Safety, and Humoral and Cell-mediated Immune Responses to Herpes Zoster Vaccine in Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To examine humoral and cellular immune responses induced by a live attenuated herpes zoster (HZ) vaccine in patients with rheumatoid arthritis (RA) compared with osteoarthritis (OA) patients.

Methods. This was an observational study of a live attenuated HZ vaccine in 41 patients with RA receiving conventional disease-modifying antirheumatic drugs (cDMARD) and/or low-dose glucocorticoids (GC) and in 28 patients with OA. Blood samples were obtained before and at 12 weeks after HZ vaccination. Immunogenicity was assessed using varicella zoster virus (VZV)-specific interferon gamma ELISA and an in-house ELISA. Clinical outcomes, including adverse events, HZ occurrence, and RA flares, were analyzed.

Results. No patients developed vaccination-induced HZ during the followup period (median = 1.6 yrs). The HZ vaccine induced a significant increase in the VZV-specific enzyme-linked immunospot spot-forming units and anti-VZV immunoglobulin G antibodies in patients with RA and OA. The number of spot-forming units was lower in patients with RA than in patients with OA both at baseline and at 12 weeks after vaccination. The disease activity index for patients with RA was similar at baseline and at 12 weeks after vaccination. However, 6 patients with RA (14.6%) experienced a flare during the 12 weeks. Overall, 17 (24.6%) participants reported a mild adverse event such as an injection site reaction (11.6%).

Conclusion. The HZ vaccine induced VZV-specific cellular and humoral responses in patients with RA. Although patients with RA showed a weaker vaccine-induced VZV-specific cellular immune response than patients with OA, the vaccine may be considered in patients with RA receiving cDMARD and/or low dose GC. (J Rheumatol First Release February 1 2018; doi:10.3899/jrheum.170936)

Key Indexing Terms:
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Herpes zoster (HZ) infection is caused by reactivation of latent varicella zoster virus (VZV) and usually occurs decades after a primary infection (i.e., chickenpox)[1]. Defects in cell-mediated immunity (CMI) are important in reactivation of latent infection and subsequent development of HZ[2].

The overall rate of HZ infection in patients with rheumatoid arthritis (RA) is greater than that in the general population, and the risk is even greater in individuals receiving conventional disease-modifying antirheumatic drugs (DMARD) or biologics[3,4,5]. The use of glucocorticoids (GC) to treat RA is an important predisposing factor for HZ, and when taken in conjunction with DMARD, the risk is increased beyond that associated with DMARD alone[3,6].

The HZ vaccine is a live attenuated vaccine approved (in 2006) for use in individuals aged ≥ 50 years; the aim is to reduce the risk and severity of HZ infection[7]. The Shingles Prevention Study revealed that the HZ vaccine shows clinical efficacy in terms of reducing the incidence of HZ (by 51.3%) and postherpetic neuralgia (by 66.5%)[8]. The vaccine is thought to boost VZV-specific CMI in older adult subjects[9]. However, a population-based study reported lower vaccine

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efficacy in individuals with comorbid conditions such as diabetes mellitus, RA, or systemic lupus erythematosus[10].

Current guidelines issued by the American College of Rheumatology (ACR)[11] and the European League Against Rheumatism (EULAR)[12] recommend using the HZ vaccine before starting DMARD or biologics. It can be given to those already taking DMARD[11]. Because the HZ vaccine is a live attenuated preparation, there are some safety concerns. To our knowledge, to date there are no published data regarding the tolerability and immunogenicity of the HZ vaccine in patients with RA. Therefore, the aim of our present study was to examine VZV-specific humoral and cellular immune responses to the HZ vaccine in patients with established RA being treated with DMARD and/or low-dose GC. We also examined the tolerability and protective efficacy of the HZ vaccine in these patients.

MATERIALS AND METHODS

Study population and design. This was an observational cohort study that enrolled patients with RA or OA attending the Rheumatology Center, Seoul St. Mary's Hospital in South Korea between October 2014 and December 2015. All participants were aged ≥ 50 years and had serologic evidence of primary varicella infection. Exclusion criteria included receipt of any vaccine and/or any antiviral agent within 6 weeks of enrollment; known human immunodeficiency virus infection; or malignancy within 5 years of enrollment. To evaluate possible differences in immunogenicity, patients with OA were used as controls. All patients with RA eligible for the study fulfilled the 2010 ACR/EULAR classification criteria for RA[13]. Patients taking biologics, cyclophosphamide, prednisolone, or the equivalent (≥ 20 mg) within 3 months of enrollment were excluded. The patients with OA were not taking DMARD and/or oral GC. The study was approved by the institutional review board of Seoul St. Mary's Hospital (KC14OISI0058), and all subjects provided written informed consent.

