REVIEW

Advancements in the Treatment of Cutaneous Lupus Erythematosus and Dermatomyositis: A Review of the Literature

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Background: Cutaneous lupus erythematosus (CLE) and dermatomyositis (DM) are autoimmune diseases that present with a wide variety of cutaneous manifestations. In both cases, first-line therapy includes topical corticosteroids. Patients may present with more widespread disease requiring systemic treatments, including corticosteroids, traditional immunosuppressants, or antimalarials. Due to their complex nature, both CLE and DM remain difficult to treat and continue to cause significant distress to patients.

Objective: To summarize the most recent literature on the safety and efficacy of novel treatment modalities for CLE and DM.

Methods: A literature search was conducted on PubMed using search terms "(dermatomyositis) AND (treatment)" and "(cutaneous lupus) AND (treatment)". Additional search terms included specific names of biologic agents, phosphodiesterase inhibitors (apremilast), and JAK inhibitors.

Results: JAK inhibitors, PDE-4 inhibitors, and biologics have shown promise in reducing cutaneous symptoms of both CLE and DM, including reduction in SLE Disease Activity Index 2000 (SLEDAI-2K), Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI), British Isles Lupus Assessment Group (BILAG), Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI), and Disease Activity Score (DAS).

Conclusion: While there have been recent advancements in the treatment for CLE and DM, further research and clinical trials are required to better elucidate which therapy is best for individual patients.

Keywords: biologics, cutaneous lupus erythematosus, dermatomyositis, JAK inhibitors, PDE-4 inhibitors

Introduction

Lupus erythematosus (LE) is an autoimmune disease that can present with a wide variety of cutaneous and systemic manifestations.¹ In cutaneous lupus erythematosus (CLE), cutaneous manifestations may occur in the absence of systemic symptoms.² Due to its broad spectrum of findings, CLE can be divided into three main subtypes: acute cutaneous lupus erythematosus (ACLE), subacute cutaneous lupus erythematosus (SCLE), and chronic cutaneous lupus erythematosus (CCLE).¹ Current recommendations for treatment of CLE include strict adherence to a sunscreen regimen³ and topical corticosteroids.^{4,5} If there is significant disease progression, systemic corticosteroids, oral antimalarials (hydroxychloroquine, chloroquine, and quinacrine), immunosuppressants (methotrexate and mycophenolate mofetil), and monoclonal antibodies (rituximab) may be used.⁶

Dermatomyositis (DM) is another autoimmune condition that presents with cutaneous abnormalities as well as extracutaneous symptoms like proximal muscle weakness and inflammation.⁷ Similar to CLE, first-line therapy begins with topical corticosteroids, with widespread disease requiring more aggressive treatment options, including antimalarials, systemic corticosteroids, IVIG, and immunosuppressants.⁸

Both CLE and DM are difficult conditions to treat, often recalcitrant to currently available therapies and thus causing debilitating disease to those affected. However, various newer agents, including biologics, phosphodiesterase (PDE)

inhibitors (apremilast), and janus kinase (JAK) inhibitors used for the treatment of other rheumatologic and dermatologic conditions are currently under investigation as potential therapies for CLE and DM.⁹ The aim of this review is to summarize the data regarding the safety and efficacy of novel treatments of CLE and DM.

Methods

A literature search was conducted on PubMed using search terms "(dermatomyositis) AND (treatment)" and "(cutaneous lupus) AND (treatment)". Additional search terms included the names of biologic agents, phosphodiesterase inhibitors (apremilast), and JAK inhibitors. Articles written after the year 2000 and in the English language were screened for content by reading the abstract. Only articles studying the use of novel therapies for the treatment of cutaneous manifestations of CLE or DM were included in the manuscript. Each article's references were screened to ensure completeness of the literature search. Articles meeting criteria after reading the abstract were reviewed for the type of study, treatment under study, and treatment outcome.

Results

CLE

Table 1 summarizes the studies describing safety and efficacy of novel treatments for CLE.

First Author (Year)	Type of Study	Treatment	Outcome
Topical Therapy			
Presto (2018) ¹⁰	RCT	Topical R333 6% (janus kinase and spleen tyrosine kinase inhibitor) vs placebo twice daily for 4 weeks	Four weeks of R333 treatment did not result in significant improvement in lesion activity.
JAK Inhibitors			
You (2019) ¹¹	Retrospective	Tofacitinib 5mg BID	Out of 10 patients: 7 patients achieved clinical remission, one patient was relieved with a decreased SLE Disease Activity Index 2000 (SLEDAI-2K) and physician's global assessment (PGA) score but not clinical remission, one did not improve, and one experienced a flare during the follow-up. Four patients quickly achieved resolution of arthritis and six patients of rash (SLEDAI-2K), respectively. However, the effectiveness of tofacitinib in rash was uncertain in two patients and completely lack of efficacy in another patient. Both SLEDAI-2K (p=0.011) and PGA (p=0.042) were improved significantly at the third month. No significant serological improvement was observed in level of C3 (p=0.319) and anti-dsDNA (p=0.259) at the third month.
Chen (2021) ¹²	Case report	Tofacitinib 5mg BID	A 29-year-old female SLE patient with a 10-year history of refractory severe diffuse non-scarring alopecia who experienced dramatic hair regrowth with tofacitinib. Prominent hair regrowth on the scalp was observed after 4 weeks, without any rash.
Wenzel (2016) ¹³	Case report	Ruxolitinib 20mg BID	A 69-year-old female with erythrosquamous skin lesions with acral distribution secondary to chilblain lupus erythematosus. Resulted in complete remission of all lesions within 4 months.

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Table I (Continued).

