

REVIEW ARTICLE

Non-psoriatic dermatologic uses of monoclonal antibody therapy

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Abstract

Monoclonal antibodies have been employed in the treatment of dermatologic disease for quite some time, primarily for psoriasis. Nevertheless, there are numerous case reports detailing successful and unsuccessful treatment of non-psoriatic dermatologic disease with these agents. In most cases, their use is off-label, as the FDA has approved monoclonal antibody use for only a few dermatologic diseases. The most commonly used monoclonal antibodies in dermatology are omalizumab, infliximab, rituximab, adalimumab, and efalizumab, and the disorders of interest include but are not limited to hidradenitis suppurativa, atopic dermatitis, pyoderma gangrenosum, and various blistering diseases. A review of these cases will hopefully encourage the use of monoclonal antibodies in dermatology via development of large, adequately powered clinical trials. This will hopefully result in FDA approval of monoclonal antibodies for a larger variety of recalcitrant, difficult-to-treat dermatologic illnesses.

Key words: *Adalimumab, anti-IgE therapy, infliximab, monoclonal antibodies, omalizumab, rituximab*

Introduction

Monoclonal antibody therapy is a relatively new arena for medicine. Pharmaceutical companies and genetic engineers have come together and applied recombinant DNA technology to create antibodies against specific disease-causing immunological mediators in the body.

There are few dermatologic FDA-approved uses for most monoclonal antibody medications, but many reports of successful off-label treatment. Here, we review over 50 reports of monoclonal antibody use for non-psoriatic dermatologic conditions. This is not an exhaustive study, but it does convey the steps dermatologists are taking with new treatment options, the need for more experimental data, and the vast potential that lies in monoclonal antibody therapy.

Efalizumab

Mechanism of action

Efalizumab is a recombinant humanized monoclonal antibody against leukocyte function-associated antigen

(LFA)-1. LFA-1 binds adhesions molecules on keratinocytes and endothelial cells to increase adhesion and migration of leukocytes. Efalizumab binds LFA-1, thus decreasing the activation and attraction of T-lymphocytes to the epidermis, and thus limits the overall inflammatory infiltrate in the skin (1,2).

Dose

Efalizumab is administered 0.7 mg/kg subcutaneously once followed by 1 mg/kg each week for maintenance thereafter (1,3).

FDA-approved uses

Psoriasis (3).

Off-label dermatologic uses

Lichen planus (LP) [two cases] LP is an autoimmune papulosquamous diseases associated with pruritic papules on the trunk and extremities. LP is associated with elevated LFA-1 expression, and, therefore, efalizumab treatment has been effective (1). Cheng

and Mann reported a case of oral erosive lichen planus having 75% improvement after 10 weeks of efalizumab, enabling the patient to eat and drink normally (2). Bohm and Luger reported a case of cutaneous LP that had complete remission of pruritis and lichenoid lesions after one dose of 0.7 mg/kg followed by doses of 1.0 mg/kg per week. This patient initially had mild side effects of vertigo and abdominal discomfort which subsided throughout the course of treatment, though she later felt fatigued immediately following treatment (1). Additionally, both reported cases had post-inflammatory hyperpigmentation after resolution of their LP lesions.

Adverse effects

Acne, leukocytosis, lymphocytosis, backache, headache, flu-like illness, infection, and hypersensitivity reaction are established side effects (3).

Mild vertigo, abdominal discomfort, fatigue, and post-inflammatory hyperpigmentation have been reported in the cited cases (1,2).

Infliximab (Remicade®)

Mechanism of action

Infliximab inhibits tumor necrosis factor α (TNF- α), a pro-inflammatory cytokine. By inhibiting TNF- α from binding to its receptor, infliximab limits the activation and recruitment of leukocytes, neutrophils, eosinophils, and interleukin-1 and -6 pro-inflammatory cytokines. In this way, TNF- α decreases the overall inflammatory immune response (3).

