

The Safety and Immunogenicity of Live Zoster Vaccination in Patients With Rheumatoid Arthritis Before Starting Tofacitinib

A Randomized Phase II Trial

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Objective. Patients with rheumatoid arthritis (RA) are at increased risk of herpes zoster, and vaccination is recommended for patients ages 50 years and older, prior to starting treatment with biologic agents or tofacitinib. Tofacitinib is an oral JAK inhibitor for the treatment of RA. We evaluated its effect on the immune response and safety of live zoster vaccine (LZV).

Methods. In this phase II, 14-week, placebo-controlled trial, patients ages 50 years and older who had active RA and were receiving background methotrexate were given LZV and randomized to receive tofacitinib 5 mg twice daily or placebo 2–3 weeks postvaccination. We measured humoral responses (varicella zoster virus [VZV]-specific IgG level as determined by glycoprotein enzyme-linked immunosorbent assay) and cell-mediated responses (VZV-specific T cell enumeration, as determined by

enzyme-linked immunospot assay) at baseline and 2 weeks, 6 weeks, and 14 weeks postvaccination. End points included the geometric mean fold rise (GMFR) in VZV-specific IgG levels (primary end point) and T cells (number of spot-forming cells/10⁶ peripheral blood mononuclear cells) at 6 weeks postvaccination.

Results. One hundred twelve patients were randomized to receive tofacitinib (n = 55) or placebo (n = 57). Six weeks postvaccination, the GMFR in VZV-specific IgG levels was 2.11 in the tofacitinib group and 1.74 in the placebo group, and the VZV-specific T cell GMFR was similar in the tofacitinib group and the placebo group (1.50 and 1.29, respectively). Serious adverse events occurred in 3 patients in the tofacitinib group (5.5%) and 0 patients (0.0%) in the placebo group. One patient, who lacked preexisting VZV immunity, developed cutaneous vaccine dissemination 2 days after starting tofacitinib (16 days postvaccination). This resolved after tofacitinib was discontinued and the patient received antiviral treatment.

Conclusion. Patients who began treatment with tofacitinib 2–3 weeks after receiving LZV had VZV-specific humoral and cell-mediated immune responses to LZV similar to those in placebo-treated patients. Vaccination appeared to be safe in all of the patients except 1 patient who lacked preexisting VZV immunity.

Herpes zoster (HZ), or shingles, is a common and sometimes debilitating disease that disproportionately affects elderly individuals and those who are immunocompromised (1). Patients with rheumatoid arthritis (RA) have a 1.5–2-fold higher risk of developing HZ compared with healthy adults (2), and treatment with some disease-

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modifying antirheumatic drugs (DMARDs) has been shown to further increase this risk (3,4). Tofacitinib is an oral JAK inhibitor for the treatment of RA. The efficacy and safety of tofacitinib at dosages of 5 mg twice daily and 10 mg twice daily, administered as monotherapy or in combination with DMARDs, in patients with active RA have been demonstrated in phase II, phase III, and long-term extension (LTE) studies (5–13). Tofacitinib has been shown to increase the risk of developing HZ, particularly when it is given in combination with methotrexate (MTX) or prednisone (14–16).

Given the preventable nature of HZ, the American College of Rheumatology (ACR), the European League Against Rheumatism (EULAR), and other committees, such as the Advisory Committee on Immunization Practices (ACIP), recommend vaccinating patients with RA (1,17–19). Due to the live nature of the zoster vaccine, there is a theoretical risk of dissemination in immunosuppressed patients, and it is recommended that treatment with a biologic agent or tofacitinib should not be started until 2–4 weeks after the vaccination (1,20). However, guidelines for the timing of the vaccination relative to the start of immunosuppressive therapy are conflicting. According to the ACR guidelines, RA patients ages ≥ 50 years should be vaccinated with the live zoster vaccine (LZV) at least 2 weeks prior to starting therapy with a biologic agent or tofacitinib (18,21). The 2011 EULAR guidelines suggest general avoidance of this vaccine in immunosuppressed patients but emphasize the potential importance of the vaccine and the need to give it to those with positive findings on serologic tests for varicella zoster virus in combination with temporary cessation of immunosuppressive drug therapy (19). The ACIP recommends administration of the vaccine to persons ages ≥ 60 years, including those with chronic medical conditions such as RA (1).