All study participants received a commercially available zoster vaccine (0.65 ml). At baseline, subjects underwent physical examination and review of concomitant medications, comorbid conditions, and history of HZ reactivation. RA disease activity was assessed using the 28-joint Disease Activity Score (DAS28). All participants were provided with a telephone number and instructed to call at the first signs of rash, vesicles, or arthritis flare. A followup examination was performed at 12 weeks postvaccination. Subjects were also asked about any adverse events (AE). For patients with RA, the DAS28 was assessed at baseline, at the 12-week visit, and whenever swollen and/or tender joints occurred. An RA flare was defined as an increase in DAS28 by > 1.1 (ΔDAS28 > 1.1). Peripheral blood samples were obtained prior to vaccination and at 12 weeks after vaccination. Peripheral blood mononuclear cells (PBMC) were isolated on the day of blood drawing, frozen, and stored in liquid nitrogen until required.

Immunologic measurements. PBMC isolated at baseline and at 12 weeks after vaccination were analyzed on the same day. Only PBMC samples containing ≥ 90% viable cells after thawing were used in the VZV-specific interferon-γ (IFN-γ) enzyme-linked immunospot (ELISPOT) assay. Thawed PBMC were incubated overnight in culture medium (RPMI 1640 supplemented with 10% fetal bovine serum).

Multiscreen Immobilon-P membrane 96-well plates were prepared as per the manufacturer's instructions (BD ELISPOT Human IFN-γ Set; BD Biosciences). An ultraviolet-irradiated (5000 J/m^2) HZ vaccine (MSD) was used as the antigen. Subsequently, 4×10^5 PBMC were added to each well in duplicate. Phytohemagglutinin was used as a positive control, and PBMC in culture medium alone were used as negative controls.

ELISPOT plates were incubated for 48 h at 37°C/5% CO_2 in a humidified incubator. The plates were then washed and developed in accordance with the manufacturer's instructions. Spots were developed for 10 min, and wells were airdried overnight at room temperature. Spots were then counted in an EliSpot Reader (AID; Autoimmun Diagnostika GmbH) and reported as the net number of VZV-specific IFN-γ spot-forming units (SFU) per 10^6 PBMC. The mean SFU in the negative control samples was subtracted from the mean SFU in the VZV-stimulated wells, and reported as the net number of VZV-specific IFN-γ SFU per 10^6 PBMC.

Anti-VZV immunoglobulin G (IgG) activity in serum was measured using an in-house ELISA, both prior to vaccination (baseline) and at 12 weeks after. Results were reported as the index value, and the sample was considered negative if the index value was < 0.8. The highest reference index value was 10.

Statistical analysis. The normality of the variables was assessed using the Shapiro-Wilk test. Comparisons between groups were made using the Mann-Whitney U test. The Wilcoxon signed- rank test was used to compare ELISPOT and ELISA results at baseline and at 12 weeks postvaccination. Categorical data were compared using the chi-square test or Fisher's exact test as appropriate. A p value < 0.05 was considered statistically significant. Results are expressed in median (IQR) or n (%). Statistical analysis of pooled data was performed using SAS software (Version 9.4; SAS Institute Inc.).

RESULTS

Demographic characteristics of the study subjects. In total, 41 patients with RA and 28 with OA were enrolled. The characteristics of the participants are shown in Table 1. Age, sex, and comorbid conditions were similar between groups. Most patients with RA were seropositive (92.7%).

Among the patients with RA, 39 (95%) were in remission (DAS28 < 2.6) before HZ vaccination whereas the other 2 (5%) showed low disease activity (2.6 ≤ DAS28 ≤ 3.2). All

Table 1. Baseline characteristics of the HZ vaccine recipients. Values are n (%) or median (IQR).

