HUMAN VACCINES & IMMUNOTHERAPEUTICS
2019, VOL. 15, NO. 1, 45–48
https://doi.org/10.1080/21645515.2018.1514228

Taylor & Francis
Taylor & Francis Group

COMMENTARY

Herpes zoster vaccination in systemic lupus erythematosus: the current status

Chi Chiu Mok

Department of Medicine, Tuen Mun Hospital, Hong Kong, China

ABSTRACT

Among the inflammatory rheumatic diseases, SLE is associated with the highest risk of herpes zoster reactivation relative to age. The reported incidence of herpes zoster infection in SLE ranges from 6.4 to 91.4/1000 patient-years, with main risk factors being major organ disease, immunosuppressive and biological therapies. Although herpes zoster in SLE is manageable with anti-viral treatment, complications such as superimposed bacterial infection, post-herpetic neuralgia may ensue. The low rate of herpes zoster vaccination in SLE is related to the lack of awareness, fear of the risk of vaccine-induced infection and disease flare, cost, as well as the lack of explicit recommendations of vaccine use for the paucity of data in immunocompromised and younger subjects. The recent availability of the non-live subunit and inactivated herpes zoster vaccines has provided more opportunities for SLE patients to be protected against this viral infection. More clinical trials are clearly needed in SLE to confirm safety, immunogenicity and efficacy of the herpes zoster vaccines.

ARTICLE HISTORY
Received 23 July 2018
Accepted 11 August 2018

KEYWORDS
vaccine; herpes; zoster; lupus; complication

Introduction

Herpes zoster (HZ) (Shingles) is a painful skin eruption caused by reactivation of the varicella zoster virus (VZV) that remains dormant in the dorsal sensory ganglion after primary infection. Shingles may lead to persistent post-herpetic neuralgia which substantially impairs quality of life.[1] In immunocompromised individuals, HZ infection may disseminate and cause life-threatening disease.[2] Patients with systemic lupus erythematosus (SLE) are prone to HZ reactivation. This is contributed by the intrinsic immune aberration of the disease and immunosuppressive therapies. A recent meta-analysis of 62 studies showed that SLE patients had increased risk of HZ infection (pooled relative risk 2.10 [1.40–3.15]).[3] Another case-control study also reported an increase incidence of HZ reactivation in SLE patients relative to age-matched patients with other non-inflammatory musculoskeletal conditions (hazard ratio 1.70 [1.08–2.71]).[4]

Not until recently, the live HZ vaccine, Zostavax, has been the only vaccine available for prevention of HZ reactivation.[5] As the vaccine is live attenuated, it is relatively contraindicated in immunocompromised persons due to a paucity of data on vaccine safety and efficacy in these patients. Guidelines for the use of the live HZ vaccine in patients with rheumatic diseases receiving immunosuppressive therapies are ambiguous.[6,7] The European League of Association of Rheumatology (EULAR) recommends that HZ vaccination may be considered in less seriously immunosuppressed patients with autoimmune inflammatory rheumatic diseases.[6] However, the definition for "less seriously immunosuppressed" state is not explicit. The Advisory Committee on Immunization Practices (ACIP) of the US Centers for Disease Control and Prevention (CDC) suggests that the live HZ vaccine can be administered in patients using lower doses of immunosuppressive drugs.[7] However, the dosages cut-off of the drugs that constitute safety to live vaccine are based on expert opinions only. Moreover, not all drugs used in SLE such as mycophenolate mofetil and belimumab are included.[7]

Subunit and inactivated HZ vaccines have recently been studied and demonstrated efficacy in both immunocompetent and immunocompromised individuals.[8-11] As they are not live-virus vaccines, they offer the opportunity for immunocompromised subjects to be immunized for protection against HZ reactivation. In this article, the current status of HZ vaccination in patients with SLE is discussed.

