Increased Incidence of Giant Cell Arteritis After Introduction of a Live Varicella Zoster Virus Vaccine

William A. Agger,[1,2] Jake A. Deviley,[2] Andrew J. Borgert,[2] and Cary M. Rasmussen[2]

[1]Department of Infectious Disease, Gundersen Health System, La Crosse, Wisconsin, USA, and [2]Department of Medical Research, Gundersen Health System, La Crosse, Wisconsin, USA

Background. Varicella zoster virus (VZV) has been associated with giant cell arteritis (GCA). The introduction of a live attenuated vaccine against this virus (ZVL) might have changed the incidence of GCA.

Methods. The incidence of GCA was retrospectively measured using 2 matched cohorts seen in a regional health system located in the Midwestern United States: ZVL recipients from the years 2007 through 2015 following the introduction of the vaccine and nonrecipients from the years 2000 through 2015.

Results. In the ZVL cohort, a significant increase of GCA was associated with clinical criteria alone for the diagnosis of GCA (hazard ratio [HR], 2.70; 95% CI, 1.48–4.45; $P = .004$). In addition, using only pathologically confirmed GCA, the same matched cohort comparison analysis also found that ZVL recipients were at significantly higher risk than those who did not receive ZVL (HR, 2.70; 95% CI, 1.48–4.95; $P = .001$).

Conclusion. Using a matched cohort, retrospective comparison, ZVL was associated with an increased incidence of GCA.

Keywords. giant cell arteritis; live attenuated varicella zoster vaccine.

Giant cell arteritis (GCA), or *temporal arteritis*, a mononuclear and giant cell vasculitis of uncertain etiology, causes inflammation in the walls of medium and large elastic arteries of the head, which can manifest as headaches, jaw claudication, scalp tenderness, visual changes, and, rarely, strokes.

Human herpesvirus 3, or varicella zoster virus (VZV), causes chicken pox, an acute viral, vesicular, exanthematous illness. After primary infection, VZV often becomes latent, without production of viral proteins or infectious particles, in ganglionic neurons [1, 2]. This viral latency is controlled by complex mechanisms, including cell-mediated immunological modulation [2] that, during the natural aging process, can become immunosenescent [3]. This, along with other immunocompromised states [4, 5], frequently allows VZV to reactivate, usually recognized as a dermatomal vesicular rash called herpes zoster or shingles. During a zoster attack, by axonally traveling down the efferent nerves, the VZV can progressively infect arterial tunica adventitia, tunica media, and tunica intima, initiating a vasculitis of the cranial arteries [4], and is known to produce strokes [6].

While some studies have failed to find VZV by polymerase chain reaction (PCR) in GCA [7, 8], recent studies have found VZV DNA in 73% of temporal artery (TA) biopsies pathologically positive for GCA vs 22% of pathologically normal TA biopsies (from cases clinically suspicious for GCA) [9]. A study by Gilden and Nagel showed VZV antibodies and antigen (VZV-Ag) and VZV PCR positivity in noncontiguous lesions of all GCA biopsy specimens and no VZV-Ag in any control biopsy samples [10].

The finding of VZV-Ag in arterial walls has led to the hypothesis that localized areas of arteritis with VZV reactivation are involved with GCA [11]. If VZV reactivation acts as a factor in GCA, theoretically, VZV vaccination might decrease or increase the incidence of GCA by multiple possible mechanisms.

A live attenuated herpes zoster vaccine (ZVL) was approved by the US Food and Drug Administration (FDA) in May 2006 for individuals 60 years and older and was expanded to those 50 years and older in 2011. This vaccination boosts host immunity to VZV, decreasing reactivation by ~50%, but with declining immunity over time [12]. Herein, we report a retrospective review using a cohort-controlled study conducted to determine whether the introduction of ZVL affected the incidence of GCA.

METHODS

Following approval of the study by the Gundersen Clinic, Ltd., Human Subjects Committee/Institutional Review Board, the study

was conducted in a large, independent, academic group practice with a stable, upper Midwestern US population of ~330 000, 90% of whom are of Northern European descent. To evaluate the potential association of ZVL and GCA, the electronic health records (EHRs) for the years 2000 through 2015 of 2 cohorts of patients (ZVL vaccinated and nonvaccinated) age 60 years or older who received their primary care in the group practice were retrospectively reviewed. The immunization records of all cases of confirmed GCA were reviewed and verified with the Iowa, Minnesota, and Wisconsin state immunization registries. Among the other patient demographics queried were age and female sex, 2 factors that are associated with GCA. Patients who were immunocompromised, owing either to underlying disease or/and therapy, were excluded because such states or therapy might obscure the diagnosis of GCA (see below).