First Author (Year)	Type of Study	Treatment	Outcome
Kreuter (2021) ¹⁴	Case report	Baricitinib 4mg daily for 2 months, then ongoing 2mg daily maintenance	A 62-year-old woman with a 4-year history of FFA and SCLE resistant to several previous medications including chloroquine, hydroxychloroquine, methotrexate, azathioprine and rituximab. Resulted in complete clearance of SCLE and stopped further progression of FFA.
Zimmermann (2018) ¹⁵	Case series	Baricitinib 4mg daily for 3 months	All patients received a diagnosis of FCL with onset in early childhood. Patient I was a woman in her 20s with FCL. Patient 2 was a man in his 70s, and patient 3 was a woman in her 50s. All 3 patients (2 females and I male) showed significant improvement of cutaneous lupus lesions.
Joos (2021) ¹⁶	Case report	Baricitinib 4mg daily for 6 months	A 54-year-old man presented with a severe progressing widespread rash affecting predominantly trunk and extremities secondary to SCLE. Improvement in CLASI from 21 at baseline to 3 after 6 months of baricitinib treatment.
Fornaro (2019) ¹⁷	Case report	Baricitinib 4mg daily for 4 weeks	A 49-year-old SLE female with papulosquamous subacute lesions. Baricitinib 4 mg daily was started and after 4 weeks with near complete resolution of active skin lesions, and, for the first time, the patient was able to stop glucocorticoids.
Maeshima (2020) ¹⁸	Case report	Baricitinib 4 mg daily along with prednisolone, mycophenolate mofetil and hydroxychloroquine	A 27-year-old Japanese woman who was diagnosed with SLE at age 21, requiring corticosteroid and tacrolimus treatment. No progression of hair loss was observed after 4 weeks of treatment, and prominent hair regrowth was observed after 8 weeks. At 12 weeks, the prednisolone dose was gradually reduced to 12.5 mg, and no lesions—including alopecia—relapsed.
PDE-4 Inhibitor			
De Souza (2012) ¹⁹	Prospective	Apremilast 30 mg BID	CLASI showed a significant (P<0.05) decrease after 85 days of treatment in 8 patients with active DLE.
Biologic Therapy			
Mazgaj (2020) ²⁰	Case report	Ustekinumab 45 mg SC at weeks 0, 4, then every 12 weeks	A 65-year-old patient with SCLE and psoriasis. The patient reported only partial remission of psoriatic plaques with ustekinumab 45 mg, hence the dose was increased to 90 mg every 8 weeks, leading to long- term resolution of both psoriasis and CLE with excellent tolerance.
Dahl (2013) ²¹	Case report	Ustekinumab 45mg SC at 0, 4, 16, and 34 wks	A 79-year-old woman presenting with persistent CLE. Using the CLASI scoring system, prior to treatment, the disease activity score was 23, the damage score was 19 and the VAS score was 10. After 34 weeks, the disease activity score decreased to 14, the damage score was unchanged and the VAS score was 5. Objectively, the erythema on the patient's face, scalp and fingers were improved and the ulcers on her fingertips were healed. The erythema on her toes was unchanged. The patient reported feeling better than she had for many years.
van Vollenhoven (2020) ²³	RCT	Ustekinumab (~6 mg/kg single IV infusion, then 90 mg SC every 8 weeks) vs placebo, with standard-of-care therapy	At week 112, 79% and 92% of patients in the ustekinumab and placebo groups, respectively, had an SRI-4 response, 92% in both groups had \geq 4-point improvement from baseline in SLEDAI-2K score, 79% and 93%, respectively, had \geq 30% improvement from baseline in PGA, 86% and 91%, respectively, had \geq 50% improvement in active joint (pain and inflammation) count, and 79% and 100%, respectively, had \geq 50% improvement in CLASI activity score.

(Continued)

Table I (Continued).

First Author (Year)	Type of Study	Treatment	Outcome
Ismail (2019) ²⁴	Case report	Tildrakizumab 100 mg SC at weeks 0, 4, and 16	A 39-year-old man with a 15-year history of treatment-resistant lupus erythematosus tumidus. After two doses of tildrakizumab, there was significant improvement in the facial plaques. The response was sustained at week 24.
Merrill (2018) ²⁵	Post hoc analysis	Anifrolumab 300 mg SC every 4 weeks	More anifrolumab-treated patients demonstrated resolution of rash by SLEDAI-2K versus placebo: 39/88 (44.3%) versus 13/88 (14.8%), OR (90% Cl) 4.56 (2.48 to 8.39), p<0.001; BILAG: 48/82 (58.5%) versus 24/85 (28.2%), OR (90% Cl) 3.59 (2.08 to 6.19), p<0.001; and \geq 50% improvement by mCLASI: 57/92 (62.0%) versus 30/89 (33.7%), OR (90% Cl) 3.31 (1.97 to 5.55), p<0.001.
Morand (2019) ²⁶	RCT	Anifrolumab (300 mg) SC vs placebo every 4 weeks for 48 weeks	The percentage of patients who had a BILAG-based BICLA response was 47.8% in the anifrolumab group and 31.5% in the placebo group (difference, 16.3 percentage points; 95% confidence interval, 6.3 to 26.3; $P = 0.001$). Among patients with a high IFN gene signature, the percentage with a response was 48.0% in the anifrolumab group and 30.7% in the placebo group; among patients with a low IFN gene signature, the percentage was 46.7% and 35.5%, respectively.
Furie (2019) ²⁷	RCT	Single dose of BIIB059 SC (humanized IgGI mAb) ranging from 0.05 mg/kg to 20 mg/kg	BIB059 administration in patients with SLE decreased expression of IFN response genes in blood, normalized MxA expression, reduced immune infiltrates in skin lesions, and decreased CLASI-A score.
Werth (2017) ²⁸	RCT	Single dose AMG 811 SC180 mg (anti-IFNγ antibody) vs placebo	AMG 811 treatment reduced the IGBS score (which was elevated in DLE patients at baseline) in both the blood and lesional skin. The keratinocyte IFNy RNA score was not affected by administration of AMG 811. Serum CXCL10 protein levels (which were elevated in the blood of DLE patients) were reduced with AMG 811 treatment. The AMG 811 treatment was well tolerated but did not lead to statistically significant improvements in any of the efficacy outcome measures.

Abbreviations: SLE, Systemic Lupus Erythematosus; CLE, Cutaneous Lupus Erythematosus; SCLE, Subacute Cutaneous Lupus Erythematosus; DLE, Discoid Lupus Erythematosus; CLASI, Cutaneous Lupus Erythematosus; Disease Area and Severity Index; FFA, Frontal Fibrosing Alopecia; SLEDAI-2K, SLE Disease Activity Index 2000; PGA, Physician's Global Assessment; VAS, Visual Analog Scale; SRI-4, SLEDAI-2K Responder Index-4; BILAG, British Isles Lupus Assessment Group; mCLASI, Modified Cutaneous Lupus Erythematosus Disease Area and Severity Index; BICLA, British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment; IFN, Interferon; IGBS, IFNγ Blockade Signature; BID, Twice daily; IV, Intravenous; SC, Subcutaneous; mAb, Monoclonal Antibody; OR, Odds Ratio; CI, Confidence Interval; SD, Standard Deviation; MxA, Myxovirus Resistance Gene A; CXCL10, C-X-C motif chemokine ligand 10; FCL, Familial Chilblain Lupus.