SLE and herpes zoster reactivation

The increase in incidence of HZ reactivation with advancing age indicates that the progressive decline in T-cell immunity against the virus is an important factor. In addition to age, other risk factors of HZ infection include the female gender, family history of HZ infection, the white race, chronic illnesses, malignant diseases and other immunocompromised states such as chronic kidney disease, dialysis, organ transplantation, HIV infection and immunosuppressive therapies.[3,12] Among patients with various chronic medical illnesses, the pooled relative risk of HZ infection was highest with SLE (2.10[1.40–3.15]), followed by rheumatoid arthritis (1.67[1.41–1.98]), chronic obstructive pulmonary disease (1.31[1.22–1.41]), diabetes mellitus (1.30 [1.17–1.45]) and asthma (1.25[1.13–1.39]).[3] Patients with SLE had a 70% higher rate of HZ infection than age-matched subjects with non-inflammatory musculoskeletal diseases.[4] According to information derived from insurance databases in the US, among seven autoimmune or inflammatory diseases, SLE patients had the highest rate of HZ infection in all age strata below 70 years.[13]

CONTACT Chi Chiu Mok, MD, FRCP ccmok2005@yahoo.com Department of Medicine, Tuen Mun Hospital, New Territories, Hong Kong, SAR, China

HZ infection was more frequent in SLE patients at all ages than immunocompetent healthy elderly above 70 years of age.[13]

The incidence of HZ infection in SLE patients ranges from 6.4 to 91.4 cases per 1000 person-years,[4,14–19] with the highest figure reported in Japan[14,18] and lowest figure reported in Brazil.[17] In general, HZ infection rate is higher in Asian countries (32.5–91.4/1000 person-years)[14–16,18] than in the US (12–19.9/1000 person-years).[4,13,19] The majority of HZ infection occurred at the age range of 30–40 years. Among patients with SLE, risk factors identified for HZ infection included high-dose glucocorticoid (GC) and non-GC immunosuppressive therapies,[4,17,19–23] increasing age,[4] lymphopenia,[20] glomerulonephritis[15,19,21–23] or other major organ diseases,[19,21,24] co-morbidities such as diabetes mellitus, renal insufficiency, HIV infection and malignancies,[21,22] reduced functional status[4] and the presence of certain autoantibodies (anti-Ro/Sm/nRNP).[15,21] However, owing to the difference in study design, sample size, patient selection and method of analyses, these risk factors are inconsistent across studies. Although HZ reactivation is more frequent during the initial presentation of SLE,[20,24] it has also been reported in those with low disease activity not receiving heavy immunosuppression during the later course of the disease.[17,19,23]

The outcome of HZ infection in SLE is generally satisfactory. With anti-viral therapy, no mortality was reported in previous studies,[17,20,22–24] although disseminated disease has been described in the old literature (11–14.5%).[22,23] Superimposed bacterial infection occurred in 8.7% to 47.4% of patients[17,20,24] and post-herpetic neuralgia was described in 14.5% to 19.6% of cases.[17,20,22] Hospitalization due to severe HZ infection was required in 17.6% of patients in one study[17] and the mean length of hospital stay was 8.8 days in another study of pediatric SLE patients.[24]

Efficacy of the herpes zoster vaccines in immunocompetent subjects

Zostavax is essentially a larger-than-normal dose of the chickenpox vaccine, which contains the Oka strain of live attenuated VZV.[5] The vaccine has been shown to be safe and protective in immunocompetent elderly populations (> 60 years of age) by reducing reactivation of HZ by 61.1% and post-herpetic neuralgia by 66.5%.[25] Another study also demonstrated efficacy of Zostavax in reducing HZ infection by 69.8% in adults aged 50–59 years.[26] However, the vaccine efficacy appears to be slightly lower in subjects > 70 years of age (55.4%) and in women (57.3%).[25]

