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REVIEW

Mechanisms Underlying Lichen Planus in Association with Biologic Therapy

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Abstract: Cutaneous reactions, including lichen planus (LP) and related lichenoid eruptions have been increasingly reported in association with biologic therapies including immune checkpoint inhibitors and tumor necrosis factor-α inhibitors. Since the immunologic mechanisms underlying biologic-associated LP remain unclear, we aimed to summarize current evidence on biologic-induced LP, outline implicated drug classes, and propose mechanistic models. We conducted a comprehensive systematic analysis of PubMed literature, reviewing 145 publications that identified 157 cases of biologic-associated LP and proposed several overlapping immunological mechanisms, including cytokine imbalances, T cell immune pathway shifts, antigen unmasking, keratinocyte apoptosis dysregulation, and host susceptibility. Management of biologic-associate LP includes withdrawal of the offending biologic and adjunctive treatment. Further research is needed to clarify mechanistic pathways, define incidence, and identify predictive biomarkers that may guide risk stratification.

Keywords: lichen planus, lichenoid eruption, drug reaction, biologic therapy, immunologic mechanisms

Introduction

Lichen planus (LP) is a chronic, inflammatory, and immune-mediated disorder that may affect the skin, nails, hair, and mucous membranes, with an estimated worldwide prevalence of 0.22–5%.[1] The traditional six "P's" of LP, "Pruritic, Purple, Polygonal, Planar, Papules, and Plaques" describe the typical cutaneous presentation of LP as polygonal, flat-topped, violaceous papules and plaques, though there are many morphological variants.[2–4] Although etiology is often idiopathic, LP may be triggered by exogenous factors, including viral infections, such as hepatitis C,[5] vaccines,[6–9] and pharmacological agents, such as anti-hypertensives, nonsteroidal anti-inflammatory agents, and antimalarials.[10]

With expanding use of biologic therapies in oncology, rheumatology, dermatology, and gastroenterology, LP and drug-induced lichenoid reactions are increasingly recognized as adverse events. These drug eruptions can complicate the long-term management of patients with chronic inflammatory diseases and necessitate therapeutic reassessment, due to the complexity of these targeted, immune-modulating treatments. Since the mechanisms underlying biologic-associated LP remain incompletely defined, this review aims to summarize current evidence on biologic-induced LP, outline implicated drug classes, and propose mechanistic models for its development.

Materials and Methods

Searches for peer-reviewed journal articles were conducted on August 12, 2025 using the PubMed/MEDLINE database with the search terms "lichen planus", "lichenoid", "biologics", "drug-induced", and "mechanism." Additional search terms included "biological therapy", "TNF inhibitor", "checkpoint inhibitor", "IL-17 inhibitor", "IL-23 inhibitor", "adalimumab", "etanercept", "infliximab", "ustekinumab", "secukinumab", "dupilumab", "nivolumab", and "pembrolizumab." Filters included "Case Reports", "Clinical Study", "Clinical Trial", "Meta-Analysis", "Review", and "Systematic Review." Articles were included if they presented example(s) of patients with lichenoid eruption following