Topical Therapies

The use of topical R333, a JAK/spleen tyrosine kinase inhibitor, has been explored in the treatment of CLE. Topical R333 was applied to 36 patients for four weeks, while a control group consisting of 18 patients received placebo. No significant improvement in lesion activity was observed.¹⁰

JAK Inhibitors

The efficacy of various JAK inhibitors in the treatment of CLE is currently being explored. Using the SLE Disease Activity Index 2000 (SLEDAI-2K) to evaluate outcomes, a retrospective study of 10 patients receiving 5 mg of tofacitinib BID showed resolution of rash in 6 patients.¹¹ Additionally, the same dosing of tofacitinib resulted in significant hair regrowth in a 29-year-old female patient experiencing non-scarring alopecia secondary to systemic lupus erythematosus (SLE).¹²

Ruxolitinib, a JAK1/2 inhibitor, has also shown promise in the treatment of CLE. Ruxolitinib 20 mg BID resulted in complete remission of skin lesions after 4 months in a 69-year-old female with chilblain lupus erythematosus.¹³

Multiple case reports have shown the benefits of baricitinib in the treatment of CLE. A 62-year-old woman showed complete clearance of SCLE after treatment with baricitinib 4 mg daily for 2 months followed by an ongoing daily

maintenance dose of 2 mg. Interestingly, the treatment also halted the progression of this patient's frontal fibrosing alopecia (FFA).¹⁴ A case series of three patients with familial chilblain lupus (FCL) showed significant improvement of all cutaneous lesions after three months of baricitinib 4 mg daily.¹⁵ Additional case reports displaying baricitinib's efficacy are shown in Table 1.^{16–18}

PDE-4 Inhibitors

Another class of drugs showing potential in the treatment of CLE is PDE-4 inhibitor apremilast. In a prospective trial of eight patients with DLE, apremilast 30 mg BID showed a significant reduction in Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) (p < 0.05) after 85 days.¹⁹

Biologic Therapies

The use of monoclonal antibodies (mAb) in the treatment of CLE is well documented in the literature. Various case reports and randomized controlled trials (RCT) highlight the efficacy of ustekinumab, an mAb that targets IL-12 and IL-23, for cutaneous manifestations of SLE. In these studies, patients were treated with 45 mg or 90 mg subcutaneously (SC). Partial or complete remission of cutaneous eruptions, erythema, and ulcerations was observed in all cases.^{20,21} In one RCT, van Vollenhoven et al showed that ustekinumab 6 mg/kg IV infusion followed by a 90 mg SC dose every eight weeks led to significant improvement compared to placebo.²² A prolonged Phase II study was conducted over two years with 46 patients, which showed further improvement in CLASI without significant adverse effects.²³

Tildrakizumab, a high-affinity anti-IL-23p19 mAb, was found to significantly improve facial plaques in a 39-year-old man with a 15-year history of treatment-resistant tumid lupus.²⁴

Injections of anifrolumab 300 mg SC weekly, an mAb that targets the type I interferon (IFN) receptor, showed a greater disease reduction in SLE patients when compared to placebo based on the British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA) after 48 weeks (p = 0.001).²⁵ Furthermore, the response to treatment as measured by the Modified Cutaneous Lupus Erythematosus Disease Area and Severity Index (mCLASI) was greater in patients with a higher baseline level of interferon genes (p < 0.001).²⁶

BIIB059 is a humanized IgG1 mAb that binds to blood DC2 antigen (BDCA2). The use of a single dose of BIIB059 ranging from 0.05 mg/kg to 20 mg/kg was explored in 12 patients with SLE and active skin disease when compared to placebo. The treatment group showed decreased CLASI-A scores, decreased IFN response gene expression, and a normalized Myxovirus Resistance Gene A (MxA) expression.²⁷

A single dose of 180mg SC of AMG 811, an anti-IFN γ antibody, did not lead to statistically significant improvements in any of the outcome measures in DLE patients compared to placebo. However, serum C-X-C motif chemokine ligand 10 (CXCL10) levels, which were elevated in the blood of patients with DLE, were reduced in the treatment group.²⁸

DM

Table 2 summarizes the studies describing the safety and efficacy of novel treatments for DM.

JAK Inhibitors

There was a total of 13 publications evaluating the effectiveness of tofacitinib in DM.^{29–41} Partial or complete improvement of cutaneous manifestations of DM – evaluated by the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI), Disease Activity Score (DAS), or clinical examination – was observed in a total of 33 retrospective patient cases. Non-cutaneous disease manifestations such as calcifications, muscle weakness, and arthritis also improved with therapy in many cases.^{30,33,38,41} These retrospective observations were supported by a recent prospective open-label trial, which showed a statistically significant (p = 0.0005) mean CDASI improvement from 28 \pm 15 to 9.5 \pm 8.5 after 12 weeks of tofacitinib 11mg daily in 10 patients.³⁴

Ruxolitinib has been evaluated in a total of 5 retrospective studies, case reports, and case series.^{42–46} All 17 patients experienced improvement of cutaneous manifestation of DM with 8 out of 17 patients having complete resolution of symptoms. Non-cutaneous symptoms of DM also resolved in many cases with ruxolitinib therapy.^{43,45,46} Notably, a study