A new non-live vaccine, known as Shingrix (HZ/su), was recently marketed in some countries. It is a subunit vaccine containing VZV glycoprotein E (gE) and the AS01B adjuvant system.[8] VZV gE is the most abundant glycoprotein on the surface of infected cells and is the primary target of VZV specific humoral and cell-mediated immune responses.[27] A phase III randomized controlled trial (RCT) (ZOE-50) has confirmed safety and efficacy of Shingrix in adults ≥ 50 years of age.[28] Participants in this study were assigned to receive two intramuscular doses of the vaccine or placebo 2 months apart. After 3.2 years, the overall vaccine efficacy in reducing HZ infection was 97.2%, which was similar across different age groups (96.6–97.9%) and ethnicities. Another RCT using a similar protocol was carried out in subjects ≥ 70 years of age (ZOE-70).[29] The efficacy of the vaccine was 89.8% and similar in participants 70–79 years (90.0%) and ≥ 80 years of age (89.1%). In both studies, injection site reaction and systemic reactions (eg. myalgia, fatigue) within 7 days post-injection were significantly more frequent in vaccinated subjects but these symptoms were self-limiting in all cases. Other serious adverse events (SAEs) was not more frequent in vaccinated patients. Pooled data of the ZOE-50 and ZOE-70 studies reported a vaccine efficacy of 91.3% against HZ and 88.8% against post-herpetic neuralgia.[29] A long-term study showed that in adults aged ≥ 60 years, the immunogenicity of the subunit HZ vaccine remained above pre-vaccination levels for at least nine years post-vaccination.[30]

Although direct comparison across different RCTs may be inappropriate, it appears that the vaccine efficacy is better with the adjuvanted subunit than live-attenuated HZ vaccine. A comparative study on the efficacy and immunogenicity of the live and subunit HZ vaccine is in progress (NCT02114333).

Efficacy of the herpes zoster vaccines in SLE patients

Data regarding the live HZ vaccine in immunocompromised hosts are scant because it is generally contraindicated in these patients. Zostavax has been demonstrated safety in patients with treated HIV infection, end stage renal failure and hemic malignancies[31] but the sample size is too small to allow detection of rare SAEs.

An observational study involving 463,541 US patients with inflammatory arthritis and inflammatory bowel disease reported that 4% of these patients had received Zostavax vaccination.[32] After a median of 2 years, the rate HZ reactivation among vaccinated patients was significantly lower than that of unvaccinated group (hazard ratio 0.61[0.52–0.71]). Among 633 patients exposed to biologics at the time of vaccination, no cases of HZ or varicella infection occurred in the subsequent 42 days. Thus, the live vaccine appears to be safe in patients with autoimmune rheumatic diseases, including those receiving the biological agents.

There is a paucity of data regarding the safety of the live HZ vaccine in SLE. A small pilot case-control study did not observe any episodes of HZ reactivation, vesicular rash, serious adverse events, or disease flares in 10 SLE patients after vaccination with Zostavax.[33] Enhanced immune response to VZV was demonstrated in all subjects but the magnitude of improvement was smaller in SLE patients.

The efficacy and safety of the subunit HZ vaccine in immunocompromised subjects is being investigated.[8,34] Preliminary data have confirmed immunogenicity and safety of the subunit HZ vaccine in patients with HIV infection and hemopoietic stem cell transplant recipients.[10,11] Recently, a HZ vaccine inactivated by gamma irradiation was tested in patients who underwent autologous stem cell transplantation.[9] A total of 1230 patients were randomly assigned to the vaccine consistency lot, high-antigen lot or placebo groups. After a mean of 2.4 years, the estimated vaccine efficacy in reducing HZ infection was 63.8%. The incidence of vaccine-related SAEs was similar between the vaccinated and placebo groups of patients.

Similar to other HZ vaccines, injection site adverse events were significantly more common in the vaccinated patients.

There are still no data regarding the efficacy of the subunit and inactivated HZ vaccines in SLE patients. Two recent phase IIb RCTs on the monoclonal antibodies against the type I interferons have reported a high incidence of HZ infection after 52 weeks' treatment (5.9%-9.5%) compared to placebo (0.9%-2.0%).[35,36] Although the type I interferons are important pathogenic mediators in patients with SLE,[37] they are also essential cytokines for the defense against viral infection. As these novel biological agents are evolving therapies for SLE, clinical trials of the non-live HZ vaccines in SLE patients are necessary.

