Review Article

Biologics in Dermatology: Off-Label Indications

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Abstract

Skin and subcutaneous diseases affect millions of people worldwide, causing significant morbidity. Biologics are becoming increasingly useful for the treatment of many skin diseases, particularly as alternatives for patients who have failed to tolerate or respond to conventional systemic therapies. Biological therapies provide a targeted approach to treatment through interaction with specific components of the underlying immune and inflammatory disease processes. Advances in the understanding of disease pathophysiology for inflammatory skin diseases and in drug development have ushered in biologic therapies in dermatology. Biologic therapies are molecules that target specific proteins implicated in immune-mediated disease. This review article highlights the increasing evidence base for biologics in dermatology for off-label use.

Keywords: *Biologics, rituximab, secukinumab, TNF-α*

Introduction

Off-label use of pharmaceutical drugs for an indication, age group, dosage, or route of administration refers to the use of the drug that is not approved by the regulatory agencies or is not declared in the prescribing information for the product. Regulatory agencies based on clinical trials and available literature evidence approves a drug for a particular indication, dose, formula and route of administration.[1] Off-label use of drug is not illegal, unless it is within ethical guidelines and other safety regulations. Based on the reliable data and perfect evidence drug can be used in for off-label indication to patients who have drained all other approved therapeutic options.[2]

Biopharmaceuticals also known as Biologic drug, or biological medicinal product are genetically engineered proteins produced in living organisms such as bacteria, yeast, or human cell lines or derived from recombinant DNA and/or controlled gene expression methods. Examples include biological proteins (cytokines, clotting factors, and hormones), vaccines, monoclonal antibodies (mABS), cell, and tissue-based therapies.[3]

Biologics are proving their worth as treatment modalities for many skin diseases, particularly as alternatives for patients who have failed respond to approved therapeutic options. Biologic therapy has shown its efficacy in the treatment of inflammatory diseases and their use in the effective treatment of Psoriasis (PsO) and other skin diseases is well established.[4] Biologics or biologicals are large complex molecules produced in living organisms. They cover a range of molecules including peptide (human insulin), small protein (Erythropoietin) and large proteins like mABS. Biologics have transformed several areas of medical therapeutics, mainly chronic inflammatory diseases such as rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), inflammatory bowel disease (IBD), PsO and more recently, Pemphigus group of diseases.[5] The European Medicines Agency (EMA) defines biologics as medical products which contain one or more active substances produced by the living organism or originated in a living organism. Unlike for synthesized medicines, due to the very nature of the biological process it is not possible to produce identical copies of biological medicine batch to batch, and variability is an inherent feature of biological medicines.[6]

The number of currently available biological agents in dermatology is growing with new developments every passing day.

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Most of the biologic drugs target PsO but several other dermatologic diseases seem to respond to biologic therapy. Common biologic therapies encountered include tumor necrosis factor (TNF) α inhibitors, interleukin (IL)-12/IL-23 inhibition, IL-17 inhibitors, rituximab, immunoglobulin E (IgE) antagonists, and intravenous immunoglobulin.[7]

The introduction of new biological treatment in recent years has dramatically altered the practice of dermatology.[8] The interest of clinicians in exploring biological therapy in various skin conditions has fundamentally increased over the years. This article discusses the off-label indication of biologics in dermatology. List of the different biologics commonly prescribed along with their specifications is shown in Table 1. Common off-label indications of various biologics are listed in Table 2.

Off-Label Use of Tumor Necrosis Factor (TNF) Inhibitors

TNF-α is a pleiotropic cytokine which plays a key role in chronic inflammatory diseases such as PsO and PsA. Biologic agents that inhibit TNF include a fusion protein, etanercept, and mABS such as infliximab and adalimumab. Levels of TNF- α are increased in many inflammatory diseases of the skin and are supposed to be a key player in the entire immune pathogenesis. The TNF-α inhibitors have been prescribed as an off-label indication for several dermatologic conditions.[9] Review of several case reports and case series in the literature show that the TNF-α inhibitors can be used in the management of a growing number of inflammatory skin conditions.

Following are amongst the ever-growing list of inflammatory dermatoses where TNF-α inhibitors have been successfully used but are awaiting relevant clearances to be the first line therapeutic options.

Off-Label Uses of TNF-α Inhibitors

Sarcoidosis

It is an idiopathic granulomatous inflammatory disease with multisystem involvement.[10] TNF-α is thought to play an important role in the pathogenesis of sarcoidosis.[11] The TNF gene, which is in the class III region of the major histocompatibility complex (MHC) on chromosome 6 suggested that the several genes in this region are useful in defining the disease susceptibility and prognosis in sarcoidosis. In particular, a biallelic functional polymorphism in the TNF-α promoter leads to variations in TNF-α production, which shows an association with distinct sarcoidosis subtypes.[12-15] Various reports describe the off-label use of TNF-α inhibitors in the treatment of sarcoidosis. Use of Infliximab[16-18] and Etanercept[19] has been described in various case reports. There have been two reports of the successful use of adalimumab for the treatment of cutaneous sarcoidosis.[20,21]

Pyoderma Gangrenosum (PG)

It is a rare ulcerative disorder of the skin in association with systemic involvement such as IBD, polyarthritis, monoclonal gammopathy, and hematological malignancy. Due to the complexity and wide variety of clinical appearance, it can be challenging to treat.[22] The pathogenesis of PG remains unclear, but may be related to TNF-α.[23] Use of Infliximab,[24-27] Etanercept[28] and