Table 2 Studies Examining Treatments for Dermatomyositis

First Author (Year)	Type of Study	Treatment	Outcome
PDE-4 inhibitor			
Bitar (2019) ⁵²	Case series	Apremilast 30 mg BID for 3 months	Patient 1. 57-year-old female with DM with heliotrope sign, V-sign with poikiloderma over chest, shawl sign on back: CDASI improved from 43 to 0 after 3 months of treatment Patient 2. 64-year-old female with DM complicated by calcinosis cutis with heliotrope sign, erythematous patches and papules, V-sign with poikiloderma, scalp pruritus, and scale: CDASI improved from 41 to 7 after 3 months of treatment Patient 3. 62-year-old female with DM with heliotrope rash, diffuse violaceous plaques with crusting and ulceration, and periorbital edema: CDASI improved from 62 to 18 after 3 months of treatment
Charlton (2019) ⁵³	Case report	Apremilast 30 mg BID for 3 months	A woman in her 50s with refractory cutaneous dermatomyositis with severe scalp pruritus After 3 months of treatment, she experienced resolution of her heliotrope rash, facial erythema, refractory scalp rash, and pruritus. She also had significant improvement of Gottron's sign over the extensor aspects of her elbows, but continued to have minimal erythema
Konishi (2021) ⁵¹	Prospective open label trial	Apremilast 30 mg BID for 3 months	Patient 1. 71-year-old female with DM Patient 2. 65-year-old female with DM Patient 3. 64-year-old female with DM Patient 4. 39-year-old female with DM Patient 5. 37-year-old female with clinically amyopathic DM Patients 4 and 5 withdrew from study. However, when analyzing the remaining three patients, median CDASI score decreased 30.8 after 12 weeks.
JAK inhibitors			
Hornung (2014) ⁴²	Case report	Ruxolitinib 5 mg BID during months 0–2 15 mg BID from months 2–12 10 mg BID from months 13+	A 72-year-old female with refractory DM with periorbital erythema and rash in sun exposed areas. After 12 months of treatment, CDASI improved from 30 to 0.
Le Voyer (2021) ⁴³	Retrospective review	Ruxolitinib for at least 6 months Patient 1: 15 mg BID Patient 2: 10 mg BID Patient 3: 10 mg BID Patient 6: 7.5 mg BID Patient 7: 20 mg BID Patient 8: 10 mg BID Patient 10: 0.7 mg/kg/d Baricitinib for at least 6 months Patient 4: 2 mg BID Patient 5: 4 mg BID Patient 9: 4 mg BID	Ruxolitinib Patient 1. 13-year-old female with DM: Skin DAS score reduced from 4/9 to 0/9 in 2.6 months. Patient 2. 8-year-old female with DM: Skin DAS score reduced from 8/9 to 0/9 in 5.3 months Patient 3. 10-year-old female with DM: Skin DAS score reduced from 2/9 to 0/9 in 5 months Patient 6. 7-year-old female with DM: Skin DAS score reduced from 7/9 to 0/9 in 3 months Patient 7. 12-year-old male with DM: Skin DAS score reduced from 8/9 to 4/9 in 3 months Patient 8. 11-year-old female with DM: Skin DAS score reduced from 8/9 to 4/9 in 3 months Patient 8. 11-year-old female with DM: Skin DAS score reduced from 8/9 to 0/9 after 3 months. Patient 10. 3-year-old male with DM: Skin DAS score reduced from 8/9 to 0/9 after 3 months. Baricitinib Patient 4. 12-year-old female with DM: Skin DAS score reduced from 3/9 to 0/9 after 1.7 months Patient 5. 5-year-old female with DM: Skin DAS score reduced from 6/9 to 0/9 after 5 months.

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Heinen (2020) ⁴⁴	Case report	Ruxolitinib 30 mg daily for 170 days	A 14-year-old male with juvenile DM with diffuse moderate erythema and palate telangiectasia continued long-term ruxolitinib therapy due to initial clinical improvement on medication after 3 months. On day 170, the sternal rash had diminished, leaving a pale scar-like area
Aeschlimann (2018) ⁴⁵	Case report	Ruxolitinib 10 mg BID for 10 months	A 13-year-old female with severe vasculopathic refractory juvenile DM with diffuse moderate erythema and palate telangiectasia. Skin DAS improved from 4/9 to 0/9 after 2 months of treatment
.adislau (2018) ⁴⁶	Case series	Ruxolitinib 40 mg daily for 3 months	Patient 1. 59-year-old female with DM for 5 years: CDASI improved from 26 to 15 Patient 2. 79-year-old female with DM for 4 years: CDASI improved from 27 to 7 Patient 3. 84-year-old female with DM for 1 year: CDASI improved from 44 to 14 Patient 4. 45-year-old female with DM for 6 years: CDASI improved from 40 to 15
Kurtzman (2016) ²⁹	Case series	Tofacitinib for mean treatment period of 9.6 months. Patient 1: 10 mg BID Patient 2: 5 mg BID Patient 3: 5 mg BID	Patient I. A female in her 30s with DM for 5 years: CDASI improved from 30 to 14 Patient 2. A female in her 40s with DM for 5 years: CDASI improved from 23 to 10 Patient 3. A female in her 50s with DM for 8 years: CDASI improved from 32 to 25
Moghadam-Kia 2019) ³⁰	Case series	Tofacitinib 5 mg BID for 6 months	Patient 1. 55-year-old female with DM with heliotrope rash, facial erythema, left upper extremity subcutaneous nodules, and inflammatory polyarthropathy: After 3 months of treatment, there was a 50% reduction in facial rash. After 6 months of treatment, she had only minimal erythema over eyelids and subtle facial flushing. Patient 2. 67-year-old female with DM with facial and truncal erythema in addition to inflammatory polyarthropathy: After 3 months of treatment in addition to inflammatory polyarthropathy: After 3 months of treatment, her facial and truncal erythema persisted but normalized serum muscle enzyme. After 6 months of treatment, she had near resolution of her DM skin rash. Patient 3. 42-year-old male with DM with erythematous rash over forearms, antecubital area, and inflammatory polyarthropathy. After 3 months of treatment, he had 50% skin improvement. After 6 months of treatment, he had 50% skin improvement. After 6 months of treatment of his rash. Patient 4. 59-year-old male with DM complicated by discoid lupus with facial and scalp erythema, gottron sign, poikilodermatous changes, and inflammatory arthropathy. After 3 months of treatment, there was a clear improvement in his rash and arthropathy with less pruritus and scaling of his scalp.

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Table 2 (Continued).