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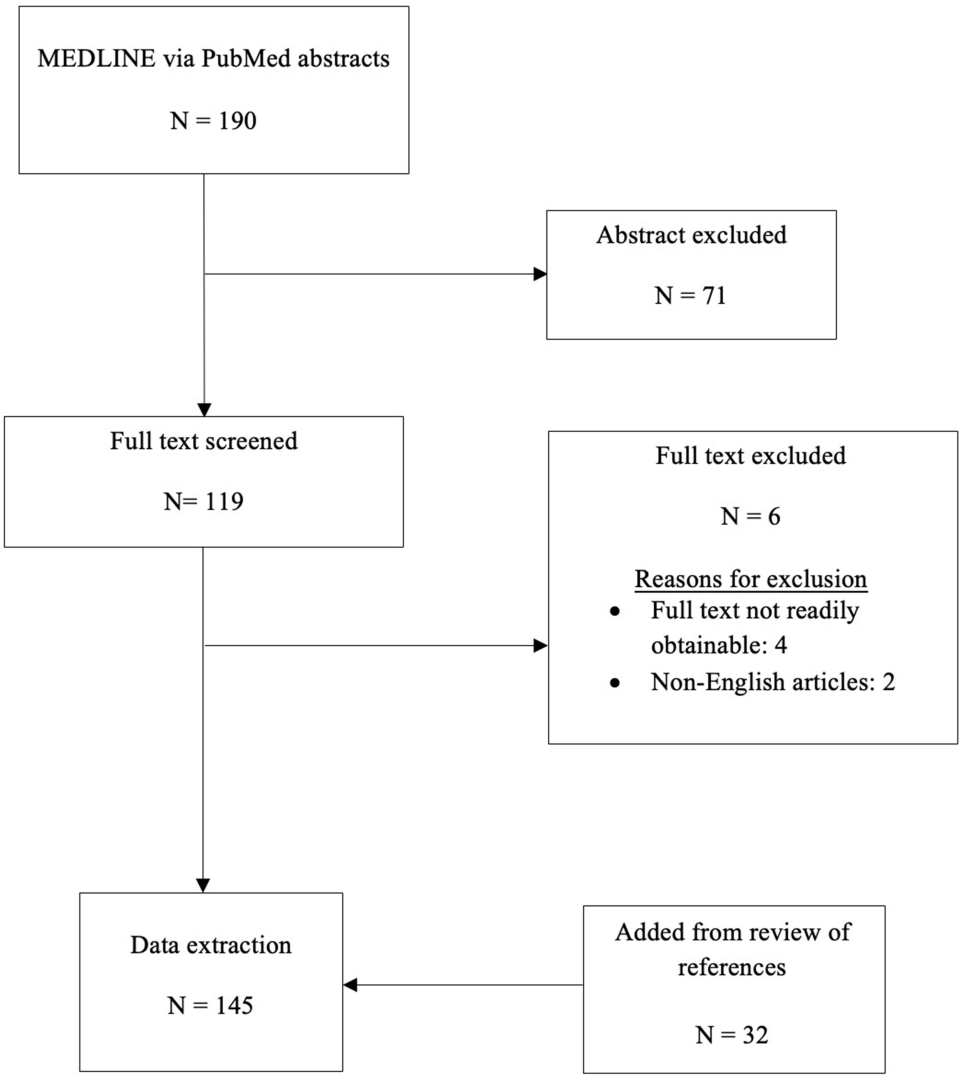

Figure 1 Flowchart diagram for selection of studies.

biologic therapy or discussed the phenomenon. Exclusion criteria included studies that did not mention lichenoid reactions and biologic therapy, vaccine-induced LP, and studies with discussion of biologic therapy as treatment for LP without presentation of LP after initiation of the therapeutic. Reference lists from these articles were used to find additional articles. Studies without readily obtainable full text in English were excluded (Figure 1).

Pathogenesis of Lichen Planus

The pathogenesis of LP is incompletely understood, but converging evidence supports that LP is driven by a cytotoxic immune response that induces apoptosis of basal keratinocytes at the dermoepidermal junction.[3,4] On immunohistochemistry of both mouse model and human biopsy samples, there is a predominance of CD8+ T lymphocytes in the lichenoid infiltrate, though CD4+ T cells, in particular T-helper-1 (Th1) cells, also play an important role in driving basal keratinocyte apoptosis.[4,11–13] Increased expression of intracellular adhesion molecule-1 (ICAM-1) by basal keratinocytes enhances this interaction, which is a unique feature of LP in comparison to other interface dermatoses, such as subacute cutaneous lupus erythematous and erythema multiforme.[14,15] Several cytokines are upregulated in this process, including tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), nuclear factor kappa B (NFκB), interleukin-1 (IL-1), IL-6, IL-8, and IL-10.[16,17] Apoptosis-related molecules, such as Fas/Apo-1 and Bcl-2, are also implicated.[18] Plasmacytoid dendritic cells (pDCs) contribute to pathogenesis by producing type I interferons, a pathway which may link viral infections and

LP through recruitment of CD8+ lymphocytes.[19] Overall, LP likely reflects a breakdown of self-tolerance, with keratinocytes acting as both targets and amplifiers of immune injury. This immune pathogenesis contributes to the histopathological lichenoid tissue reaction pattern characteristic of LP.