Previous studies have shown that in immunocompetent individuals, the efficacy of LZV for protection against HZ was 51% in those ages ≥ 60 years over a follow-up period of 4.9 years and 70% in those ages 50–59 years over a follow-up period of 1.3 years (17). Despite the higher risk of HZ in patients with RA, there has been no large interventional clinical study of LZV in the setting of RA. The immunogenicity and safety of LZV in patients receiving DMARDs (including tofacitinib) are unknown. Accordingly, we sought to evaluate the safety and immunogenicity of LZV in a group of patients with RA, prior to starting tofacitinib therapy.

PATIENTS AND METHODS

We enrolled patients with active RA who were receiving stable background doses of MTX into a phase II, 14-week,

randomized, double-blind, parallel-arm, placebo-controlled trial (study A3921237; ClinicalTrials.gov identifier: NCT02147587). Patients were randomized (1:1) to receive tofacitinib at a dosage of 5 mg twice daily or placebo 2–3 weeks after vaccination with LZV, to specifically assess the effect of tofacitinib 5 mg twice daily on the safety and immunogenicity of LZV. The study was conducted at 27 centers across the US, between June 2014 and July 2015 (see Supplementary Information, available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40187/abstract>). RA patients ages 50 years and older were eligible if they had at least 4 tender/painful joints and ≥ 4 swollen joints (28 assessed) at the time of screening or at baseline (before vaccination), and a C-reactive protein level of >3 mg/liter or a Clinical Disease Activity Index (22) score of >10 at the time of screening or at baseline. Patients were enrolled if they met the 2010 ACR/EULAR criteria for an RA score of ≥ 6 (23). Prior to screening, patients must have received continuous treatment with MTX at a dosage of 15–25 mg/week for at least 4 months. Exclusion criteria were any of the following: recent history of serious infection (within 6 months), recent infection requiring treatment (within 2 weeks), active hepatitis B or hepatitis C virus infection, untreated latent tuberculosis, any history of malignancy (except nonmelanoma or squamous cell skin cancer or cervical carcinoma in situ), a history of recurrent (>1 episode) or disseminated HZ, prior exposure to LZV, or a history of any other vaccination in the past 6 weeks (see inclusion/exclusion criteria, available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40187/abstract>).

Study conduct. Eligible patients were vaccinated and then randomized (1:1) to receive either tofacitinib 5 mg twice daily or placebo, initiated 2–3 weeks postvaccination (see Supplementary Figure 1, available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40187/abstract>). Patients continued to receive their current dose of MTX. Concomitant treatment with prednisone or equivalent at a dosage of ≤ 10 mg/day was allowed. A history of varicella was not investigated, and patients were not screened for VZV antibodies. RA disease activity was measured only at baseline, prior to vaccination. Other demographic, comorbidity, and other clinical data for the participants were collected at baseline. The study concluded after 12 weeks of treatment with tofacitinib or placebo (14 weeks postvaccination), and the patients were given the option of joining a separate LTE study at that time (see Supplementary Figure 2, available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40187/abstract>). These studies were approved by the institutional review board and/or independent ethics committee at each center and were carried out in accordance with the Declaration of Helsinki and in compliance with all International Conference on Harmonisation Good Clinical Practice guidelines.

Immunogenicity analyses. We evaluated both humoral and cell-mediated responses at baseline (just prior to vaccination) and at 2, 6, and 14 weeks after vaccination (day 1, week 4, and week 12 of treatment with tofacitinib or placebo). Measures included VZV-specific IgG levels, as determined by purified glycoprotein enzyme-linked immunosorbent assay (gpELISA), and VZV-specific T cell responses, as determined by enumeration of interferon- γ (IFN γ) spot-forming cells (SFCs) using an enzyme-linked immunospot (ELISpot) assay.

The primary end point of the trial was the geometric mean fold rise (GMFR) in VZV-specific IgG levels at 6 weeks postvaccination. Secondary and additional end points included

Table 1. Characteristics of the patients, including measures of VZV immunity on the day of LZV immunization*