First Author (Year)	Type of Study	Treatment	Outcome
Min (2022) ³¹	Retrospective review	Tofacitinib for mean treatment duration of 27.2 months Patient 1: 10 mg BID Patient 2: 5 mg BID (14 months) and 10 mg BID (10 months) Patient 3: 10 mg BID Patient 4: 5 mg BID (5 months), 10 mg BID (10 months), and 10 mg daily alternating with 10 mg BID (11 months) Patient 5: 10 mg BID Patient 6: 10 mg BID (25 months), and 10 mg daily (3 months) Patient 7: 10 mg BID Patient 8: 5 mg BID (5 months), and 10 mg daily alternating with 20 mg daily (25 months) Patient 9: 10 mg BID Patient 10: 11 mg extended-release daily (21 months), and 11 mg extended-release BID (3 months) Patient 11: 5 mg BID	Patient 1. 31-year-old female with amyopathic DM: CDASI improved from 30 to 14 Patient 2. 50-year-old female with amyopathic DM: CDASI improved from 32 to 10 Patient 3 59-year-old female with amyopathic DM: CDASI improved from 27 to 8 Patient 4 31-year-old male with amyopathic DM: CDASI improved from 27 to 8 Patient 5 54-year-old female with amyopathic DM: CDASI improved from 22 to 7 Patient 6 74-year-old female with classic DM: CDASI improved from 30 to 10 Patient 7 58-year-old female with classic DM: CDASI improved from 17 to 4 Patient 8. 39-year-old female with classic DM: CDASI improved from 23 to 9 Patient 9. 53-year-old female with classic DM: CDASI improved from 26 to 6 Patient 10. 26-year-old female with juvenile DM: CDASI improved from 20 to 9 Patient 11. 19-year-old female with juvenile DM: CDASI improved from 29 to 6
Shneyderman (2021) ³²	Case series	Tofacitinib Unspecified dose for 3 months	Patient I. 50-year-old female with refractory DM for 14 years. There was an improvement in her skin disease after 3 months with an unspecified CDASI score improvement. Patient 2. 55-year-old female with refractory DM for 5 years. There was an improvement in her skin disease after 3 months with an unspecified CDASI score improvement. Patient 3: 35-year-old female with refractory DM for 10 years. There was an improvement in her skin disease after 3 months with an unspecified CDASI score improvement.
Williams (2020) ³³	Case report	Tofacitinib 11 mg daily for 6 months	39-year-old woman with DM with facial rash, arthralgias, and worsening lower extremity edema After 6 months of treatment, there was substantial improvement with regained muscle strength, hair regrowth, resolution of her rash, and minimal arthralgias
Paik (2021) ³⁴	Prospective open label study	Tofacitinib 11 mg daily for 12 weeks	10 adult patients 18 years and older with DM. After 12 weeks, there was a statistically significant (p = 0.0005) mean CDASI improvement from 28 ± 15 to 9.5 ± 8.5
Yu (2021) ³⁵	Case series	Tofacitinib 5 mg BID for at least 6 months	Patient 1. I I-year-old female with juvenile DM: Skin DAS improved from 5/9 to 0/9 after 6 months of therapy Patient 2. 10-year-old female with juvenile DM: Skin DAS improved from 2/9 to 0/9 after 6 months of therapy Patient 3. 10-year-old male with juvenile DM: Skin DAS improved from 7/9 to 0/9 after 6 months of therapy
Crespo (2019) ³⁶	Case report	Tofacitinib 5 mg BID for 2 weeks	49-year-old female with DM with itching and localized skin lesions in sun exposed areas After 2 weeks of treatment, all skin lesions and itching improved significantly
Ishikawa Y (2020) ³⁷	Case report	Tofacitinib 10 mg daily for one year	57-year-old female with amyopathic DM complicated by ILD. 6 months after starting treatment, the patient's skin lesions improved, and ulcerations epithelialized. One year after starting treatment, her prednisone dose was reduced, and disease activity did not re-exacerbate.

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Sozeri (2020) ³⁸	Case series	Tofacitinib 5 mg BID for 3 months	Patient 1. 7-year-old male with heliotrope rash, Gottron's papules, muscle weakness, and skin and muscle calcifications Skin and muscle calcifications completely resolved after 3 months of therapy. Patient 2. 9-year-old female with heliotrope rash, Gottron's papules, muscle weakness, arthritis, and skin and muscle calcifications: 50% improvement in skin and muscle calcifications after 3 months of therapy
Sabbagh (2019) ³⁹	Case series	Tofacitinib 5 mg BID Patient 1: 6 months Patient 2: 12 months	Patient 1. 12-year-old male with anti-MDA5 autoantibody-positive JDM with malar and heliotrope rashes and Gottron's papules: CDASI improved from 21 to 12 within 6 months of therapy. Patient 2. 15-year-old female with anti-MDA5 autoantibody-positive JDM with malar rash, digital erythema and ulcers, and hair loss: CDASI improved from 21 to 7 after 1 year of therapy.
Ohmura (2021) ⁴⁰	Case report	Tofacitinib 5 mg BID for first 25 days 20 mg daily for next 162 days 10 mg daily maintenance afterwards	55-year-old male with Gottron's signs and itchy confluent macular erythema over upper back, posterior neck, shoulders, and lateral thighs. The patient experienced complete symptom resolution of ulcerating skin lesions after 27 days of treatment. Skin lesions continued to show marked improvement on follow up visits.
Paik (2017) ⁴¹	Case report	Tofacitinib 5 mg BID for 6 months during the study and later continued at same dosage for maintenance therapy.	55 year old female with severe, refractory DM with shawl sign, heliotrope rash, Gottron's papules, periungual erythema, and holster sign. Patient experienced improvement of Gottron's papules, shawl and V-neck sign, and muscle strength after 2 months of therapy.
Kim (2021) ⁴⁷	Prospective open label study	Baricitinib 4–8 mg daily (mean 7.25 mg/day) divided two times per day for 24 weeks	4 patients ranging from 5.8 to 20.7 years old with chronically active juvenile DM who had failed 3–6 immunomodulatory medications. There was a statistically significant (p < 0.01) decrease in CDASI scores at the 4, 8, 12, and 24 week timepoints.
Delvino (2020) ⁴⁸	Case report	Baricitinib 4 mg daily for 3 months	58-year-old female with DM with proximal limb muscle fatigue, facial erythema with swelling of the eyelids and orbits, Gottron's papules at the metacarpophalangeal joints, oropharyngeal dysphagia for solids and liquids, inflammatory polyarthralgias and high-spiking fever. The patient achieved a rapid and remarkable improvement of her cutaneous lesions, subjective muscle weakness, and polyarthritis after 3 months of treatment
Papadopoulou (2019) ⁴⁹	Case report	Baricitinib 6 mg BID for 12 months	A 11.5-year-old male of non-consanguineous descent diagnosed with juvenile DM at age 2.5 years with heliotrope rash, gottron's papules, and proximal muscle weakness. Modified skin DAS improved from 5/5 at baseline to 1/5 after 6 months of treatment. At 12 months of

(Continued)

treatment, patient stopped taking all medication against medical advice causing a flare showing modified DAS

score returning to 5/5.

