Review

Current concepts and advances in dermatomyositis: a dermatological perspective

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ABSTRACT

Dermatomyositis (DM) is an autoimmune disorder in which clinically amyopathic DM, characterised by hallmark cutaneous findings in the absence of clinical weakness, represents 20% of patients. This review will highlight current concepts and recent advances made in DM from a dermatological perspective, with a discussion of skin-predominant DM and its distinct challenges regarding diagnosis and management as well as their implications in clinical trials. An update will be presented with respect to classification criteria, pathogenesis in cutaneous DM, myositis-specific autoantibodies and their associations with cutaneous findings, skin-specific outcome measures and new therapeutics with their efficacy in skin disease.

Introduction

Dermatomyositis (DM) is an autoimmune disease characterised by hallmark cutaneous findings along with a risk of involvement of various organs including the muscles and lungs. DM is classified as classic DM (CDM) or clinically amyopathic DM (CADM), distinguished by the presence or absence of clinical weakness. The latter includes amyopathic DM (ADM), with no evidence of clinical or laboratory muscle involvement for ≥6 months, and hypomyopathic DM (HDM), where subclinical myopathy is found following laboratory evaluation or more intensive testing (1). CADM comprises at least 20% of DM patients (2-4). DM represents a diagnostic challenge. In a recent study, 55% were given a different diagnosis initially, mainly lupus erythematous (LE) and undifferentiated connective tissue disease, with a median delay of 15.5 months before diagnosis (5). Clinically amyopathic patients are even more frequently misdiagnosed (5). This is of clinical relevance as they are also at risk of interstitial lung disease (ILD) and malignancy, being highest in the first 1-2 years after disease onset (2-4, 6, 7). Furthermore, cutaneous DM significantly impacts patients' quality of life (QoL) (8, 9). This review highlights the recent progress made in DM while giving insight into DM skin disease, recognising skin-predominant DM as a distinct entity and the inherent challenges regarding both diagnosis and management.

Classification criteria and skin-predominant dermatomyositis

The idiopathic inflammatory myopathies (IIMs) are a heterogenous group of inflammatory muscle diseases that can also affect other organs (10). IIM classification has undergone substantial progress in last decade, leading to different subgroup descriptions based on clinico-histopathological findings. It is only relatively recently that classification schema has recognised skin-predominant DM in this spectrum of disorders (10, 11).

In 1975, Bohan and Peter introduced the first leading set of criteria for IIMs which have been widely used for the diagnosis of polymyositis and DM in clinical practice and research (12, 13). By definition, some form of muscle involvement was required, and polymyositis was differentiated from DM by the presence of a DM rash, consisting of heliotrope, Gottron's sign or Gottron's papules. These criteria completely excluded skin-predominant DM patients.

Sontheimer published in 2002 a proposed minimal set of hallmark cutaneous manifestations of DM while recognising that CADM should be included within the IIMs classification (1, 14). Several DM skin findings were incor-

porated, and a diagnostic skin biopsy was required. The purpose was to stimulate discussion and consensus in defining CADM to allow for more inclusive and uniform populations for studies, but these criteria were not validated.

In 2017, a multidisciplinary group of international experts developed and validated the European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) classification criteria for adult and juvenile IIMs (15). These criteria generate a total score corresponding to the probability of having IIM where a score above 55% defines the minimum threshold for IIM. The presence of 2/3 skin variables among heliotrope rash, Gottron's papules and Gottron's sign, allows CADM diagnosis, although a confirmatory cutaneous biopsy is recommended. A subsequent study showed that this new classification criteria did not capture 26% of ADM (16). These misclassified patients presented with other various DM skin findings. The EULAR/ACR criteria represent a major improvement, but there remains a need for more sensitive criteria, and additional variables are currently being evaluated (17).