Low rate of herpes zoster vaccination in SLE

Despite the high incidence of HZ reactivation, a very low rate of HZ vaccination (7.1%) has been reported in patients with SLE.[4] Possible reasons include the lack of awareness of vaccine availability, concern about the risk of live vaccines in causing disseminated infection, cost, and the worry about SLE exacerbation by the vaccine or its adjuvants. In fact, there is so far no evidence of induction of autoimmunity related to Zostavax according to a 10-year post-marketing adverse experience review.[38] The live HZ vaccine is licensed in many parts of world for immunocompetent subjects older than the age of 50 years. The subunit HZ vaccine is also recently licensed in some countries for persons of the same age. As SLE patients are generally younger, there is also a concern about the safety of the HZ vaccines in these subjects, who were excluded in the pivotal trials. The subunit and inactivated HZ vaccines have great potential in SLE patients receiving intense immunosuppression as they do contain the live virus that may cause disseminated infection. More clinical data regarding the safety and efficacy of the HZ vaccines in SLE and other immunocompromised patients are eagerly awaited.

Summary and expert opinions

Among the inflammatory rheumatic disorders, SLE patients are particularly at risk of HZ infection. This is contributed by the intrinsic disease-related immunological abnormalities and immunosuppressive therapies, including the biological agents. HZ infection in SLE is associated with significant morbidity and impairment of quality of life. Despite a high incidence of HZ reactivation, vaccination rate is low in patients with SLE. Currently, limited data in the literature have demonstrated safety of the HZ vaccine in SLE patients. HZ vaccination may be considered in all SLE patients before intensive immunosuppressive therapies. The vaccine should best be administered when SLE is quiescent and requires minimal immunosuppression. In SLE patients receiving higher doses of immunosuppressive drugs, the decision and timing for HZ vaccination should be individualized and the non-live HZ vaccines are preferred if they are available. More data on the safety and efficacy of the live and non-live HZ vaccines in SLE are needed to enhance the vaccination rate so that more patients can be protected.

Disclosure of potential conflicts of interest

No potential conflict of interest was reported by the author.

ORCID

Chi Chiu Mok http://orcid.org/0000-0003-3696-1228

References

1. Johnson RW, Bouhassira D, Kassianos G, Leplège A, Schmader KE, Weinke T. The impact of herpes zoster and post-herpetic neuralgia on quality-of-life. BMC Med. 2010;8:37. doi:10.1186/1741-7015-8-37.
2. Freer G, Pistello M. Varicella-zoster virus infection: natural history, clinical manifestations, immunity and current and future vaccination strategies. New Microbiol. 2018;41(1).Epub ahead of print
3. Kawai K, Yawn BP. Risk factors for Herpes Zoster: a systematic review and meta-analysis. Mayo Clin Proc. 2017;92:1806–1821. doi:10.1016/j.mayocp.2017.10.009.
4. Chakravarty EF, Michaud K, Katz R, Wolfe F. Increased incidence of herpes zoster among patients with systemic lupus erythematosus. Lupus. 2013;22:238–244. doi:10.1177/0961203312470186.
5. Doan HQ, Ung B, Ramirez-Fort MK, Khan F, Tyring SK. Zostavax: a subcutaneous vaccine for the prevention of herpes zoster. Expert Opin Biol Ther. 2013;13:1467–1477. doi:10.1517/14712598.2013.830101.
6. van Assen S, Agmon-Levin N, Elkayam O, Cervera R, Doran MF, Dougados M, Emery P, Geborek P, Ioannidis JPA, Jayne DRW, et al. EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis. 2011;70:414–422. doi:10.1136/ard.2010.137216.
7. Harpaz R, Ortega-Sanchez IR, Seward JF. Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC). Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2008;57(RR–5):1–30.
8. Cunningham AL. The herpes zoster subunit vaccine. Expert Opin Biol Ther. 2016;16:265–271. doi:10.1517/14712598.2016.1134481.
9. Winston DJ, Mullane KM, Cornely OA, Boeckh MJ, Brown JW, Pergam SA, Trociukas I, Žák P, Craig MD, Papanicolaou GA, et al. V212 Protocol 001 Trial Team. Inactivated varicella zoster vaccine in autologous haemopoietic stem-cell transplant recipients: an international, multicentre, randomised, double-blind, placebo-controlled trial. Lancet. 2018;391:2116–2127. doi:10.1016/S0140-6736(18)30631-7.
10. Stadtmauer EA, Sullivan KM, Marty FM, Dadwal SS, Papanicolaou GA, Shea TC, Mossad SB, Andreadis C, Young J-AH, Buadi FK, et al. A phase 1/2 study of an adjuvanted varicella-zoster virus subunit vaccine in autologous hematopoietic cell transplant recipients. Blood. 2014;124:2921–2929. doi:10.1182/blood-2014-04-573048.
11. Berkowitz EM, Moyle G, Stellbrink HJ, Schürmann D, Kegg S, Stoll M, et al. Safety and immunogenicity of an adjuvanted herpes zoster subunit candidate vaccine in HIV-infected adults: a phase 1/2a randomized, placebo-controlled study. J Infect Dis. 2015;211:1279–1287. doi:10.1093/infdis/jiu606.
12. Cohen JI. Clinical practice: herpes zoster. N Engl J Med. 2013;369:255–263. doi:10.1056/NEJMcp1302674.
13. Yun H, Yang S, Chen L, Xie F, Winthrop K, Baddley JW, Saag KG, Singh J, Curtis JR. Risk of Herpes Zoster in autoimmune and inflammatory diseases: implications for vaccination. Arthritis Rheumatol. 2016;68:2328–2337. doi:10.1002/art.39670.
14. Nagasawa K, Yamauchi Y, Tada Y, Kusaba T, Niho Y, Yoshikawa H. High incidence of herpes zoster in patients with systemic lupus erythematosus: an immunological analysis. Ann Rheum Dis. 1990;49:630–633.
15. Kang I, Park SH. Infectious complications in SLE after immunosuppressive therapies. Curr Opin Rheumatol. 2003;15:528–534.

