Herpes Zoster Vaccination in SLE: A Pilot Study of Immunogenicity

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ABSTRACT. **Objective.** Patients with systemic lupus erythematosus (SLE) are at increased risk of herpes zoster (HZ). Although a vaccine for HZ has been approved by the US Food and Drug Administration, its use in immunocompromised individuals remains controversial because it is a live-attenuated virus vaccine. We performed a pilot study of the immunogenicity of the HZ vaccine (Zostavax) in patients with SLE.

Methods. Ten patients with SLE and 10 control subjects ≥ age 50 years participated in this open-label vaccination study. All were seropositive for varicella zoster virus (VZV). Patients with SLE were excluded for SLE Disease Activity Index (SLEDAI) > 4, or use of mycophenolate mofetil, cyclophosphamide, biologics, or > 10 mg prednisone daily. Followup visits occurred at 2, 6, and 12 weeks. Clinical outcomes included the development of adverse events, particularly HZ or vesicular lesions, and SLE flare. Immunogenicity was assessed with VZV-specific interferon-γ-producing enzyme-linked immunospot (ELISPOT) assays and with antibody concentrations.

Results. All subjects were women. Patients with SLE were slightly older than controls (60.5 vs 55.3 yrs, p < 0.05). Median baseline SLEDAI was 0 (range 0–2) for patients with SLE. No episodes of HZ, vesicular rash, serious adverse events, or SLE flares occurred. Three injection site reactions occurred in each group: mild erythema or tenderness. The proportion of subjects with a > 50% increase in ELISPOT results following vaccination was comparable between both groups, although absolute SLE responses were lower than controls. Antibody titers increased only among controls following vaccination (p < 0.05).

Conclusion. The HZ vaccination yielded a measurable immune response in this cohort of patients with mild SLE taking mild-moderate immunosuppressive medications. No herpetiform lesions or SLE flares were seen in this small cohort of patients. ClinicalTrials.gov ID:NCT01474720. (First Release Sept 15 2013; J Rheumatol 2013;40:1875–80; doi:10.3899/jrheum.130170)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS   HERPES ZOSTER   VACCINE
ZOSTAVAX   INFECTION   CLINICAL TRIAL

Herpes zoster (HZ) is caused by reactivation of latent varicella zoster virus (VZV) that usually occurs decades following initial exposure. The rash usually lasts 7–10 days, during which the virus may be transmissible through airborne particles. Complications include postherpetic neuralgia, bacterial superinfection, and disseminated disease with meningoencephalitis. HZ incidence increases with age, presumably as cell-mediated immunity (CMI) naturally wanes. Studies of VZV-CMI in unvaccinated individuals estimate a 2.7%–3.9% decrease with each year of age after 60, whereas VZV-specific antibody levels remain essentially unchanged[1].

Several studies have shown that HZ is more common and can present with more severe manifestations among patients with systemic lupus erythematosus (SLE)[2,3,4,5,6,7,8,9,10,11,12]. Some studies suggest that the incidence may be increased in SLE even in the absence of immunosuppressive medications[3,9] and during periods of relative disease quiescence[13], possibly because of an inherent deficiency in CMI associated with the disease process itself.

The HZ vaccine (Zostavax) is a live, attenuated version of the Oka/Merck strain of VZV. It has at least 14 times the potency of the varicella vaccine. The HZ vaccine was licensed in the United States and Europe in 2006 for adults aged ≥ 60 years based on a large phase III clinical trial that showed a reduction in the incidence of HZ by 51.3%[14]. It is now licensed for individuals ≥ 50 years[15]. An immuno-

logical substudy of the Shingles Prevention Study demonstrated a clear association between increased CMI and protection from the development of HZ, although a threshold level could not be identified[16]. In contrast, VZV-specific antibody titers were not associated with protection.

The US Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices has published guidelines regarding use of the HZ vaccine[17] stating that vaccination should be safe for persons taking moderate doses of prednisone, methotrexate (MTX), or azathioprine (AZA) for autoimmune diseases; however, this is not based upon any evidence of safety in these populations.