Dose

Infliximab is administered as 5–10 mg/kg IV at weeks 0, 2, and 6, followed by every 4 weeks (3).

FDA-approved uses

Ankylosing spondylitis, Crohn's disease, plaque psoriasis, psoriatic arthritis, rheumatoid arthritis, and ulcerative colitis (3).

Off-label dermatologic uses

Hidradenitis suppurativa (HS) [15+ cases] HS is a chronic inflammatory disease of the apocrine hair follicles. Over 20 case studies have shown partial improvement of HS with infliximab, marked by decreased pain, itching, and exudate over the course of treatment, but never complete resolution of symptoms

(4,5). A retrospective study by Fernández-Vozmediano and Armario-Hita resulted in four out of six subjects demonstrating marked improvement and the remaining two demonstrating moderate improvement with between 5 and 10 mg/kg of infliximab at weeks 0, 2, and 6, and then maintenance doses every 4 weeks (4). There was a decline in treatment efficacy with successive doses in three patients, and all patients ultimately relapsed. The only reported side effect was an infusion reaction headache. Fardet et al. reported seven severe, chronic HS patients treated with 5 mg/kg at weeks 0, 2, and 6, and five patients receiving a fourth dose at week 10 (5). At 6 weeks, five of seven patients had moderate improvement, and at 10 weeks, two of five had marked improvement, two of five had minor improvement, and one of five had no improvement. Three patients experienced severe side effects including a grade 3 allergic reaction, colon cancer, and a motor neuropathy interfering with daily living. These results were not as successful as other studies, but perhaps this is due to the severity of HS and exclusion criteria that the patients were not allowed to have concurrent Crohn's disease (5).

Pyoderma gangrenosum (PG) [40+ cases] PG is an idiopathic inflammatory condition involving chronic ulcerative lesions. It is associated with inflammatory bowel disease and is probably caused by some type of hyperimmune response. Infliximab has been shown to improve PG associated with Crohn's disease and independent of any inflammatory bowel disease (IBD). A randomized, double-blind, controlled trial with 29 patients showed significant improvement in 20/29 patients treated with infliximab (6). Six of the 29 had complete remission after 6 weeks of infliximab therapy, while 9/29 had no response to treatment. Adverse effects were reported in four patients and involved muscle aches 48 hours post-infusion, oral herpes simplex lesions, congestive heart failure with atrial fibrillation, and MRSA septicemia. Other case reports reflect more successful results, although the patients with no improvement may not be reported as readily in an isolated case report (7). Further studies are needed directly comparing corticosteroids and cyclosporine with infliximab for PG treatment (6).

Acne conglobata [one case] Acne conglobata is a therapy-resistant, inflammatory, nodulocystic condition involving pustules, abscesses, and frequent secondary infections usually found on the chest, back, and buttocks. Shirakawa et al. reported a patient with concurrent rheumatoid arthritis who experienced several resolving lesions and decreased pain when treated with 3 mg/kg infliximab at weeks 0, 2, and 6, and then every 8 weeks thereafter (8). Acne conglobata is similar

to hidradenitis suppurativa in that they are both inflammatory adnexal conditions, so successful treatment of HS suggests that infliximab may also be efficacious with acne conglobata.

Granulomatous skin disease [one case] Interstitial granulomatous dermatitis (IGD) is a rare skin disease involving erythematous plaques and patches on the lateral trunk, and is associated with autoimmune diseases. Furthermore, IGD can resolve spontaneously within 1–10 months. Kreuter et al. reported a patient with complete regression of the exanthem within 1 month after 5 mg/kg infliximab treatment at weeks 0, 2 and 6. They do note, however, that it is unclear whether this regression was due to treatment or natural/spontaneous disease course (9). Other granulomatous skin conditions such as granuloma annulare, cutaneous sarcoidosis, and necrobiosis lipoidica have responded to infliximab as well (9).