Characteristics	RA, n = 41	OA, n = 28	p
Age, yrs	60 (55–63)	62 (58–67)	0.074
Sex, female	38 (92.7)	24 (85.7)	0.347
Disease duration, yrs	7.5 (2.4–14.6)	—	
Seropositive RA	38 (92.7)	—	
RF, > 20 IU/ml	30 (73.2)	—	
ACPA, > 7 U/ml	35 (85.4)	—	
Comorbid conditions			
Diabetes mellitus	4 (9.8)	1 (3.6)	0.642
Hypertension	13 (31.7)	9 (32.1)	0.970
Previous HZ	5 (12.2)	3 (10.7)	> 0.999
Medications			
GC	25 (61.0)	—	
Daily dose, mg	2.5 (0–5)		
MTX	38 (92.7)	—	
Weekly dose, mg	10 (7.5–12.5)		
SSZ	3 (7.3)	—	
LEF	9 (22.0)	—	
HCQ	9 (22.0)	—	
Baseline ESR, mm/h	21 (12–37)		
Baseline CRP, mg/l	0.01 (0.01–0.04)		

ACPA: anticitrullinated protein antibodies; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; GC: glucocorticoids; HCQ: hydroxychloroquine; HZ: herpes zoster; IQR: interquartile range; LEF: leflunomide; MTX: methotrexate; OA: osteoarthritis; RA: rheumatoid arthritis; RF: rheumatoid factor; SSZ: sulfasalazine.

patients with RA received DMARD, and 44% received combination DMARD therapy: MTX and leflunomide (n = 8; 19.5%), MTX and hydroxychloroquine (n = 8; 19.5%), or MTX and sulfasalazine (n = 2; 4.9%). Low-dose GC (prednisolone or equivalent dose ≤ 7.5 mg/day) were prescribed for 61% of patients with RA.

Immunogenicity. Twelve weeks after vaccination, we noted a significant increase in the number of VZV-specific ELISPOT SFU and in anti-VZV IgG levels in both RA and OA patients (Figure 1). The baseline and 12-week followup median of VZV-specific ELISPOT SFU were lower in patients with RA than in patients with OA [baseline: 5 (3–10) and 9 (3–35), respectively, p = 0.056; 12 weeks: 18 (9–53) and 56 (20–119), respectively, p = 0.001; Figure 1A].

The baseline anti-VZV IgG index value was lower in patients with RA than in patients with OA [5.5 (2.6–8.0) and 8.0 (4.8–10), respectively; p = 0.022]. Because the values at 12 weeks after vaccination were increased in all participants, the anti-VZV IgG index values were not significantly different between the 2 groups (Figure 1B).

Clinical outcomes. There were no hospitalizations or episodes of HZ during the 12 weeks. Participants were followed up for a median 1.6 (1.4–1.8) years after receiving the HZ vaccination. No HZ infection was identified in any participants during followup.

Among the 69 participants, 17 (24.6%) experienced an AE within 7 days following vaccination. The most frequently reported AE was a reaction at the injection site, which was observed in 4 patients with RA and 4 patients with OA. All these injection site reactions comprised erythema and/or mild swelling, and all resolved spontaneously. All participants were afebrile (< 38°C) after vaccination. Overall, 8 (11.6%) participants experienced mild systemic AE, such as general weakness, headache, or rash.

In patients with RA, the median DAS28–C-reactive protein (CRP) did not change from baseline to 12 weeks after HZ vaccination [1.1 (1.1–1.5) and 1.4 (1.1–1.7), respectively; p = 0.506]. In addition, the erythrocyte sedimentation rate and CRP levels did not change significantly from baseline to 12 weeks. At 12 weeks after HZ vaccination, 36 patients (87.8%) remained in remission, 3 (7.3%) showed low-level disease activity (2.6 ≤ DAS28 ≤ 3.2) and 2 (4.9%) showed moderate disease activity (3.2 < DAS28 ≤ 5.1). Six patients with RA (14.6%) experienced an arthritis flare (ΔDAS28 > 1.1) between 6 and 12 weeks after HZ vaccination; 4 of these had transient arthritis and recovered spontaneously or after treatment with additional low-dose GC, whereas the other 2 were switched to antitumor necrosis (TNF)-α therapy (Table 2).

DISCUSSION

This prospective observational study evaluated VZV-specific cellular and humoral immune responses after live attenuated HZ vaccination of patients with RA taking DMARD and/or low-dose GC. The HZ vaccine induced an increase in VZV-specific ELISPOT and anti-VZV IgG levels in patients with RA. The vaccinated patients with RA had not developed HZ for a median 1.6 (1.4–1.8) years, and had no serious AE.

