Long-term effectiveness of live herpes zoster vaccine in patients with rheumatoid arthritis subsequently treated with tofacitinib

Herpes zoster (HZ) incidence is higher in patients with rheumatoid arthritis (RA) compared with the general population,[1] and it may be further increased with disease-modifying antirheumatic drugs (DMARDs).[2] Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. Real-world data indicate that HZ incidence is approximately twofold higher with tofacitinib versus biologic DMARDs (bDMARDs).[3]

Current American College of Rheumatology guidelines conditionally recommend that patients with RA aged ≥50 years receive HZ vaccine prior to tofacitinib or bDMARDs.[4] We previously evaluated the immunogenicity of a live attenuated zoster vaccine (LZV), administered 2–3 weeks prior to tofacitinib or placebo with background conventional synthetic DMARDs. Both groups had similar varicella zoster virus (VZV)-specific immune responses, and overall immune responses were comparable with those of healthy volunteers in previous studies.[5] We have now followed this patient cohort in an open-label, long-term extension (LTE) study of tofacitinib.

Patients enrolled in the index study (A3921237; NCT02147587)[5] could join ORAL Sequel (LTE study; A3921024; NCT00413699) 14 weeks post-vaccination, where they received open-label tofacitinib 5 or 10 mg two times per day (online supplementary figure S1); background RA therapy was also allowed. Patients were followed for 27 months. Post-vaccination, adverse events (AEs), including discontinuations due to AEs, were recorded during the study within 28 days of the last dose. Incidence rates (IRs; patients with events/100 patient-years (PY)) and 95% CIs for HZ post-vaccination were calculated based on time to first event (patients not reporting an event were censored at last treatment dose). Short-term VZV-specific immunity was evaluated at baseline and week 6 post-vaccination during the index study.

Vaccine-related AEs in the index study included mild injection-site pain, swelling, redness, itching and myalgia. Disseminated vaccine-strain varicella was also reported in a patient with no previous exposure to VZV.[5] After rollover into ORAL Sequel, 100 patients received an average tofacitinib dose of 5 mg (n=46) or 10 mg (n=54) two times per day. Mean (range) tofacitinib exposure was 489 (46–811) days and overall exposure was 139 PY.

LZV did not provide adequate protection to all patients. Five HZ cases (#1–5) occurred in the LTE study 218, 280, 748, 741 and 544 days post-vaccination, respectively (IR=3.60 (1.17, 8.39); table 1). Cases #1–4 were monodermatomal and case #5 involved five dermatomes. All HZ events were mild/moderate in severity and resolved with antiviral treatment.

VZV humoral immunity (immunoglobulin G (IgG) titre) and VZV cell-mediated immunity (interferon-γ enzyme-linked immunosorbent spot (ELISPOT)) in patients receiving

Table 1 Patient profiles of HZ cases

	Case #1	Case #2	Case #3	Case #4	Case #5
Age, years	65	60	77	74	74
Sex	Female	Male	Female	Male	Male
Race	White	White	White	White	White
Study drug (A3921237)	Tofacitinib 5 mg two times per day	Tofacitinib 5 mg two times per day	Placebo	Placebo	Placebo
Study drug (ORAL Sequel)	Tofacitinib 10 mg two times per day	Tofacitinib 5 mg two times per day	Tofacitinib 5 mg two times per day	Tofacitinib 10 mg two times per day	Tofacitinib 10 mg two times per day
Background RA drugs	MTX 15 mg/week Prednisone 5 mg/day	MTX 20 mg/week	None	None	MTX 20 mg/week
Type of HZ	Monodermatomal	Monodermatomal	Monodermatomal	Monodermatomal	5 dermatomes
Severity of HZ*	Moderate	Mild	Moderate	Mild	Mild
Duration of HZ, days	49	14	14	16	10
Action to study drug	No action taken	Stopped temporarily	No action taken	No action taken	Stopped temporarily
Outcome of HZ	Resolved with acyclovir	Resolved with famciclovir	Resolved with acyclovir and azithromycin	Resolved with valacyclovir	Resolved with valacyclovir
Occurrence of HZ					
Time after LZV vaccination, days	218	280	748	741	544
Time after initiation of tofacitinib, days	202	267	702	699	466
VZV humoral immunity (IgG titre), U/mL†					
Baseline	224.3	36.9	96.6	237.3	208.3
Week 6	444.0	70.9	186.9	231.5	222.5
Change from baseline (fold rise at week 6)	1.98	1.92	1.93	0.98	1.07
VZV cell-mediated immunity, SFCs/10^6 PBMCs‡					
Baseline	25	41	25	25	25
Week 6	25	76	51	25	25
Change from baseline (fold rise at week 6)	1.00	1.85	2.04	1.00	1.00