Table 1: Characteristics of the different biologic agents available in India

	Infliximab	Etanercept	Adalimumab	Golimumab	Rituximab	Secukinumab
Type	Monoclonal antibody against TNF-α	TNF soluble receptor	Monoclonal antibody against TNF-α	Monoclonal antibody against TNF-α	Anti-CD20 Monoclonal antibody	Interleukin-17A monoclonal antibody
Composition	Chimeric antibody	Recombinant fusion protein	Recombinant mnoclonalantibodyo	Monoclonal antibody	Chimeric antibody	Monoclonal antibody
Dose	3-5 mg/kg at weeks 0, 2, and 6; then, every 4-8 weeks	25-50 mg once or twice a week	40 mg every other week	50 mg once monthly	500 mg every other week weekly for 4-8 consecutive weeks The off-label protocol in the literature is a 375-mg/m^2 IV infusion once weekly for 2-4 consecutive weeks	Initial: 300 mg SC at weeks 0, 1, 2, 3, and 4 Monthly maintenance: Beginning at week 8, give 300 mg SC once monthly
Route of administration	Intravenous	Subcutaneous	Subcutaneous	Subcutaneous	Intravenous	Subcutaneous
Indications	AS, CD, PsA, PsO, RA, UC	AS, JIA, PsA, PsO, RA	AS, CD, JIA, PsA, PsO, RA, UC, HS, NIU	AS, PsA, RA, UC	CLL, NHL, RA, GPA, MPA, PV	PsO, PsA, AS
Biosimilar Available	Yes	Yes	Yes	No	Yes	No

AS: Ankylosing Spondylitis; RA: Rheumatoid Arthritis; JIA: Juvenile idiopathic Arthritis; PsA: Psoriatic Arthritis; PsO: Psoriasis; IBD: Inflammatory Bowel Disease; HS: Hidradenitis Suppurativa; UC: Ulcerative Colitis; CD: Crohn's Disease; NIU; Non Infectious Uvetits; CLL: Chronic Lymphocytic Leukemia; NHL: Non Hodgkins Lymphoma; GPA: Granulomatosis with polyanglitis; MPA: Microscopic Polyangitis; PV: Pemphigus Vulgaris

Table 2: List of off-label indications of biologics

Biologic	Off-label Use
Etanercept	Pyodrma gangrenosum
	Sarcoidosis
	Necrobiosis lipoidica diabeticorum
	Hidradenitis suppurativa
	Sweet's syndrome
	Vasculitis
	Behcet Disease
	Atopic Dermatitis
	Pityriasis Rubra Pilaris
	Lichen Planus
	SAPHO syndrome
	Toxic Epidermal Necrolysis
	Pruritus
	Keloid
Infliximab	Sarcoidosis
	Hidradenitis suppurativa
	Pyodrma gangrenosum
	Necrobiosis lipoidica diabeticorum
	Giant Cell Arteritis
	Vasculitis
	Behcet Disease
	Atopic Dermatitis
	Toxic Epidermal Necrolysis
Adalimumab	Sarcoidosis
	Pyodrma gangrenosum
	Behcet Disease
	Pityriasis Rubra Pilaris
	Lichen Planus
	Alopecia Areata
	SAPHO syndrome
Rituximab	Chronic graft-versus-host disease
	Dermatomyositis
Secukinumab	Pityriasis rubra pilaris
	Hidradenitis suppurativa
Omalizumab	Churg-Strauss Syndrome
	Bullous pemphigoid
	Atopic dermatitis
	Angioedema
Anakinra	Pyoderma gangraenosum
	PAPA syndrome
	Hidradenitis suppurativa

Adalimumab,[24] are described in a considerable number of reports in the treatment of PG.1

Necrobiosis lipoidica diabeticorum (NLD)

A rare chronic and granulomatous skin disorder with unknown etiology. Legs are the most commonly affected site of NLD.[29] Raised levels of TNF-α have been found in the NLD patient's sera and skin. Promising results were observed with TNF-α inhibitors treatment.[30] Few cases of necrobiosis lipoidica diabeticorum have been reported to be cured with infliximab[31] and etanercept.[32]

Hidradenitis suppurativa (HS)

It is characterised by chronic inflammation of the skin, affecting apocrine gland-rich areas of the body with the presence of painful nodules, abscesses, sinus tracts, and scarring.[33] Adalimumab is the only approved biologic in the treatment for HS. Off label, moderate improvement with infliximab[34] has been reported in one case study. There is another report of six patients with refractory HS treated with etanercept, 25 mg twice weekly.[35] TNF-α antagonists may lead to an improvement in HS by inhibiting the effects of TNF- α.[36] which has been described as the key inflammatory marker in the disease's pathophysiology.

Sweet's syndrome

Cytokines play an etiological role, directly or indirectly in the development of Sweet's syndrome.[37] In particular, serum Granulocyte colony-stimulating factor (G-CSF) levels have been reported much higher in patients with active Sweet's syndrome.[38] One published report with two patients with Sweet's syndrome and RA achieved complete skin clearance after etanercept administration.[39]

Vasculitis

TNF-α is having an important role in inducing the membrane expression of proteinase-3 or myeloperoxidase, which could be recognized by ANCA later in ANCA-associated vasculitis (AAV).[40]

Infliximab provided remission in 88% of the patients in a prospective trial of patients suffering from small vessel vasculitis with systemic complications.[41] Etanercept has also been evaluated for the possible treatment of vasculitis. However, results have not been remarkable.[42]

Giant cell arteritis (GCA)

The raised tissue concentraions of TNF-α led to hypothesis that anti-TNF-α agents will be a promising treatment in GCA.[43] In a study where 44 patients with GCA were treated with placebo or glucocorticoids plus infliximab have shown a significant difference in the therapeutic effect.[44]

Behcet disease (BD)

It is an idiopathic inflammatory disorder affecting multiple organ systems with a chronic-relapsing course. TNF-α is a central inflammatory mediator in BD with the involvement of Human Leukocyte Antigens (HLA)-51 gene.[45] Etanercept in a trial with 40 patients with BD has shown significant improvement in oral ulcers, papulopustular lesions, and nodular lesions, but has not shown significant resolution of the genital lesions.[46] In another case study, infliximab (3 mg/kg) and methotrexate provided remission to patients resistant to etanercept with RA and Behcet disease.[47] Adalimumab in its randomized, prospective study with a large number of patents has proven its efficacy in the treatment of BD.[48]

Atopic dermatitis (AD)

In AD, the TNF-α production has been found to be up-regulated by keratinocytes, mast cells, monocytes, and dendritic cells. However, some conflicting results have

been observed regarding the efficacy of TNF-α inhibitors in treatment in AD.[49] Use of infliximab in nine patients with AD showed 53% clinical improvement at week 2 of the treatment.[50] Etanercept has also been reported to be used in the management of chronic AD in two patients who achieved remission after 11 months of therapy.[51]