Childhood cutaneous polyarteritis nodosa (CPAN) [one case] CPAN is a necrotizing vasculitis of the small-to-medium sized arteries of the skin, muscles, and joints. It presents with painful inflammatory nodules and can be associated with fatigue, myalgia, and other generalized symptoms. CPAN's standard treatment of long-term steroid therapy can have severe side effects. Vega Gutierrez et al. reported a case of infliximab treatment for CPAN which resulted in complete initial remission at 20 days, but relapse flares 1 month after treatment cessation. The boy achieved successful long-term remission with injections every 2 months and reported no adverse effects (10).

Erythema nodosum (EN) [two cases] a) Chronic: although the exact cause of EN is not clear, it presents as acute subcutaneous inflammation, and is associated with IBD. Treatment of IBD with infliximab demonstrated concurrent remission of EN in a case report by Clayton et al. The patient, who received infliximab injections every 3 months, no longer requires steroid therapy. However, it is unclear whether the regression of IBD or the infliximab treatment, itself, caused the EN regression (11).

b) Leprosom: a case reported by Faber et al. discussed recurrent EN associated with leprosy improving within hours of receiving infliximab, prednisone, acetaminophen, and cetirizine. Infliximab infusions were repeated at 2 and 6 weeks, resulting in full remission of the erythema nodosum and no reported adverse effects. Infliximab should be considered as an alternative therapy for EN leprosum (12).

Chronic wounds [14 cases] TNF- α is elevated in chronic wounds, and may even prevent the proper healing of

wounds. Based on this information, Streit et al. tested 10 mg/ml topical infliximab solution on eight patients with 14 chronic ulcers with varying etiologies (13). After 8 weeks, 12 of the 14 ulcers had positive responses to infliximab with five wounds healing completely. Although there were no adverse effects in this study, further studies are needed to determine the efficacy and safety of topical infliximab (13).

Mucous membrane pemphigoid (MMP) [one case] MMP is an autoimmune inflammatory disease involving IgG, IgA, and IgM auto-antibodies which target the epithelial basement membrane. It presents with blistering lesions, ulcerations, and subsequent scarring on a variety of mucous membranes, including the oral mucosa, cornea, nasopharynx, larynx, and skin. TNF- α levels are high in patients with MMP and may propagate the inflammatory pathology; thus, infliximab is a possible second-line therapy for the disease. Heffernan and Bentley reported a patient with severe MMP involving her eyes, oropharynx, and esophagus refractory to steroid, cyclophosphamide, and dapsone treatments (14). With 5 mg/kg infusions of infliximab at weeks 0, 2, 6, and every 8 weeks thereafter, she quickly improved and had complete remission of oral lesions within 6 months.

Pityriasis rubra pilaris (PRP) [seven cases] PRP is a rare idiopathic papulosquamous condition associated with perivascular inflammation and erythroderma. There is no clearly established treatment for PRP, and in some cases it regresses spontaneously. The common therapeutic approaches to PRP are similar to those of psoriasis, a condition effectively treated with infliximab. Ruiz-Genao et al. (15) reported a case of PRP achieving complete resolution with 5.0 mg/kg at weeks 0, 2, and 6 with three follow-up doses, one given every 8 weeks for 24 weeks. Six other PRP patients have been reported to be responsive to infliximab treatment, so perhaps it should be considered as an alternative treatment (15).

Vitiligo [one case] Vitiligo is an idiopathic, benign, and psychologically devastating depigmentation disorder. Simon and Burgos-Vargas reported a patient with ankylosing spondylitis and concurrent vitiligo treated with 350 mg infliximab IV at weeks 0, 2, 6 and one dose every 8 weeks thereafter for 10 months (16). In addition to his improved ankylosing spondylitis symptoms, the patient noticed a decline in spread of his vitiligo and repigmentation of several macules after 6 months of infliximab treatment. The spread of two large macules was halted, and five macules were reported as decreased by 30% (16). These results suggest that TNF- α may play a role in the pathogenesis of vitiligo and physiological melanogenesis.

Adverse effects

Abdominal pain, headache, fatigue, and severe or complicated infection due to immunosuppression are established side effects (3).