Because the HZ vaccine is a live-attenuated vaccine, theoretical concerns remain about the safety of vaccination in immunocompromised patients, including patients with SLE. To date, there are no published data regarding the tolerability and immunogenicity of the HZ vaccine in subjects with autoimmune diseases; therefore, its use in this population remains the subject of debate despite documented increased risk of HZ reactivation. Indeed, current guidelines from the European League Against Rheumatism and the American College of Rheumatology (ACR) recommend against the HZ vaccine in many individuals with autoimmune diseases[18,19].

We performed a pilot study to ascertain preliminary estimates of immunogenicity to the HZ vaccine in patients with SLE compared to healthy control subjects.

MATERIALS AND METHODS

Study design. We performed a pilot, open-label, prospective 12-week study of the commercially available HZ vaccine in 10 subjects with SLE and a comparison cohort of 10 healthy subjects (ClinicalTrials.gov ID:NCT01474720). SLE subjects were recruited from the Oklahoma Rheumatic Disease Research Center (NIH AR053483) and clinics. Healthy controls were recruited from participants in the Oklahoma Immune Cohort (NIH GM103510). The study received local institutional review board approval prior to initiation, and all subjects provided written informed consent.

Inclusion criteria were age ≥ 50 years; serologic evidence of primary varicella infection; diagnosis of SLE according to 1992 modified ACR criteria[20], or healthy subject. Patients with SLE were required to have stable, mild disease activity defined by a clinical SLE Disease Activity Index (SLEDAI)[21] score ≤ 4 (clinical SLEDAI excluded complement levels or double-stranded DNA antibodies); acceptable immunosuppressive medications had to be stable for 60 days prior to screening and were limited to prednisone ≤ 10 mg daily; hydroxychloroquine (HCQ) ≤ 6.5 mg/kg daily; MTX ≤ 20 mg weekly; or AZA ≤ 150 mg daily. Other immunosuppressive or biologic medications, including mycophenolate mofetil (MMF), were excluded from the study because they were not addressed in the CDC guidelines for the HZ vaccine. Changes in medications were permitted only in situations where increased immunosuppression may be needed to treat disease flare.

Exclusion criteria included any prior receipt of a VZV-containing vaccine (primary varicella or zoster); history of HZ reactivation within 5 years of screening; receipt of any live vaccine within 6 weeks or recombinant vaccine within 2 weeks of enrollment; known hepatitis B or C virus or human immunodeficiency virus infection; diabetes mellitus; malignancy within 5 years of screening; contraindication to use of famciclovir; active lupus nephritis or cerebritis; proteinuria > 1.5 g/day; serum creatinine > 1.5 mg/dl; MMF within 3 months of screening; and cyclophosphamide within 6 months or rituximab within 2 years of screening. Healthy subjects were excluded if they were taking corticosteroids or other immunosuppressive medications for any reason.

Study assessments. At baseline, subjects underwent physical examination and review of concomitant medications. SLE disease activity was assessed using the SLEDAI and the SLEDAI flare index[22]. Peripheral blood and urine samples were obtained for clinical assessments; plasma and peripheral blood mononuclear cells (PBMC) were collected for assays of VZV-specific immune response. Following baseline study assessments, all subjects received a single subcutaneous dose of commercially purchased HZ vaccine (Merck; ≥ 19,400 plaque-forming units), according to the manufacturer's directions. Subjects were provided with telephone numbers and instructed to call for any signs of rash or vesicles near the injection site. Followup assessments occurred at Weeks 2, 6, and 12. At each visit, subjects were assessed for adverse events, with particular focus on injection site reactions and development of vesicular or bulliform lesions around the injection site. All other adverse events and medication changes were recorded. SLEDAI and the SLEDAI Flare Index were assessed for all SLE participants. Peripheral blood and urine samples were collected for clinical assessments. Plasma and PBMC were processed and frozen for batched analyses of VZV-specific immune response.

Preparation of frozen PBMC. PBMC from each study timepoint were isolated and stored in liquid nitrogen. Cell samples from all visits for a lupus case and a control subject were analyzed on the same day. Frozen cells were suspended in 37º C media supplemented with 25 U/ml benzonase (Sigma). Cells were centrifuged at 1000 rpm for 8 min, washed twice. The viable cell concentration (cells/ml) was determined, and the concentration was adjusted to 2×10^5 cells/ml and 1×10^6 cells/ml.