	Placebo	Tofacitinib 5 mg BID
Baseline demographics		
Age, mean \pm SD years	62.0 \pm 8.7	61.7 \pm 6.2
Female	38 (66.7)	42 (76.4)
BMI, mean \pm SD kg/m ²	30.7 \pm 6.1	31.4 \pm 7.1
Background MTX	57 (100.0)	54 (98.2)
MTX dose, mean \pm SD mg/week	16.9 \pm 4.3	17.1 \pm 4.7
Prednisone daily equivalent	21 (36.8)	26 (47.3)
Prednisone, or equivalent, dose, mean \pm SD mg/day	7.1 \pm 4.8	5.9 \pm 2.2
No prior biologic DMARD exposure	20 (35.1)	29 (52.7)
Inadequate response to prior biologic DMARD	37 (64.9)	26 (47.3)
More than 1 biologic DMARD failure	12 (21.1)	8 (14.5)
RA assessments at screening		
CRP, mean \pm SD mg/liter	1.3 \pm 1.3	1.6 \pm 2.9
ESR, mean \pm SD mm/hour	41.1 \pm 22.9	47.1 \pm 29.3
Tender/painful joint count (28 assessed), mean \pm SD	14.6 \pm 6.6	14.5 \pm 6.5
Swollen joint count (28 assessed), mean \pm SD	10.8 \pm 5.8	11.0 \pm 5.6
Measurement of immunity to VZV at baseline		
VZV-specific IgG level, GMT (80% CI) [range]	182.3 (151.3–219.8) [8.3–1,176.9]	201.0 (166.0–243.2) [0.32–2,370.8]
VZV-specific T cell response, GMC (80% CI) [range]†	43.2 (36.4–51.3) [25–559]	48.4 (40.6–57.7) [25–309]

* The numbers of patients in the placebo and tofacitinib groups are as follows: for baseline demographics, n = 57 and n = 55, respectively; for rheumatoid arthritis (RA) assessments at screening, n = 57 and n = 55, respectively; for measurement of immunity to varicella zoster virus (VZV), n = 53 and n = 54, respectively. Except where indicated otherwise, values are the number (%). LZV = live zoster vaccine; BID = twice daily; BMI = body mass index; MTX = methotrexate; DMARD = disease-modifying antirheumatic drug; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; GMT = geometric mean titer; 80% CI = 80% confidence interval; GMC = geometric mean count.

† Measured by enumeration of interferon- γ spot-forming cells, using enzyme-linked immunospot assay.

the proportion of patients achieving a ≥ 1.5 -fold increase in VZV-specific IgG levels, the absolute VZV-specific IgG levels, the absolute numbers of VZV-specific reactive T cells, and the GMFR in VZV-specific reactive T cells between baseline and 2, 6, and 14 weeks postvaccination.

For gpELISA measures, we used a validated assay (PPD Vaccines and Biologics) used for licensure of Zostavax and widely used in research settings. For gpELISA output, the geometric mean titer was defined as the geometric mean of 3 independent assay measurements of each blood sample.

ELISpot results were obtained using an assay qualified to quantify the number of IFN γ -secreting cells (performed at the Pfizer Inc Vaccine Research Unit, Pearl River, NY). Four hundred thousand peripheral blood mononuclear cells (PBMCs) isolated from whole blood samples obtained from the patients were plated on 96-well plates in triplicate. After a mean \pm SD of 18 \pm 2 hours of incubation (37°C in 5% CO₂) with processed VZV from Oka vaccine strain, reactive T lymphocytes were enumerated. The number of SFCs/10⁶ PBMCs was recorded (24).

Safety assessments. The safety end points were evaluated for 12 weeks after randomization and included adverse events (AEs), serious AEs (SAEs), clinically significant laboratory abnormalities, vaccine-related AEs (including injection-site reactions and HZ-like lesions), and clinical HZ events. Patients who developed rashes during this time period were instructed to be seen by their study physician, and a biopsy specimen of the involved skin was to be obtained if the rash was clinically suggestive of VZV infection. For any patients needing a biopsy, specimens were to be transferred in viral transport media and then

sent to the Centers for Disease Control and Prevention (CDC) for VZV testing. Real-time Förster Resonance Energy Transfer-based polymerase chain reaction (PCR) analysis using a LightCycler platform was performed to target different vaccine-associated single-nucleotide markers in the VZV genome. If VZV infection was identified, samples were tested for markers in open-reading frame 38 (ORF 38) and ORF 54 (to discriminate the Oka vaccine strain from other wild-type strains) and for 2 vaccine strain-specific markers in ORF 62, to confirm VZV infection and to robustly discriminate the vaccine strain from wild-type strains.

Sample size determination. The number of patients (up to ~ 70 in each treatment group) was selected based on a literature review and clinical considerations (25). Specifically, for the primary end point of fold increase from baseline in VZV-specific IgG antibodies at 6 weeks postvaccination (week 4 of treatment with the study drug), assuming a common SD of 1.33 on the logarithmic scale (~ 3.8 -fold on the original scale), a sample size of up to 70 patients in each group would yield a halfwidth of ~ 0.288 on the logarithmic scale for a 2-sided 80% confidence interval (80% CI) of the ratio of the GMFRs between the tofacitinib 5 mg twice daily group and the placebo group (tofacitinib/placebo), ensuring that the GMFR is estimated with reasonable precision.