Annual incidence of GCA was defined as the number of newly diagnosed GCA-positive cases divided by the number of patients at risk for GCA seen in that given year. Patients' first and last dates of contact were established for each patient aged 60 years or older. Patients were defined as at risk and counted toward the denominator (total population ≥60 years of age) in the year of first contact at age ≥60 years, the year of last contact, and all intervening years. For example, a patient who was first seen in 2008 at age 60 and last seen in 2015 was counted in our denominator for the years 2008 through 2015.

After identifying the number of at-risk patients for each year, the EHR system was queried to determine which of these patients' records contained a GCA diagnosis code using the *International Classification of Diseases, Ninth Revision* (ICD-9), and *International Classification of Diseases, Tenth Revision* (ICD-10), codes for GCA: ICD9: 446.5 and 447.6; ICD10: M31.5, M31.6, I77.6. The EHR and pathology records for each patient with a GCA diagnosis code were then reviewed, and dates surrounding the first coded date were reviewed to determine whether the patient had received a TA biopsy positive for GCA or had undergone a course of treatment consistent with a GCA diagnosis, defined as at least 6 months of treatment with a glucocorticoid.

In 1990, the American College of Rheumatology (ACR) criteria for a GCA diagnosis were defined as meeting at least 3 of the following 5 criteria: age at onset ≥50 years, new headache, TA abnormality, elevated erythrocyte sedimentation rate (≥50 mm/hr), and/or abnormal result of TA biopsy [13]. To ensure that study patients had GCA, additional case criteria were incorporated for study case selection. Cases that met either of the following definitions for GCA in any given year were included in the numerator of our incidence fraction for that year: (1) a clinical diagnosis: 3 of 5 ACR criteria for GCA diagnosis met and a clinical course consistent with GCA treatment ordered, or active GCA diagnosed by a rheumatologist/ophthalmologist and a clinical course consistent with GCA treatment

ordered; or (2) a pathological diagnosis only: a TA biopsy result positive for GCA.

Using these 2 GCA case criteria, matched comparisons were done. First, ZVL recipients were compared with unvaccinated patients by standard demographics, such as age, sex, and the development of GCA. In order to measure for a possible health care utilization bias between GCA cases and non-GCA cases, contacts per year, follow-up years, and the use of pneumococcal vaccine were measured before GCA developed in GCA cases. In addition, rates of patient–provider contact were defined as the ratio of numbers of years with at least 1 provider–patient contact divided by the number of years at risk.

The ZVL recipients were matched with unvaccinated patients on age (+/-5 years), sex, and date of first contact (+/-5 years). Patients with a history of HIV/AIDS, leukemia, lymphoma, myeloma, and myelodysplastic syndrome were excluded, as were patients on any prescription of the immunomodulating drug anti-IL6, B-cell blockade, calcineurin inhibitors, costimulation blockade, disease-modifying antirheumatic drugs, interleukin-1 inhibitors, interleukin-17 inhibitors, monoclonal TNF-alpha antibody, mammalian target of rapamycin (mTOR) inhibitors, tumor necrosis factor (TNF) inhibitors, chemotherapy, and 2 or more prescriptions of glucocorticoids within the past year, as these therapies potentially could obscure GCA. For all patients, age, comorbidities, and medication status were determined using either the date of first contact (for patients whose first contact was at age ≥60) or the patient's 60th birthday (patients whose first contact was at <60 years of age).

Statistics

GCA-free survival analysis was performed on the matched cohort using a proportional hazards regression model with a time-varying ZVL vaccination status. ZVL-vaccinated patients were counted as unvaccinated during the time between the date of first contact or 60th birthday and the date of ZVL vaccination and were counted as vaccinated from the date of ZVL vaccination to the date of last contact or GCA diagnoses. For this analysis, patient follow-up was censored at the date of last contact or the date of death. All analyses were performed using the SAS software suite, version 9.4 (SAS Foundation, Cary, NC, USA).