Studies show that the HZ vaccination rate among patients with RA is 1.2–2.5%[7,14]. When considering the risk-to-benefit ratio of the HZ vaccine in individuals with underlying autoimmune diseases such as RA, safety concerns are paramount. One of the main safety concerns is direct infection from the vaccine itself because patients with RA are usually taking several immunosuppressive medications.

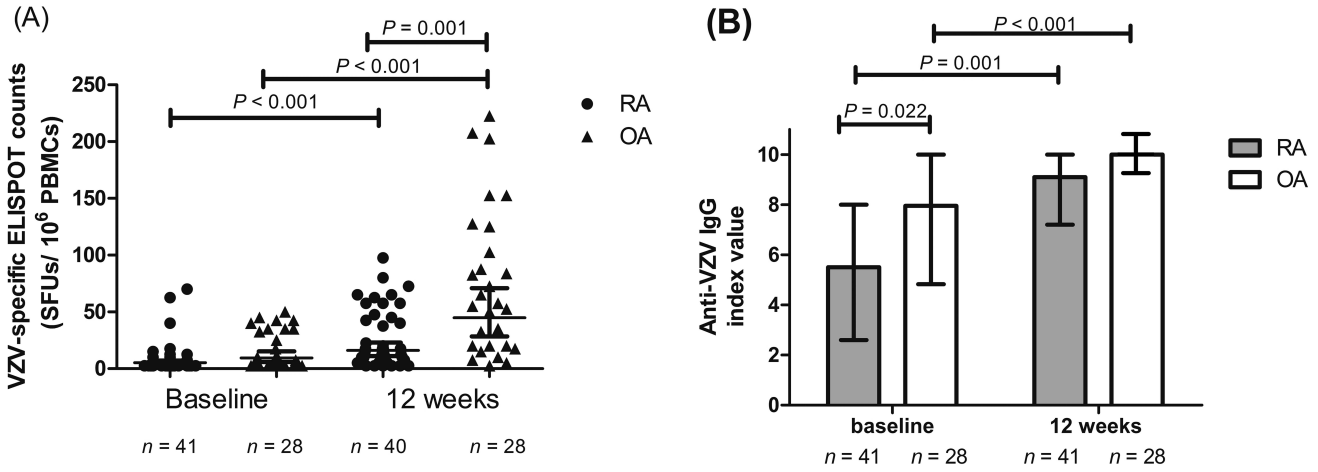

Figure 1. Vaccine-induced cellular and humoral immune response to VZV in patients with RA and OA. A. Number of interferon-γ ELISPOT SFU for VZV stimulation (according to timepoint) for patients with RA (circles) and OA (triangles) after HZ vaccination. B. Assay of anti-VZV IgG antibodies in serum from patients with RA and OA at baseline and at 12 weeks after vaccination. Data are expressed as median and IQR. Statistical significance was calculated using the Wilcoxon log-rank test and Mann-Whitney U test as appropriate. VZV: varicella zoster virus; RA: rheumatoid arthritis; OA: osteoarthritis; ELISPOT: enzyme-linked immunospot; SFU: spot-forming units; HZ: herpes zoster; IgG: immunoglobulin G; IQR: interquartile range; PBMC: peripheral blood mononuclear cells.

Table 2. Detailed characteristics of patients experiencing an RA flare within 12 weeks of HZ vaccination.

Sex/Age	RF, IU/ml*/ ACPA, U/ml†	Remission Duration‡, mos	Medication	Baseline DAS28	TJC/SJC	Onset, wk	Flare DAS28	TJC/SJC	Location	Remark
F/60	55.2/–	8.8	MTX 7.5 mg, PSL 7.5 mg	1.0	0/0	7	2.8	1/1	Right knee	Positive joint effusion: WBC 9000/μl; IA triamcinolone; started anti–TNF-α therapy 20 wks later
F/55	5.8/> 100	26.2	MTX 7.5 mg, LEF 10 mg, PSL 2.5 mg	1.0	0/0	12	2.9	2/2	Left 2nd, 3rd MCP	Recovered spontaneously
F/61	13.3/329	7.3	LEF 10 mg, PSL 10 mg	1.1	0/0	9	2.5	1/1	Right shoulder	Biceps tenosynovitis on ultrasound; IA triamcinolone injection
F/56	103.4/303	10.0	MTX 10 mg, SSZ 1 g	2.0	0/0	12	3.4	2/2	Both 2nd MCP	Right ankle synovitis on ultrasound; started anti–TNF-α therapy 5 wks later
F/67	2.9/< 0.05	33.0	MTX 10 mg	1.1	0/0	9	2.6	2/2	Left 2nd, 3rd PIP	Recovered spontaneously
F/54	160.7/–	14.7	SSZ 1 g	1.1	0/0	12	3.4	6/2	Both wrists	Added PSL 5 mg, temporary

