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The Case for Zostavax Vaccination in Systemic Lupus Erythematosus

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Introduction

Herpes zoster (HZ) is the painful reactivation of latent varicella zoster virus (VZV) in the sensory ganglion that frequently occurs decades after primary infection. It is seen with increasing incidence in older individuals, likely due to a slow, progressive decline in cell mediated immunity (CMI) affiliated with advancing age[1]. Although rarely life threatening, HZ can be extremely painful and associated with a reduced quality of life[2]. Post herpetic neuralgia (PHN) is a debilitating neuropathic pain syndrome that is often associated with HZ and can last months to years following acute HZ reactivation [3]. The pain often disrupts sleep, work and activities of daily living, and is associated with a reduced quality of life. Individuals with autoimmune diseases, including systemic lupus erythematosus (SLE), appear to be at increased risk for HZ, possibly due to inherent immune dysregulation associated with the disease, immunosuppressive therapies, or a combination of the two.

The Zostavax vaccine (Merck) is a live-attenuated virus vaccine approved for the reduction of HZ risk in individuals ≥50 years of age. Conflicting recommendations have been published about the safety of this vaccine in immunocompromised hosts, including SLE. The Advisory Committee on Immunization Practices [4] has published recommendations on the use of the vaccine for the prevention of herpes zoster with guidelines regarding vaccine use in immunocompromised individuals [4]. These recommendations, based on consensus expert opinion rather than on clinical data, state that the vaccine should not be administered to persons on immunosuppressive therapy including biologic immunosuppressive medications used to treat autoimmune diseases; subjects receiving such medications should be vaccinated prior to the initiation of therapy or hold therapy for at least 1 month prior to vaccination. Low-to-moderate immunosuppression, including prednisone <20 mg daily, low

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dose methotrexate, azathioprine, or 6-mercaptopurine are not contraindicated as they are "not considered sufficiently immunosuppressive to create vaccine safety concerns" [4]. Guidelines do not differentiate safety concerns for different immunosuppressant medications based upon mechanism of action, but rather on perceived degree of overall immunosuppression. Unfortunately, the ACIP guidelines do not mention several medications that are commonly used to treat SLE including mycophenolate mofetil or belimumab, leaving many practitioners weary of the safety of vaccination in patients chronically receiving such medications. Vaccination guidelines from United States and European rheumatology organizations conform to the ACIP recommendations [5,6]. To date, there is little to no clinical data from which to base vaccination guidelines for patients with autoimmune diseases. Herein, we present arguments in favor of vaccinating SLE patients against HZ.

1. SLE patients are at increased risk for herpes zoster

Accumulating data suggests that HZ occurs more frequently and at younger ages in SLE patients (Table 1)[7–20]. Incidence in adult SLE populations range from 6.4 to 91.4 cases/1000 patient-years: the majority occurring during the 4th decade[7,9–12,16]. In contrast, incidence in the general population ranges from 2.6 to 5.0/1000 person-years, with highest rates among the elderly (Table 2)[21–23]. The increased risk of HZ is likely due, in part, to degree of disease activity as well as immunosuppressive medication use. However, studies have shown that the incidence of HZ is elevated among SLE patients with low disease activity and who are on minimal immunosuppressive medications [16,24]. Outside of pediatric onset SLE, no particular subset of SLE has been consistently shown to have higher risk of HZ. It can be argued that young adults with SLE have HZ rates that supercede those of elderly immunocompetent individuals, for whom zoster vaccination is recommended. Despite this increased risk, rates of zoster vaccination are lower among SLE patients than controls, even among those at ages for which the vaccine is approved[15]. Concerns by both physicians and patients about the safety of live-attenuated vaccines in immunosuppressed populations and lack of clear, evidence-based, guidelines for vaccination is perhaps the main reason for such low vaccination rates. Clearer understanding of risk:benefit analyses for the use of Zostavax in people with autoimmune diseases may help increase vaccination rates in appropriate populations.

2. Delaying therapy or drug holidays may not be feasible for lupus patients

The ACIP and guidelines published by Rheumatology organizations for vaccinating individuals with autoimmune diseases requiring more than mild immunusuppression advise vaccination at least two weeks prior to initiating therapy or after a 1-month drug holiday [4–6]. While this is a reasonable option in some patient populations with relatively mild disease, it may not be advisable in all situations.

SLE commnly manifests with flares and periods of relative remission. Often, disease onset is dramatic, presenting with active internal organ disease requiring immediate induction immunosuppression. In these settings, delaying therapy for the purposes of vaccination would place the patient at unacceptable risk of prolonged or worsening disease activity as well as incremental organ damage in the interval prior to immunosuppression.