Table 2 (Continued).

First Author (Year)	Type of Study	Treatment	Outcome
Fischer (2022) ⁵⁰	Case series	Baricitinib 4mg daily Patient 1: 5 months Patient 2: 6 months Patient 3: 4 weeks	 Patient I. Female with 25-year history of recurrent DM with recent cutaneous flare with normal muscle enzymes. Complete resolution of her neck, facial, and periungual erythema occurred after the treatment period. Patient 2. Individual with anti-NXP2 antibody positive DM with severe muscle aches, erythema of the face and abdomen, and DM-related panniculitis of the back. Improvement and gradual resolution of the panniculitis occurred after therapy. Patient 3. Individual with anti-MDA5 antibody positive DM with severe skin involvement and minimal muscle or lung activity. Cutaneous lesions greatly improved in terms of CDASI only after 4 weeks of therapy.
Biologic agents			
Xie (2020) ⁶³	Case report	Adalimumab 40 mg weekly for 4 weeks, followed by q2weeks for 12 weeks. Etanercept 50 mg weekly (medication changed due to pregnancy) Adalimumab 40 mg q2weeks for 18 months, then q4weeks for 6 months, then q6weeks for 6 months	24-year-old female with DM and 3 month history of eyelid swelling and a 1-year history of a nonpruritic erythematous rash affecting her chest, face and arms, associated with migraines and with wrist and phalangeal joint pains Patient had an excellent clinical response within 6 months of treatment, with a reduction in symptoms, skin rash, clearing of Gottron's papules, increase in muscle bulk and strength, and softening and improvement of calcinosis
Campanilho-Marques (2020) ⁵⁴	Retrospective review	Infliximab 6mg/kg q4weeks alone for 12 months OR Adalimumab 24 mg/m ² q2weeks alone for 12 months OR Infliximab 6mg/kg q4weeks for mean treatment time of 2.3 months followed by Adalimumab 24 mg/m ² q2weeks for remaining time until 12 months	60 children with juvenile DM with mean age of onset of 5.2 years old. Infliximab alone: Significant modified skin DAS decrease from 4/5 to 2/5 after 6 months ($p = 0.002$) and to 1/5 after 12 months ($p = 0.0006$) of treatment. Adalimumab alone: Statistical analysis limited by low patient number ($n = 4$) but showed modified skin DAS change from 2/5 to 3/5 at 6 months and 1/5 after 12 months of treatment. Infliximab to Adalimumab: No significant changes in modified skin DAS at 6 months ($p = 0.7$) or 12 months ($p = 0.2$) of treatment.
Park (2012) ⁶²	Case report	Adalimumab 40mg q2weeks for 18 doses	48-year-old female with DM with 60 day history of scaled erythematous rash involving the face, elbows, knuckle areas, and proximal muscle weakness. After 18 doses of therapy, skin lesions were improved completely.
Yamada-Kanazawa (2019) ⁵⁵	Case report	Infliximab 5mg/kg for I year	44-year-old female with DM with itchy erythema all over body for 1 month. Skin and joint symptoms improved completely after 1.5 months of treatment.
Huang (2020) ⁵⁶	Case report	Infliximab 5 mg/kg at weeks 0, 2 and 6, then q8weeks thereafter for an unspecified duration	57-year-old female with DM with eyelid edema, limb weakness, and swallowing difficulties Patient had clinical improvement in rash, muscle pain, and weakness on all subsequent follow up visits.
Chen (2013) ⁵⁷	Retrospective review	Infliximab 5 mg/kg at weeks 0, 2 and 6, then q8weeks thereafter	14 females with average age 52.57 years old with DM. 10/14 patients had a favorable response, with improved motor strength, reduced rashes, and lung improvement on CT images. The remaining 4 died due of grave respiratory failure.

Riley (2008) ⁵⁸	Case series	Infliximab 3mg/kg at weeks 0, 2 and 6, then q8weeks thereafter for treatment durations below Patient 1: 24 months Patient 2: 30 months Patient 3: 18 months Patient 4: 12 months Patient 5: 8 months	Patient 1. 8-year-old female with refractory juvenile DM with continuous active muscle and skin disease. VAS improved from 78 to 15 after 24 months. There was a reduction in calcinosis, which was softer and no longer painful. Patient 2. 8-year-old male with juvenile DM with muscle weakness, active skin disease, and painful calcinosis. VAS improved from 41 to 15 after 30 months. Only mild skin disease and calcinosis persisted at the end of treatment Patient 3. 7.5-year-old male with refractory juvenile Dm with muscle weakness, profound lethargy, skin disease, and painful calcinosis. VAS from 24 to 6 after 18 months. Only livedo reticularis remained of his skin disease. Patient 4. 6.5-year-old female with DM with severe facial erythema, moderate muscle weakness, lethargy, and progressive soft calcinosis. VAS remained at 20 after 12 months of treatment. However, patient's parents noted an improvement in energy levels. Patient 5. 6-year-old female with DM with muscle weakness, severe lethargy, arthralgia, and soft calcinosis: VAS improved from 50 to 40 after 8 months of treatment. The calcified nodules became softer and smaller.
Dold (2007) ⁵⁹	Case series	Patient 1: Infliximab 5 mg/kg every 2 weeks for three doses Patient 2: Infliximab 3 mg/kg every 2 weeks for three doses	Patient I. 40-year-old female with DM with symmetric muscle weakness and rash on her face, neck, and metacarpophalangeal joints: After three doses of infliximab, she experienced improved muscle strength and normalized serum CK levels. The patient had a sustained clinical and laboratory response Patient 2. 29-year-old female with proximal symmetric muscle weakness, heliotrope rash, Gottron's papules, and malar rash involving the nasolabial folds: After three doses of infliximab, her dysphagia resolved; rash became faintly visible, and proximal muscle strength improved.
Hassan (2021) ⁶⁰	Case report	Infliximab 5 mg/kg at week 0, 2, 6 then q8week thereafter for 3 months	54-year-old female with DM with widespread erythematous rash and generalized weakness After 3 months of treatment, all manifestations improved, including skin rashes, swallowing, and GI vasculopathy.
Roddy (2002) ⁶¹	Case report	Infliximab 5mg/kg at 0, 2, and 6 weeks for 3 total doses.	48-year-old female with DM with arthralgia and florid violaceous rash on face and extensor aspects of hands. There was no improvement in this patient's skin disease.