RESULTS

Pre Matched Population

A total of 92 153 patients met initial criteria for inclusion in the study. In this unmatched population, 21 312 patients received ZVL at some point during their follow-up, and there were 207 GCA diagnoses. After matching, the matched cohorts contained a total of 71 008 patients (21 308 in the ZVL cohort and 49 700 in the non-ZVL cohort) age 60 years or older without a history of immunosuppression who were seen by their primary care provider at some point in the years 2000 through 2015 (Figure 1).
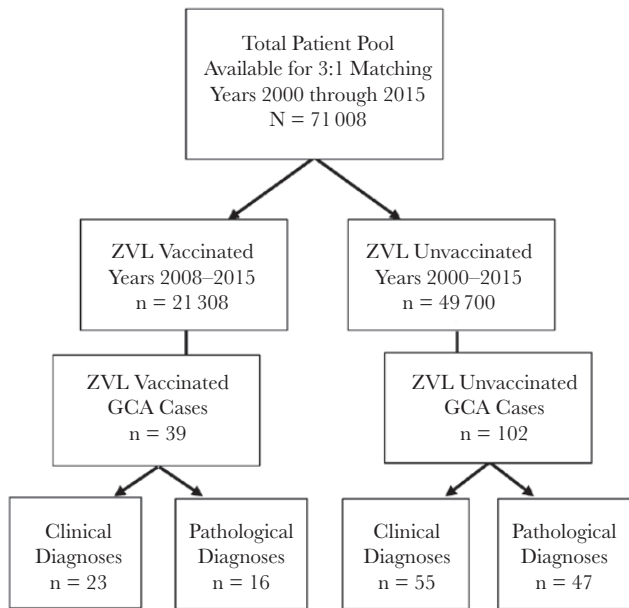
Figure 1. Study population flowchart. After applying selection criteria and matching on age, sex, and date of first primary care contact, 141 GCA cases (39 ZVL vaccinated and 102 unvaccinated) were included in the final analysis. Abbreviations: GCA, giant cell arteritis; ZVL, live attenuated herpes zoster vaccine.

Demographics of Vaccinated and Unvaccinated Patients After Matching

The populations of the ZVL and non-ZVL patients were, for the most part, balanced; the median age (range) of GCA cases was 74.3 (61.3–95.6) years in ZVL-vaccinated cases and 73.1 (61.7–91.6) years in unvaccinated ($P = .45$). However, women accounted for 55.6% of ZVL-vaccinated cases vs 52.3% unvaccinated ($P \leq .0001$), and for all years, health care utilization, measured by years with contacts divided by years of follow-up, was a mean of 85% +/-22% in ZVL patients vs 73% +/- 34% in non-ZVL patients ($P < .0001$).

For patients who developed GCA, health care utilization was determined. In ZVL recipients, only utilization before receipt of ZVL was included in the calculations. Utilization before GCA diagnosis was a mean of 80% +/- 28% of at-risk years vs 77% +/-31% of at-risk years for non-GCA patients ($P = .24$). A secondary measure of utilization, the number of pneumococcal immunizations received during the follow-up period, was also examined. Before the development of GCA, patients who developed GCA received an average of 0.67 +/- 0.77 pneumococcal immunizations, compared with 1.0 +/- 1.0 immunizations in non-GCA patients ($P < .0001$).

In the combined cohorts, 141 had received an ICD code for GCA and met GCA case criteria for inclusion (Figure 1). Thirty-nine GCA cases were diagnosed after ZVL vaccinations out of a total 80 546 patient-years at risk (4.8 cases per 10 000 person-years), and 102 GCA cases were diagnosed in ZVL-naïve patients out of a total 470 982 patient-years at risk (2.2 cases per 10 000 person-years).

Of the 39 cases diagnosed after ZVL vaccination, 16 (41%) were diagnosed via positive biopsy, and 23 (59%) by nonpathological ACR clinical criteria. Of the 102 cases diagnosed in ZVL-naïve patients, 47 (46%) cases were diagnosed via biopsy and 55 (54%) via other ACR criteria. There was no significant association between ZVL status and either GCA diagnostic case criterion ($P = .71$).