Interferon-γ (IFN-γ) enzyme-linked immunospot (ELISPOT) assay for VZV response. Multiscreen Immobilon-P membrane plates were prepared per manufacturer's instructions (ELISPOT Human IFN-γ Set, BDBiosciences). On day of assay, fresh media were added to each well and the plates were incubated at room temperature for 2 h. Phytohemagglutinin-M (PHA-M) and antigens [Vero uninfected cell extract and VZV-Vero inactivated cell extract (Advanced Biotechnologies Inc.)] used for stimulation were prepared in media. Preincubation media were removed from the wells, and 100 μl of PHA-M (50 μg/ml) or antigen (30 μg/ml) was added to the appropriate wells. One hundred microliters of the 2×10^5 cells/ml cell suspension was plated for the PHA-M positive control wells, and 1×10^6 cells/ml was plated for the antigen wells. The plate was then incubated at 37°C, in a 5% CO_2 and humidified incubator for 18 h, then washed and developed according to manufacturer's instructions. Spots were allowed to develop for 15–20 min, and wells were washed with water and then air-dried at room temperature overnight. Spots were enumerated manually using an ELISPOT plate reader. Each sample was run in duplicate. The results are a comparison of the median number of spot-forming units (SFU) of duplicate wells between patients with SLE and control subjects at the different timepoints.

VZV-specific IgG antibody assessments. Anti-VZV IgG reactivity was assessed using the commercial Varicella-Zoster Virus IgG ELISA II kit (Wampole) according to manufacturer's instructions. Positive and negative controls and calibrators were included in the kits. Results were assessed by determining a "cutoff OD value" for the positive sample using the following formula:

$$CF \times mean\ OD_{(calibrator)} = OD_{(cutoff)}$$

where CF is the correction factor provided by the manufacturer for each lot of the kit. An "index" value (or OD ratio) for each sample is then calculated by dividing the OD (sample) by the OD (cutoff). The sample is considered negative if the index value is < 0.90, equivocal if the value varies between

0.91 and 1.09, and positive for IgG antibodies against VZV if > 1.1. Higher index values semiquantitatively reflect increased anti-VZV titers.

Study design and endpoints. The study was designed to provide preliminary experience with the HZ vaccine in a small cohort of patients with SLE compared to healthy subjects to obtain estimates of tolerability and immunogenicity. Clinical outcomes included the development of lesions suspicious for VZV or clinical HZ following vaccination; development of vaccine-related adverse events, including injection site reactions; and flare or significant increase in SLEDAI among patients with SLE. Immunogenicity endpoints included increase in VZV-specific IFN-γ-producing ELISPOT SFU and change in anti-VZV IgG concentrations following vaccination.

Statistical analyses. Because there are no previous data on immunogenic response to HZ vaccine in SLE populations from which to compute power estimates, sample size was determined by feasibility of recruitment at a single site within a reasonable time frame. One of the goals of our study was to derive initial estimates of immunogenic response, to power future studies. Therefore, our study was designed without statistical comparisons between groups. Descriptive results were presented as mean (SD) or median (range) as appropriate. Comparisons between cell-mediated or antibody response to vaccination were performed using the Mann-Whitney test, with significance set at $\alpha = 0.05$.

To determine potential relationships between SLE-related immunological variables and cell mediated response, Spearman's correlation coefficients were determined individually for total leukocyte count, absolute lymphocyte count, complement 3 and complement 4, and VZV-specific or PHA-mediated ELISPOT results. This analysis was performed only for patients with SLE.

RESULTS

Baseline characteristics of study population. Ten patients with SLE and 10 healthy subjects were recruited from January through March 2012. Patients with SLE were slightly older than healthy subjects (60.5 vs 55.3 yrs, p = 0.03; Table 1). Four patients with SLE and 2 controls had a clinical history of HZ prior to enrollment. Seven patients with SLE were receiving HCQ; 2 were taking low-dose MTX; and 4 were taking low-dose prednisone. The median SLEDAI score at baseline was 0 (range 0–2). By entry criteria, no control subjects were receiving corticosteroids or other immunosuppressant medications. Aside from age, there were no statistically significant differences between baseline demographics or history of HZ between the groups.