Pityriasis rubra pilaris (PRP)

It is an uncommon inflammatory papulosquamous skin disorder which is often refractory to conventional therapies. The off-label use of Infliximab has shown significant improvement in two weeks of therapy,[52] Etanercept has proved its efficacy in both type I and type II PRP.[53] Adalimumab mono-therapy has also been reported in the successful treatment of PRP.[54] A PRP type I patient who was treated with adalimumab, achieved clinical remission after four months. An increased level of mRNA of TNF-alpha was found in the lesional and perilesional skin at the time of active disease but was found to be normal after remission. This finding was consistent with the observed clinical remission and supported the use of anti-TNF-alpha for the treatment of PRP. It may be possible that although biologics are effective in a subset of PRP cases, their success is over-represented in the literature.[55]

Lichen planus (LP)

Genetic polymorphisms of several cytokines associated with the clinical presentation of LP, an increase in the frequency of 308A (TNF-α) allele may contribute to the development of more skin involvement.[56] Several case reports mention that severe erosive LP has improved with Etanercept. Adalimumab also has been reported in the treatment of LP.[57]

Alopecia areata (AA)

TNF-α inhibitors have been shown to induce AA/worsen symptoms.[58,59] TNF-α inhibitors are believed to regulate the production of interferon (IFN), which has been implicated in AA.[60] Adalimumab has been reported in the successful treatment of a patient with alopecia universalis which was unresponsive to multiple treatments.[61]

Synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome (SAPHO syndrome)

It is an autoimmune disorder characterized by the association of neutrophilic cutaneous involvement and chronic osteomyelitis.[62] TNF-α plays an important role in the occurrence and development of SAPHO syndrome. High expression of TNF-α in mandibular biopsy specimens of SAPHO syndrome patients have been demonstrated in a study. Several clinical reports have also established the definite efficacy of TNF-α inhibitors in management of SAPHO syndrome.[63] Palmoplantar pustulosis and HS which can be associated with SAPHO syndrome have also been treated with TNF inhibitors.[64-66] In a report, SAPHO syndrome associated with acne conglobata was effectively treated with a combination of etanercept and isotretinoin.[67] In a report, Adalimumab in combination with isotretinoin has led to remission of most of the features of SAPHO syndrome; however the osteoarticular manifestation continued to remain progressive.[68]

Toxic epidermal necrolysis (TEN)

TNF-α and IFN-gamma drive and perpetuate the pathogenesis of TEN. In a reported case series with ten participants with TEN, the use of single dose of Etanercept has shown complete healing.[69] Infliximab also has been reported to induce successful healing of TEN in one patient.[70]

Pruritus

In a 51-year-old man with Grover's disease who was non-responsive to conventional therapy, a reduction in pruritus by 98% was observed with use of Etanercept and the response was maintained for four months.[71]

Keloid

Etanercept has been shown to be associated with favorable therapeutic effect in the treatment of Keloid in a single case report.[72]

Erythema nodosum leprosum (ENL)

In Leprosy, the clinical spectrum is associated with the immunity of the patient. Around 30–50% of the patients develop acute inflammatory episodes known as type I reaction or reverse reaction and type II reaction ENL. This reaction may remain recurrent after being released from the hospital, requiring long-term use of thalidomide and or prednisone, thus increasing the risk of side effects. Two reports of infliximab and etanercept with a good response was found in the literature.[73]

Infliximab (5 mg/kg) was used successfully refractory ENL to conventional drugs including prednisone, pentoxifylline, and thalidomide in a patient with dimorphic lepromatous leprosy The symptoms of ENL were significantly reduced after 24 h. No further episodes of ENL were described after two infliximab administrations during weeks 2 and 6 and a follow-up of one year.[74]

Off-Label Uses of Rituximab

Rituximab is an anti-CD20 monoclonal antibody and currently approved for the treatment of relapsed or refractory, low-grade or CD20 positive follicular B-cell lymphoma.[75] Rituximab can be useful for dermatologic diseases where B cells play a major role in pathogenesis.[76] Chronic graft-versus-host disease and dermatomyositis (DM) are two of the most reported indications for off-label use of rituximab.[77]

Pemphigus

Rituximab has finally been approved as the first drug in the last 60 years in the management of moderate to severe

Pemphigus vulgaris. This approval has finally been obtained in June 2018 after years of off label and successful use in this clinical condition. Rituximab however still continues to be an off-label indication for other pemphigus variants and bullous pemphigoid (BP). This approval is a landmark shift in the spectrum of off-label and approved indication for biologics wherein a drug was approved after evidence of its off-label use. The previous practice of labeling a biologic for a particular indication and then obtaining its long term patient response was reversed in this case and an off-label indication was finally approved.[77]

Chronic graft-versus-host-disease

GVHD is the most promising indication reported in dermatology with Rituximab.[78,79] More than four case series have reported the successful use of Rituximab at a dose of 375 mg/m^2 in GVHD, wherein 70% of the patients achieved clinical response with the therapy.[80]

Dermatomyositis (DM): Since B cell plays a vital role in the pathogenesis of DM, Rituximab can be a promising treatment option.[79] Rituximab has shown therapeutic improvement in several cases.[77,79,81]

Off-Label Uses of Secukinumab

Secukinumab is an interleukin-17A monoclonal antibody approved for the treatment of Psoriasis, PsA, and AS. Secukinumab can be useful for the dermatological disease where IL-17 plays a key role,[82]

Hidradenitis suppurativa (HS)

Therapeutic response to secukinumab in a case of HS refractory to conventional local, systemic therapies as well as biolohgics including anti-TNF and anti-IL12/23 antagonists has been reported. However, the role of IL-17 in HS pathogenesis is lacking.[83] In other two case reports, it was reported that secukinumab may be beneficial in HS for the short term.[84,85] A patient suffering from both PsO and HS, was successfully treated with secukinumab in a single case report.[86] Contemporary research confirms the presence of increased IL-17 levels in patients with HS.[87]

Pityriasis rubra pilaris (PRP)

