placebo-controlled trials with cyclic vitamin D3 and 5-fluorouracil cream after cryotherapy for hyperkeratotic actinic keratoses treatment are needed to confirm these findings. Similarly, monotherapy studies with cyclic topical calcipotriene 0.005% foam for actinic keratoses treatment may be warranted to confirm any association of improved efficacy and decreased irritation and possible effect on subsequent squamous cell carcinoma development.

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A retrospective cohort study confirms that prophylactic vaccination is underused in patients on tumor necrosis factor inhibitors

To the Editor: Biologics place patients at increased risk for infection.[1] The medical boards of the National Psoriasis Foundation, the American College of Rheumatology, and the European League Against Rheumatism advocate influenza, pneumococcal, and varicella zoster vaccines for this high-risk patient population.[2-4] Unfortunately, low use of pneumococcal vaccine among Veterans Affairs patients prescribed tumor necrosis factor inhibitors (TNFi) has been noted.[5]

We performed a retrospective cohort study accessing the MarketScan Commercial Claims and Encounters Database (IBM, Armonk, NY) containing data from >150 million Americans to explore vaccine use in TNFi-treated patients. We used National Drug Codes to identify commercially insured patients, aged 18 to 60 years, prescribed adalimumab, etanercept, or infliximab continuously for ≥6 months between 2014 and 2016. National Drug Codes or Current Procedural Terminology (American Medical Association, Chicago, IL) entries, or both, for influenza, varicella zoster, or pneumococcal pneumonia vaccines were used to classify individuals as vaccinated or unvaccinated. *International Classification of Disease* 9 and 10 codes were used to identify patients diagnosed with influenza, varicella zoster, or pneumococcal pneumonia and capture those hospitalized for relevant infections. Infection rates and frequency of subsequent hospitalization were compared between vaccinated and unvaccinated patients. Odds ratios were constructed for each comparison.

Included were 89,098 patients prescribed TNFi for ≥6 months (19,878 on adalimumab, 12,167 on etanercept, and 57,053 on infliximab). Only a fraction of the patients were vaccinated for influ-

Table I. Vaccination rate of patients on biologic therapy from 2014 to 2016*

Vaccination	Vaccine received	Number	% of total
Influenza vaccination	In 2014	31,117	34.92
	In 2015	32,854	36.87
	In 2016	35,344	39.67
Zoster vaccination	In 2014-2016	2963	3.33
Pneumococcal	In 2014-2016	9406	10.56

*Number and rates of patients who received influenza, zoster and pneumococcal vaccination from 2014-2016.

Table II. Inflection rates and hospitalizations based on vaccination status from 2014-2016*

Variable	Vaccinated, %	Unvaccinated, %	χ^2 test	*P* value	OR	95% CI	*P* value
Infections							
Influenza	0.44	7.37	3291.90	<.00001	17.83	15.5999-20.3789	<.0001
Zoster	1.11	1.73	6.5526	.010473	1.5672	1.1078-2.2171	.0111
Pneumococcal pneumonia	2.32	3.71	47.7092	<.00001	1.6258	1.4145-1.8688	<.0001
Hospitalization for							
Those infected	12.09	13.45	0.7311	.39252	1.1301	0.8536-1.4962	.3928
All individuals on TNFi	0.09	0.47	192.8935	<.00001	5.2889	4.0654-6.8806	<.0001

CI, Confidence interval; *OR*, odds ratio; *TNFi*, tumor necrosis factor inhibitor.
*Data for influenza, zoster, and pneumococcal infections in those vaccinated vs unvaccinated for those diseases from the years 2014-2016 as well as percentage of infections that required hospitalization and percentage of all individuals who acquired an infection severe enough to require hospital admission. Also included are the χ^2 analysis, odds ratio of developing the condition if unvaccinated, confidence intervals, and associated *P* values.

enza (34.92% in 2014, 36.87% in 2015, and 39.67% in 2016), zoster (3.33%), and pneumococcal pneumonia (10.56%) (Table I). Unvaccinated individuals were more likely to develop subsequent infection of influenza, pneumococcal pneumonia, and varicella zoster, with odds ratios of 17.83, 1.6258, and 1.5672, respectively (Table II). Of those infected, 59 vaccinated patients (12.09%) and 954 unvaccinated patients (13.45%) were hospitalized, although this difference did not achieve significance (Table II). Individuals who received no vaccinations had a significantly higher risk of subsequent hospitalization, with an odds ratio of 5.2889 (Table II).

