVL was safe and had reasonable short-term effectiveness (based on the 6-week immunogenicity results) in participants receiving TNFis for a broad range of indications. Although country-specific labeling requirements may continue to discourage use of a live virus vaccine in immunosuppressed patients receiving biologic therapies, use of this ZVL in TNFi-treated patients may be a reasonable option, especially in the absence of an alternative zoster vaccine.

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Note: Drs. Curtis, Cofield, and Winthrop take responsibility for the integrity of the data and the accuracy of the data analysis.

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Data Sharing Statement: The following data will be made available with publication: deidentified participant data on request to Dr. Curtis, the principal investigator (e-mail, jcurtis@uab.edu). These data will be made available to researchers with a signed data use agreement whose proposed use of the data has been approved by the principal investigator per the trial steering committee.

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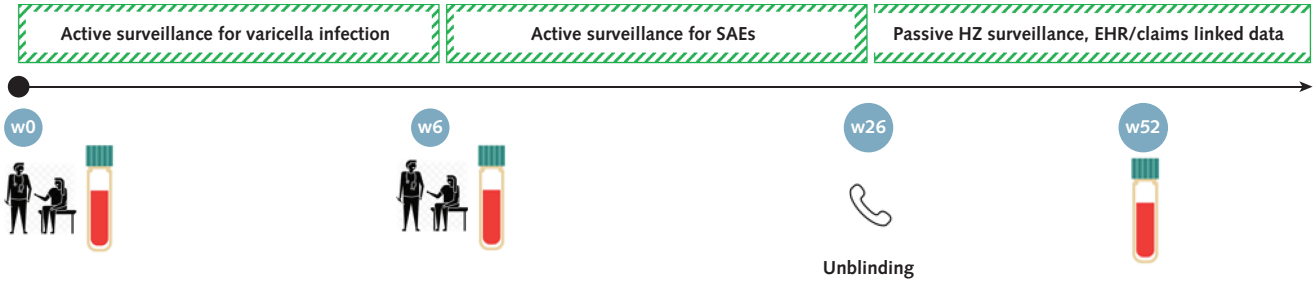
Appendix Table 1. Sensitivity Analysis for Trial Termination Before Month 6*

Characteristic	Completed Month 6 (*n* = 536)	Terminated Before Month 6 (*n* = 81)	*P* Value
Treatment group			
Live attenuated zoster vaccine	276 (89.0)	34 (11.0)	0.110
Placebo	260 (84.7)	47 (15.3)	–
Mean age (SD), *y*	62.1 (7.5)	62.1 (7.9)	0.99
Female sex	357 (66.6)	56 (69.1)	0.65
Race/ethnicity (*n* = 441; Hispanic or Latino, *n* = 442)	380	62	–
Non-Hispanic White	348 (91.5)	49 (79.0)	0.021†‡
Non-Hispanic Black	26 (6.8)	10 (16.1)	–
Other/multiple	6 (1.6)	3 (4.8)	–
Hispanic/Latino	21 (5.5)	5 (8.1)	0.70§
Specific TNFi used			
Adalimumab	180 (33.6)	22 (27.2)	0.24
Certolizumab	30 (5.6)	5 (6.2)	0.84
Etanercept	113 (21.1)	18 (22.2)	0.82
Golimumab	49 (9.1)	7 (8.6)	0.88
Infliximab	164 (30.6)	29 (35.8)	0.35
Concurrent medication use			
Methotrexate	257 (48.0)	39 (48.2)	0.97
Glucocorticoid	51 (9.5)	14 (17.3)	0.047‡
TNFi indication, *n (%)*‖			
Arthritis-related			
Ankylosing spondylitis	42 (7.8)	8 (9.9)	0.54
Inflammatory bowel disease–related arthritis	21 (3.9)	2 (2.5)	0.50
Other inflammatory arthritis	35 (6.5)	4 (4.9)	0.57
Psoriatic arthritis	138 (25.8)	16 (19.8)	0.24
Reactive arthritis	2 (0.4)	1 (1.2)	0.35§
Rheumatoid arthritis	318 (59.3)	50 (61.7)	0.68
Undifferentiated arthritis	1 (0.2)	1 (1.2)	0.25§
Non–arthritis-related			
Crohn disease	29 (5.4)	3 (3.7)	0.79§
Ulcerative colitis	13 (2.4)	2 (2.5)	>1.00§
Sarcoidosis	8 (1.5)	2 (2.5)	0.63§
Psoriasis	15 (2.8)	0 (0.0)	0.24§
Participants with event report			
Adverse event	170 (31.7)	25 (30.9)	0.88
Serious adverse event	14 (2.6)	4 (4.9)	0.28§

TNFi = tumor necrosis factor inhibitor.
* Values are numbers (percentages) unless otherwise indicated.
† Black participants were less likely than White participants to complete month 6 ($P = 0.013$). No other differences were identified; however, the sample size is too small to make definitive conclusions.
‡ Statistically significant.
§ Fisher exact test.
‖ Indications are not mutually exclusive.

Appendix Figure. Study schema showing time course of assessment intervals.



EHR = electronic health record; HZ = herpes zoster; SAE = serious adverse event; w = week.