Clinical outcomes. All subjects completed the 12-week study. No serious adverse events, hospitalizations, episodes of HZ, or SLE flares occurred (Table 2). No immunosuppressive or other medication changes occurred during the 12-week study. Three patients in each group experienced injection site reactions: all were mild and consisted of self-limited erythema and/or tenderness. No vesicular or herpetiform lesions occurred, and no systemic complaints (fever, myalgias) were reported. The median SLEDAI was 0–1 (range 0–3) over the 12-week study (p = NS). In 5 subjects, SLEDAI did not change over time. In all other cases, SLEDAI changed by only 2 points during the study, all reflecting minor changes in complement levels that crossed the threshold of the lower limit of normal. These modest changes were considered normal variations of stable disease and were not deemed clinically significant.

Cell-mediated response. At each timepoint, median VZV-specific ELISPOT results were lower in patients with SLE compared to controls (Figure 1A). The proportion of subjects with a 50% increase in the frequency of SFU over baseline was similar in patients with SLE and controls (63% SLE vs 60% controls at 2 weeks; 44% SLE vs 56% controls at 6 weeks; and 44% in both SLE and controls at 12 weeks after vaccination). To determine whether the difference in VZV-specific cell-mediated response was a function of a generally depressed cellular immunity in patients with SLE, IFN-γ ELISPOT results following stimulation with PHA were compared between groups at each timepoint (Figure 1B). Among control subjects, the interquartile range of SFU was similar at all timepoints, and did not change substantially following the vaccination. Except for the 6-week timepoint where patients with SLE had statistically lower median VZV-specific results (p = 0.006), differences between patients with SLE and controls were not clinically or statistically significant, and fewer than 20% of subjects in either group experienced a 50% increase in PHA-mediated response at any time following vaccination.

Table 1. Baseline demographic and clinical characteristics of participants.

Characteristics	SLE	Healthy
n	10	10
% female	100	100
Age, yrs, mean (SD)	60.5 (5.4)*	55.3 (4.2)
White, n	7	7
African American, n	3	3
History of shingles, n	4	2
Taking prednisone, n	4	0
Mean daily dose, mg	6.9	—
Taking HCQ, n	7	0
Taking MTX, n	2	0
Baseline SLEDAI, median (range)	0 (0–2)	—

* p < 0.05 compared to healthy subjects. HCQ: hydroxychloroquine; MTX: methotrexate; SLE: systemic lupus erythematosus; SLEDAI: SLE Disease Activity Index.

Table 2. Adverse events and SLE disease activity following HZ vaccine.

	SLE	Healthy
HZ, n	0	0
Serious adverse event, n	0	0
ISR (any), n	3	3
Erythema, tenderness, n	3	3
Vesicular lesions, n	0	0
2-week SLEDAI, median (range)	0 (0–3)	—
6-week SLEDAI, median (range)	1 (0–3)	—
12-week SLEDAI, median (range)	0 (0–3)	—
SLE flare, n	0	—

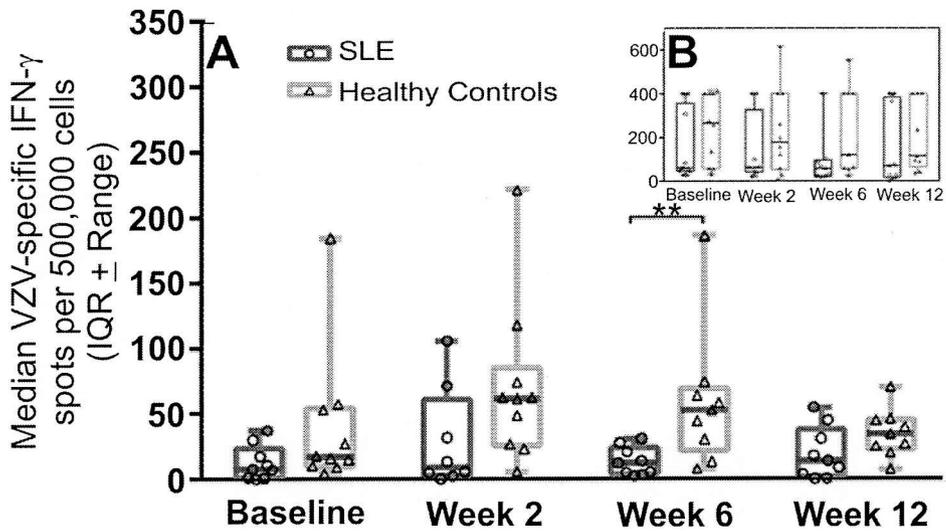ISR: injection site reaction; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; HZ: herpes zoster.