Limitations include the retrospective nature of MarketScan data. The nonrandom sample may contain biases or fail to generalize well to other populations worldwide and were collected before the widespread use of the recombinant zoster vaccination was commercially available. We did not exclude patients with other indications for vaccination due to poor understanding of adherence in these populations (ie, organ transplant or HIV). Therefore, our already surprisingly low results likely overstate vaccination use purely for the indication of TNFi therapy.

Although prophylactic influenza, pneumococcal, and varicella zoster vaccination for patients on TNFi therapy is recommended,[2-4] our study confirms shockingly low use of prophylactic vaccination across patients treated with adalimumab, etanercept, and infliximab. This underuse is associated with higher infection rates for influenza, varicella zoster, and pneumococcal pneumonia in unvaccinated TNFi users. Unvaccinated patients prescribed TNFi have a substantially higher rate of hospitalization compared with individuals receiving even just 1 of the vaccinations.

Literature cites confusion among prescribers of TNFi therapy regarding who carries responsibility for suggesting vaccination: specialists or primary practicioners.[5] We believe the TNFi prescriber should discuss recommendations for vaccination and administer personally or communicate with primary care. Our data suggest improving vaccination adherence in TNFi-treated patients could prevent considerable morbidity and cost within our health system.

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Efficacy of antihistamines in combination with topical corticosteroid and superficial cryotherapy for treatment of alopecia areata: A retrospective cohort study

To the Editor: Despite advancements in our understanding of the pathomechanism of alopecia areata (AA), optimal therapies and means to predict treatment responses remain elusive. Cases of AA with improvement after topical diphenylcyclopropenone (DPCP) immunotherapy and antihistamine treatment have been reported.[1] Hence, we investigated the role of adjuvant antihistamines in combination with a topical corticosteroid (TC) and superficial cryotherapy (SC) for AA.

We retrospectively analyzed patients with AA who visited our hospital from February 2012 to November 2018. At our hospital, we administer a treatment protocol consisting of TC and SC at 4- to 8-week intervals for patients with mild to moderate AA who are not candidates for topical DPCP immunotherapy and systemic corticosteroids. The patients included in the analysis were divided into 2 groups: those who were or were not treated with adjuvant antihistamines during the follow-up period. Notably, we did not consider whether the antihistamines were used intentionally for the treatment of AA or unintentionally for some other indication. The antihistamines included in the analysis were fexofenadine (180 mg/d for adults and 30 mg/d for pediatric patients) and ebastine (10 mg/d for adults). Demographic data and clinical progress were compared using the Kaplan-Meier method between both groups.

Twenty-four patients were treated with an adjuvant antihistamine—in combination with TC and SC—and 121 patients were not. There were no significant differences in sex, age, disease duration, type of episode, initial Severity of Alopecia Tool (SALT) score, history of atopy, or total follow-up period between groups (Table I). In the group treated with adjuvant antihistamines, the mean duration of antihistamine use within the AA treatment period was 6.29 months. A cumulative

Table I. Characteristics of patients treated with and without adjuvant antihistamines

Characteristics	TC + SC + AH	TC + SC	*P* value
Number of patients	24	121	
Age, y, mean ± SD	44.00 ± 13.74	39.31 ± 14.49	.147
Duration, mo, mean ± SD	8.71 ± 10.96	5.22 ± 10.80	.162
Sex, n (%)			.456
Male	9 (37.5)	50 (41.3)	
Female	15 (62.5)	71 (68.7)	
Type of current episode, n (%)			.315
First time	19 (79.2)	86 (71.7)	
Recurrent	5 (20.8)	34 (28.3)	
Initial SALT score, n (%)			.518
0-30	22 (91.7)	113 (93.4)	
31-50	2 (8.3)	8 (6.6)	
History of atopic diathesis,* n (%)			.399
Yes	3 (12.5)	21 (17.5)	
No	21 (87.5)	99 (82.5)	
Family history of AA, n (%)			.181
Yes	1 (4.2)	16 (13.3)	
No	23 (95.8)	104 (86.7)	
Total follow-up period, mo, mean ± SD	9.43 ± 8.03	7.28 ± 6.61	.229

AA, Alopecia areata; *AH*, antihistamine; *SALT*, Severity of Alopecia Tool; *SC*, superficial cryotherapy; *SD*, standard deviation; *TC*, topical corticosteroid.
*History of atopic diathesis included atopic dermatitis, asthma, allergic rhinitis, eosinophilic esophagitis, or anaphylactic reaction to food.