Overview of Implicated Biologic Therapies

Biologic-associated LP and lichenoid eruptions have been reported in association with multiple therapeutic classes, most prominently programmed cell death protein-1 (PD-1)/PD-ligand 1 (PD-L1) inhibitors, such as pembrolizumab and nivolumab,[20,21] and TNF-α-inhibitors, such as infliximab, adalimumab, and etanercept.[22,23] In an observational study of 82 melanoma patients, 17% of patients developed lichenoid drug eruption associated with anti-PD-1 antibody treatment.[24] Biologics, such as those targeting IL-17 and IL-23 have also been associated with lichenoid reactions.[25] Our literature review identified 157 cases of lichenoid drug eruptions following biologic therapy with 24 distinct medications (Table 1). Clinical presentations were heterogenous, encompassing classic cutaneous LP (Figure 2), 50 cases of oral LP, 22 cases of lichen planus pemphigoides (LPP), 7 cases of nail LP (Figure 3), and 6 cases of lichen planopilaris. The wide spectrum of presentation suggests that the potential disruption of multiple inflammatory pathways may precipitate biologic-induced lichenoid reactions, highlighting the need to examine the immunologic mechanisms.

Proposed Mechanisms of Biologic-Induced Lichen Planus

Biologic-associated lichenoid eruptions have been reported across multiple biologic classes, suggesting that these reactions are attributable to nuanced immunological mechanisms. They appear to result from disruptions to immune homeostasis that ultimately favor cytotoxic T cell-mediated injury at the dermoepidermal junction.[28] Several mechanistic models emerge from the literature, including cytokine imbalances, immune pathway redirection, unmasking of antigens and epitope spreading, dysregulation of keratinocyte apoptosis pathways, and potential genetic or host susceptibility factors.

Cytokine Imbalances

One of the most widely proposed mechanisms for biologic-induced LP involves cytokine imbalance following targeted inhibition of specific inflammatory pathways. In idiopathic LP, type I interferons, especially IFN-α, play important roles in modulating keratinocyte damage.[19] Conversely, TNF-α normally exerts an inhibitory effect on pDCs, limiting IFN-α production. Thus, TNF-α blockade by biologics like adalimumab and etanercept may lead to upregulation of cytokines including IFN-α, activating pDCs and cytotoxic T cells and generating an inflammatory response.[29–31] Inhibition of TNF-α has also been hypothesized to increase the expression of IL-17A and IL-23, stimulating the Th17 pathway.[32]

Similar cytokine shifts have been hypothesized with IL-17 inhibitors, such as secukinumab.[33] It has been proposed that IL-17 inhibition may activate pDCs and promote the production of inflammatory cytokines such as IL-23, IL-12, and TNF-α, contributing to LP development.[32,33] Additionally, hydroxychloroquine is occasionally used to treat biologic-associated LP, because it interferes with toll-like receptor signaling and decreases proinflammatory cytokine production.[34]

Although direct mechanistic studies remain limited, cytokine imbalance provides a strong potential mechanism for why certain biologics precipitate lichenoid reactions. Further research using serum cytokine profiling may delineate the precise immune shifts associated with each biologic class.

T Lymphocyte Immune Pathway Shifts

Another proposed mechanism for biologic-associated LP is the activation of a Th1-mediated immune response that stimulates autoreactive CD8+ T cell populations, resulting in basal keratinocyte apoptosis.[25] For example, the PD-1 pathway typically inhibits T cell activation, allowing malignant cells to escape the immune response. Therefore, biologic agents that inhibit PD-1, such as pembrolizumab and nivolumab, can remove the block on previously suppressed T cells, inducing T cell activation.[35,36] These inflammatory T lymphocytes may then proliferate and attack autoantigens in the skin, resulting in LP.[36] Furthermore, it has been proposed that the production of type I IFNs is closely associated with the recruitment of cytotoxic lymphocytes and pDCs via CXCR3 ligands, indicating a Th1-mediated immune response.[19,29,30]