Figure 1. A. Number of interferon-γ (IFN-γ) enzyme-linked immunospot (ELISPOT) spot-forming units with varicella zoster virus (VZV) stimulation by timepoint for patients with systemic lupus erythematosus (SLE) and control subjects. Inset panel B displays the number of IFN-γ ELISPOT spot-forming units with phytohemagglutinin stimulation by timepoint for patients with SLE and control subjects. The median number of spots is displayed as a horizontal bar within the box plot with the interquartile range (IQR) ± range graphed. **Statistical significance using a Mann-Whitney U test with α = 0.05.

Humoral response. Although not protective, VZV-specific IgG concentrations were quantitated at the baseline and at each followup visit (Figure 2). Values were statistically increased from baseline at all timepoints among healthy adults, but no statistical significance was seen in change of

IgG concentrations among patients with SLE over time. By 12 weeks, fewer than 25% of subjects in either group had concentrations that were 50% higher than baseline levels.

Correlations between leukocyte count or complement and CMI. When all study visits were combined, a moderate
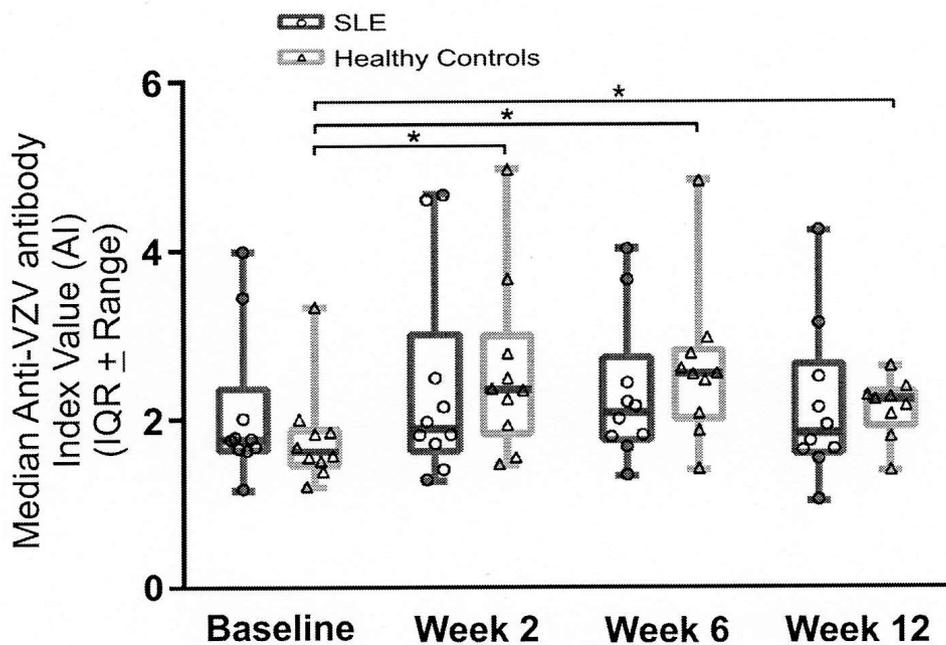

Figure 2. Median [interquartile range (IQR)] anti-varicella zoster virus (VZV) IgG index value at each timepoint for patients with systemic lupus erythematosus (SLE) and control subjects. *Statistical significance using a Mann-Whitney U test with α = 0.05.

positive correlation was seen between total leukocyte count and VZV-specific ELISPOT results (r = 0.59, p = 0.02). At the baseline visit and 2-week visit, total leukocyte count, but not absolute lymphocyte count, had a stronger positive correlation with VZV-specific CMI (r = 0.78, p = 0.02 and r = 0.77, p = 0.02, respectively), but this pattern was not seen at 6 or 12 weeks. At the baseline visit only, C3 level was strongly positively correlated with VZV-specific ELISPOT results (r = 0.82, p = 0.007). And at the 2-week visit only, C4 was positively correlated (r = 0.71, p = 0.047). No significant correlations were noted between any of the variables and PHA-mediated ELISPOT results.