Statistical analysis. The final analysis included only patients who were deemed “evaluable” and had a complete set of assay results for gpELISA at both baseline and 6 weeks postvaccination, had started the study drug according to the protocol 2–3 weeks postvaccination, and had been $\geq 80\%$ compliant with the

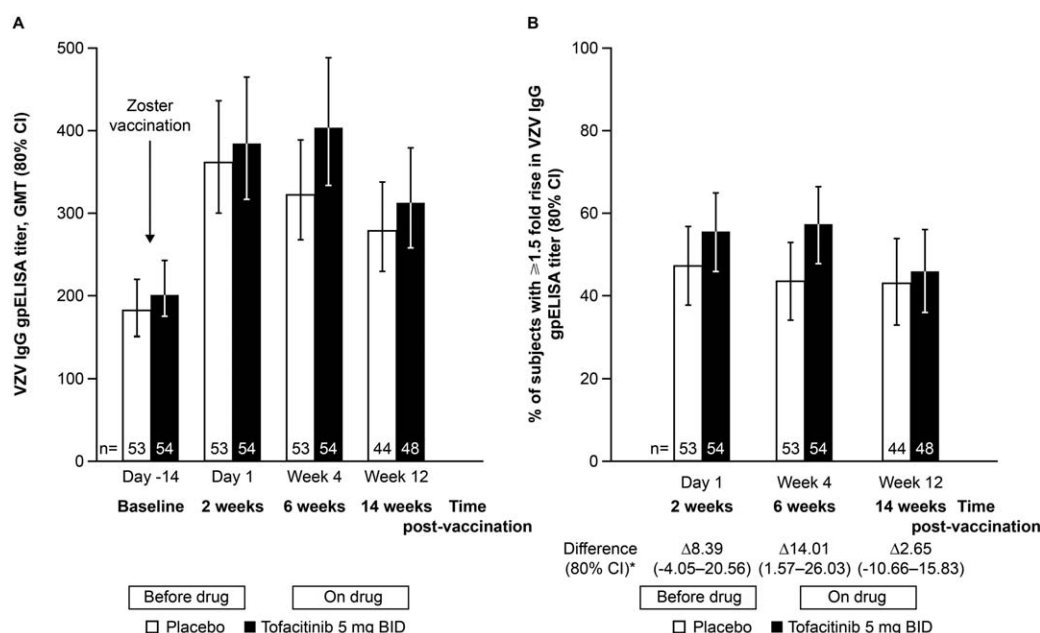


Figure 1. Analyses of varicella zoster virus (VZV)-specific IgG levels. Live zoster vaccine was given on day -14; a blood sample from each subject was obtained at that time to evaluate the baseline immune response to VZV immediately before vaccination. **A**, Mean absolute VZV-specific IgG levels (glycoprotein enzyme-linked immunosorbent assay [gpELISA] titer) in the tofacitinib group and the placebo group at baseline (day -14, before vaccination) and 2, 6, and 12 weeks postvaccination. **B**, Proportion of patients with a ≥ 1.5 -fold change in VZV-specific IgG levels (gpELISA titer) in the tofacitinib group and the placebo group at 2, 6, and 12 weeks postvaccination. * = The 80% confidence intervals (80% CIs) were calculated using the Clopper-Pearson exact method. GMT = geometric mean titer; BID = twice daily.

study drug until 6 weeks postvaccination. The study was not designed to test any statistical hypotheses; therefore, all comparisons described herein are based on the observed magnitudes of the estimates only. For the primary outcome in this group, we compared measures at baseline with those obtained at week 6 postvaccination. We calculated an adjusted estimation of the GMFR ratios (tofacitinib/placebo) using a linear mixed model (analysis of covariance) with repeated measures that included age, sex, randomization stratum (biologic agent-naïve versus prior biologic nonresponder) and baseline value as covariates, and study treatment, visit after vaccination, and treatment-by-visit interaction as fixed effects. The GMFR ratios (tofacitinib/placebo) from baseline were computed. The 2-sided 80% CI of this ratio was obtained from this model (back-transformation).

Additionally, the primary end point was analyzed using descriptive methods (GMFR, geometric SD, minimum, and maximum, according to treatment group and visit following vaccination). Two-sided 80% CIs for the geometric mean constructed by back-transformation of the CI for the mean of the logarithmically transformed end point (computed using Student's *t*-distribution) were calculated.