In 2018, the European Neuromuscular Centre proposed classification criteria for DM based on international consensus. In addition to the 3 classic DM skin signs mentioned above, they incorporated ulcers on hand joints (for anti-MDA-5 disease), DM-specific autoantibodies and skin and muscle histopathology (18). These criteria allow a CADM diagnosis based on a combination of clinico-sero-pathological findings, although validation studies are still needed. In this classification, anti-synthetase syndrome (ASS), even with DM rash, is distinguished from DM. It is currently a widely held belief that ASS defines its own entity, based on differential phenotypes, interferon (IFN) signatures, muscle, and skin histopathology (18). However, ASS classification is subject to debate. A recent study of lesions at different sites (arm, leg and trunk) demonstrated comparable increased myxovirus resistance protein (MxA) and IFN-β (type I IFN-inducible proteins) upregulation in both ASS and DM patients with similar inflammatory pathways (19). This is in contrast with a previous study of lesions on the fingers in a mechanics hand distribution that did not show a type I interferon signature (20). Of interest, the clinical manifestations of ASS and DM can overlap in terms of the presence of ILD, Raynaud's phenomenon (RP), mechanic's hands, and DM rash (21). The role of ASAs is of interest since DM rash is more frequently reported with anti-Jo-1/EJ/PL-7/PL-12 (22). Certain clinical-pathological overlap is present between ASS and DM. A lack of definition consensus may explain current discrepancies in the literature, and there is ongoing work to define ASS (23).

An international collaboration between dermatology and rheumatology experts was created to develop skin-focused classification criteria to distinguish cutaneous DM from mimickers while providing a more inclusive definition of skin-predominant DM (17). In 2020, Concha *et al*. published a provisional list of 25 retained items resulting from several rounds of Delphi consensus (Fig. 1). Eponyms were replaced by descriptive terms to better characterise DM skin features and DM-specific autoantibodies were integrated. Data are currently being prospectively collected in a multicenter effort to construct these criteria. These classification criteria will complement the EULAR/ACR criteria for patients not meeting the latter or function as a standalone for skin-predominant cases.

Establishment of validated criteria for skin-predominant DM patients is essential as misclassification leads to a delay in diagnosis (with potential for missed systemic comorbidities), inadequate treatment, and exclusion from clinical and translational studies (5). The latter is detrimental to skin-predominant DM patients as it may prevent them to benefit from novel therapies investigated in clinical trials done largely in CDM.

Pathophysiology and biomarkers in cutaneous dermatomyositis

The pathogenesis of DM is not yet completely understood, but increasing studies point towards type I IFN dysregulation as a key player in the disease, since marked upregulation of downstream biomarkers of this pathway has been demonstrated in skin, muscle, and blood (24-27). In a study analysing genome-wide expression in DM skin, a strong upregulation of IFN-inducible genes was observed and was more closely related to transcript levels of genes induced by type I rather than type II IFN (24). Despite this, both INF-β and IFN-γ transcript levels were highly correlated with IFN signature. Increased IFN-inducible proteins MxA and CXCL9/10 were also reported in lesional DM skin, and the authors proposed that these chemokines may attract CXCR3-bearing lymphocytes, leading to inflammation and keratinocyte necrosis (28, 29). Recent studies have demonstrated that myeloid dendritic cells (mDCs) are the predominant dendritic cell type in the skin of DM relative to plasmacytoid dendritic cells (pDCs) (30). In another study, highly multiplexed mass cytometry revealed a predominance of mDCs, CD14+ macrophages and T-cells in DM skin, and all were major producers of IFN-β (31). pDCs were also increased but were the highest relative producers of IFN-γ. IL-4/31+ mDCs as well as IL-31 levels correlated with itch score (32). Lesional mDCs were later confirmed to produce IFN-β and be associated with hydroxychloroquine refractoriness (30).

Significant association between skin disease activity and type I IFN signature has been reported using a skin-specific 10-cm VAS (33). Consistent with this finding, a recent study demonstrated moderate correlation between CDASI-A and type 1 IFN-inducible gene signature in the blood (34). CDASI-A score has also been found to be significantly associated with serum levels of CXCL10 and IFN-β, suggesting the potential role of IFN-β as a biomarker (34, 35).

Potentially precipitating or aggravating factors for DM have been identified, including immunostimulatory herbal supplements such as Spirulina, Aphanizomenon, Chlorella, Echinacea, and alfalfa (36). Compared to healthy and autoimmune disease controls, DM patients were found to be more likely to use herbal supplements (19.5%), especially Spirulina (37). Spirulina has been dem-