In a recent study, the gene expression analysis revealed an increase in T-helper (Th) 1 cytokines levels in PRP. In particular, Th17 cytokines, such as IL-17A, IL-22, and IL-23 were found to be increased.[88] High levels of IL-17 have been found in a previous PRP patient providing a rationale for targeting IL-17 in some PRP patients.[89] In a case report of two patients with refractory PRP, it has been effectively treated with secukinumab. In both cases, the patients' erythematous plaques resolved or had a near complete resolution by week 4 of the treatment.[90]

Off-label use of Omalizumab

Omalizumab is a recombinant DNA-derived humanized IgG1 monoclonal antibody that selectively binds to free and membrane-bound IgE. It has been licensed for use in severe allergic asthma and chronic urticaria. Patients are required to have a baseline serum IgE between 30 and 700 IU/ml and body weight not more than 150 kg. Diseases in which IgE maybe or certainly has an important role such as bullous pemphigoid, angioedema, atopic dermatitis, Churg-Strauss syndrome (CSS) are reported off-label indications for Omalizumab.[91]

Churg-Strauss syndrome (CSS)

Eosinophilic granulomatosis with polyangitis (EGPA) also termed as Churg-Strauss syndrome is an extremely rare autoimmune allergic granulomatosis that causes inflammation of small- and medium-sized blood vessels. Omalizumab has been used to successfully treat this condition, and it has also been shown to aggravate this syndrome. A poorly understood link between Omalizumab and CSS has been hypothesized. Various case studies have been published about the association of Omalizumab with CSS. Omalizumab treatment may unmask CSS due to the weaning of corticosteroids in some asthma patients or may delay corticosteroid treatment allowing for CSS to manifest.[92,93]

Bullous pemphigoid (BP)

Bullous pemphigoid is an acquired, autoimmune, bullous disease presenting with subepidermal blistering, eosinophilia, and severe itch that is characterized by autoantibodies against bullous pemphigoid antigen within basal keratinocytes.[94] IgE antibodies specific for the BP180 autoantigens are detected in sera and biopsy samples from the majority of BP patients. A successful treatment of BP with Omalizumab was observed in a case report.[95] In another study with six patients followed up for 42 weeks reported therapeutic benefit with Omalizumab.[96]

Angioedema

A case reported by Ozturk and Kocaturk in a 47-year-old male patient with severe idiopathic recurrent attacks of angioedema was controlled by Omalizumab treatment.[97]

Atopic dermatitis

Various studies have been published on the effective treatment of AD with Omalizumab. A case series on 11 patients with severe AD treated with Omalizumab showed improvement in SCORing Atopic Dermatitis (SCORAD) scores.[98]

Anakinra

It is approved for the treatment of RA and cryopyrin-associated periodic syndromes. Anakinra is currently reported in case reports as an option for the treatment of skin conditions such as psoriasis, atopic dermatitis, photo-ageing, melanoma, Schnitzler syndrome, pyoderma gangraenosum, PAPA syndrome, HS, lamellar ichthyosis, Sweet's syndrome, panniculitis, Muckle-Wells

syndrome, familial Mediterranean fever, SAPHO syndrome, and other disorders.[99] However, the use of Anakinra due to its availability and cost is very limited.

Pyoderma gangraenosum (PG)

Abnormal immune cells identified in PG lesions including neutrophils, T cells, the inflammatory mediators IL-1β, IL-8, IL-17, and TNF-α lend themselves to new therapeutic approaches.[22] A successful treatment of PG with anakinra in a patient with Wiskott–Aldrich syndrome has been reported.[100]

PAPA syndome

PAPA syndrome is characterized by the triad of sterile pyogenic arthritis, PG, and acne. Due to the genetic backgro und of PAPA syndrome resulting in permanent elevation of IL-1b levels, the IL-1 receptor antagonist anakinra seems to be the choice of treatment. A quick and effective response of Anakinra in a patient with PAPA syndrome was reported.[100]

Hidradenitis suppurativa

In a study on cases with PG and HS, one patient was successfully treated with Anakinra and responded with good therapeutic effect.[101]

Safety profile of biologics

Immunogenicity is an important safety concern for biologics, which may induce immune responses, including mild hypersensitivity, infusion reactions, or cross-reactions to endogenous molecules. This could result in a loss of efficacy or deficiency syndromes (e.g., thrombocytopenia as a result of neutralizing antibodies blocking endogenous thrombopoietin after treatment with recombinant thrombopoietin or neutralizing antibodies with human growth hormone).[102]

Biologic-related immunologic reactions include systemic inflammatory reactions such as cytokine release syndrome (CRS) or cytokine storms, and TGN1412, a humanized anti-CD28 monoclonal antibody. During pre-clinical studies, no proinflammatory reactions were detected. But in phase I clinical trial, the enrolled patients developed multi-organ failure, lymphopenia, thrombocytopenia, and elevations in cytokine levels. These outlined the clinical picture of a CRS.[103,104] Such reactions were also documented for infliximab, rituximab, and alemtuzumab.[105] Severe or life-threatening CRS induced by chimeric antigen receptor T cells was reported with tocilizumab.[106]

Adverse drug reactions associated with individual biologics due to their mechanism of action. Biologics associated with serious infections including tuberculosis reactivation, malignancies (e.g., anti-TNF-α agents), and progressive multifocal leukoencephalopathy (e.g., natalizumab and rituximab). Wound-healing complications or arterial thromboembolic events observed for angiogenesis inhibitors (e.g., bevacizumab). Dermatologic toxicities observed for epidermal growth factor receptor inhibitors (cetuximab and panitumumab) and B-cell lymphocyte depletion from anti-CD20 antibodies (rituximab).[107-112]

Ongoing Trials and Future Perspective

Dupilumab (Dupixent®) a monoclonal antibody against the IL-4 receptor is the first biologic approved to treat AD.[113] 52 weeks phase III randomized clinical trial (RCT) demonstrated the long-term efficacy of dupilumab in combination with topical corticosteroids. This displayed an acceptable safety profile with only injection site reactions and conjunctivitis more commonly occurred in dupilumab-treated subjects. Results from the preliminary phase II trials on lebrikizumab and tralokinumab were promising with eczema area and severity index (EASI), 50 improvements in 82.4% (n = 51), and 73.4 (n = 52) at week 12.[114]

