ARTICLES · Online first, February 09, 2026

Recombinant herpes zoster vaccine in patients with autoimmune rheumatic diseases in Brazil: a double-blind, randomised, placebo-controlled, phase 4, non-inferiority study

Nadia E Aikawa, MD PhD [a,b,†] · Ana C Medeiros-Ribeiro, MD PhD [a,†] · Sandra G Pasoto, MD PhD [a] · Leonard V K Kupa, PhD [a] · Luciana P C Seguro, MD PhD [a] · Ana P Luppino-Assad, MD PhD [a] · et al. Show more

Show Outline

Summary

Background

Patients with autoimmune rheumatic diseases are at high risk of developing herpes zoster due to immunosuppressive treatment. We evaluated the effect of a recombinant zoster vaccine in patients with autoimmune rheumatic diseases compared with placebo and in healthy controls.

Methods

This single-centre, double-blind, randomised, placebo-controlled, phase 4, non-inferiority, study was done at a tertiary centre in Brazil. Eligible patients were aged 18 years or older with an autoimmune rheumatic disease diagnosis. All patients had to have been managed with glucocorticoids, immunosuppressives, or disease-modifying antirheumatic drugs, provided the doses were stable for at least 4–12 weeks before the initial study visit. Patients were randomly assigned (1:1) to receive two doses of recombinant zoster vaccine or placebo, 6 weeks apart, according to computer-generated sequences, without blocks or stratification. Investigators and participants were masked to treatment allocation. Healthy controls were also included from the same centre and received two doses of the recombinant zoster vaccine. Following the double-blind phase, patients with autoimmune rheumatic diseases who initially received placebo entered an open-label phase and received two doses of the vaccine. The primary outcome was the number of patients with autoimmune rheumatic diseases with worsening of disease activity (flare) up to day 84 after the first dose of the recombinant zoster vaccine compared with placebo in the double-blind phase of the study. Non-inferiority of recombinant zoster vaccine would be declared if the upper boundary of the one-sided 95% CI for the rate of worsening in disease activity in the group receiving recombinant zoster vaccine versus the placebo group was less than 5%. The primary analysis (flare rates) and the safety analysis were done in all participants who received at least one vaccine dose. There was no involvement of people with lived experience of autoimmune rheumatic diseases in the study design. The study is registered with ClinicalTrials.gov (NCT05879419) and is complete.

Findings

Between May 25, 2023, and Nov 27, 2024, 1192 patients were enrolled in the study and were randomly assigned to receive either the recombinant zoster vaccine (n=590) or placebo (n=602). 559 (95%) of 590 patients in the recombinant vaccine group and 577 (96%) of 602 in the placebo group received at least one dose of the recombinant zoster vaccine or placebo and were included in the primary outcome and safety analyses; 891 (78%) of 1136 were female, 245 (22%) were male, 555 (49%) were of African descent, and 552 (49%) were White. An additional 393 healthy controls were enrolled in the study: 380 received both doses of the recombinant zoster vaccine and were included in the safety analyses. For the primary outcome of worsening of disease activity (flare) up to day 84 for patients with autoimmune rheumatic diseases, non-inferiority was shown for the recombinant zoster vaccine group compared with placebo. 80 (14%) of 559 patients in the recombinant zoster vaccine group had a flare compared with 84 (15%) of 557 in the placebo group, equating to a between-group difference in flare rate of –1·2% (95% CI –4·7 to 2·2; $p_{non-inferiority}$=0·0018). Adverse events were less frequently reported after both vaccine doses in patients with autoimmune rheumatic diseases compared with the healthy control group (after first dose: 430 [77%] of 559 in the recombinant zoster vaccine group *vs* 179 [31%] of 577 in the placebo group *vs* 341 [90%] of 380 in the healthy control group; after the second dose: 402 [72%] *vs* 148 [26%] *vs* 307 [81%]). Serious adverse events were similar across the groups after the first dose (five [1%] *vs* six [1%] *vs* none) and second dose (nine [2%] *vs* five [1%] *vs* two [1%]) of the recombinant zoster vaccine.