Table 1 Characteristics of Reported Biologic-Associated Lichenoid Eruptions from the Literature, Summarized by Agent and Class

Biologic, Class	Number of Cases, n	Most Common Indications	Type(s) of LP Produced	Sex (% Male)	Median Time to LP Onset (Months), Range	Biologic Continued, n	LP Resolved, n
Pembrolizumab, PD-1-inhibitor	46	Lung cancer, melanoma, RCC, other carcinoma (eg, breast, urothelial)	Classic, oral, LPP, lichen planopilaris	41.3	4, 0.25–26	13	30
Nivolumab, PD-1-inhibitor	39	Lung cancer, melanoma, RCC	Classic, oral, LPP, nail, lichen planopilaris	66.6	5, 0.1-20	12	22
Infliximab, TNF-inhibitor	14	Psoriasis, IBD, arthritis	Classic, oral, lichen planopilaris	42.9	3.75, 0.5-48	5	10
Adalimumab, TNF-inhibitor	12	Psoriasis, IBD, arthritis	Classic, oral, lichen planopilaris	50.0	6, 0.5–52	4	7
Etanercept, TNF-inhibitor	9	Psoriasis, RA	Classic, nail	44.4	4, 0-12	2	8
Imatinib, tyrosine kinase inhibitor	6	CML, GIST	Classic, oral, nail	66.6	3, 0.1-12	3	6
Secukinumab, IL-17 inhibitor	5	Psoriasis, RA	Classic, oral	60.0	5, 0.25-8	0	5
Denosumab, RANKL-inhibitor	4	Osteoporosis	Classic	25.0	1, 1-2	0	4
Atezolizumab, PD-L1-inhibitor	4	Lung cancer	Classic, oral, LPP	50.0	4, 0.5–5.5	2	3
Dupilumab, IL-4Rα-inhibitor	3	Atopic dermatitis	Classic, oral	33.3	11, 4-24	1	3
Miscellaneous, various	15	Lung cancer, psoriasis, IBD	Classic, oral, LPP, nail	40.0	1.6, 0.1-26	4	12

Notes: Miscellaneous biologic therapies include: cadonilimab, CT-P13, durvalumab, ipilimumab, lenvatinib, MK-4830, TAK-981, sintilimab, lenercept, certolizumab pegol, casirivimab/imdevimab, ixekizumab, tislelizumab, and sitravatinib. **Abbreviations**: %, percentage; LP, lichen planus; PD-1, programmed cell death protein-1; RCC, renal cell carcinoma; LPP, lichen planus pemphigoides; TNF, tumor necrosis factor; IBD, inflammatory bowel disease; IL, interleukin; RA, rheumatoid arthritis; CML, chronic myeloid leukemia; GIST, gastrointestinal stromal tumor; RANKL, receptor activator of nuclear factor kappa-β ligand; PD-L1, programmed cell death-ligand 1; IL-4R, interleukin-4 receptor.