Currently, several new biological preparations MABp1, CJM112, and bimekizumab are under investigation for the management of HS.[115]

Conclusion

Development of biological therapy has a remarkable impact on several dermatologic diseases. TNF blocker has widely been reported in several off-label indications without any trial-based evidence except data provided by case reports and case series. Due to limited and unsatisfactory therapeutic options, many dermatological diseases have been successfully managed with biologics, although the indication may not have been approved by the regulatory authorities. A large number of potential targets for the treatment of these chronic inflammatory skin conditions show the complexity and knowledge gaps in the pathogeneses of these diseases. This depicts the need for future larger scale studies. Further research in this field is needed to support the development of new treatments option. We expect that the off-label use of biologics will continue to grow in the field of dermatology. With the addition to new literature in off-label indication, we will acquire more knowledge about the rational use of these agents for other dermatological disorders.

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Conflicts of interest

There are no conflicts of interest.

Reference

1. Divatia J, Gota V. Off-label use of drugs: An evil or a necessity? Indian J Anaesth 2015;59:767.
2. Gupta SK, Nayak RP. Off-label use of medicine: Perspective of physicians, patients, pharmaceutical companies and regulatory authorities. J Pharmacol Pharmacother 2014;5:88-92.

3. Crommelin DJ, Storm G, Verrijk R, de Leede L, Jiskoot W, Hennink WE. Shifting paradigms: Biopharmaceuticals versus low molecular weight drugs. Int J Pharm 2003;266:3-16.
4. Chandler D, Bewley A. Biologics in dermatology. Pharmaceuticals 2013;6:557-78.
5. Kinch MS. An overview of FDA-approved biologics medicines. Drug Discov Today 2015;20:393-8.
6. Neumann PJ, Sandberg EA, Bell CM. Are pharmaceuticals cost-effective? A review of the evidence. Health Aff 2000;19:92-109.
7. Morrow T, Felcone LH. Defining the difference: What makes biologics unique. Biotechnol Healthc 2004;1:24-9.
8. George H. Biologics in dermatology beyond psoriasis. Cutis 2014;93:E21-7.
9. Lis K, Kuzawinska O, Bałkowiec-Iskra E. State of the art paper tumor necrosis factor inhibitors – State of knowledge. Arch Med Sci 2014;6:1175-85.
10. Valeyre D, Prasse A, Nunes H, Uzunhan Y, Brillet P, Müller-Quernheim J. Sarcoidosis. Lancet 2014;383:1155-67.
11. Mallbris L, Ljungberg A, Hedblad MA, Larsson P, Ståhle-Bäckdahl M. Progressive cutaneous sarcoidosis responding to anti-tumor necrosis factor-alpha therapy. J Am Acad Dermatol 2003;48:290-3.
12. Seitzer U, Gerdes J, Muller-Quernheim J. Genotyping in the MHC locus: Potential for defining predictive markers in sarcoidosis. Respir Res 2002;3:6.
13. Seitzer U, Gerdes J, Muller-Quernheim J. Evidence for disease phenotype associated haplotypes (DR.TNF) in sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 2001;18:279-83.
14. Wilson AG, di Giovine FS, Blakemore AI, Duff GW. Single base polymorphism in the human tumour necrosis factor alpha (TNF alpha) gene detectable by NcoI restriction of PCR product. Hum Mol Genet 1992;1:353.
15. Wilson AG, Symons JA, McDowell TL, McDevitt HO, Duff GW. Effects of a polymorphism in the human tumor necrosis factor alpha promoter on transcriptional activation. Proc Natl Acad Sci U S A 1997;94:3195-9.
16. Haley H, Cantrell W, Smith K. Infliximab therapy for sarcoidosis (lupus pernio). Br J Dermatol 2004;150:146-9.
17. Pritchard C, Nadarajah K. Tumour necrosis factor alpha inhibitor treatment for sarcoidosis refractory to conventional treatments: A report of five patients. Ann Rheum Dis 2004;63:318-20.
18. Baughman RP, Lower EE. Infliximab for refractory sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 2001;18:70-4.
19. Khanna D, Liebling MR, Louie JS. Etanercept ameliorates sarcoidosis arthritis and skin disease. J Rheumatol 2003;30:1864-7.
20. Heffernan MP, Smith DI. Adalimumab for treatment of cutaneous sarcoidosis. Arch Dermatol 2006;142:17-9.