RESULTS

Baseline characteristics of the patients. One hundred twelve patients were randomized to receive placebo ($n = 57$) or tofacitinib ($n = 55$). Overall, patients in both treatment groups were similar with regard to sex, age, baseline disease activity, and baseline VZV immune

measures (Table 1). Among the 112 patients vaccinated and subsequently randomized, 16 discontinued because of AEs not related to the study drug (2 patients in the tofacitinib group and 7 patients in the placebo group), AEs related to the study drug (2 patients in the tofacitinib group and 2 patients in the placebo group), or an insufficient clinical response (1 patient in the tofacitinib group and 2 patients in the placebo group) (see Supplementary Figure 3, available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40187/abstract>).

Immunogenicity. Most patients (53 [93%] of those in the placebo group and 54 [98%] of those in the tofacitinib group) were evaluable for the immune response end points. Among these individuals, the GMFR for VZV-specific IgG levels at 6 weeks postvaccination was similar between the tofacitinib-treated and placebo-treated patients.

The mean VZV-specific IgG levels at 6 weeks postvaccination (4 weeks after treatment initiation) were 403.42 units/ml and 322.49 units/ml in tofacitinib-treated and placebo-treated patients, respectively (Figure 1A), and the GMFRs from baseline at this time point were 2.11 (80% CI 1.87–2.37) and 1.74 (80% CI 1.55–1.95), respectively. VZV-specific IgG levels were also evaluated on day 1 (2 weeks postvaccination) and after 3 months (14 weeks

Table 2. GMFR in VZV-specific IgG levels from baseline over the 12-week treatment period*

Visit, treatment	GMFR (80% CI)	GMFR ratios (tofacitinib/placebo) (80% CI)
Day 1 (2 weeks postvaccination)		
Tofacitinib 5 mg BID (n = 54)	2.01 (1.78–2.26)	1.03 (0.88–1.21)
Placebo (n = 53)	1.95 (1.73–2.19)	
Week 4 (6 weeks postvaccination)		
Tofacitinib 5 mg BID (n = 54)	2.11 (1.87–2.37)	1.21 (1.03–1.42)
Placebo (n = 53)	1.74 (1.55–1.95)	
Week 12 (14 weeks postvaccination)		
Tofacitinib 5 mg BID (n = 48)	1.64 (1.45–1.85)	1.09 (0.92–1.29)
Placebo (n = 44)	1.50 (1.32–1.69)	

* GMFR = geometric mean fold rise; VZV = varicella zoster virus; 80% CI = 80% confidence interval; BID = twice daily.

postvaccination) of tofacitinib or placebo treatment. At all postvaccination time points, there was a trend toward numerically higher GMFRs in tofacitinib-treated patients (Table 2), but the differences were small and not statistically significant. Furthermore, the proportion of patients developing a ≥ 1.5 -fold postvaccination increase in IgG levels at 6 weeks postvaccination trended higher for those receiving tofacitinib (57.4%) compared with those receiving placebo (43.4%) (Figure 1B). Similar results were observed in a subpopulation of patients who were not treated with corticosteroids and with data stratified

according to age (see Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40187/abstract>).

An ELISpot assay to enumerate VZV-specific IFN γ -secreting T cells was performed. For this cell-mediated immune response, the absolute VZV-specific reactive cell counts were 69.97 and 56.39 SFCs/10⁶ PBMCs 6 weeks postvaccination in the tofacitinib group and the placebo group, respectively (Figure 2). The GMFR in VZV-specific T cell responses at 6 weeks was similar in tofacitinib-treated patients (1.50; 80% CI