For patients who achieve remission or have low disease activity while taking chronic immunosuppressive medications, drug holidays for the purpose of vaccination may pose undue risks for disease flare. Even for hydroxychloroquine, which is not itself immunosuppressive, holidays can place stable SLE patients at increased risk for mild-to-moderate and even severe flares[25]. Little data is available for the safety of withdrawal of azathioprine, mycophenolate mofetil, or other chronic immunosuppressive medications

following periods of disease quiescence, so discontinuing for the sole purpose of vaccination may not be advisable. In these cases, the benefits of vaccination while on chronic immunosuppressant therapy, even if the response is sub-optimal, may outweigh the risk of discontinuing therapy and potentially inducing disease flare.

Vaccination should probably be delayed in the setting of acute moderate-to-severe SLE activity or flares, and for times when high dose corticosteroids or alkylating agents are required. Once disease activity has stabilized and patients no longer require induction therapy, vaccination may be considered, even in the setting of background immunosuppressive therapy.

3. Zoster vaccination does not introduce live-attenuated virus into a naïve population

In contrast to other vaccines which are designed to prevent primary infection from a virus that the vaccinee is naïve to, the zoster vaccine is designed to reduce the reactivation of latent VZV that permanently resides in sensory ganglia following primary infection. Primary VZV infection mostly occurs during childhood; even if clinical disease is not recalled, approximately 98% of the adult population has serologic evidence of exposure, and are at risk for HZ [1]. Vaccination is essentially a “booster” of an existing, if waning, memory response rather than an introduction of a novel virus into an unprimed host. To avoid introducing a live-attenuated virus vaccine into a naïve population, readily available serologic testing for varicella-specific IgG may be performed to document previous exposure. This recommendation is not made by the ACIP prior to vaccination in the general population, but has been suggested by the American College of Rheumatology[6] and the European League Against Rheumatism [5] because of safety concerns regarding live-attenuated vaccine administration in immunocompromised hosts.

Although VZV-specific serologies confirm prior exposure, either through infection or vaccination, antibodies do not confer protection against viral reactivation. Rather, protection requires a robust CMI response. In an immunological sub-study of the Shingles Prevention Study (SPS), higher CMI was associated with lower risk of and reduced severity of HZ, whereas antibody titers were not; however, no threshold of CMI was found to confer protection [26]. The gradual decline in overall CMI with age is thought to be among the major contributors to the increasing incidence of HZ with advancing age. Similarly, defects in CMI due to the disease itself or immunosuppressive therapy may help explain the increased risk of HZ seen in SLE patients [1].

4. Heat-inactivated or recombinant zoster vaccines are not currently available

The live-attenuated formulation is the only currently available zoster vaccine. Two zoster vaccines are currently in development: one recombinant vaccine (Glaxo Smith Kline) and one inactivated zoster vaccine (Merck). The timeline to licensure for these products is unknown, as is the relative efficacy of these vaccines compared to live-attenuated preparations. Because there may be a long delay before licensure, waiting for these to become commercially available may place many SLE patients at risk for zoster in the interval.

5. Zostavax has been shown to be safe and effective in other populations

Zostavax received licensure in the US and Europe largely based upon the randomized, placebo-controlled study of over 38,000 individuals ≥60 years old that found a 51% reduction in HZ among vaccinated individuals and a reduction of PHN by 66% [27]. Among vaccine recipients who did develop HZ, the severity of illness was markedly reduced. Results remained similar for the 17,799 participants ≥ 70 years old, who have the highest degree of age-related immunosenescence. In that pivotal Shingles Prevention Study (SPS),

injection site reactions occurred more frequently in vaccine recipients (48%) than placebo (17%). Most were mild and transient [27]. Of varicella-like lesions that occurred within 42 days of vaccine/placebo administration, none were confirmed to be from the vaccine strain of VZV. Additionally, no transmission of vaccine virus from vaccine recipients to contacts were seen. Viremia was not evaluated in these studies [4,27].

Since publication of the SPS, the safety and efficacy of Zostavax administration has been studied in several immunosuppressed populations. Most notably, Zhang, et al. performed an observational study evaluating HZ and vaccination rates among subjects with immune mediated diseases. There was a 40% reduction in HZ seen in the 18,683 vaccinated patients [28]. Among the 633 receiving biologic therapy at the time of vaccination, no cases of varicella or HZ was identified within 42 days of vaccination, suggesting vaccine-induced HZ risk was low. Thus, safety of vaccination and reduction of subsequent HZ was similar in this population compared to the larger SPS. Other published studies of adults with hematologic malignancy and HIV have demonstrated similar safety of HZ vaccination [29,30]. No studies of vaccine-strain viral transmission or viremia were discussed in any of these reports. These studies involved populations too small to determine efficacy results. Trials in subjects with autoimmune diseases including SLE and RA, transplant recipients, corticosteroid users, HIV, and frail elderly nursing-home residents are listed on ClinicalTrials.gov.

