

Brief Report

Increased Herpes Zoster Risk With Inhaled Corticosteroid Use for Those With Chronic Obstructive Pulmonary Disease

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Herpes zoster (HZ) or shingles is a common painful condition that occurs in about one third of the general population by age 80 years. While for many shingles is limited to a day to 2 week long symptomatic prodromal period followed by one to four weeks of painful rash, many older individuals will experience one or more HZ complications including HZ ophthalmicus and post herpetic neuralgia that can linger for months with marked decline in the person's quality of life and ability to continue usual activities.^{1,2} Several chronic medical conditions (rheumatic, inflammatory bowel and chronic lung diseases including COPD) and associated treatments such as corticosteroids have been shown to increase the annual risk of HZ by 20 to 60%.³

Up to 75% of people diagnosed with COPD receive daily inhaled corticosteroid (ICS) therapy often augmented over several years by bursts of oral corticosteroid treatment for exacerbations. But studies reporting on the risk of HZ in those with COPD exposed to daily ICS⁴⁻⁸ only provide relative risk (RR) or hazard ratio (HR) in comparison to individuals without COPD. This brief report compares groups with and without ICS exposure within the COPD population to better determine the risk of HZ when adding ICS to COPD therapy. This is especially important since real world data shows that many people with COPD are prescribed daily ICS without meeting the recommendations for inclusion of ICS in COPD maintenance therapy---frequent COPD exacerbations, high total eosinophil count or concomitant asthma and COPD.^{4,9}

To test the hypothesis that longer duration of ICS as part of COPD therapy is associated with increased HZ risk using real world data from the DARTNet Practice Performance Registry and selected additional databases, we compare the risk of HZ in people with COPD and no or <3 months (short-term/no) versus 24+ months (long-term) ICS exposure. The DARTNet Practice Performance Registry is a Center for Medical and Medicaid Services quality improvement registry. In the time frame included in this study, over 7000 clinical organizations from solo clinicians to large integrated healthcare system provided electronic health record (EHR) data for various periods of time.^{10,11} All individuals in the cohorts had a clinical diagnosis of COPD based on 2 separate visits with a COPD diagnosis separated by at least 3 months or one visit for COPD with prescription of a daily COPD maintenance medication (LAMA, LABA or ICS or any combination of those) or a hospitalization for COPD. We developed both a COPD prevalence cohort; had a COPD diagnosis at entry into the observation period, and an inception cohort; had new diagnosis of COPD 6+ months after entry into the database or 2 visits within the first 6 months of observations without a COPD diagnostic code. The individuals within each cohort were propensity matched, through the use of genetic exact matching, based on multiple demographic factors. The duration of ICS exposure was based on prescribing data and oral corticosteroids exposure was collected for all groups. HZ vaccination and spirometry data were not available. For analysis, the people who previously had HZ were dropped after matching.

Data are presented separately for the two cohorts comparing HZ occurrence for the long-term versus short-term/no ICS exposed individuals. The first occurrence of an HZ episode during the observation period was based on the presence of any HZ related code with no HZ codes in the prior 12 months. Recurrences were not assessed. Simple relative risk (RR; univariate analysis, not corrected for demographics or bursts) and hazard ratios (HR; Cox proportional hazards) from modeling to account for differing demographics and numbers of oral corticosteroid bursts per

person were calculated. Burst frequency is important for total corticosteroid exposure and as a proxy for COPD exacerbations and COPD severity. Mean and median duration of follow up were 3.98 and 4.00 years respectively with s.d 3.06.

For the prevalence cohort, the long-term ICS exposure group vs short-term/no exposure (N=242,623) included more women (57.4% vs 53.7%, $P<.001$) with a younger mean age [66.8 years (s.d. 10.4) versus 68.2 years (s.d. 11.3), $p<.001$] and fewer with Charlson-Deyo Scores of >2 (22.8% vs 25.8%, $P<.001$). The demographics of the inception cohort (COPD diagnosed after 6 months in the database, N=147,279) were similar with more women (58.0% versus 54.3%, $p<.001$), lower mean age [66.8 years (s.d. 10.5) versus 68.6 years (s.d. 11.2), $p<.001$] and fewer with baseline Charlson-Deyo score of >2 (24.1% versus 31.0%, $p<.001$) in long-term versus short-term/no ICS exposure groups.