Infusion reaction headache, colon cancer, allergic reaction, motor neuropathy, muscle aches 48 hours post-infusion, oral herpes simplex lesions, congestive heart failure with atrial fibrillation, MRSA septicemia, hypertriglyceridemia, hypercholesterolemia, visual disturbances, and dry mouth and skin have been reported in the cited cases (5,6,8).

Adalimumab*Mechanism of action*

Similar to infliximab, adalimumab is a TNF- α inhibitor and blunts the inflammatory response. While infliximab is a chimeric monoclonal antibody, adalimumab is the first fully human monoclonal antibody against TNF- α , and thus less likely to spark an antibody response (17).

Dose

Adalimumab is administered as 40 mg subcutaneous injections every other week (3). This subcutaneous mode eliminates the need for frequent office visits, an associated inconvenience with infliximab (17).

FDA-approved uses

Ankylosing spondylitis, Chron's disease, juvenile idiopathic arthritis, psoriasis (plaque or with arthropathy), and rheumatoid arthritis (3).

Off-label dermatologic uses

Pyoderma gangrenosum (PG) [two cases] PG is an idiopathic inflammatory condition involving chronic ulcerative lesions and often associated with IBD. As stated above, there has been successful treatment of PG with infliximab – another TNF- α antagonist. Pomerantz et al. reported a patient who had an unspecified systemic reaction to infliximab, but achieved complete remission with adalimumab given 40 mg bi-monthly (18). Heffernan et al. reported a case of a 3 $\times$ 3.5 cm PG lesion treated with 80 mg/week adalimumab for the first 2 weeks, followed by 40 mg each week thereafter (17). The lesion healed completely after 5.5 months of treatment with no reported adverse effects.

Chronic erythema nodosum (CEN) [one case] CEN is an idiopathic panniculitis associated with painful nodular lesions. CEN shows similarities to granulomatous

diseases, in which TNF- α plays a large etiological role. Ortego-Centeno et al. reported a case of CEN treated with 40 mg adalimumab given bi-monthly resulting in asymptomatic presentation during the 7 months of follow-up with no adverse effects. Adalimumab and anti-TNF- α monoclonal antibodies, in general, should be considered as an alternative treatment for CEN (19).

Hidradenitis suppurativa (HS) [one case] As mentioned above, infliximab has been very successful in treating HS. With a similar mechanism to infliximab and the added convenience of at-home subcutaneous administration, Moul and Korman administered 40 mg adalimumab every other week to a patient with severe HS (20). They reported significant improvement with localized decreased sinus drainage immediately after one injection, decreased erythema, resolution of pain, and localized decrease in drainage after 1 month of treatment, and minimal drainage in all lesion locations after 4 months of treatment.

Ulcerative cutaneous sarcoidosis [one case] Sarcoidosis is a non-necrotizing granulomatous disease that can involve the skin. As TNF- α plays an important role in the granulomatous processes, Philips et al. administered adalimumab therapy to a patient with a 9.8 $\times$ 3.8 cm ulcer caused by sarcoidosis (21). After 9 weeks of 40 mg/week of adalimumab, the ulcer was completely healed.

Adverse effects

Hypertension, injection site reaction, antinuclear antibody (ANA) positivity, antibodies against adalimumab, headache, sinusitis, and upper respiratory infection are established side effects (3).

No additional side effects were cited in the reviewed cases.

Omalizumab*Mechanism of action*

Omalizumab is a recombinant humanized monoclonal antibody targeting IgE. It binds IgE and prevents mast cell and basophil activation, allergic sensitization, and the allergic cascade (22).

Dose

Omalizumab is administered as 150–375 mg subcutaneously every 2 or 4 weeks (3,23).

FDA-approved uses

Allergic asthma (3).

Table I. Monoclonal antibodies with associated dose, mechanism of action, off-label use, number of cases, efficacy, and adverse effects.