6. VZV strain in Zostavax is susceptible to standard anti-viral therapy

The Oka vaccine strain of VZV the was attenuated by serial passages in cell cultures rendering it avirulant as compared to wild type strains and is susceptible to standard antivirals[31]. Antivirals have been shown to reduce the duration of the skin lesions of HZ by only 1–2 days[32]. However, the prodromal pain and rash may present for several days before medical advice is sought and therapy can be instituted. In contrast, individuals who receive the zoster vaccine know precisely the time of exposure and can be instructed to recognize very early clinical signs of potential vaccine-induced infection and receive promt antiviral therapy. Since clinical disease may be identified much earlier, it is theoretically possible to further reduce the severity and duration of lesions with early antiviral therapy.

Summary

Data published thus far demonstrate that the HZ vaccine has been well tolerated by most individuals, immunocompetent and immunocompromised. It is currently licensed for healthy adults ≥ 50 years old. In the healthy population, advancing age is the greatest risk factor for the development of HZ, with highest rates seen in those ≥70 years of age, likely due to age-related diminution of CMI. HZ incidence is higher in SLE patients compared to healthy people at all ages. Hence, SLE patients, even as young adults, have higher reported HZ incidence than 80 year-old healthy adults, and should be considered a similar high-risk population who are most likely to derive meaningful benefit from vaccination. Even if the efficacy of vaccination in the SLE population proves to be less than seen in the immunocompetent elderly population, the reduction in incidence and severity of both acute HZ and PHN will provide benefit. Until results of randomized clinical trials of Zostavax in SLE patients are reported, we must rely on clinical assessment of potential risks and benefits of vaccinating this population.

Risks of complications directly attributible to zoster vaccination, including the theoretic possibility of vaccine-induced infection, can be mitigated by several means. First, prior exposure to VZV can be easily confirmed by commercially available serology, thereby avoiding the introduction of live-attenuated VZV into naive patients. In these subjects, the varicella vaccine (Varivax (Merck) or Varilrix (GlaxoSmithKline)), which has significantly

lower potency than Zostavax and is intended for primary prevention of varicella, may be considered.

Vaccination should be delayed until acute flares have resolved and induction therapy has been completed and patients are receiving only maintenance immunosuppressive therapy. Discontinuing disease modifying therapy for the sole purpose of vaccination should only be undertaken after careful consideration of the risks of inducing flare of underlying disease after withdrawal of therapy.

Finally, the OKA vaccine strain was attenuated by serial passages in cell cultures and is avirulant as compared to wild type strains. Furthermore, it is susceptible to standard antiviral therapy, shall any vaccine-induced infection occur.

Clinical trials addressing the safety and efficacy of Zostavax in SLE will provide more definitive information upon which to base vaccination decisions. However, results remain years away. In the mean time, vaccination among stable SLE patients ≥50 years old should be strongly considered.

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Table 1

Reported Incidence and Prevalence of Zoster in Adult SLE Patients

Author	Years *of Study*	*Country*	Sample Size	Prevalence	Incidence*	Average Age at HZ Diagnosis
Retrospective Studies						
Wang [7]	1975–1981	Malaysia	184	13%	NR	34.6 (14–35)¥
Manzi [8]	1979–1989	United States	321	15%	NR	NR
Nagasawa [9]	1979–1989	Japan	92	43%	91.4	36.8 (19–68)¥
Sayeeda [10]	1982–2006	Saudi Arabia	624	5.1%	NR	31.4 (11–60)¥
Kang [11]	1990–2000	Korea	303	13.9%	32.5	34.1 (11.6)§
Chen [12]	1996–2006	Taiwan	10,337	N/A	37.7	34.8 (14.3)§
Borba [13]	1999–2006	Brazil	1,145	4.45%	6.4	39 (13.7)§
Hata [14]	2001–2007	Japan	1,077	NR	53.7	51.2 (20.9)§
Chakravarty [15]	2001–2009	United States	1,485	NR	12	NR
Case Control Studies						
Moutsopoulos [16]	1978	Greece	83	21%	NR	NR
Strom [17]	1985–1987	United States	195	9.2%	NR	NR
Khal [18]	1994	United States	348	13.5%	16	NR
Ishikawa [19]	1999	Japan	58	46.6%	NR	40.2 (13.4)§
Pope [20]	2004	United Kingdom	61	19%	NR	49 (2)§

*Incidence given in cases/1000 person-years

NR = Not reported

¥Mean (Range)

§Range (Standard Deviation)

Table 2

Incidence of Zoster in General Population (unless otherwise noted includes all ages and all health states) Incidence rates given as cases/1000 patient-years.

Author	Years of Study	Country of Study	Incidence ¥	Incidence at youngest compared to oldest age range §
Brisson [21]	1979 1997	Canada	2.58 3.48	(5–14) 1.2 (65+) 8.1
Brisson [21]	1979 1997	United Kingdom	3.15 3.82	(5–14) 1.7 (65+) 7.7
Insinga [22]	2000–2001	United States	3.2	(0–14) 1.1 (80+) 10.9
Jih [23]	2000–2006	Taiwan	4.89	(0–20) 2.07 (80+) 13.7

¥Note: 2.58, 3.48 and 3.15, 3.82; incidence rates for respective years.

§Represented as (Age) incidence