studies are needed to understand the pathogenesis for PRP eruptions associated with pharmacologic agents.

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Development of morphea in patients receiving biologic therapies: A systematic review

To the Editor: An infrequently reported cutaneous complication of biologic treatment is the onset of localized scleroderma or morphea. Given the increasing use of biologic therapy worldwide, it is essential for health care providers to anticipate and manage potential adverse effects. This review aims to summarize reports of morphea development in patients receiving biologic therapies targeting inflammatory pathways implicated in psoriasis.

An EMBASE and MEDLINE search was conducted on May 8, 2020, in accordance with PRISMA

Table I. Summary of included cases of morphea in patients receiving biologics

Study characteristics and demographic information		Biologic information				Patient characteristics			Characteristics of morphea				Morphea resolution				
Sources	Age (y)/sex	Drug	Biologic mechanism	Dose and frequency	Indication	Comorbidities	Other medications (dose and frequency)	Latency period (months)	Morphea type	No. of morphea lesions	Morphea present at the injection site	Location	Treatment for morphea (dose, frequency)	Postdiagnosis follow-up (months)	Complete (CR) or partial (PR) morphea resolution	Morphea course (months)	Potential reason for morphea resolution
1	45/M	Etanercept	TNF-α inhibitor	50 mg twice weekly for 3 mo, followed by once-weekly for 1 mo	Psoriasis	NR	NR	18	Plaque	Multiple	Yes	Right lower aspect of abdomen, thighs, flanks, back	Intralesional corticosteroids	3	PR	NR	NR
2	54/M	Etanercept	TNF-α inhibitor	25 mg twice weekly	Rheumatoid arthritis	NR	Sulphasalazine (2 g daily)	36	Plaque	Multiple	NR	Lumbar area	Topical corticosteroid, vitamin E oil preparation and sulphasalazine 2 g daily for 3 mo; methylprednisolone, 100 mg every 2 wk; rituximab, 1000 mg every 2 wk	14	PR	14	Resolved after etanercept was stopped
3	37/M	Adalimumab	TNF-α inhibitor	NR	Ankylosing spondylitis	NR	NR	12	Plaque	Multiple	No	Left and right legs	Topical corticosteroids, dose and frequency NR	18	PR	18	Resolved after adalimumab was stopped
4	17/F	Adalimumab	TNF-α inhibitor	40 mg every 14 d	Crohn's disease	Tuberculosis	Isoniazid (300 mg/d)	2.8	Plaque	Single	Yes	Abdomen	Topical corticosteroids, dose and frequency NR	12	CR	2	NR
5	42/F	Adalimumab	TNF-α inhibitor	NR, for 2 mo	Psoriasis	Lichen planus, neutrocytopenia, hypothyroidism	Prednisolone (20 mg, daily) after discharge	6	Pansclerotic	Multiple	No	Limbs and trunk	narrowband ultraviolet B therapy (dose NR, for $\geq$3 mo) and calcipotriol (dose NR, for $\geq$3 mo)	NR	PR	3	Resolved after tx
6	NR/M Mean age 16.4 $\pm$ 3.2	Adalimumab	TNF-α inhibitor	NR	Crohn's disease	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
7	58/F	Golimumab	TNF-α inhibitors	NR	Ankylosing spondylitis	4 episodes of uveitis	Systemic corticosteroids, methotrexate, anti-inflammatory drugs, leflunomide	23	Linear	Multiple	No	Lower limbs	NR	NR	NR	NR	NR
8	63/F	Ustekinumab	IL-12/IL-23 antagonist	NR	Psoriasis	NR	Phototherapy	6	Plaque	Multiple	No	Left and right legs	Phototherapy, dose and frequency NR	NR	NR	NR	Resolved after ustekinumab was stopped

9	48/F	Ustekinumab	IL-12/IL-23 antagonist	NR	Ulcerative colitis	Presumed psoriasis	Antibiotics, tofacitinib, mesalamine	12	Plaque	Multiple	No	Back, trunk, bilateral upper and lower aspect of extremities	Nonmodified cyclosporine, 200 mg daily	12	CR	2	Resolved after tx

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CR, Complete resolution; *F*, female patient; *IL*, interleukin; *M*, male patient; *NR*, not reported; *PR*, partial resolution; *TNF*, tumor necrosis factor; *tx*, treatment; *y*, years.

guidelines, using key words "biologic" specific to psoriasis AND "morphea" (Supplemental Tables I and II available via Mendeley at 10.17632/bjgghsp5gn.2). Of the 262 records identified, 9 studies met the inclusion criteria and a total of 9 patients with a mean age of 45.5 years were added (Table I, Fig 1). Men accounted for 44% of the cases (n = 4) and women accounted for 56% of cases (n = 5). Overall, morphea was reported while patients were receiving tumor necrosis factor α inhibitors in 7 cases (adalimumab, n = 4; etanercept, n = 2; and golimumab, n = 1) and interleukin (IL) 12 and 23 antagonists in 2 cases (ustekinumab, n = 2). Of these patients, 6 had plaque, 1 pansclerotic, 1 linear morphea, and 1 not reported. Their location included legs, upper extremities, chest, abdomen, trunk, and back.