21. Callejas-Rubio JL, Ortego-Centeno N, Lopez-Perez L, Benticuaga MN. Treatment of therapy-resistant sarcoidosis with adalimumab. Clin Rheumatol 2006;25:596-7.
22. Ahn C, Negus D, Huang W. Pyoderma gangrenosum: A review of pathogenesis and treatment. Expert Rev Clin Immunol 2018;14:225-33.
23. Reguia Z, Grange F. The role of anti-tumor necrosis factor-α therapy in pyoderma gangrenosum associated with inflammatory bowel disease. Am J Clin Dermatol 2007;8:67-77.
24. Hinterberger L, Müller C, Vogt T, Pföhler C. Adalimumab: A treatment option for pyoderma gangrenosum after failure of systemic standard therapies. Dermatol Ther 2012;2:6.
25. Jenne L, Sauter B, Thumann P, Hertl M, Schuler G. Successful treatment of therapy-resistant chronic vegetating pyoderma gangrenosum with infliximab (chimeric antitumour necrosis factor antibody). Br J Dermatol 2004;150:380-2.
26. Singh M, Andrew SM, Lear JT. Infliximab as a treatment for recalcitrant pyoderma gangrenosum. Clin Exp Dermatol 2004;29:196-7.
27. Grange F, Djilali-Bouzina F, Weiss A, Polette A, Guillaume J. Corticosteroid-resistant pyoderma gangrenosum associated with Crohn's disease: Rapid cure with Infliximab. Dermatology 2002;205:278-80.
28. McGowan JW 4th, Johnson CA, Lynn A. Treatment of pyoderma gangrenosum with etanercept. J Drugs Dermatol 2004;3:441-4.
29. Kota S, Kota S, Modi K, Jammula S, Meher L. Necrobios lipoidica diabeticorum: A case-based review of literature. Indian J Endocrinol Metab 2012;16:614.
30. Suárez-Amor O, Pérez-Bustillo A, Ruiz-González I, Rodríguez-Prieto MA. Necrobiosis lipoidica therapy with biologicals: An ulcerated case responding to etanercept and a review of the literature. Dermatology 2010;221:117-21.
31. Cummins DL, Hiatt KM, Mimouni D, Vander Kolk CA, Cohen BA, Nousari CH. Generalized necrobiosislipoidica treated with a combination of split-thickness auto grafting and immunomodulatory therapy. Int J Dermatol 2004;43:852-4.
32. Zeichner JA, Stern DW, Lebwohl M. Treatment of necrobiosis lipoidica with the tumor necrosis factor antagonist etanercept. J Am Acad Dermatol 2006;54(Suppl):S120-1.
33. Kurzen H, Kurokawa I, Jemec GB. What causes hidradenitis suppurativa? Exp Dermatol 2008;17:455-72.
34. Sullivan TP, Welsh E, Kerdel FA, Burdick AE, Kirsner RS. Infliximab for hidradenitis suppurativa. Br J Dermatol 2003;149:1046-9.
35. Cusack C, Buckley C. Etanercept: Effective in the management of hidradenitis suppurativa. Br J Dermatol 2006;154:726-9.
36. Robert C, Kupper TS. Inflammatory skin diseases, T cells, and immune surveillance. N Engl J Med 1999;341:1817-28.
37. Reuss-Borst MA, Pawelec G, Saal JG, Horny HP, Müller CA, Waller HD. Sweet's syndrome associated with myelodysplasia: Possible role of cytokines in the pathogenesis of the disease. Br J Haematol 1993;84:356-8.
38. Kawakami T, Ohashi S, Kawa Y, Takahama H, Ito M, Soma Y, *et al.* Elevated serum granulocyte colony-stimulating factor levels in patients with active phase of Sweet syndrome and patients with active Behçet disease: Implication in neutrophil apoptosis dysfunction. Arch Dermatol 2004;140:570-4.
39. Yamauchi PS, Turner L, Lowe NJ, Gindi V, Jackson JM. Treatment of recurrent Sweet's syndrome with coexisting rheumatoid arthritis with the tumor necrosis factor antagonist etanercept. J Am Acad Dermatol 2006;54(Suppl):S122-6.
40. McAdoo SP, Pusey CD. Is there a role for TNFα blockade in ANCA-associated vasculitis and glomerulonephritis?. Nephrol Dial Transplant 2017;32(Suppl 1):i80-8.
41. Booth A, Harper L, Hammad T, Bacon P, Griffith M, Levy J, *et al.* Prospective study of TNF alpha blockade with infliximab in anti-neutrophil cytoplasmic antibody associated systemic vasculitis. J Am Soc Nephrol 2004;15:717-21.
42. Stone JH, Uhlfelder ML, Hellmann DB, Crook S, Bedocs NM, Hoffman GS. Etanercept combined with conventional treatment in Wegener's granulomatosis: A six-month open-label trial to evaluate safety. Arthritis Rheum 2001;44:1149-54.
43. Hernandez-Rodriguez J, Segarra M, Vilardell C, *et al.* Tissue production of pro-inflammatory cytokines (IL-1beta, TNFalpha and IL-6) correlates with the intensity of the systemic inflammatory response and with corticosteroid requirements in giant-cell arteritis. Rheumatology (Oxford) 2004;43:294-301.