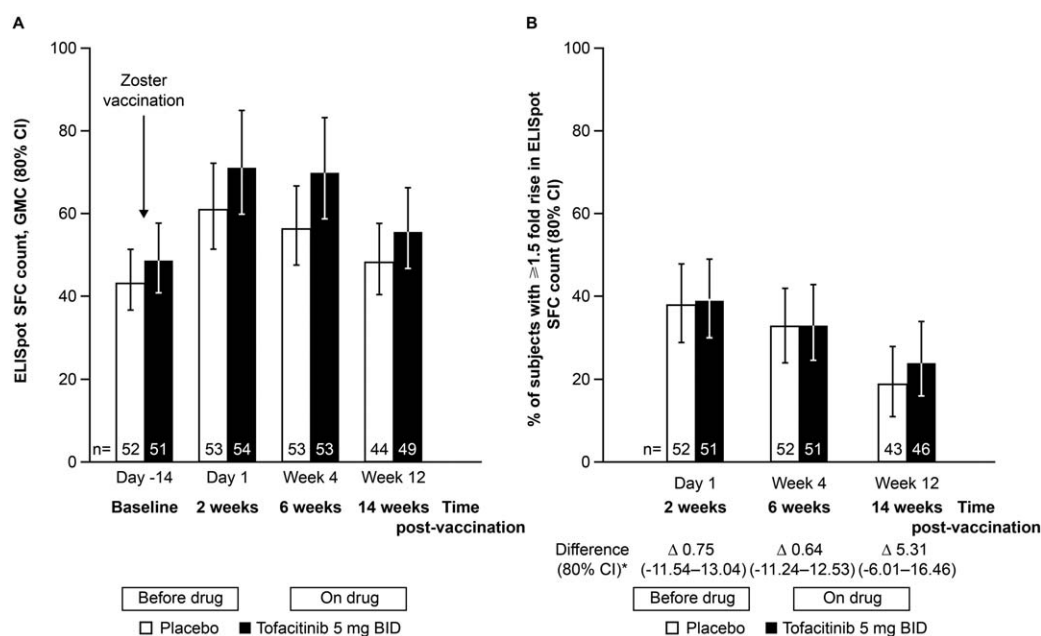


Figure 2. Analyses of VZV-specific T cell responses, measured by enumeration of interferon- γ spot-forming cells (SFCs) using enzyme-linked immunospot (ELISpot) assay. Live zoster vaccine was given on day -14; a blood sample from each subject was obtained at that time to evaluate the baseline immune response to VZV immediately before vaccination. **A**, Mean absolute values of VZV-specific reactive T cells, as determined by ELISpot assay, in the tofacitinib group and the placebo group at baseline (day -14, before vaccination) and 2, 6, and 12 weeks postvaccination. **B**, Proportion of patients with a ≥ 1.5 -fold change in the VZV-specific T cell response, as determined by ELISpot assay, in the tofacitinib group and the placebo group at 2, 6, and 12 weeks postvaccination. * = The 80% confidence intervals (80% CIs) were calculated using the Clopper-Pearson exact method. GMC = geometric mean count (see Figure 1 for other definitions).

Table 3. GMFR in VZV-specific T cell responses over the 12-week treatment period*

Visit, treatment	GMFR (80% CI)	Ratio of GMFRs tofacitinib/placebo (80% CI)
Day 1 (2 weeks postvaccination)		
Tofacitinib 5 mg BID (n = 51)	1.54 (1.35–1.75)	1.10 (0.92–1.31)
Placebo (n = 52)	1.40 (1.23–1.58)	
Week 4 (6 weeks postvaccination)		
Tofacitinib 5 mg BID (n = 51)	1.50 (1.31–1.70)	1.16 (0.97–1.38)
Placebo (n = 52)	1.29 (1.14–1.46)	
Week 12 (14 weeks postvaccination)		
Tofacitinib 5 mg BID (n = 46)	1.17 (1.02–1.34)	1.05 (0.88–1.27)
Placebo (n = 43)	1.11 (0.97–1.27)	

* GMFR = geometric mean fold rise; VZV = varicella zoster virus; 80% CI = 80% confidence interval; BID = twice daily.

1.31–1.70) and placebo-treated patients (1.29; 80% CI 1.14–1.46) (Table 3). This increase was also similar at weeks 2 and 14 postvaccination. The proportion of patients developing a ≥ 1.5 -fold postvaccination increase in the T cell response was similar between groups at 6 weeks postvaccination (33.3% in the tofacitinib group and 32.7% in the placebo group), as well as other postvaccination time points (Figure 2B). Similar results were observed when we analyzed a subgroup of patients who did not receive concomitant glucocorticoids (see Supplementary Table 2, available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40187/abstract>).

Safety. One patient in the placebo group discontinued treatment following abnormal results for the absolute neutrophil count; other nonserious vaccine-related AEs were identified in 7 patients in the tofacitinib group and 5 patients in the placebo group (see Supplementary Table 3, available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40187/abstract>). These AEs included mild injection-site swelling, redness, or itching.

SAEs occurred in 3 patients in the tofacitinib group (5.5%) and 0 patients in the placebo group (0%). The 3

SAEs included 1 case each of cholangitis and bronchitis, and 1 case of disseminated primary varicella. Onset of the disseminated rash occurred 16 days postvaccination (2 days after starting tofacitinib), on the patient's trunk (back and abdomen) and right ipsilateral arm. The patient discontinued tofacitinib and was treated with antiviral (valacyclovir) therapy for 7 days, and the rash resolved. She was not hospitalized and continued to receive background oral MTX (15 mg/week) and oral prednisone (4 mg/day) for RA, as per prior and upon vaccination. Biopsy specimens from both her abdomen and forearm showed mixed deep granulomatous perivascular inflammation with fibrinoid degeneration of vessel walls, which was morphologically compatible with VZV infection. Molecular testing in the abdominal specimen showed PCR positivity for VZV DNA, with subsequent genomic work-up at the CDC confirming that VZV was the Oka vaccine strain.