The latency period between biologic initiation and morphea onset ranged from 2.8 to 36 months (mean 14.5 months). Specifically, tumor necrosis factor α inhibitors had a mean latency period of 16.3 months (adalimumab = 6.9 months, etanercept = 27 months, and golimumab = 23 months), whereas IL-12 and -23 antagonists (ie, ustekinumab) had a latency period of 9 months. Of the 5 patients who reported morphea resolution periods, remission ranged from 2 to 18 months (mean 7.8 months). In 33% of patients (n = 3), morphea resolution was attributed to the discontinuation of biologics, whereas 20% (n = 2) experienced remission after treatment, which included narrowband ultraviolet B therapy and calcipotriol (n = 1) and cyclosporine (n = 1).

Our search identified 7 cases in which morphea occurred in patients receiving tumor necrosis factor α inhibitors. These inhibitors have secondary effects on transforming growth factor β, which may cause fibroblast proliferation, extracellular matrix protein synthesis, and ultimately skin thickening characteristic of morphea.[1] However, in our analysis the greater proportion of patients developing morphea while receiving adalimumab (n = 4; 44.4%) may be a reflection of greater prescription rates of adalimumab compared with other biologics.[2] Although cutaneous manifestations of IL-12 and -23 inhibition have rarely been reported,[3] this group of biologics was associated with morphea in 2 cases. The classic pathway of IL-12 and -23 ultimately activates T-helper 17 cells, which release proinflammatory cytokines such as IL-17A; animal studies have illustrated elevated levels of T-helper 17 cells, IL-23, and IL-17A in the peripheral blood or fibrotic sites of systemic sclerosis.[4] Also, trauma may be a contributing

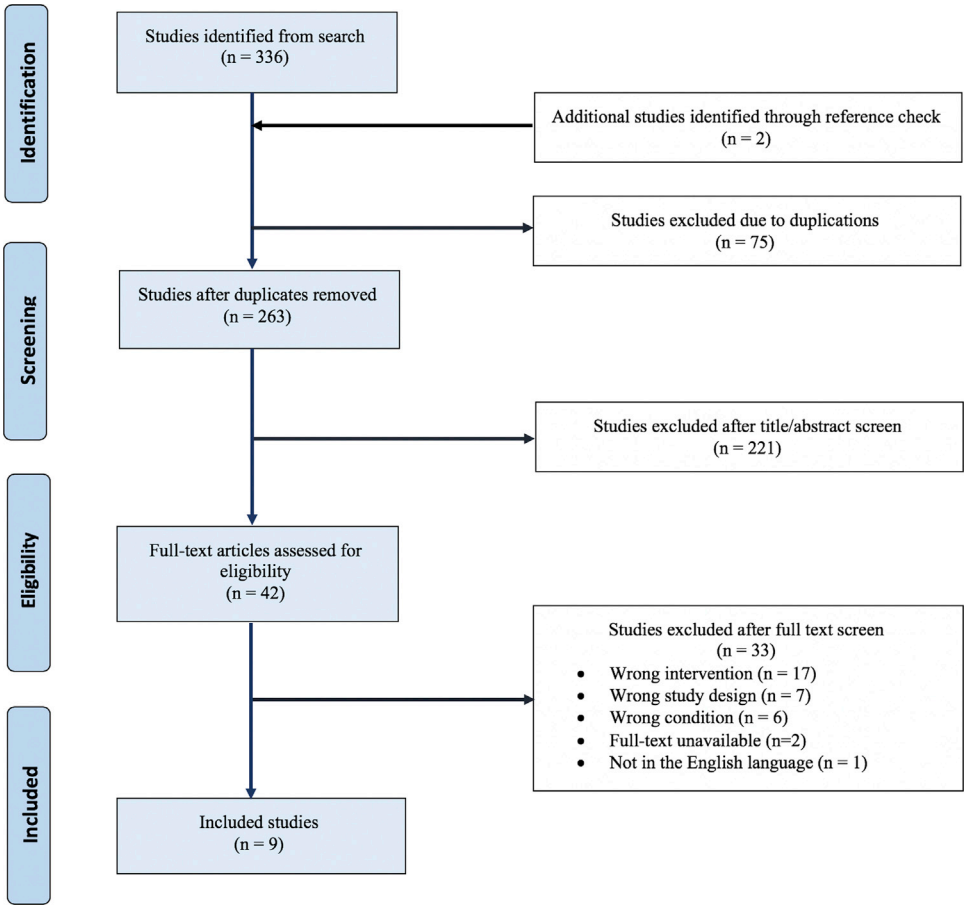

Fig 1. Flow diagram of literature screening using the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. Figure adapted from http://prisma-statement.org.

factor in morphea development in 2 patients who developed morphea at the injection site.