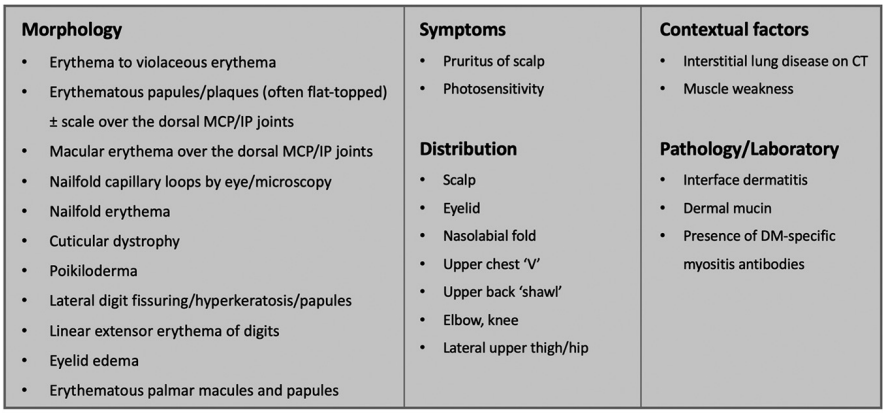

Fig. 1. List of 25 potential items for classification criteria of skin-predominant dermatomyositis proposed by the Skin Myositis Delphi Group.

onstrated to stimulate TNF-α and IFN-γ production via Toll-like receptor (TLR)-4 activation of monocytes and dendritic cells in DM patients *in vitro* (38). Weight loss powder IsaLean was also reported to be used in 3 DM patients, and dose-dependent increase secretion of IFN-α and IFN-β from IsaLean-treated cells was revealed *in vitro* (39).

COVID-19 vaccination has been increasingly reported to trigger DM. Sprow *et al*. systematically and prospectively assessed 402 autoimmune patients, especially LE and DM, and among fully vaccinated subjects, 14.8% experienced exacerbations while 6.7% required treatment escalation (40). DM patients were more likely to flare compared to LE (22.7% *vs*. 8.5%; p=0.009). Most autoimmune exacerbations occurred after the first (20%) and second dose (82%) within 7 and 14 days. In another study, 7.9% had DM exacerbations following vaccination, although flares were mostly mild (41). A cluster of new IIMs was reported in the Yorkshire region induced by COVID-19 vaccination (42). A recent review reported 21 cases of DM occurring after either COVID-19 infection or vaccination (43). Given COVID-19 infection-associated risks, vaccination should not be avoided in this population as it is generally safe in IIMs, but clinicians must be aware of this potential sequela (44).

Dermatomyositis clinical phenotypes associated with myositis-specific and autoantibodies

Discovery of multiple myositis-specific autoantibodies (MSAs) in recent years has led to the identification of biologically relevant subgroups of IIMs (45). It is unclear to what level (if any) these antibodies are pathogenic versus merely being reflective of a T-cell driven immune pathology. In this regard, it is interesting that several studies have suggested that plasma adsorption/exchange can result in clinical improvement of patients with anti-MDA-5 antibodies (46). Many methodologies for the detection of MSAs exist (immunoprecipitation, ELISA, line immunoblot assay, immunodot) and laboratories have their own proprietary assays for testing that diverge widely, leading to inconsistent results (47). Despite the usefulness of MSAs as a diagnostic tool, there is a need for standardisation as currently used detection platforms do not demonstrate high level of agreement for selected antigens.

DM has been associated with several MSAs that appear to define different subgroups with characteristic cutaneous and systemic manifestations. These antibodies include anti-Mi-2/TIF-1γ/NXP-2/MDA-5/SAE-1/2. These MSAs may also be associated with differing muscle histopathology, HLA subtypes, microRNA profiles and IFN levels (47, 48).

Anti-Mi-2 autoantibodies

The prevalence of anti-Mi-2 autoantibodies in adult DM ranges from 2-38% (48). Classic skin findings include a heliotrope eruption, Gottron's sign and papules, V-neck sign, Shawl sign, Holster sign, periungual erythema and cuticular overgrowth (49, 50). Punctate haemorrhages of the perionychium were reported in Japan (51). Proximal muscle weakness is almost always present, and creatine kinase levels are usually higher (49, 51-53). Most studies suggest that anti-Mi2 antibodies confer a decreased risk of ILD and malignancy as compared to anti-Mi-2-negative DM (51-53). However, a French study of 64 anti-Mi-2-positive DM patients supported an increased risk of malignancy with a standardised incidence ratio of 5.1 (p<0.001) compared to the general population (54). Overall, the prognosis is favourable with a good response to treatments, although a risk of recurrence is present.