Subsequent evaluation of this patient's baseline blood specimens showed that she lacked preexisting immunity to VZV. Unlike any other patient in the study, she had no measurable VZV-specific T cell response and a negative gpELISA titer at baseline (Table 4). Interestingly, at 2 weeks after vaccination (and just prior to starting tofacitinib treatment), this patient had no measurable

Table 4. VZV-specific immune response evaluations in the patient with disseminated HZ*

Immune response, assay	Day -14, before vaccination (1/13/15)	Day 1, 2 weeks after vaccination (1/27/15)	Early termination, 6 weeks after vaccination (2/24/15)	Notes
VZV IgG, gpELISA	Undetectable	Undetectable	96.64 gpELISA units/ml	None
IFN γ response to VZV antigen, ELISpot	25 SFCs/10 ⁶ PBMCs \dagger	25 SFCs/10 ⁶ PBMCs	566 SFCs/10 ⁶ PBMCs	25 SFCs: negative response (no VZV-specific T cells)
VZV IgM, ELISA	0.54 units/ml	0.55 units/ml	>5.00 units/ml	≤ 0.90 units/ml: negative response (no VZV-specific IgM)

* VZV = varicella zoster virus; HZ = herpes zoster; gpELISA = glycoprotein enzyme-linked immunosorbent assay; IFN γ = interferon- γ ; ELISpot = enzyme-linked immunospot.

\dagger Limit of detection = 25 spot-forming cells (SFCs)/10⁶ peripheral blood mononuclear cells (PBMCs).

response to vaccination, since the results of both the gpELISA and ELISpot assay remained negative. After developing disseminated vaccine-strain varicella, the patient developed robust immunity, as evidenced by 6-week postvaccination assessments in which the gpELISA titer was 96.6 units/ml and the ELISpot count was 566 SFCs/10⁶ PBMCs. Additional VZV-specific IgM and IgG avidity testing also showed negative responses at baseline and 2 weeks after zoster vaccination, followed by robust responses at week 6. These findings are consistent with a primary VZV infection.

DISCUSSION

To our knowledge, this study is the first to directly assess the safety and immunogenicity of the LZV in patients with RA. We observed that patients with active RA developed robust immune responses to this vaccine, and that starting tofacitinib treatment 2–3 weeks after vaccination had no negative impact on the established immune response. Patients treated with tofacitinib had similar or even numerically higher VZV-specific humoral and cell-mediated immune responses to the vaccine compared with placebo-treated patients. Importantly, although our results suggest that the vaccine is safe for RA patients with prior VZV exposure, they also indicate the potential need to either screen for prior exposure before giving this vaccine or waiting longer than 2–3 weeks before starting immunosuppression with tofacitinib.

Patients with RA are known to respond less robustly to certain vaccines (26,27). This is likely attributable to disease activity as well as, potentially, DMARD and corticosteroid use. LZV is currently contraindicated in patients receiving high-dose steroids (>20 mg/day prednisone or equivalent) or MTX at a dosage of >25 mg/week. Below these dosing thresholds, the vaccine is thought to be safe and effective, although this recommendation has been based on expert opinion in the absence of data (1). Importantly, the current study provides data for this recommendation, because the vaccine appeared to be adequately immunogenic as well as safe in patients receiving standard doses of MTX and/or lower doses of steroids. Although we did not enroll patients without RA in our study, for context it is useful to compare the magnitude of response observed in our study with that observed in studies in healthy individuals—the Shingles Prevention Study (SPS) (28) and the Zostavax Efficacy and Safety Trial (ZEST) (29). The SPS study enrolled more than 38,000 individuals ages ≥60 years, none of whom had RA. In the SPS Immunology Substudy, 1,395 individuals were evaluated using the same outcomes measures used in our study. They observed an average increase in VZV-specific IgG levels (gpELISA

titer) between baseline and 6 weeks postvaccination of 1.7-fold, and an ~2.0-fold increase was observed for the VZV-specific ELISpot measures (1,24,28,29). In the ZEST study, 2,269 healthy volunteers ages 50–59 years had a VZV-specific IgG increase of 2.3 at 6 weeks postvaccination (25). This magnitude of IgG responses in immunocompetent individuals was similar to what we observed. Although the magnitude of cell-mediated responses was slightly less than that observed in healthy individuals within the ZEST study, it is possible that this could be attributable to the older age of our study population, the impact of RA, or the therapies being used for these patients.