44. Hoffman GS, Cid MC, Rendt-Zagar KE. Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis: A randomized trial. Ann Intern Med 2007;146:621-30.
45. Hatemi G, Christensen R, Bang D, Bodaghi B, Celik A, Fortune F, *et al.* 2018 update of the EULAR recommendations for the management of Behçet's syndrome. Ann Rheum Dis 2018;213-25.
46. Melikoglu M, Fresko I, Mat C. Short-term trial of etanercept in Behcet's disease: A double blind, placebo controlled study. J Rheumatol 2005;32:98-105.
47. Sommer A, Altmeyer P, Kreuter A. A case of mucocutaneous Behcet's disease responding to etanercept. J Am Acad Dermatol 2005;52:717-9.
48. Ishigatsubo Y, Ueda A, Takeno M. Adalimumab in the management of Behcet's disease. Ther Clin Risk Manag 2015;11:611-9.
49. Ibler KS, Jemec GB. Novel investigational therapies for atopic dermatitis. Expert Opin Investig Drugs 2015;24:61-8.
50. Jacobi A, Antoni C, Manger B, Schuler G, Hertl M. Infliximab in the treatment of moderate to severe atopic dermatitis. J Am Acad Dermatol 2005;52:522-6.
51. Drosou A, Kirsner RS, Welsh E, Sullivan TP, Kerdel FA. Use of infliximab, an anti-tumor necrosis alpha antibody, for inflammatory dermatoses. J Cutan Med Surg 2003;7:382-6.
52. Lu R, George SJ, Hsu S. Pityriasis rubra pilaris: Failure of combination treatment with acitretin and infliximab. Dermatol Online J 2006;12:18.
53. Walling HW, Swick BL. Pityriasis rubra pilaris responding rapidly to adalimumab. Arch Dermatol 2009;145:99-101.
54. Irla N, Schneiter T, Haneke E, Yawalkar N. Nail lichen planus: Successful treatment with etanercept. Case Rep Dermatol 2010;2:173-6.
55. Zhang YH, Zhou Y, Ball N, Su MW, Xu JH, Zheng ZZ. Type I pityriasis rubra pilaris: Upregulation of tumor necrosis factor alpha and response to adalimumab therapy. J Cutan Med Surg 2010;14:185-8.
56. Carrozzo M, Uboldi de Capei M, Dametto E, Fasano ME, Arduino P, Broccoletti R, *et al.* Tumor necrosis factor-alpha and interferongamma polymorphisms contribute to susceptibility to oral lichen planus. J Invest Dermatol 2004;122:87-94.
57. Holló P, Szakonyi J, Kiss D, Jokai H, Horváth A, Kárpáti S. Successful treatment of lichen planus with adalimumab. Acta Derm Venereol 2012;92:385-6.
58. Strober B, Buonanno M, Clark JD, Kawabata T, Tan H, Wolk R, *et al.* Effect of tofacitinib, a Janus kinase inhibitor, on haematological parameters during 12 weeks of psoriasis treatment. Br J Dermatol 2013;169:992-9.
59. Navarro R, Daude´n E, Gallo E, Santiago Sa´nchez-Mateos D, Garcı´a-Diez A. Alopecia areata during treatment of psoriasis with adalimumab and leflunomide: A case and review of the literature. Skin Pharmacol Physiol 2012;25:107-10.
60. Ghoreishi M, Martinka M, Dutz JP. Type 1 interferon signature in the scalp lesions of alopecia areata. Br J Dermatol 2010;163:57-62.
61. Gorcey L, Spratt EAG, Leger MC. Alopecia universalis successfully treated with adalimumab. JAMA Dermatol 2014;150:1341-4.
62. Zhao Z, Li Y, Li Y, Zhao H, Li H. Synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome with review of the relevant published work. J Dermatol 2010;38:155-9.
63. Wollina U, Hansel G, Koch A, Schönlebe J, Köstler E, Haroske G. Tumor necrosis factor-alpha inhibitor-induced psoriasis or psoriasiform exanthemata: First 120 cases from the literature including a series of six new patients. Am J Clin Dermatol 2008;9:1-14.
64. Ben Abdelghani K, Dran DG, Gottenberg JE, Morel J, Sibilia J, Combe B. Tumor necrosis factor-α blockers in SAPHO syndrome. J Rheumatol 2010;37:1699-704.
65. Arias-Santiago S, Sanchez-Cano D, Callejas-Rubio JL, Fernández-Pugnaire MA, Ortego-Centeno N. Adalimumab treatment for SAPHO syndrome. Acta Derm Venereol 2010;90:301-2.
66. Firinu D, Garcia-Larsen V, Manconi PE, Del Giacco SR. SAPHO syndrome: Current developments and approaches to clinical treatment. Curr Rheumatol Rep 2016;18:35.
67. Su YS, Chang CH. SAPHO syndrome associated with acne conglobate successfully treated with etanercept. J Formos Med Assoc 2015;114:562-4.
68. Garcovich S, Amelia R, Magarelli N, Valenza V, Amerio P. Long-term treatment of severe SAPHO syndrome with adalimumab: Case report and a review of the literature. Am J Clin Dermatol 2012;13:55-9.
69. Paradisi A, Abeni D, Bergamo F, Ricci F, Didona D, Didona B. Etanercept therapy for toxic epidermal necrolysis. J Am Acad Dermatol 2014;71:278-83.
70. Koh MJ, Tay YK. An update on Stevens-Johnson syndrome and toxic epidermal necrolysis in children. Curr Opin Pediatr 2009;21:505-10.
71. Norman R, Chau V. Use of etanercept in treating pruritus and preventing new lesions in Grover disease. J Am Acad Dermatol 2011;64:796-8.
72. Berman B, Patel JK, Perez OA, Viera MH, Amini S, Block S, *et al.* Evaluating the tolerability and efficacy of etanercept compared to triamcinolone acetonide for the intralesional treatment of keloids. J Drugs Dermatol 2008;7:757-61.
73. Mitra D. Rare atypical presentations in type 2 Lepra reaction: A case series. Open Forum Infect Dis 2017;4:672.
74. Faber WR, Jensema AJ, Goldschmidt WF. Treatment of recurrent erythema nodosum leprosum with infliximab. N Engl J Med 2006;355:739.
75. Espana A, Ornilla E, Panizo C. Rituximab in dermatology. Actas Dermosifiliogr 2013;104:380-92.
76. Emer JJ, Claire W. Rituximab: A review of dermatological applications. J Clin Aesthet Dermatol 2009;2:29-37.
77. Schmidt E, Hunzelmann N, Zillikens D, Bröcker EB, Goebeler M. Rituximab in refractory autoimmune bullous diseases. Clin Exp Dermatol 2006;31:503-8.
78. Carr DR, Heffernan MP. Off-label uses of rituximab in dermatology. Dermatol Ther 2007;20:277-87.
79. Fatourechi MM, el-Azhary RA, Gibson LE. Rituximab: Applications in dermatology. Int J Dermatol 2006;45:1143-55.
80. Canninga-van Dijk MR, van der Straaten HM, Fijnheer R, Sanders CJ, van den Tweel JG, Verdonck LF. Anti-CD20 monoclonal antibody treatment in 6 patients with therapy refractory chronic graft-versus-host disease. Blood 2004;104:2603-6.
81. Scheinfeld N. A review of rituximab in cutaneous medicine. Dermatol Online J 2006;12:3.
82. Frieder J, Kivelevitch D, Menter A. Secukinumab: A review of the anti-IL-17A biologic for the treatment of psoriasis. Ther Adv Chronic Dis 2017;9:5-21.
83. Jorgensen A, Yao Y, Thomsen S. Therapeutic response to secukinumab in a 36-year-old woman with hidradenitis suppurativa. Case Rep Dermatol Med 2018;2018:1-3.
84. Thorlacius L, Theut Riis P, Jemec G. Severe hidradenitis suppurativa responding to treatment with secukinumab: A case report. Br J Dermatol 2018;179:182-5.