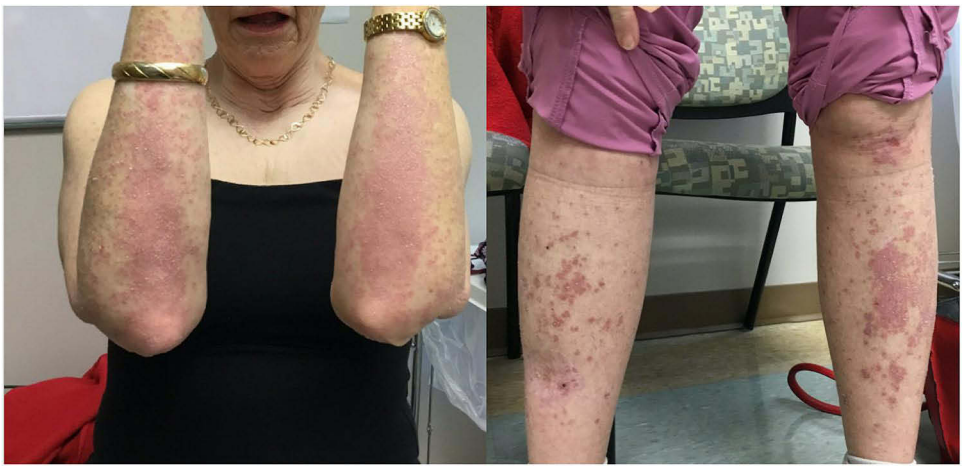

Figure 2 Multiple flat-topped violaceous papules, some coalescing into plaques, on the forearms and legs.
Notes: Copyright ©2023. Reproduced from Zemlok SK, Buuh S, Brown R et al. Nivolumab-induced lichen planus responsive to dupilumab treatment in a patient with stage III C melanoma. JAAD Case Reports, Volume 38, 23–26.[26]

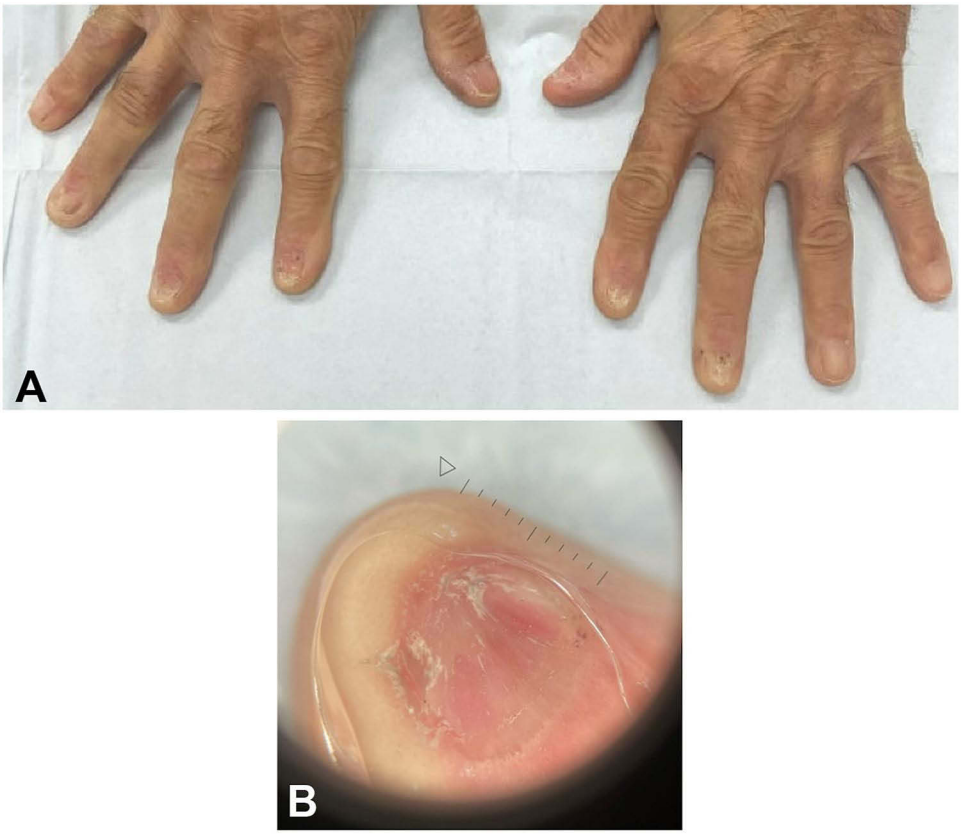

Figure 3 (**A** and **B**) A 75-year-old male with nail lichen planus secondary to imatinib use. Fingernails atrophic with pterygium on 7/10 fingernails, sparing the right thumbnail and left fourth and fifth fingernails. On dermoscopy, severe nail plate thinning and atrophy is apparent.
Notes: Copyright ©2025. Reproduced from Axler E, Loesch E,Vaidya T et al. Nail lichen planus associated with imatinib mesylate. JAAD Case Reports, Volume 58, 25–28.[27]

Furthermore, recent reports indicate that Th2 blockade by dupilumab may lead to a Th1/Th2 imbalance, shifting towards a Th1-dominated immune response that may result in dupilumab-induced LP.[37–40]