DISCUSSION

We conducted a prospective open-label pilot study of a commercially available live-attenuated zoster vaccine in patients with stable SLE receiving no more than moderate immunosuppressive medications. The goal of our study was to obtain preliminary data on the short-term safety, tolerability, and immunogenicity of the HZ vaccine in a small cohort of patients with SLE compared to healthy control subjects. Per licensure, all subjects were ≥ 50 years old. We did not identify any episodes of HZ or vesicular lesions at the injection site within 12 weeks following vaccination in any participant. Injection site reactions, consisting of mild erythema and tenderness, were seen at similar frequency in patients with SLE and controls. Although VZV-specific cell-mediated responses were diminished in patients with SLE compared to controls, similar proportions of subjects increased responses by > 50% following vaccination. Anti-VZV IgG concentrations were additionally similar between patients with SLE and controls at each timepoint. We found only minimal changes in disease activity over the 12 weeks following vaccination (all increases in SLEDAI were from minor changes in complement levels that crossed the lower limit of normal), none of which were considered clinically significant or deemed to be disease flares. Immunosuppressive medications were not increased or added during the study.

When considering the risk-to-benefit analysis of vaccination in individuals with underlying autoimmune diseases including SLE, several concerns arise: the foremost being the safety of vaccination. Particularly for live-attenuated virus vaccines, there is a concern about causing direct infection from the vaccine strain of the virus. Additional safety considerations include the potential of causing a flare of underlying disease because of generalized immune stimulation in response to vaccination. These potential risks need to be balanced against the risk in the population of developing HZ if unvaccinated, as well as the efficacy of the vaccine to induce protection following vaccination.

Cumulative evidence has identified a nearly 10-fold increased risk of HZ among patients with SLE compared to healthy individuals, and elevated rates are seen in patients with SLE at young ages[3,4,5,6,7,8,9,10,23]. Although rarely life-threatening, HZ is associated with significant pain and associated morbidity despite early institution of antiviral therapy[24,25], and may lead to disruption or discontinuation of otherwise necessary immunosuppressant medications. Given that the risk of HZ in patients of all ages who have SLE may be similar to or may supersede the risk seen in elderly immunocompetent individuals for whom the vaccine is recommended, the study of the safety and efficacy of the HZ vaccine is of high relevance. If found to be well tolerated, routine HZ vaccine administration to patients with SLE may have an important effect on the disease experience by reducing the burden of comorbid HZ.

Specific guidelines about the use of the HZ vaccine in patients with SLE have been lacking, largely owing to a theoretical concern of vaccine-induced infection as well as the lack of clinical or experimental data upon which to base recommendations[18,19].

We sought to minimize risk of vaccine-induced *de novo* HZ by confirming VZV seropositivity prior to vaccination in all subjects, and by restricting immunosuppressive medication use to those determined to be acceptable according to published guidelines. Within this restricted SLE population, no HZ-related reactions were identified.

Several limitations to our study need to be addressed. The small sample size is perhaps the greatest limitation. Others include the strict exclusion criteria and the short period of observation following vaccination. This pilot study was designed to assess the HZ vaccine in lower-risk patients with SLE for whom vaccination might be considered under current guidelines. The study design was not powered to perform meaningful statistical analyses. With the preliminary estimates of immunogenicity that have been established with our study, studies in SLE patients with expanded inclusion and restricted exclusion criteria can now be considered. Because the risk of HZ is increased even in adolescent and young adult patients with SLE, the study of the safety and efficacy of the vaccination in a wider age range is appropriate. Similarly, many patients are receiving longterm immunosuppressant therapy with MMF, which has been identified as an independent risk factor for HZ[10], and this group requires further study. The short time of followup allowed for close observation of participants during the time of highest risk for vaccine-induced HZ and early estimates of the immune response.

Future, more definitive studies will require a larger sample size, an unvaccinated control group, and longer followup to assess the role of the HZ vaccine in preventing episodes of HZ in this high-risk population. Widespread vaccination among patients with SLE should still proceed with caution, and preferably in the setting of controlled studies.

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