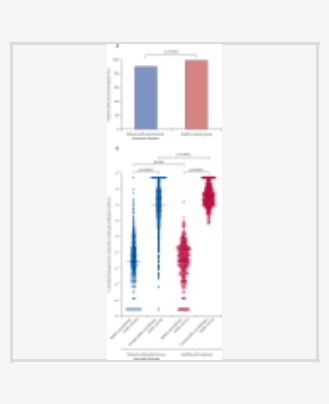
Interpretation

Recombinant zoster vaccine had an acceptable safety profile in patients with autoimmune rheumatic diseases who are immunosuppressed, and had no significant effect on short-term disease activity.

Funding

GSK and the Fundação de Amparo à Pesquisa do Estado de São Paulo.

Figures (2) Figure Viewer



Article metrics

Metric data currently unavailable

Supplementary material (1)

PDF (1.31 MB)
Supplementary appendix

References

1. Zeevaert, R · Thiry, N · Maertens de Noordhout, C · et al.
Efficacy and safety of the recombinant zoster vaccine: a systematic review and meta-analysis
Vaccine X. 2023; **15**, 100397
Google Scholar

2. Stevens, E · Weinblatt, ME · Massarotti, E · et al.
Safety of the zoster vaccine recombinant adjuvanted in rheumatoid arthritis and other systemic rheumatic disease patients: a single center's experience with 400 patients
ACR Open Rheumatol. 2020; **2**:357-361
Google Scholar

3. Kochhar, GS · Desai, A · Caldera, DO F · et al.
Effectiveness of recombinant zoster vaccine (RZV) in patients with inflammatory bowel disease
Vaccine. 2021; **39**:4199-4202
Google Scholar

4. Cunningham, AL · Heineman, TC · Lal, H · et al., the ZOE-50/70 Study Group
Immune responses to a recombinant glycoprotein E herpes zoster vaccine in adults aged 50 years or older
J Infect Dis. 2018; **217**:1750-1760
Google Scholar

5. Lal, H · Cunningham, AL · Godeaux, O · et al., the ZOE-50 Study Group
Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults
N Engl J Med. 2015; **372**:2087-2096
Google Scholar

6. Cunningham, AL · Lal, H · Kovac, M · et al., the 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
Google Scholar

7. Giannelos, N · Ng, C · Curran, D
Cost-effectiveness of the recombinant zoster vaccine (RZV) against herpes zoster: an updated critical review
Hum Vaccin Immunother. 2023; **19**, 2168952
Google Scholar

8. Desai, A · Hashash, JG · Kochhar, GS · et al.
Recombinant zoster vaccine [RZV] is effective in patients with inflammatory bowel disease: a US propensity matched cohort study
J Crohns Colitis. 2024; **18**:828-835
Google Scholar

9. Bass, AR · Chakravarty, E · Akl, EA · et al.
2022 American College of Rheumatology guideline for vaccinations in patients with rheumatic and musculoskeletal diseases
Arthritis Care Res (Hoboken). 2023; **75**:449-464
Google Scholar

10. Gupta, S · Arasaratnam, RJ · Solow, EB · et al.
A medical records review study assessing safety of zoster vaccine recombinant, adjuvanted in patients with rheumatic disease
J Clin Rheumatol. 2022; **28**:e528-e531
Google Scholar

11. Lenfant, T · Jin, Y · Kirchner, E · et al.
Safety of recombinant zoster vaccine: a retrospective study of 622 rheumatology patients
Rheumatology (Oxford). 2021; **60**:5149-5157
Google Scholar

12. Kojima, S · Iwamoto, T · Kobayashi, Y · et al.
Immunogenicity and influence on disease activity of recombinant zoster vaccine in patients with rheumatoid arthritis treated with DMARDs
RMD Open. 2024; **10**, e003902
Google Scholar

13. Park, JK · Kim, M · Jung, JI · et al.
Immunogenicity, reactogenicity, and safety of two-dose adjuvanted herpes zoster subunit vaccine in patients with systemic lupus erythematosus in South Korea: a single-centre, randomised, double-blind, placebo-controlled trial
Lancet Rheumatol. 2024; **6**:e352-e360
Google Scholar

14. Venerito, V · Stefanizzi, P · Cantarini, L · et al.
Immunogenicity and safety of adjuvanted recombinant zoster vaccine in rheumatoid arthritis patients on anti-cellular biologic agents or JAK inhibitors: a prospective observational study
Int J Mol Sci. 2023; **24**, 6967
Google Scholar