Additionally, narrowband ultraviolet B (NBUVB) phototherapy has successfully been used to treat anti-PD-1-induced LP refractory to steroidal treatment.[41,42] Since LP is associated with a Th1/Th17 response,[43] NBUVB phototherapy may

be used therapeutically to shift from a Th1/Th17 response to a Th2 milieu, promoting immunosuppression.[41,42] In addition to hydroxychloroquine's decreased proinflammatory cytokine production, it also downregulates major histocompatibility class (MHC) II-peptide complex formation, resulting in decreased CD4+ T cell activation and a suppressed immune response.[34] Therefore, NBUVB phototherapy and hydroxychloroquine may be used to treat biologic-associated LP by shifting from proinflammatory immune responses to Th2-mediated immune pathways.

Antigen Unmasking & Epitope Spreading

It has also been hypothesized that biologic therapy may precipitate lichenoid eruptions by unmasking a previously suppressed inflammatory response to pre-existing autoantigens localized to specific sites in the body.[36,44–46] In anti-PD-1 therapy in particular, biologic-associated LP is proposed to be mediated by an unmasked antigen and/or a neoantigen directly created by the anti-PD-1 antibody.[46,47] The resulting lichenoid reactions have been found to contain susceptible mutated keratinocytes that specifically express PD-L1, resulting in infiltration of the dermoepidermal junction by autoreactive T lymphocytes and keratinocyte necrosis.[48,49] This suggests that the lichenoid eruption is a target effect of the PD-1/PD-L1 pathway, rather than a nonspecific hypersensitivity reaction.[48] Interestingly, biologic-associated LP may therefore serve as a biomarker for efficacy of treatment with immune checkpoint inhibitors, encouraging the resumption or continuation of treatment of patients with immunotherapy once the reaction is managed.[47,50]

It is also reported that dermoepidermal junction damage in LP may expose previously immune-tolerated membrane antigens, eliciting an immune response through epitope spreading.[51] This phenomenon has been associated with LPP in particular, with the blistering response occurring after the formation of lichenoid lesions.[51,52] The occurrence of rare variants of biologic-associated LP, such as LPP and lichen planopilaris, suggests that distinct antigenic targets within basement membrane components or hair follicles can be unmasked by biologic agents. Finally, it has been proposed that the oral LP associated with imatinib use may be closely correlated with the altered expression of epidermal markers.[53]

Keratinocyte Apoptosis Dysregulation

Keratinocyte apoptosis is an essential component in the pathogenesis of idiopathic LP, mediated primarily through Fas/Fas ligand interactions and the perforin-granzyme B pathway.[18,54] Biologic therapy may be implicated in heightening keratinocyte vulnerability to immune-mediated injury. For example, the activation of cytotoxic T cells associated with biologic therapy may then enable T lymphocytes to secrete granules containing granulysin, perforin, and granzyme B, leading to keratinocyte apoptosis.[33] Additionally, keratinocyte apoptosis results in the release of pro-inflammatory cytokines, perpetuating the disease process.[33]

Altered apoptotic signaling may particularly be implicated in association with receptor activator of nuclear factor κB ligand (RANKL)-inhibitor therapy. Under physiologic conditions, RANK-RANKL signaling supports peripheral immune tolerance by prolonging pDC survival, promoting regulatory T cell development, and eliminating autoreactive T cells through Fas-mediated apoptosis.[55,56] Inhibition of this pathway with denosumab therapy disrupts immune tolerance, rendering keratinocytes vulnerable to autoreactive T cell-driven apoptosis, which may promote lichenoid eruptions.[56]

Genetic & Host Susceptibility Factors

While biologic therapy may provide an inciting stimulus for lichenoid reactions, not all patients exposed to immunotherapeutic agents develop LP, suggesting an important role for underlying host susceptibility. Idiopathic LP has been associated with certain HLA genotypes, such as HLA-DR1,[1] but whether similar HLA associations predispose to biologic-associated LP is unclear. However, it has been theorized that in certain genotypes, the effect of TNF-α inhibition can accelerate IFN-α production, pathologically activating T cells and pDCs.[30] Overall, biologic-associated LP likely represents an unmasking of preexisting immune vulnerability rather than a uniformly-induced pathogenic response. However, future studies involving HLA typing, immune gene sequencing, and longitudinal patient registries may aid in identifying at-risk individuals.