85. Schuch A, Fischer T, Boehner A, Biedermann T, Volz T. Successful treatment of severe recalcitrant hidradenitis suppurativa with the interleukin-17A antibody secukinumab. Acta Derm Venereol 2018;98:151-2.
86. Giuseppe P, Nicola P, Valentina C, Elena C, Salvatrice C, Rosario G, *et al.* A case of moderate hidradenitis suppurativa and psoriasis treated with secukinumab. Ann Dermatol 2018;30:462.
87. Matusiak Ł, Szczęch J, Bieniek A, Nowicka-Suszko D, Szepietowski JC. Increased interleukin (IL)-17 serum levels in patients with hidradenitis suppurativa: Implications for treatment with anti-IL-17 agents. J Am Acad Dermatol 2017;76:670-5.
88. Feldmeyer L, Mylonas A, Demaria O, Mennella A, Yawalkar N, Laffitte E, *et al.* Interleukin 23-helper T cell 17 axis as a treatment target for pityriasis rubra pilaris. JAMA Dermatol 2017;153:304-8.
89. Adnot-Desanlis L, Antonicelli F, Tabary T, Bernard P, Reguia€ı Z. Effectiveness of infliximab in pityriasis rubra pilaris is associated with pro-inflammatory cytokine inhibition. Dermatol Basel Switz 2013;226:41-6.
90. Bonomo L, Levitt JO. Secukinumab emerges as a rapidly effective therapy for pityriasis rubra pilaris. Cutis 2018;101:367-9.
91. El-Qutob D. Off-label uses of omalizumab. Clin Rev Allergy Immunol 2015;50:84-96.
92. Winchester DE, Jacob A, Murphy T. Omalizumab for asthma. N Engl J Med 2006;355:1281-2.
93. Bargagli E, Madioni C, Olivieri C, Penza F, Rottoli P. Churg-strauss vasculitis in a patient treated with omalizumab. J Asthma 2008;45:115-6.
94. Fairman KA, Curtiss FR. Regulatory actions on the offlabeluse of prescription drugs: Ongoing controversy and contradiction in 2009 and 2010. J Manag Care Pharm JMCP 2010;16:629-39.
95. Fairley JA, Baum CL, Brandt DS, Messingham KA. Pathogenicity of IgE in autoimmunity: Successful treatment of bullous pemphigoid with omalizumab. J Allergy Clin Immunol 2009;123:704-5.
96. Yu KK, Crew AB, Messingham KA, Fairley JA, Woodley DT. Omalizumab therapy for bullous pemphigoid. J Am Acad Dermatol 2014;71:468-74.
97. Ozturk AB, Kocaturk E. Omalizumab in recurring larynx angioedema: A case report. Asia Pacific Allergy 2014;4:129-30.
98. Ramirez del Pozo ME, Contreras Contreras E, Lopez Tiro J, Gomez VJ. Omalizumab (an anti-IgE antibody) in the treatment of severe atopic eczema. J Investig Allergol Clin Immunol 2011;21:416-7.
99. Pazyar N, Feily A, Yaghoobi R. An overview of interleukin-1 receptor antagonist, anakinra, in the treatment of cutaneous diseases. Curr Clin Pharmacol 2012;7:271-5.
100. Brenner M, Ruzicka T, Plewig G, Thomas P, Herzer P. Targeted treatment of pyoderma gangrenosum in PAPA (pyogenic arthritis, pyoderma gangrenosum and acne) syndrome with the recombinant human interleukin-1 receptor antagonist anakinra. Br J Dermatol 2009;161:1199-201.
101. Hsiao JL, Antaya RJ, Berger T, Maurer T, Shinkai K, Leslie KS. Hidradenitis suppurativa and concomitant pyoderma gangrenosum: A case series and literature review. Arch Dermatol 2010;146:1265-70.
102. Sharma B. Immunogenicity of therapeutic proteins. Part 3: Impact of manufacturing changes. Biotechnol Adv 2007;25:325-31.
103. Suntharalingam G, Perry MR, Ward S, Brett SJ, Castello-Cortes A, Brunner MD, *et al.* Cytokine storm in a phase 1 trial of the anti-CD28 monoclonal antibody TGN1412. N Engl J Med 2006;355:1018-28.
104. Khan DA. Hypersensitivity and immunologic reactions to biologics: Opportunities for the allergist. Ann Allergy Asthma Immunol 2016;117:115-20.
105. Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, *et al.* Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014;124:188-95.
106. US Food and Drug Administration. FDA approves tisagenlecleucel for B-cell ALL and tocilizumab for cytokine release syndrome. Available from: https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm574154.htm. [Last accessed on 2018 Jan 31].
107. Giezen TJ, Mantel-Teeuwisse AK, Straus SMJM, Schellekens H, Leufkens HG, Egberts AC. Safety-related regulatory actions for biologicals approved in the United States and the European Union. JAMA 2008;300:1887-96.
108. Erdman A, Nickas J, Brown B. Safety of biotherapeutics. In: Talbot J, Aronson JK, editors. Stephens' Detection and Evaluation of Adverse Drug Reactions: Principles and Practice. 6th ed. Chichester: Wiley-Blackwell; 2011.
109. Giezen TJ, Mantel-Teeuwisse AK, Leufkens HGM. Pharmacovigilance of biopharmaceuticals. Drug Saf 2009;32:811-7.
110. Cutroneo PM, Isgrò V, Russo A, Ientile V, Sottosanti L, Pimpinella G, *et al.* Safety profile of biological medicines as compared with non-biologicals: An analysis of the Italian spontaneous reporting system database. Drug Saf 2014;37:961-70.
111. Downing NS, Shah ND, Aminawung JA, Pease AM, Zeitoun JD, Krumholz HM, *et al.* Postmarket safety events among novel therapeutics approved by the US Food and Drug Administration between 2001 and 2010. JAMA 2017;317:1854-63.
112. Stanculeanu DL, Zob D, Toma OC, Georgescu B, Papagheorghe L, Mihaila RI. Cutaneous toxicities of molecular targeted therapies. Maedica (Buchar) 2017;12:48-54.
113. Blauvelt A, de Bruin-Weller M, Gooderham M, Cather JC, Weisman J, Pariser D, *et al.* Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): A 1-year, randomised, double-blinded, placebocontrolled, phase 3 trial. Lancet 2017;389 (10086):2287-303.
114. Simpson EL, Flohr C, Eichenfield LF, Bieber T, Sofen H, Taïeb A, *et al.* Efficacy and safety of lebrikizumab (an anti-IL-13 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical corticosteroids: A randomized, placebo-controlled phase II trial (TREBLE). J Am Acad Dermatol 2018;78:863-71.e11.
115. Włodarek K, Ponikowska M, Matusiak Ł, Szepietowski JC. Biologics for hidradenitis suppurativa: An update. Immunotherapy 2019;11:45-59.