16. Chen HH, Chen YM, Chen TJ, Lan JL, Lin CH, Chen DY. Risk of herpes zoster in patients with systemic lupus erythematosus: a three-year follow-up study using a nationwide population-based cohort. Clinics (Sao Paulo). 2011;66:1177–1182.
17. Borba EF, Ribeiro AC, Martin P, Costa LP, Guedes LK, Bonfá E. Incidence, risk factors, and outcome of Herpes zoster in systemic lupus erythematosus. J Clin Rheumatol. 2010;16:119–122. doi:10.1097/RHU.0b013e3181d52ed7.
18. Hata A, Kuniyoshi M, Ohkusa Y. Risk of Herpes zoster in patients with underlying diseases: a retrospective hospital-based cohort study. Infection. 2011;39:537–544. doi:10.1007/s15010-011-0162-0.
19. Kahl LE. Herpes zoster infections in systemic lupus erythematosus: risk factors and outcome. J Rheumatol. 1994;21:84–86.
20. Chen D, Li H, Xie J, Zhan Z, Liang L, Yang X. Herpes zoster in patients with systemic lupus erythematosus: clinical features, complications and risk factors. Exp Ther Med. 2017;14:6222–6228. doi:10.3892/etm.2017.5297.
21. Hu SC, Yen FL, Wang TN, Lin YC, Lin CL, Chen GS. Immunosuppressive medication use and risk of herpes zoster (HZ) in patients with systemic lupus erythematosus (SLE): A nationwide case-control study. J Am Acad Dermatol. 2016;75:49–58. doi:10.1016/j.jaad.2015.12.059.
22. Manzi S, Kuller LH, Kutzer J, Pazin GJ, Sinacore J, Medsger TA Jr, Ramsey-Goldman R. Herpes zoster in systemic lupus erythematosus. J Rheumatol. 1995;22:1254–1258.
23. Moutsopoulos HM, Gallagher JD, Decker JL, Steinberg AD. Herpes zoster in patients with systemic lupus erythematosus. Arthritis Rheum. 1978;21:798–802.
24. Lee PP, Lee TL, Ho MH, Wong WH, Lau YL. Herpes zoster in juvenile-onset systemic lupus erythematosus: incidence, clinical characteristics and risk factors. Pediatr Infect Dis J. 2006;25:728–732. doi:10.1097/01.inf.0000226841.03751.1f.
25. Oxman MN, Levin MJ, Johnson GR, Schmader KE, Straus SE, Gelb LD, Arbeit RD, Simberkoff MS, Gershon AA, Davis LE, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med. 2005;352:2271–2284. doi:10.1056/NEJMoa051016.
26. Schmader KE, Levin MJ, Gnann JW Jr, McNeil SA, Vesikari T, Betts RF, Keay S, Stek JE, Bundick ND, Su S-C, et al. Efficacy, safety, and tolerability of herpes zoster vaccine in persons aged 50-59 years. Clin Infect Dis. 2012;54:922–928. doi:10.1093/cid/cir970.
27. Arvin AM. Humoral and cellular immunity to varicella-zoster virus: an overview. J Infect Dis. 2008;197(Suppl 2):S58–60. doi:10.1086/522123.
28. Lal H, Cunningham AL, Godeaux O, Chlibek R, Diez-Domingo J, Hwang SJ, Levin MJ, McElhaney JE, Poder A, Puig-Barberà J, et al. ZOE-50 study group. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. N Engl J Med. 2015;372:2087–2096. doi:10.1056/NEJMoa1501184.