First Author (Year)	Type of Study	Treatment	Outcome		
Rouster-Stevens (2014) ⁶⁵	Prospective open label study	Etanercept 0.4 mg/kg 2x/week for 12 weeks	Patient 1. 12-year-old female with 7.3-year history of DM: Juvenile DM DAS improved from 14/16 to 13/16 at 24-week follow-up Patient 2. 28-year-old male with 24.6-year history of DM: Juvenile DM DAS score increased from 9/16 to 12/ 16 at 24-week follow-up Patient 3. 13-year-old female with 4.1-year history of DM: Juvenile DM DAS score improved from 6/16 to 4/ 16 at 24-week follow-up Patient 4. 7-year-old male with 4.8-year history of DM: Juvenile DM DAS score increased from 10/16 to 13/16 at 24-week follow-up Patient 5. 14-year-old female with 10.8-year history of DM: Juvenile DM DAS score improved from 11/16 to 13/16 at 24-week follow-up Patient 5. 14-year-old female with 10.8-year history of DM: Juvenile DM DAS score improved from 11/16 to 10/16 at 24-week follow-up Patient 6. 18-year-old female with 3.5-year history of DM: Juvenile DM DAS score improved from 10/16 to 8/ 16 at 24-week follow-up Patient 7. 14-year-old female with 3.3-year history of DM: Juvenile DM DAS score improved from 10/16 to 8/ 16 at 24-week follow-up Patient 7. 14-year-old female with 3.3-year history of DM: Juvenile DM DAS score improved from 14/16 to 13/16 at 24-week follow-up Patient 8. 17-year-old female with 7.2-year history of DM: Juvenile DM DAS score improved from 14/16 to 13/16 at 24-week follow-up		
Muscle study group (2011) ⁶⁴	RCT	Etanercept 50mg weekly (n = 11) or placebo (n = 5) for 24 weeks	Subjects aged 18 to 65 years old with active DM. CDASI score improved from 11.9 to 8.8 but this was not significant ($p > 0.05$) compared to placebo.		
Norman (2006) ⁶⁶	Case report	Etanercept 25 mg 2x/week for 24 weeks	42-year-old female with DM with violaceous papules over extensor forearms, gottron's papules, periungual telangiectasias, heliotrope eruption, and poikiloderma over chest, neck, and back. She experienced an excellent clinical response with improvement in both cutaneous and muscle findings after 24 weeks.		
Montoya (2017) ⁶⁷	Case report	Ustekinumab 45 mg given at week 0, week 4, and q12 weeks thereafter for 18 months.	20-year-old male with 5 years of amyopathic DM with erythematous and confluent scaling plaques in multiple skin areas. At 18 month follow up, patient had a very good clinical response, no relapses, and no adverse effects		
Kim (2018) ⁶⁸	Phase 2 double blinded RCT	IMO-8400 0.6 mg/kg, IMO-8400 1.8 mg/kg, or placebo weekly for 24 weeks (IMO-8400 is an oligonucleotide antagonist of TLR7/8/9)	30 subjects with DM with CDASI scores of 15 or greater participated in this study. CDASI score improvement of -9.3 for 0.6 mg/kg, -8.8 for 1.8 mg/kg, and -7.3 for placebo. However, there was no significant difference in CDASI improvement between placebo and treatment groups (p = 0.238)		
Cannabinoid recepto	Cannabinoid receptor agonists				
Werth (2022) ⁶⁹	Phase 2 double blinded RCT	Lenabasum 20mg daily for 28 days, then 20 mg BID for 56 days, or a placebo (Lenabasum is a cannabinoid receptor type 2 agonist)	22 subjects of \geq 18 years of age with DM and CDASI activity \geq 14 At day 113, the lenabasum treatment group, compared to the placebo group, had a lower CDASI adjusted least squares mean of 6.5 [SE = 3.1], p = 0.038.		

Abbreviations: DM, dermatomyositis; CDASI, cutaneous Dermatomyositis Disease Area and Severity Index; BID, twice daily; QAM, daily every morning; QPM, daily every evening; DAS, skin disease activity score; ILD, idiopathic lung disease; VAS, visual analog score; TLR, toll-like receptor; RCT, randomized controlled trial; SE, standard error.

composed of 7 pediatric patients <13 years old with juvenile DM showed symptomatic improvement in DAS for all patients after ruxolitinib therapy.⁴³

Baricitinib has been evaluated in a prospective open-label trial of 4 patients with DM ranging from 5.8 to 20.7 years old. This study showed a statistically significant (p < 0.01) decrease in CDASI at 4, 8, 12, and 24 weeks of therapy.⁴⁷ Four case reports with a total of 8 patients showed that 7 out of 8 patients experienced partial or complete improvement of their DM.^{43,48–50} However, one 9.5-year-old patient with an initial DAS of 6/8 did not respond to therapy after 3 months.⁴³

PDE-4 Inhibitors

A prospective open-label trial of three patients with DM treated with apremilast 30 mg BID showed a mean decrease in CDASI score of 30.8.⁵¹ Two case reports/series composed of four total patients showed marked improvement in CDASI with apremilast 30 mg BID for 3 months.^{52,53}

Biologic Therapies

Infliximab, a chimeric IgG1 κ mAb binding TNF- α , at 3 or 5 mg/kg greatly reduced or completely resolved DMassociated skin rashes in most patients.^{54–61} One retrospective review of 14 female patients with an average age of 52.6 years old found that 10 out of 14 patients experienced a favorable treatment response with both improved skin findings and motor function.⁵⁷ A similar study in a pediatric cohort of 39 children found a significant modified skin DAS decrease from a group median of 4/5 to a 2/5 after 6 months (p = 0.002) and to 1/5 after 12 months (p = 0.0006) of treatment.⁵⁴