Analysis Results of the Matched Cohorts

Using proportional hazards regression models of time to GCA by combination of both diagnostic case criteria, ZVL vaccination was associated with an increased risk of GCA diagnosis (hazard ratio [HR], 2.20; 95% CI, 1.50–3.24; $P < .0001$). In this matched analysis, the median time from ZVL vaccination to a diagnosis of GCA was a median (range) of 37.7 (4.9–104.3) months, with peaks around 15 months and 45 months (Figure 2). In the more specific, biopsy-confirmed subset of GCA cases, ZVL receipt remained a significant risk factor for GCA (HR, 2.70; 95% CI, 1.48–4.95; $P = .004$) (Table 1).
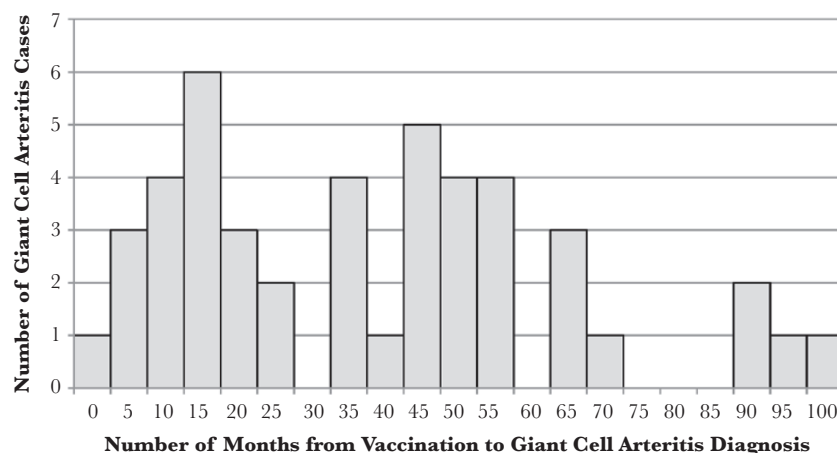

Figure 2. Number of months from patient receipt of ZVL to diagnosis of giant cell arteritis. Abbreviation: ZVL, live attenuated herpes zoster vaccine.

Table 1. Matched Cohort of ZVL-Vaccinated Cases vs Unvaccinated Results by Diagnostic Criteria

Diagnostic Criteria	ZVL Vaccinated	Unvaccinated	P Value
Clinical criteria			
2000		5/5039 (0.10)	
2001		10/18 496 (0.05)	
2002		2/21 971 (0.01)	
2003		4/24 523 (0.02)	
2004		7/26 672 (0.03)	
2005		10/28 524 (0.04)	
2006		6/33 025 (0.02)	
2007	0/3 (0.00)	10/33 018 (0.03)	.99
2008	1/7 (12.50)	3/35 149 (0.01)	.001
2009	0/1958 (0.00)	5/35 166 (0.01)	.99
2010	1/2917 (0.03)	8/36 062 (0.02)	.50
2011	4/4677 (0.09)	6/35 965 (0.02)	.003
2012	2/9010 (0.02)	7/32 929 (0.02)	.99
2013	7/12 682 (0.06)	6/29 791 (0.02)	.07
2014	7/15 036 (0.05)	1/27 827 (0.00)	.004
2015	4/16 787 (0.02)	8/25 316 (0.03)	.77
2016	13/17 430 (0.07)	4/21 407 (0.02)	.009
Combined years	39/80 508 (0.05)	102/470 880 (0.02)	<.001
Pathologic criteria only	16/80 531 (0.02)	47/470 953 (0.01)	0.02

Results are reported as No. of GCA events/No. of patients (%).

Abbreviations: GCA, giant cell arteritis; ZVL, live attenuated herpes zoster vaccine.

To account for potential changes in health care practice over time, we performed a secondary analysis incorporating only those patients from the original matched cohort whose follow-up period included the year 2008 (the first year of widespread ZVL availability and use) or any subsequent years. In this subset (n = 62 395 patients with 130 GCA diagnoses), ZVL vaccination remained a significant risk factor for GCA diagnosis via all diagnostic criteria (HR, 2.35; 95% CI, 1.58–3.47; P < .0001) and for GCA diagnosis by positive biopsy alone (57 GCA diagnoses; HR, 2.91; 95% CI, 1.57–5.38; P = .0007).

DISCUSSION

This matched comparison of ZVL vs non-ZVL patients showed that vaccinated patients had a significantly higher incidence of GCA. In their study utilizing a large Israeli claims database, Lotan and Steiner [14] also reported an increase in the incidence of GCA in the population receiving a vaccine (75.2/100 000) compared with an unvaccinated population (41.6/100 000; P = .07); however, unlike our current study, the increase they reported did not meet standard definitions of statistical significance and was not a matched cohort comparison. The modest discrepancy between the Israeli study and ours may be due to the difference in methods and populations, to the longer period over which this US population was followed, and to the larger number of vaccinated patients in our study cohort. Importantly,

our population is of ~90% northern European descent, a group known to have a high incidence of GCA.