Anti-TIF-1γ autoantibodies

Anti-TIF-1γ autoantibodies are found in both juvenile and adult DM patients across the world, and they are of high prevalence in Caucasian DM populations (38-41%) (48). The associated DM rash tends to be more severe, chronic, and psoriasiform (55). These patients appear to exhibit distinct dermatological signs: ovoid palatal patch (erythematous patch on the hard palate revealing interface dermatitis on biopsy), non-painful hyperkeratotic palmar papules, purpuric patches, and red-on-white lesions (hypopigmented patches admixed with telangiectatic macules) (55-57). Both CDM and CADM are found in this subgroup, although it appears that patients with muscle disease have relatively low CK levels (55). A negative association has been described for ILD, arthritis and RP (55, 58).

Malignancy risk associated with anti-TIF1-γ antibodies has been well substantiated in multiple cohorts (51, 58-61). In a meta-analysis pooling 312 adults, 80% of paraneoplastic DM tested positive for this autoantibody (62). Nevertheless, many anti-TIF-1γ-positive patients in the USA do not develop malignancy (55). Fiorentino *et al*. recently reported a reduced likelihood of cancer emergence in patients with a wider breadth of additional antibodies, with CCAR1 being the most frequently targeted antigen associated with cancer protection (63). Hosono *et al*. have recently reported a similar cancer-protective association with anti-Sp4 autoantibodies (64).

Anti-NXP-2 autoantibodies

The prevalence of anti-NXP-2 autoantibodies is approximately 14-25% in the USA (48). Calcinosis cutis and peripheral edema are more frequently encountered in this group (65-68). Anti-NXP-2-positive patients can often display a milder classic DM rash and some of them have actually been described as "sine dermatitis" DM (69). Systemic features include severe myositis affecting proximal and distal muscles, dysphagia, myalgia, and rarely intestinal vasculopathy (65, 66, 70, 71). An increased risk of malignancy appears to be present in some cohorts but not others, while the risk of ILD is reduced (60, 66, 70).

Anti-MDA-5 autoantibodies

Anti-MDA-5 autoantibodies are more prevalent among Asian (11–57%) than Caucasian cohorts (0–13%) (48). Several dermatological characteristics help to distinguish this group: severe non-scarring alopecia, cutaneous ulcers, painful erythematous palmar macules/papules on palmar interphalangeal joints, livedoid lesions on pulps, mechanic hands, RP, calcinosis cutis and panniculitis (51, 67, 72-76). Skin ulcerations may be complicated by gangrene and osteomyelitis. These unique findings are postulated to reflect an underlying vasculopathy of small and medium-sized vessels found in biopsies (73, 76). The ulcerative skin disease can be recalcitrant, and some experts lean towards treatment with MMF and IVIG as well as vasodilatators (75, 77). Anti-MDA-5-positive patients more frequently have ILD, including a subgroup with rapidly progressive ILD associated with high mortality (51, 76, 78-80). Skin ulcers represent a risk factor for ILD (81). Other manifestations include fever, arthritis, and myositis (51, 72, 73, 80, 82). Concomitant anti-Ro52 with anti-MDA-5 autoantibodies increase the risk of ILD and cutaneous ulcerations (83).

Anti-SAE1/2 autoantibodies

These autoantibodies are rarely encountered, with a prevalence of 5–10% in European populations (48). Anti-SAE1/2-positive patients have a typical DM rash, and cutaneous ulcers are also observed (84-88). Other findings include dark red/violaceous rash and 'angel wings' consisting of widespread erythema sparing the inferior scapula (85, 89). These patients can suffer from myopathy with frequent dysphagia (85, 88, 90). Small Asian cohorts more often have mild ILD, pulmonary arterial hypertension and malignancy (85, 86, 90).

Antisynthetase autoantibodies

These antibodies are found in ASS, and although controversy surrounds its classification, clinicopathologic overlap with DM exists. One Japanese study suggested that DM-associated skin manifestations are more commonly observed with anti-Jo-1/EJ/PL-7/PL-12 (22). Mechanic's hands represent the classic cutaneous finding: they are scaly, hyperkeratotic, fissured or hyperpigmented, affect mostly the ulnar surface of the thumb and the radial aspect of the fingers, and show interface dermatitis with mucin deposition (91, 92). Albeit characteristic, they are not pathognomonic of ASS as they are also reported in other DM subtypes, systemic sclerosis and MCTD (91). The presence of mechanic's hands is associated with a higher risk of ILD (93). The plantar equivalent is "hiker's feet" with bilateral dryness, cracking and hyperkeratosis, often seen with concomitant mechanic's hands (94). Systemic manifestations include ILD, myositis, arthritis, fever and RP (22, 93, 95). ASAs-positive patients suffering from ILD have a better prognosis than anti-MDA-5-positive patients (96).