Drug	Dose	Mechanism	Off-label dermatologic use	No. of cases	Efficacy	Adverse effects
Efalizumab	0.7 mg/kg SC once, followed by 1 mg/kg weekly for maintenance	Humanized monoclonal anti-LFA-1	Lichen planus	2	CR of cutaneous lesions (n = 2), PR 75% of oral erosive lesions (n = 1)	Acne, leukocytosis, lymphocytosis, backache, headache, infection, hypersensitivity reaction are established In these cases: mild vertigo and abdominal discomfort, fatigue, postinflammatory hyperpigmentation
Infliximab	5–10 mg/kg IV at weeks 0, 2, and 6 weeks followed every 4 weeks	Chimeric monoclonal anti-TNF- α antibody	Hidradenitis suppurativa Pyoderma gangrenosum Acne conglobata Granulomatous skin disease Childhood cutaneous PAN Erythema nodosum Chronic wounds Mucous membrane pemphigoid Pityriasis rubra pilaris Vitiligo	15+ 40+ 1 1 1 2 14 1 7 1	PR (n = 11), NI (n = 1) CR (n = 12), PR (n = 33), NI (n = 9) PR (n = 1) CR (n = 1) CR with maintenance therapy every 2 months (n = 1) CR (n = 2) CR (n = 5), PR (n = 7), relapse (n = 2) CR (n = 1) CR (n = 7) PR (n = 1)	Abdominal pain, headache, fatigue, severe or complicated infection due to immunosuppression are established In hidradenitis suppurativa cases: infusion reaction headache, colon cancer, allergic reaction, motor neuropathy In pyoderma gangrenosum cases: muscle aches 48 hours post-infusion, oral herpes simplex lesion, congestive heart failure with atrial fibrillation, and MRSA septicemia In acne conglobata case: hypertriglyceridemia, hypercholesterolemia, visual disturbances, dry mouth and skin
Adalimumab	40 mg SC every other week	Human monoclonal anti-TNF- α antibody	Pyoderma gangrenosum Chronic erythema nodosum Hidradenitis suppurativa Ulcerative cutaneous sarcoidosis	2 1 1 1	CR (n = 2) CR (n = 1) PR with continued therapy (n = 1) CR (n = 1)	Hypertension, injection site reaction, ANA+, antibodies against adalimumab, headache, sinusitis, upper respiratory infection are established None cited in reviewed cases
Omalizumab	150 mg SC every 2 or 4 weeks	Humanized monoclonal anti-IgG antibody	Atopic dermatitis Urticaria: Cholinergic Chronic Cutaneous mastocytosis	18 3 1 1	PR (n = 13), NI (n = 3), WS (n = 2) PR (n = 3) CR (n = 1) PR (n = 1)	Injection site reaction, headache, infection *None cited in reviewed cases
Rituximab	375 mg/m ² IV per week	Chimeric monoclonal anti-CD20 antibody	Pemphigus vulgaris Pemphigus foliaceus Paraneoplastic pemphigus Bullous pemphigoid Epidermolysis bullosa acquisita Dermatomyositis Cutaneous B-cell lymphoma	70+ 16 4 4 2 7 40+	CR (n = 42), PR (n = 25), NI (n = 3), death (n = 1) CR (n = 12), PR (n = 4) CR (n = 2), PR (n = 1), NI (n = 1) CR (n = 3), death (n = 1) PR (n = 2) PR (n = 7) CR (n = 35), PR (n = 13), NI (n = 5)	Puritis, nausea, vomiting, asthenia, dizziness, headache, fever, shivering are established In pemphigus vulgaris cases: infection 15%, pulmonary embolism, death (by Pneumocystis carinii pneumonia) In bullous pemphigoid cases: infection, hypogammaglobulinemia

ANA = antinuclear antibody; CR = complete remission; LFA = leukocyte function-associated antigen; NI = no improvement; PAN = polyarteritis nodosa; PR = partial remission; SC = subcutaneously; WS = worsened symptoms.