Implications for Clinical Practice

Recognition of biologic-associated LP has important implications for dermatologists, oncologists, rheumatologists, and other physicians prescribing these agents. Lichenoid eruptions can mimic idiopathic LP both clinically and histopathologically, necessitating a high index of suspicion in patients who develop new cutaneous, oral, or follicular lichenoid lesions while on biologic therapy.[57] A careful drug history is essential, as latency from drug initiation to eruption may vary widely, ranging from days to years.[21,57]

From a management standpoint, most cases of biologic-associated LP respond to withdrawal of the offending biologic and topical or systemic corticosteroids.[57,58] Steroid-sparing agents, such as acitretin, cyclosporine, methotrexate, apremilast, hydroxychloroquine, phototherapy, and other biologic agents, such as dupilumab and rituximab are also often used to treat these cutaneous reactions.[26,34,36,37,39,41,42,48,57–70] However, in patients with limited or well-controlled disease, continuation of the biologic with adjunctive treatment is often reasonable, especially if the biologic is effectively treating the underlying indication.[57,58] Nevertheless, more severe presentations of biologic-associated LP, as well as LPP and lichen planopilaris may often necessitate cessation of biologic therapy.

Importantly, management of lichenoid drug eruptions underscores the need for shared decision-making between physicians and patients. Counseling before initiation of biologic therapy should include discussion of potential cutaneous adverse events and strategies for early recognition. When considering withdrawal of biologic therapy, the balance of risks and benefits must be evaluated. Greater understanding of the mechanisms underlying biologic-associated LP may eventually enable risk stratification.

Research Gaps & Future Directions

Despite the growing number of case reports documenting biologic-associated LP, there remain several key gaps in our understanding of the pathogenesis and clinical implications. Primarily, the true incidence and risk factors remain undefined. Large, multicenter prospective studies are needed to establish incidence rates across different biologic classes and identify patient characteristics that may predispose to lichenoid eruptions, such as HLA genotype and autoimmune history. Additionally, functional studies using in vitro keratinocyte and pDC models, cytokine assays, and lesional transcriptomics may provide direct mechanistic evidence to clarify the immunologic mechanisms underlying biologic-associated LP.

Physicians and patients may also benefit from more standardized treatment algorithms. Optimal approaches to continuing versus withdrawing biologic therapy, the role of adjunctive treatments, and outcomes after rechallenge with the offending biologic remain unclear. Prospective studies evaluating therapeutic decisions and long-term outcomes are needed to streamline management strategies. Finally, studies evaluating HLA typing, immune profiling, and/or genetic testing may guide risk stratification, enabling a more individualized approach to prescribing and surveilling patients initiating biologic therapy.

Conclusion

In sum, biologic therapies are increasingly recognized as potential triggers of LP and related lichenoid eruptions. Evidence to date suggests that biologic-associated LP arise through multiple related mechanisms, including cytokine imbalance, T cell dysregulation, antigen unmasking, keratinocyte apoptosis, and host susceptibility. It is important for physicians to counsel patients regarding potential risks of biologic therapy, and carefully weigh the benefits of continuing vs withdrawing treatment. Future studies aimed at clarifying mechanisms and defining incidence, risk factors, and predictive biomarkers may improve our understanding and help guide patient care.

Abbreviations

LP, lichen planus; Th, T-helper; ICAM-1, intracellular adhesion molecule-1; TNF-α, tumor necrosis factor-α; IFN-γ, interferon-γ; NFκB, nuclear factor kappa B; IL, interleukin; pDC, plasmacytoid dendritic cell; PD-1, programmed cell death protein-1; PD-L1, programmed cell death protein-ligand 1; LPP, lichen planus pemphigoides; NBUVB,

narrowband ultraviolet B; MHC, major histocompatibility complex; RANKL, receptor activator of nuclear factor κB ligand.

Data Sharing Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Author Contributions

Ms. Podolsky contributed to formal analysis, investigation, methodology, visualization, and writing – original draft. Dr. Lipner contributed to conceptualization, project administration, supervision, and writing – review and editing. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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