*Reference range, 0–20 IU/ml. †Reference range, < 7 U/ml. ‡Duration of remission calculated from the last flare to the time of HZ vaccination. ACPA: anti-citrullinated protein antibodies; IA: intraarticular injection; DAS28: 28-joint Disease Activity Score; HZ: herpes zoster; LEF: leflunomide; MCP: metacarpophalangeal joint; MTX: methotrexate; PSL: prednisolone; PIP: proximal interphalangeal joint; RF: rheumatoid factor; SJC: swollen joint count; SSZ: sulfasalazine; TJC: tender joint count; TNF-α: tumor necrosis factor–α; WBC: white blood cells; RA: rheumatoid arthritis.

Here, we found that none of the patients taking DMARD and/or low-dose GC experienced HZ infection after vaccination. Another safety concern is a flare of the underlying disease. We found that 6 (14.6%) patients with RA experienced an arthritis flare between 6–12 weeks after HZ vaccination. However, apart from the 2 patients who were switched to anti-TNF-α therapy, the arthritis flares were transient. All flares occurred after 6 weeks, which is considered an incubation period for HZ. Thus, we could not determine that HZ vaccination had a direct effect on RA activity.

T cell receptor repertoire, fundamentally important to recognize all potential antigens, is significantly contracted in patients with RA[15]. In addition, the ability to produce naive T cells and to maintain peripheral T cell homeostasis was also impaired[16,17]. Response to vaccine is associated with repertoire maintenance and T cell proliferation after vaccination; contraction of memory T cell repertoire and abnormalities in T cell homeostasis could be explanations for reduced VZV-specific CMI in patients with RA.

The strength of the VZV-specific CMI is inversely correlated with the development of HZ[18]. In addition, HZ patients with a stronger VZV-specific CMI during the first week after HZ onset tend to have milder HZ infection and a lower incidence/severity of postherpetic neuralgia than those with weaker VZV-specific CMI[9]. Protection might be mediated by direct interaction between T cells and neurons, which prevents VZV reactivation; alternatively, VZV reactivation might be prevented by a rapid T cell response that limits the early infection before it becomes clinically apparent[19]. The HZ vaccine increases the numbers of VZV-specific T helper, memory, early effector, and cutaneous homing receptor-bearing T cells[20]. The vaccine-induced increase in VZV-specific CMI is maximal at 6 weeks after vaccination and declines rapidly between 6 weeks and 1 year after vaccination[9]. Although the response decreases over time, the CMI induced by the HZ vaccine persists for 3 years[9]. We found that the vaccine-induced VZV-specific CMI was lower in patients with RA than in those with OA. Thus, persistent vaccine efficacy may also be low in the former. Currently, it is unclear what level of VZV-specific CMI is necessary to prevent patients with RA from developing HZ. Thus, larger longitudinal studies are necessary to fully examine the preventive effects of the HZ vaccine in patients with RA.

Our study has several limitations. First, we could not compare healthy individuals and patients with RA. We used a control group comprising patients with OA not taking DMARD and/or GC. These participants were presumed to have normal immune systems. Second, we did not measure VZV glycoprotein ELISA, which is common in HZ vaccine studies. Although VZV-specific antibodies do not protect against HZ[9,18], we measured them using an in-house anti-VZV IgG ELISA. Because the detection limit of this test in our hospital is 10 index values, our study cannot provide accurate information about the degree of boosting effect on humoral immunity.

To the best of our knowledge, this is the first study to examine humoral and cellular immune responses and tolerability in patients with RA receiving a live attenuated HZ vaccine. Because our study was performed at a single center,

we were able to acquire detailed medical histories and monitor AE, including joint flares, closely. The results may inform clinical decision making regarding management of RA and future HZ vaccine testing and targeting in such patients.

The live attenuated HZ vaccine induced cellular and humoral immune responses in patients with RA taking DMARD and/or low-dose GC with no serious AE. Although the magnitude of CMI was relatively low in patients with RA, none developed HZ during the median 1.6-year observation period. Thus, administration of a live attenuated HZ vaccine to stable RA patients without biologics is likely to be of benefit.

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