Off-label dermatologic uses

Atopic dermatitis (eczema) [18+ cases] Atopic dermatitis is a chronic, inflammatory, pruritic disease associated with high serum IgE levels. Vigo et al. treated seven severe atopic dermatitis cases with varying doses between 300 mg and 375 mg of omalizumab based on their baseline IgE levels (24). The trial resulted in five out of seven patients showing marked improvement and two out of seven showing moderate improvement. Andres et al. treated 11 therapy-refractory atopic eczema patients with 150 mg omalizumab bi-monthly for 5 months (23). Six out of 11 patients improved, 3/11 had no changes, and 2/11 had worsened eczema. It is possible that variations in IgE serum levels play a role in this discrepancy (24). Further clinical trials are necessary to establish the range of omalizumab efficacy for eczema.

For many people, atopic dermatitis is the first sign in their progression to asthma and allergic rhinitis. Animal studies have shown that skin exposures can cause systemic sensitization (22). Omalizumab therapy can limit the inflammatory response of IgE, and thus may prevent or slow this systemic sensitization (22).

Urticaria [four cases] Urticaria is also caused by an IgE response, and, therefore, treatment with omalizumab may be effective. There have been case reports of successful treatment with omalizumab for both chronic and cholinergic subtypes of urticaria.

a) Chronic: Spector and Tan reported three patients with refractory chronic urticaria achieving marked improvement after treatment with omalizumab every 2 weeks (25). Two patients had complete resolution of their urticaria within 1 week and the third patient had clearing after 6 weeks.

b) Cholinergic: cholinergic urticaria is characterized by erythematous, pruritic wheal flare-ups triggered by a rise in body temperature. Antihistamines are often unsuccessful, but Metz et al. reported a patient with complete remission of symptoms after 8 weeks of 300 mg omalizumab given every 2 weeks (26).

Cutaneous mastocytosis (CM) with Ménière disease [one case] CM is a skin disease associated with mast cell infiltrates causing pruritic, pigmented, macular and urticarial eruptions over the entire body. Ménière's disease is characterized by tinnitus, vertigo, nausea, and hearing loss – possibly caused by immune pathology. Siebenhaar et al. reported a patient with Ménière's disease and CM treated with 150 mg omalizumab every 2 weeks for the first 2 months, followed by a 150 mg maintenance shot every 4 weeks thereafter (27). The patient had remission of her vertigo, nausea, pruritis, and wheals at 8 weeks. However, hearing loss remained, as did some skin pigmentation.

To our knowledge, there is no etiologic connection between Ménière's and CM, and the concurrence in this case appears to be coincidence.

Adverse effects

Injection site reaction, headache, and infection are established side effects (3).

No additional side effects were cited in the reviewed cases.

Rituximab (Rituxan®)*Mechanism of action*

Rituximab is a chimeric monoclonal antibody targeting the antibody-producing B-cell's CD20 antigen; it works by blunting antibody production and the overall immune response. Rituximab binding to CD20 results in B-cell apoptosis, antibody-mediated cytotoxicity, and complement-induced cell death (28).

Dose

Rituximab is administered as 375 mg/m² IV per week for 4 weeks ± monthly follow-up doses (3).

FDA-approved uses

Non-Hodgkin's lymphoma (CD20+) and rheumatoid arthritis (3).

Off-label dermatologic uses

Pemphigus Pemphigus is an autoimmune disease in which antibodies attack surface antigens of keratinocytes, resulting in severe blistering. Currently treated with aggressive corticosteroids and other immunosuppressive agents, there is a high co-morbidity and even 5% mortality associated with pemphigus treatment. Many recent cases report successful treatment with rituximab. There are two subtypes of pemphigus based on the specific target antigen and epidermal layer within which the antibodies deposit: pemphigus vulgaris and pemphigus foliaceus (29).