This study's limitations include a relatively small sample population of a single health care system, as well as those inherent to retrospective studies, which depend upon the accuracy and completeness of the records from which data are captured. In addition, because the EHR, including registration of ZVL vaccination, was available to providers at the time of patient visits, bias for or against a GCA diagnosis might have occurred. However, we believe this is unlikely as the clinical association of VZV (and certainly VZL) and GCA was neither widely known nor widely accepted.

While some studies, including this one, indicate an association of chronic VZV infection (now, also ZVL) and GCA, these reports are by no means consistent [15, 16]. Because postvaccine GCA cases occurred months after ZVL, acute ZVL infection does not appear to be a cause of postvaccination GCA. Further research to confirm this association and, if found, to characterize the etiology of GCA post-ZVL is needed. In this regard, in vaccinated cases, evaluation of GCA for ZVL DNA may be informative. In addition, a new recombinant zoster vaccine (ZVR), an HZ subunit adjuvanted vaccine, has been reported to have a stronger immune response than ZVL. It also would be beneficial to determine whether immunization has a long-term effect on the incidence of GCA in the era of this more potent subunit vaccine.

In summary, ZVL was found to be associated with an increased risk of GCA. This association may potentially be attributed to (1) subacute or persistent arterial wall infection with ZVL, (2) a ZVL vaccine-driven cellular immune response to VZV already present in the arterial walls, or (3) a non-viral-specific autoimmune reaction triggered by ZVL.

References

1. Eshleman E, Shahzad A, Cohrs RJ. Varicella zoster virus latency. Future Virol **2011**; 6:341–55.
2. White DW, Suzanne Beard R, Barton ES. Immune modulation during latent herpesvirus infection. Immunol Rev **2012**; 245:189–208.
3. Yoshikawa TT, Schmader K. Herpes zoster in older adults. Clin Infect Dis **2001**; 32:1481–6.

4. Deviley JA, Oldenburg D, Berg LC, Agger WA. Recurrent strokes, central nervous system vasculitis, and acquired protein S deficiency secondary to varicella zoster in a child with AIDS. J Neurovirol **2019**; 25:137–40.

5. Buchan SA, Daneman N, Wang J, et al. Incidence of hospitalizations and emergency department visits for herpes zoster in immunocompromised and immunocompetent adults in Ontario, Canada, 2002-2016. Clin Infect Dis **2020**; 71:22–9.

6. Nagel MA, Bubak AN. Varicella zoster virus vasculopathy. J Infect Dis **2018**; 218:107–12.

7. Cooper RJ, D'Arcy S, Kirby M, et al. Infection and temporal arteritis: a PCR-based study to detect pathogens in temporal artery biopsy specimens. J Med Virol **2008**; 80:501–5.

8. Alvarez-Lafuente R, Fernández-Gutiérrez B, Jover JA, et al. Human parvovirus B19, varicella zoster virus, and human herpes virus 6 in temporal artery biopsy specimens of patients with giant cell arteritis: analysis with quantitative real time polymerase chain reaction. Ann Rheum Dis **2005**; 64:780–2.

9. Nagel MA, White T, Khmeleva N, et al. Analysis of varicella-zoster virus in temporal arteries biopsy positive and negative for giant cell arteritis. JAMA Neurol **2015**; 72:1281–7.

10. Gilden D, Nagel M. Varicella zoster virus in temporal arteries of patients with giant cell arteritis. J Infect Dis **2015**; 212(Suppl 1):S37–9.

11. Gilden D, Nagel MA. Varicella zoster virus triggers the immunopathology of giant cell arteritis. Curr Opin Rheumatol **2016**; 28:376–82.

12. Cunningham AL, Levin MJ. Herpes zoster vaccines. J Infect Dis **2018**; 218:127–33.

13. Hunder GG, Bloch DA, Michel BA, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum **1990**; 33:1122–8.

14. Lotan I, Steiner I. Giant cell arteritis following varicella zoster vaccination. J Neurol Sci **2017**; 375:158–9.

15. Buckingham EM, Foley MA, Grose C, et al. Identification of herpes zoster-associated temporal arteritis among cases of giant cell arteritis. Am J Ophthalmol **2018**; 187:51–60.

16. Ostrowski RA, Metgud S, Tehrani R, Jay WM. Varicella zoster virus in giant cell arteritis: a review of current medical literature. Neuroophthalmology **2019**; 43:159–70.