The risk of HZ was significantly greater with longer exposure to ICS in both the prevalence and inception cohorts: RR = 2.40 (95% CI 2.20-2.60) for prevalence cohort and RR = 2.42 (95% CI 2.30-2.80) for the inception cohort. The HR after adjusting for demographic factors were similar: HR=2.57 (95% CI 2.55-2.60) for the prevalence cohort and 2.55 (95% CI 2.52-2.58) for the inception cohort. (Table) The absolute risk was a 1.03% increase in risk of HZ for the inception cohorts over an average period of 4 years with a NNH of 100.

This is one of the first studies to report on the increased risk of HZ in those with COPD exposed to long term versus short-term/no ICS exposure. Comparisons with previously published risk assessments are limited since most studies reported comparative risks of ICS exposure in cohorts with and without COPD. Yang et al ⁵ report HRs of 1.67 and 2.09 for those with COPD without and with ICS exposure compared to a matched Taiwanese population without COPD. From Spain Munos-Quiles et al ⁷ report RRs of 1.45 and 1.61 again comparing those with COPD without and with ICS exposure to a matched group without COPD. In a German claims-based study, Batram et al ⁸ reported increased risk of HZ in people with COPD prescribed one or more bursts of oral steroids. None of these studies are limited to COPD populations and do not report the risk from ICS added to risk from having COPD. Our study was limited by all the limitations of using HER data, lack of HZ vaccination data and no spirometric confirmation of COPD. However, these were likely to be similar for all people with clinical diagnoses of COPD regardless of ICS exposure. We are also unable to report whether the HZ risk continues to increase with more years of ICS exposure.

Within these COPD populations, an increased risk of HZ was associated with a longer duration of ICS exposure emphasizing the importance of balancing the risk and benefits from adding ICS to COPD maintenance therapy.⁹ Based on local vaccination guidelines, clinicians should consider recommending or administering HZ vaccine to their patients with COPD, especially those on long-term ICS.^{3,12}

Summary of Conflicts of Interest Statements: B.P. Yawn reports receiving honoraria from AstraZeneca, GlaxoSmithKline, Merck, TEVA, and Boehringer Ingelheim for consulting and work on advisory boards and from AstraZeneca and GlaxoSmithKline for travel to presentations. She is on the MASAC board of the COPDF (unpaid) W. Pace has received research grant support from Boehringer Ingelheim (outside of this project), AstraZeneca, PCORI, NIH, ONC, CDC, Tabula Rasa Healthcare. He is on the Advisory Board and Executive Committee member (unpaid) for COPD Foundation 360 Network; he owns stock through a trust in Johnson and Johnson, Eli Lilly, Novo-Nordisk, Pfizer, Novartis, Moderna, and Amgen. Asif Shaikh was affiliated with BI during the study, is now an employee of Sun Pharma

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Table. RR and HR for herpes zoster episodes by ICS exposure duration: Prevalence and Inception cohorts.

HZ in COPD matched prevalent cohort including asthma (N=242,623)					
ICS duration	All with COPD	No HZ during observation period	HZ during observation period	Unadjusted RR	Adjusted HR [%]
	N	n, (%)	n, (%)	Long-term vs short-term/no	
ICS 24+ months	81,159	79,950 (98.5)	1,209 (1.49)*	2.40 (2.2-2.6)	2.57 (2.55-2.60)
ICS <3 months/No ICS	161,464	160,466 (99.4)	998 (0.62)		
HZ in COPD matched inception cohort including asthma (N=147,279)					
ICS duration	All with COPD	No HZ during observation period	HZ during observation period	Unadjusted RR	Adjusted HR [%]
	N	n, (%)	n, (%)	Long-term vs short-term/no	
ICS 24+ months	73,933	72,695 (98.3)	1,238 (1.70)*	2.42 (2.3-2.8)	2.55 (2.52-2.58)
ICS <3 months/No ICS	73,346	72,855 (99.3)	491 (0.67)		

*p<.001 for ICS 24+ months vs ICS <3 months/no ICS for prevalent and incidence cohorts

% Note: Adjusted for Age at index, index year, number of steroid bursts, gender, race, ethnicity, smoking status, bmi and Carlson-Deyo Score