*Determined by the investigator.
†Assessed by gpELISA (PPD Vaccines and Biologics); mean VZV IgG titres in patients receiving tofacitinib and placebo, respectively, in the index study were 201 and 182 U/mL at baseline and 403 and 323 U/mL at week 6 (fold rise at week 6 was 2.11 with tofacitinib and 1.74 with placebo).[5]
‡Assessed by IFNγ ELISPOT (Pfizer Inc Vaccine Research Unit, Pearl River, New York, USA); limit of detection was 25 SFCs/10^6 PBMCs; values in the table shown as 25 SFCs/10^6 PBMCs may be below this threshold; mean VZV cell-mediated immunity in patients receiving tofacitinib and placebo, respectively, in the index study was 48 SFCs/10^6 PBMCs and 43 SFCs/10^6 PBMCs at baseline, and 70 SFCs/10^6 PBMCs and 56 SFCs/10^6 PBMCs at week 6 (fold rise at week 6 was 1.50 with tofacitinib and 1.29 with placebo).[5]
ELISPOT, enzyme-linked immunosorbent spot; gpELISA, glycoprotein-based enzyme-linked immunosorbent assay; HZ, herpes zoster; IFNγ, interferon gamma; IgG, immunoglobulin G; LZV, live zoster vaccine; MTX, methotrexate; PBMCs, peripheral blood mononuclear cells; RA, rheumatoid arthritis; SFCs, spot-forming cells; VZV, varicella zoster virus.

tofacitinib or placebo in the index study[5] are shown in table 1. In terms of immunity after LZV in this analysis, cases #1, #4 and #5 had undetectable VZV cell-mediated immunity, at baseline and week 6; cases #2 (patient received tofacitinib 5 mg two times per day in index and LTE studies) and #3 (patient received placebo and tofacitinib 5 mg two times per day in index and LTE studies, respectively) responded adequately to vaccination by both IgG and ELISPOT measures but had lower than average VZV IgG levels at baseline (case #2: 36.9 U/mL vs average of 201 U/mL; case #3: 96.6 U/mL vs average of 182 U/mL) and week 6 (case #2: 70.9 U/mL vs average of 403 U/mL; case #3: 186.9 U/mL vs average of 323 U/mL; table 1).

HZ incidence was similar to that in patients receiving tofacitinib in phase 1/2/3/LTE studies up to 9.5 years (IR=3.6 (3.4, 3.9); n=782/7061]),[6] although the present analysis was limited due to the small number of patients, and 95% CIs were wide. Cell-mediated responses in cases #2 and #3 may have been short-lived; however, serial longitudinal data are required to confirm this.

These results suggest that LZV may not provide adequate long-term protection, as previously demonstrated in healthy individuals aged ≥60 years 3 years post-vaccination, in which HZ risk was reduced by 51%.[2] While it is possible that LZV booster vaccinations may improve vaccine efficacy, to date there is a lack of data on the use and timing of booster vaccinations, and no recommendations on the use of LZV booster vaccinations currently exist. This highlights the importance of evaluating the newly approved subunit non-live vaccine (Shingrix) in patients with RA receiving tofacitinib.

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REFERENCES

1 Yun H, Yang S, Chen L, *et al*. Risk of herpes zoster in autoimmune and inflammatory diseases: implications for vaccination. *Arthritis Rheumatol* 2016;68:2328–37.
2 Winthrop KL, Furst DE. Rheumatoid arthritis and herpes zoster: risk and prevention in those treated with anti-tumour necrosis factor therapy. *Ann Rheum Dis* 2010;69:1735–7.
3 Curtis JR, Xie F, Yun H, *et al*. Real-world comparative risks of herpes virus infections in tofacitinib and biologic-treated patients with rheumatoid arthritis. *Ann Rheum Dis* 2016;75:1843–7.
4 Singh JA, Saag KG, Bridges Jr SL, *et al*. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol* 2016;68:1–26.
5 Winthrop KL, Wouters AG, Choy EH, *et al*. The safety and immunogenicity of live zoster vaccination in patients with rheumatoid arthritis before starting tofacitinib: a randomized Phase II trial. *Arthritis Rheumatol* 2017;69:1969–77.
6 Cohen S, Tanaka Y, Mariette X, *et al*. Long-term safety of tofacitinib up to 9.5 years: a comprehensive integrated analysis of the RA clinical development program [abstract]. *Arthritis Rheumatol* 2018;70:Abstract 963.