29. Cunningham AL, Lal H, Kovac M, Chlibek R, Hwang SJ, Díez-Domingo J, Godeaux O, Levin MJ, McElhaney JE, Puig-Barberà J, et al. ZOE-70 study group. Efficacy of the Herpes Zoster Subunit vaccine in adults 70 years of age or older. N Engl J Med. 2016;375:1019–1032. doi:10.1056/NEJMoa1603800.
30. Schwarz TF, Volpe S, Catteau G, Chlibek R, David MP, Richardus JH, Lal H, Oostvogels L, Pauksens K, Ravault S, et al. Persistence of immune response to an adjuvanted varicella-zoster virus subunit vaccine for up to year nine in older adults. Hum Vaccin Immunother. 2018;14:1370–1377. doi:10.1080/21645515.2018.1442162.
31. Levin MJ, Bresnitz E, Popmihajlov Z, Weinberg A, Liaw KL, Willis E, Curtis JR. Studies with herpes zoster vaccines in immune compromised patients. Expert Rev Vaccines. 2017;16:1217–1230. doi:10.1080/14760584.2017.1395703.
32. Zhang J, Xie F, Delzell E, Chen L, Winthrop KL, Lewis JD, Saag KG, Baddley JW, Curtis JR. Association between vaccination for herpes zoster and risk of herpes zoster infection among older patients with selected immune-mediated diseases. JAMA. 2012;308:43–49. doi:10.1001/jama.2012.7304.
33. Guthridge JM, Cogman A, Merrill JT, Macwana S, Bean KM, Powe T, Roberts V, James JA, Chakravarty EF. Herpes zoster vaccination in SLE: a pilot study of immunogenicity. J Rheumatol. 2013;40:1875–1880. doi:10.3899/jrheum.130170.
34. Bharucha T, Ming D, Breuer J. A critical appraisal of 'Shingrix', a novel herpes zoster subunit vaccine (HZ/Su or GSK1437173A) for varicella zoster virus. Hum Vaccin Immunother. 2017;13:1789–1797. doi:10.1080/21645515.2017.1317410.
35. Khamashta M, Merrill JT, Werth VP, Furie R, Kalunian K, Illei GG, Drappa J, Wang L, Greth W. CD1067 study investigators. Sifalimumab, an anti-interferon-α monoclonal antibody, in moderate to severe systemic lupus erythematosus: a randomised, double-blind, placebo-controlled study. Ann Rheum Dis. 2016;75:1909–1916. doi:10.1136/annrheumdis-2015-208562.
36. Furie R, Khamashta M, Merrill JT, Werth VP, Kalunian K, Brohawn P, Illei GG, Drappa J, Wang L, Yoo S. CD1013 Study Investigators. Anifrolumab, an Anti-Interferon-α Receptor Monoclonal Antibody, in Moderate-to-Severe Systemic Lupus Erythematosus. Arthritis Rheumatol. 2017;69:376–386. doi:10.1002/art.39962.
37. Crow MK. Type I interferon in the pathogenesis of lupus. J Immunol. 2014;192:5459–5468. doi:10.4049/jimmunol.1002795.
38. Willis ED, Woodward M, Brown E, Popmihajlov Z, Saddier P, Annunziato PW, Halsey NA, Gershon AA. Herpes zoster vaccine live: A 10 year review of post-marketing safety experience. Vaccine. 2017;35:7231–7239. doi:10.1016/j.vaccine.2017.11.013.