Adalimumab, a human IgG1 mAb binding TNF- α , at 40 mg every two weeks for 18 doses was found to completely resolve DM skin lesions for a 48-year-old female with erythema of the face, elbows, and knuckle areas.⁶² A 24-year-old female who received adalimumab 40 mg every 2 to 6 weeks was switched to etanercept 50mg weekly during pregnancy and continued to have improvement in her skin rash and clearing of her Gottron's papules after 6 total months of treatment.⁶³

Notably, one study with 15 patients found no significant change in modified skin DAS at 6 months (p = 0.7) or 12 months (p = 0.2) when patients were first treated with infliximab 6 mg/kg every 4 weeks for an average duration of 2.3 months and then transitioned to adalimumab 24 mg/m2 every 2 weeks for 12-months.⁵⁴

Etanercept, a soluble TNF receptor that binds and inhibits TNF- α and TNF- β , was studied in an RCT composed of 11 patients with active DM.⁶⁴ After a 24-week treatment period with etanercept 50 mg weekly (n = 11) or placebo (n = 5), no significant CDASI score improvement was observed.⁶⁴ On the other hand, a prospective open-label study testing etanercept 0.4 mg/kg twice weekly for 12 weeks observed improvement in juvenile DM DAS scores in 6 out of 8 patients at 24-week follow-up.⁶⁵ One case report studying etanercept at 25 mg twice weekly for 24 weeks demonstrated improved cutaneous and muscle findings in a 42-year-old female.⁶⁶

One case report has been published regarding the use of ustekinumab in DM.⁶⁷ Ustekinumab 45 mg every 12 weeks for 18 months provided a 20-year-old male with marked clinical improvement.⁶⁷

IMO-8400, an oligonucleotide antagonist of toll-like receptor (TLR) 7/8/9, was evaluated in one RCT.⁶⁸ Patients receiving 0.6 mg/kg or 1.8mg/kg for 24 weeks experienced a decrease in CDASI scores of 9.3 and 8.8, respectively, but these improvements were not significant (p = 0.238) when compared to control.⁶⁸

Cannabinoids

Lenabasum, a selective cannabinoid 2 receptor agonist, was evaluated with a Phase 2 double-blinded RCT composed of 22 patients.⁶⁹ On day 113 of the trial, participants in the treatment group experienced a statistically significant decrease of 6.5 in their adjusted least square mean CDASI (p = 0.038). Similarly, there were statistically significant differences in secondary outcomes in biomarker changes, such as in IFN-beta and IFN-gamma (p < 0.05).⁶⁹

Discussion

A wide array of novel therapies for the treatment of both CLE and DM are currently being explored, including JAK inhibitors, PDE-4 inhibitors, and biologic therapies. This literature review sought to elucidate the most up-to-date information regarding the safety and efficacy of each therapy.

A review of the literature on CLE treatment revealed that the topical JAK inhibitor R333 was not effective in improving lesion activity when compared to placebo.¹⁰ Conversely, systemic JAK inhibitors – including tofacitinib, ruxolitinib, and baricitinib – showed significant improvements in both skin lesions and hair regrowth.^{11–14,16,17} The use of apremilast, a PDE-4 inhibitor, was also found to be efficacious in the treatment of CLE, with one study citing a significant reduction in CLASI after 85 days.¹⁹ Additionally, the use of biologic therapies – including ustekinumab, tildrakizumab, anifrolumab, and BIIB059 – were effective in reducing cutaneous manifestations of CLE.^{20–27} However, the anti-IFN_Y antibody AMG 811 was not found to be effective in the treatment of DLE when compared to placebo.²⁸

Research has shown that the pathophysiology of CLE lesions is, in part, attributable to aberrant type I IFN production [32141953].⁷⁰ Thus, biologic therapies that target its receptor, such as anifrolumab, have shown promise for treatment of CLE. The pathogenesis of CLE has also been linked to environmental factors, such as ultraviolet (UV) light, and a subsequent amplified immune response orchestrated by a plethora of cytokines and chemokines.⁷¹ This has led to the use of various other biologic agents and JAK inhibitors, which target immune cells and pro-inflammatory mediators contributing to the cycle.

A review of the literature on DM treatment found strong evidence on the effectiveness of JAK inhibitors. Tofacitinib and baricitinib demonstrated significant improvement in CDASI activity, while ruxolitinib led to the resolution of cutaneous and non-cutaneous DM symptoms in multiple retrospective studies.^{29,30,32–41,43–50} The PDE-4 inhibitor apremilast has been studied to a lesser degree, but data similarly showed reduction in mean CDASI activity.⁵¹ Biologic therapies targeting the TNF-alpha pathway – infliximab, adalimumab, and etanercept – generally showed reductions in DM activity by either CDASI or DAS score, but statistical significance was not achieved in an RCT studying etanercept.^{54–66} Applications of other biologics such as ustekinumab and IMO-8400 have shown some limited success in single patients, although the former is limited to one case report and the latter was found to result in no significant difference by an RCT.^{67,68} The cannabinoid agonist, lenabasum, was found to significantly decrease patient mean CDASI.⁶⁹

The pathogenesis of DM is complex and not fully understood, but it appears to rely on cytokines and interferons from CD4+ T cells, B cells, mast cells, and dendritic cells among others.⁷² DM patients have elevated levels of IL-6, IL-15, IL-17, IL-18, and interferon-inducible proteins.⁷² Additionally, genetic polymorphisms in the TNF-alpha promoter appear to influence the risk and severity of DM.^{73,74} Therefore, disease improvement following pharmacologic blockade of these key inflammatory molecules is consistent with the current literature. Indirectly modulating these pathways with non-biologic therapies such as JAK inhibitors or cannabinoids may provide more accessible and cheaper therapeutic alternatives.

One of the main limitations of this review was the lack of robust studies, such as randomized controlled trials and meta-analyses, from which data could be gleaned. Additionally, the failure to find significance in some studies may be in part due to small sample sizes, and future large-scale studies are needed.

Conclusion

Both CLE and DM are autoimmune conditions that can cause devastating disease to those afflicted. Advancements in therapies, including biologics, JAK inhibitors, and PDE-4 inhibitors have shown promise in the treatment of both conditions. However, further research and clinical trials are required so that clinicians can confidently make decisions regarding which therapy is best for their patients.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; 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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