Our study provides the first data regarding use of LZV in patients with RA and suggests that these patients, even those being treated with nonbiologic DMARDs at the time of vaccination, are capable of mounting adequate immune responses to this vaccine. Furthermore, our data suggest that the use of tofacitinib following VZV vaccination in patients with RA did not negatively impact the vaccine immunogenicity or the time course of the immune response to the vaccine. Interestingly, immune responses in RA patients receiving tofacitinib 5 mg twice daily or placebo were comparable with those expected in healthy individuals (24,25). From a safety standpoint, our study highlights the potential for vaccine dissemination in an immunocompromised host. In the SPS trial, in which >19,000 patients received the vaccine, no cases of local or disseminated HZ with this vaccine strain occurred in the first 42 days after vaccination (28). Although we observed only 1 such case in a study of 112 patients, it is notable given the lack of such cases in a study as large as SPS. The SPS study did not check for preexisting VZV immunity before administering the vaccine (similar to our study design); however, it is highly likely that at least a handful of such individuals were entered into the study but did not develop vaccine dissemination. Interestingly, 100% of the 1,395 individuals analyzed in an immunology substudy had serologic evidence of prior VZV exposure, suggesting that the number of individuals lacking prior exposure within the SPS study was likely small (25). Based on the SPS experience, the vaccine is licensed and approved for patients ages 50 or older regardless of a history of VZV (30). In our 1 case of disseminated primary varicella, the patient developed an injection-site reaction the day she started receiving tofacitinib and a disseminated rash on day 16 after vaccination, just 2 days after starting tofacitinib. It is known that patients can have circulating virus for several weeks after vaccination, and a small number of individuals may shed virus in saliva for up to 4 weeks postvaccination (31). Given this temporal sequence, it is possible that tofacitinib may have played a role in vaccine dissemination. Because of this potential for prolonged viremia, some time lag between

vaccination and the start of immunosuppression makes theoretical sense, in order to further decrease the possibility of dissemination. Current recommendations suggest that this time lag should be 2–4 weeks (1,20), but our data would suggest that 4 weeks might be preferable. Alternatively, testing patients who do not recollect a history of chickenpox, to ensure prior exposure to VZV before vaccinating them, would also potentially mitigate this risk. In this case, our patient who lacked preexisting immunity would not have been a candidate for LZV.

A limitation of the current study is that the long-term effectiveness of the vaccine in RA patients was not investigated. However, this point is being investigated in the patients who joined an open-label LTE study of tofacitinib. In addition, because this study was conducted specifically to assess vaccine responses and not the efficacy of tofacitinib, further RA disease activity measures were not obtained. Last, our study was small in nature such that our conclusions regarding the safety of this vaccine and in RA patients in general are limited. Although only 1 case of vaccine dissemination occurred, in a patient lacking preexisting immunity, it is possible that other such cases could occur in the RA setting. Larger studies should be conducted to better understand the risk of this complication in RA patients in general.

In summary, we have conducted the first clinical study evaluating the use of LZV in patients with RA who are receiving nonbiologic DMARDs. In accordance with guidelines, our patients were vaccinated 2–3 weeks prior to starting tofacitinib therapy. Importantly, our data suggest that starting tofacitinib according to these guidelines does not hinder the immunogenicity of this vaccine, and that these patients were able to mount humoral and cell-mediated responses similar to those seen in other studies in healthy volunteers who do not have RA.

From a safety standpoint, the single event of disseminated shingles vaccine (Oka) virus in a patient without prior immunity suggests that patients should be screened for prior immunity (i.e., by eliciting a history of chickenpox or testing with commercially available VZV serologic tests) before receiving this vaccine, or that the time periods between vaccination and initiation of tofacitinib treatment should be longer (e.g., 4 weeks). Further research is necessary to understand the risk of this complication as well as the long-term effectiveness of this LZV to prevent HZ in this high-risk population.

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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. Dr. Winthrop 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.

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ROLE OF THE STUDY SPONSOR

The manuscript was drafted by Dr. Winthrop, with all authors providing subsequent critical revision. All authors interpreted the results, approved the final draft, and made the final decision to submit the manuscript for publication. Pfizer Inc did not control the analysis or interpretation of the study results. Pfizer Inc provided editorial assistance, performed by Sandrine M. Dupré, PhD, at Complete Medical Communications, funded by Pfizer Inc. Publication of this article was not contingent upon approval by Pfizer Inc.

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