a) **Pemphigus vulgaris (PV) [70+ cases]** Pemphigus vulgaris is characterized by anti-desmoglein 3 antibodies resulting in suprabasilar blisters (29). El Tal et al. reviewed 17 severe cases of PV treated with a combination of immunosuppression (corticosteroids, cyclophosphamide, methotrexate, mycophenolate, IVIg, and/or cyclosporine) and 375 mg/m² rituximab (30). Ten of the 17 patients had complete remission of symptoms

and another five of 17 had partial improvement; furthermore, 10 continued their treatments after the study concluded. One patient had no improvements and another died of treatment complications. Reported side effects included three patients with systemic infection and one death from *Pneumocystis carinii* pneumonia. Ahmed et al. treated 11 PV patients, who were unresponsive to steroids, with a combination of rituximab and immune globulin (31). Patients received 375 mg/m² rituximab once a week for 3 weeks, with 2 g/kg immune globulin on the fourth week for 3 months. Then, for 4 months following, the patients received a single 375 mg/m² per month dose of rituximab and a single infusion of 2 g/kg per month immune globulin. All 11 study participants noticed improvement by 6 weeks, and nine of the 11 had complete remission after 2–3 years of treatment. The authors concluded that there may be a synergistic effect of rituximab with IgG for PV. Goh et al. treated five PV patients with 4 weeks of adjuvant rituximab at 375 mg/m² per week (32). Two of the five patients achieved complete remission after 2–8 months, two of five had clinical remission with continued therapy, and one did not respond. Faurschou and Gniadecki reported two PV patients achieving remission with two courses of 375 mg/m² weekly rituximab for 4 weeks, but without the added immunosuppressive therapy (33). Although it appears that about half of patients treated with rituximab achieve complete remission, there is still the benefit of a tapered corticosteroid treatment for other patients (30,33).

b) Pemphigus foliaceus (PF) [16 cases] Pemphigus foliaceus is characterized by anti-desmoglein 1 antibodies resulting in subcorneal blisters (28). There have not been as many reported PF cases treated with rituximab, but its similar pathogenesis to pemphigus vulgaris is encouraging in this regard. Fernando et al. reported a relapsing PF patient who had failed corticosteroid and plasmapheresis therapies, but achieved stable remission with two courses of 375 mg/m² rituximab (34). Similarly, Serrao et al. reported a recalcitrant PF patient who had near-complete lesion resolution and B-cell depletion after 4 weeks of 375 mg/m² per week rituximab (35).

c) Paraneoplastic pemphigus (PNP) [four cases] Paraneoplastic pemphigus is an autoimmune disease that targets plakin proteins and presents with stomatitis and cutaneous eruptions of the oropharynx. It is associated with malignancy, particularly B-cell lymphomas; thus, it is unclear whether its response to rituximab is direct or secondary to treatment of the underlying malignancy. Four PNP patients treated with 375 mg/m² per week rituximab for 4 weeks had variable responses,

ranging from slight improvement to complete remission. Two case reports of PNP secondary to non-Hodgkin's lymphoma achieved complete remission, one report had full-body skin improvements with less dramatic oropharynx improvements, while a fourth patient showed only slight improvement (36).

Bullous pemphigoid (BP) [four cases] BP is a blistering skin disease involving auto-antibodies against the hemidesmosomes which link keratinocytes to the epidermal basement membrane. Schmidt et al. analyzed the efficacy and adverse events of adjuvant 375 mg/m² per week rituximab on autoimmune bullous diseases including two BP patients (37). A 2-year-old boy with BP achieved full clinical remission with four follow-up doses of rituximab 8 months after the initial therapy. He also received 320 mg mycophenolate mofetil daily, 1.5 mg prednisone daily, and 22 mg dapsone daily during his treatment with rituximab and continued with a maintenance dose of 3.5 mg prednisone. The other patient in Schmidt et al.'s study was a 63-year-old woman treated with 10 mg prednisone daily in addition to the 4-weekly rituximab treatments. She had over a 50% reduction of lesions initially but died due to nosocomial pneumonia at 6 weeks post-treatment. Both patients had several infectious complications due to their combination of immune suppression and rituximab therapy. Saouli et al. reported complete remission in two BP patients with 375 mg/m² per week rituximab for 4 weeks as monotherapy for their concurrent chronic lymphocytic leukemia (38).