Limitations of our review include the small sample size, making it difficult to generalize our findings. Additionally, a causal relationship between biologic use and morphea cannot be elucidated because of the observational nature of the studies. No studies conducted causality assessment using published criteria, thus indicating the potential for publication bias. Further studies are required to confirm our findings.

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Lichen planus associated with hepatitis B, hepatitis C, and liver cirrhosis in a nationwide cohort study

To the Editor: Although associations between lichen planus (LP) and hepatopathies have been established since 1978,[1] previous studies focused only on LP associated with hepatitis B virus (HBV) and hepatitis C virus (HCV) infection.[2,3] HBV and HCV may cause chronic liver damage and induce liver cirrhosis and even hepatocellular carcinoma. Some studies showed that CD 8^+ T cells showed similar profiles of cytokines and chemokines between LP and liver cirrhosis.[4,5] However, no epidemiologic studies have investigated the association between LP and liver cirrhosis. This study aimed to investigate the incidence of hepatitis B or C and liver cirrhosis in patients with LP by a nationwide case-control study from the National Health Insurance Research Database in Taiwan.

We collected data from patients diagnosed as having diseases with International Classification of Disease, Ninth Revision—Clinical Modification (ICD-9-CM) codes of 697.0 (LP) by dermatologists or dentists from 2000 to 2011 from the Longitudinal Health Insurance Database 2000, which comprises 2 000 000 individuals randomly sampled from the general Taiwanese population (23 million people) of the National Health Insurance Research Database. We recruited the control group by age, sex, and index year matching with 1 to 2 ratios without significant differences. We also identified the diagnoses of viral hepatitis in the study and control cohorts by ICD-9 codes for hepatitis B, hepatitis C, and liver cirrhosis without a history of alcoholism.

This study included 2454 patients with LP and 4768 age- and sex-matched control individuals. The incidence of hepatitis C in patients with LP (1.8%) was significantly higher than in control individuals (0.6%; $P < .001$). The incidence of hepatitis B in patients with LP (2.2%) was also significantly higher than in control individuals (1.1%; $P < .001$). The incidence of liver cirrhosis in patients with LP (1.7%) was also significantly higher than in control individuals (0.9%; $P = .003$). We also used univariable and multivariable Cox proportional hazards models to evaluate independent predictors of new-onset liver cirrhosis to show adjusted hazard ratios as 1.71 (95% confidence interval, 1.11-2.61) for the LP group. In the subgroup Cox regression model for the association between LP and liver cirrhosis, we identified that women, those older than 60 years, and those without HBV or HCV infection in the LP subgroup were more prone to developing new-onset liver cirrhosis than in the non-LP subgroup (Table I). The Kaplan-Meier analysis showed higher cumulative incidences of liver cirrhosis in patients with LP than in those without LP (Fig 1).

The main limitation of the current study design was the lack of validation of liver cirrhosis diagnosis by imaging studies. More experimental studies are

Table I. Subgroup analysis of Cox' regression model for the association between LP and LC

Model	Patients, n	LC, n (%)	Hazard ratio (95% CI)	*P* value
Main model				
Non-LP	4768	44 (0.92)	1.00	
LP	2454	42 (1.71)	1.71 (1.11-2.61)	.014*
Age, y				
20-40				
Non-LP	1321	3 (0.23)	1.00	
LP	662	2 (0.30)	1.37 (0.23-8.18)	.732
40-60				
Non-LP	1943	18 (0.93)	1.00	
LP	987	14 (1.42)	1.45 (0.72-2.93)	.295
≥60 y				
Non-LP	1504	23 (1.53)	1.00	
LP	805	26 (3.23)	1.95 (1.10-3.46)	.022*
Sex				
Female				
Non-LP	2657	16 (0.60)	1.00	
LP	1360	22 (1.62)	2.32 (1.20-4.48)	.013*
Male				
Non-LP	2111	28 (1.33)	1.00	
LP	1094	20 (1.83)	1.30 (0.73-2.32)	.370
HBV				
No				
Non-LP	4714	41 (0.87)	1.00	
LP	2400	38 (1.58)	1.74 (1.12-2.72)	.014*
Yes				
Non-LP	54	3 (5.56)	1.00	
LP	54	4 (7.41)	1.34 (0.30-6.08)	.705
HCV				
No				
Non-LP	4738	43 (0.91)	1.00	
LP	2409	36 (1.49)	1.61 (1.03-2.51)	.036*
Yes				
Non-LP	30	1 (3.33)	1.00	
LP	75	6 (13.33)	3.54 (0.39-32.62)	.264

CI, Confidence interval; *HBV*, hepatitis B virus; *HCV*, hepatitis C virus; *LC*, liver cirrhosis; *LP*, lichen planus.
*Cox proportional hazards model.