15. Källmark, H · Bergström, T · Nagel, J · et al.
Serologic immunogenicity and safety of herpes zoster subunit vaccine in patients with rheumatoid arthritis receiving Janus kinase inhibitors
Rheumatology (Oxford). 2024; **63**:2024-2033
Google Scholar

16. Kupa, LVK · Medeiros-Ribeiro, AC · Aikawa, NE · et al.
Disease safety, immunogenicity, and efficacy of recombinant herpes zoster vaccine (RZV or Shingrix) in autoimmune rheumatic diseases: launching a randomized phase 4 study
J Clin Rheumatol. 2025; **31**:e104-e111
Google Scholar

17. Calabrò, A · Accardi, G · Aiello, A · et al.
Sex and gender affect immune aging
Front Aging. 2023; **4**, 1272118
Google Scholar

18. WHO
WHO draft guidelines for adverse event reporting and learning systems
https://iris.who.int/server/api/core/bitstreams/ca6b372b-e56b-4229-8b47-349480a4e8b9/content
Date: 2005
Date accessed: December 24, 2025
Google Scholar

19. Felten, R · Scherlinger, M · Guffroy, A · et al.
Incidence and predictors of COVID-19 and flares in patients with rare autoimmune diseases: a systematic survey and serological study at a national reference center in France
Arthritis Res Ther. 2021; **23**:188
Google Scholar

20. Medeiros-Ribeiro, AC · Aikawa, NE · Saad, CGS · et al.
Immunogenicity and safety of the CoronaVac inactivated vaccine in patients with autoimmune rheumatic diseases: a phase 4 trial
Nat Med. 2021; **27**:1744-1751
Google Scholar

21. Shoenfeld, Y · Agmon-Levin, N
'ASIA' - autoimmune/inflammatory syndrome induced by adjuvants
J Autoimmun. 2011; **36**:4-8
Google Scholar

22. Araujo, CSR · Medeiros-Ribeiro, AC · Saad, CGS · et al.
Two-week methotrexate discontinuation in patients with rheumatoid arthritis vaccinated with inactivated SARS-CoV-2 vaccine: a randomised clinical trial
Ann Rheum Dis. 2022; **81**:889-897
Google Scholar

23. Saad, CG · Borba, EF · Aikawa, NE · et al.
Immunogenicity and safety of the 2009 non-adjuvanted influenza A/H1N1 vaccine in a large cohort of autoimmune rheumatic diseases
Ann Rheum Dis. 2011; **70**:1068-1073
Google Scholar

24. Claudino Formiga, FF · Silva, CA · Pedrosa, TDN · et al.
Influenza A/Singapore (H3N2) component vaccine in systemic lupus erythematosus: a distinct pattern of immunogenicity
Lupus. 2021; **30**:1915-1922
Google Scholar

25. Tonacio, AC · do Nascimento Pedrosa, T · Borba, EF · et al.
Immunogenicity and safety of primary fractional-dose yellow fever vaccine in autoimmune rheumatic diseases
PLoS Negl Trop Dis. 2021; **15**, e0010002
Google Scholar

26. Manaï, M · van Middendorp, H · Veldhuijzen, DS · et al.
How to prevent, minimize, or extinguish nocebo effects in pain: a narrative review on mechanisms, predictors, and interventions
Pain Rep. 2019; **4**:e699
Google Scholar

27. Vijenthira, A · Gong, I · Betschel, SD · et al.
Vaccine response following anti-CD20 therapy: a systematic review and meta-analysis of 905 patients
Blood Adv. 2021; **5**:2624-2643
Google Scholar

28. Petri, M · Joyce, D · Haag, K · et al.
Effect of systemic lupus erythematosus and immunosuppressive agents on COVID-19 vaccination antibody response
Arthritis Care Res (Hoboken). 2023; **75**:1878-1885
Google Scholar

29. Levin, MJ · Weinberg, A
Immune responses to zoster vaccines
Hum Vaccin Immunother. 2019; **15**:772-777
Google Scholar

30. Schmid, DS · Miao, C · Leung, J · et al.
Comparative antibody responses to the live-attenuated and recombinant herpes zoster vaccines
J Virol. 2021; **95**:e00240-e00321
Google Scholar

31. Laing, KJ · Ouwendijk, WJD · Koelle, DM · et al.
Immunobiology of varicella-zoster virus infection
J Infect Dis. 2018; **218**(suppl 2):S68-S74
Google Scholar

View full text