Epidermolysis bullosa acquisita (EBA) [two cases] EBA is an autoimmune bullous skin disease similar to BP, but involving auto-antibodies against collagen VII on the dermal side of the basement membrane. It presents with spontaneous blisters, fragile skin, scarring, and nail loss. As EBA is quite rare, there is little data on treatment outcomes. With a similar pathogenesis as the other bullous autoimmune skin diseases, several physicians have tried rituximab. Crichlow et al. reported a case of EBA treated with 375 mg/m² per week rituximab, 1 g mycophenolate mofetil twice daily, and 30 mg prednisone once daily (39). The patient achieved partial remission within a week, increased her quality of life, and was able to decrease her corticosteroid dose. Wallet-Faber et al. reported another patient with EBA and corticosteroid co-morbidities from prior unsuccessful treatment. Three months after four doses of 375 mg/m² per week rituximab treatment, her skin cleared up completely with only a few lesion relapses in the following year (40).

Dermatomyositis [seven cases] Dermatomyositis is an idiopathic inflammatory disease that causes muscle weakness and erythematous rash over joints, face, and back (41). B-cell perivascular infiltrates are typical of dermatomyositis; thus, rituximab has been used for treatment of refractory cases. Levine constructed an open label study of seven refractory dermatomyositis patients treated with 375 mg/m² per week of rituximab for 4 weeks (36). All patients demonstrated improvements in their rash and alopecia, but there were varying responses in terms of regaining muscle strength.

Cutaneous B-cell lymphoma (CBCL) [40+ cases] CBCL is a rare skin presentation of non-Hodgkin's B-cell lymphoma. As they are CD20+ neoplasms, rituximab is a logical treatment option. Similar to other lymphomas, CBCLs can be further classified based on cytogenetics and histopathology. Gitelson et al. reported five patients with varying subtypes of CBCL who achieved success with 375 mg/m² per week rituximab therapy for 4 weeks, followed by maintenance doses of 375 mg/m² once every 2–3 months (42). Three patients with follicular CBCL achieved complete clinical remission with rituximab. Another patient had incomplete CBCL remission with rituximab, but then progressed to diffuse CBCL and required radiation. The last patient, an 88-year-old man, with severe co-morbidities and cutaneous small lymphocytic lymphoma, achieved full remission with rituximab alone. A review by Kyrtonis et al. included two patients with multiple primary cutaneous marginal zone lymphoma lesions who achieved complete clinical remission with rituximab (43). Overall, about two out of three CBCLs treated with rituximab achieve full remission, but relapse is not uncommon (36).

Adverse effects

Pruritis, nausea, vomiting, asthenia, dizziness, headache, fever, shivering are established side effects (3).

Infection (bacterial sepsis, varicella zoster, sepsis), pulmonary embolism, infusion reaction with first infusion, and cardiac complications have been reported in the cited cases (36,44).

Conclusion

Based on preliminary evidence, monoclonal antibody therapy may be the key to treating otherwise chronic and life-altering skin disease. Nevertheless, the majority of data regarding the efficacy and use of monoclonal antibodies for non-psoriatic indications are primarily from isolated case reports and small clinical trials. Almost all cases of successful treatment are qualified

with the need for further efficacy and side-effect evaluation – certainly, there is a need for larger-scale clinical trials. As a new frontier in dermatology, there are only a handful of approved therapeutic monoclonal antibodies, but the potential is vast and limitless. Current monoclonal antibody therapies target particular immune mediators and are, therefore, quite useful in treating selected autoimmune diseases. Further research will elucidate other immune targets, hopefully resulting in the development of new monoclonal antibodies. Furthermore, better characterization of autoimmune disorders will lead to monoclonal antibodies that are more specific, more sensitive, and more tolerable for patients.

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