Outcomes measures in dermatomyositis

Optimal management of cutaneous DM necessitates reliable and validated skin outcome instruments to assess disease progression, treatment efficacy, and evaluate new therapies in clinical trials. These encompass the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI), Physician Global Assessment Score (PGA), VAS and Investigator Global Assessment Score (IGA) among others (97). Standardised instruments for patients' QoL include the Skindex-29 and Dermatology Life Quality Index (DLQI) (97).

The CDASI is a skin outcome instrument employed with success in clinical studies and trials (98). It was developed in 2008 by a group of dermatologists expert in DM, and later refined in 2010 (99). The instrument defines skin disease activity, based on erythema, scale, and erosion/ulceration, and skin damage, based on poikiloderma and calcinosis. 15 anatomical locations are scored, in addition to Gottron's papules on the hands, periungual changes and alopecia (99). The activity and damage subscore ranges from 0-100 and 0-32 respectively, with a higher score indicating greater disease severity.

The CDASI showed good construct validity when correlated with the PGA using VAS and Likert scale and good overall inter-rater reliability when compared to the PGA and CAT-BM (binary method) (100). As DM may require interdisciplinary collaboration, a study confirmed that CDASI inter- and intra-reliability were overall good to excellent across rheumatologists, neurologists, and dermatologists, aside from the activity inter-reliability and damage intra-reliability that were moderate (but acceptable) among neurologists (101).

A CDASI-activity score of 14 or greater differentiates mild from moderate-to-severe skin disease (102). Higher CDASI activity (CDASI-A) has been shown to be associated with poorer QoL (9). The CDASI has been shown to be responsive to change. A decrease of 4 to 5 points in CDASI-A reflects a minimal clinically significant improvement, corresponding to a 2-cm improvement in the PGA VAS (gold standard) (102). Using the 4-point decrease, a significant improvement in QoL was shown in responders *versus* non-responders (103). It was determined that for initial CDASI-A >14, a 40%-change between 2 visits illustrates a meaningful improvement in QoL according to Skindex-29 and DLQI (103, 104). A review of 171 DM patients revealed that improvement in QoL measures correlated with decreasing CDASI-A scores. Quality of life was not improved below CDASI-A cut-off values of 4-10, suggesting that total clearance of skin findings may be irrelevant as a meaningful outcome for patients (105). This is of crucial relevance as cutane-

ous DM is refractory. Use of meaningful outcomes will optimise the development and accessibility of much needed therapeutics for cutaneous DM.

It was recently observed that among CDASI, IGA and Skindex-Symptoms, CDASI was best at discriminating small improvements in overall skin disease. DM-specific IGA performed the least well, which limits its usefulness in clinical trials (106). The IGA is a 5-point scale to evaluate the overall skin disease (from "clear to "severe") by the investigator based on the overall description of each category (107). Furthermore, the CDASI has been used in translational studies and appears to reflect certain candidate DM biomarker, such as type 1 IFN signature, serum IFN-β and CXCL10 levels (34, 35).

The Total Improvement Score (TIS) has gained a considerable attention as an outcome measure in myositis clinical trials (108). This composite response score was developed in 2016 by an international collaboration of experts and encompasses 6 weighted core set measures (CSM) using absolute percent changes (109). The TIS (0-100) is determined by summing each CSM subscore. Thresholds of ≥20, ≥40 and ≥60 define minimal, moderate, and major improvements. The overall skin activity disease is assessed in the 'Extramuscular Global Activity' CSM using 10-cm VAS based on listed clinical features. It is then incorporated within the extramuscular global activity VAS with other organ involvement, thus further reducing skin-disease activity's weight in the overall scoring. While being useful to show a response in patients with active myositis, further investigations are warranted to evaluate the applicability of TIS in skin-predominant DM patients and its sensitivity to discriminate different improvement levels of skin activity. Primary endpoints that directly account for both skin and muscle disease may be more sensitive in discerning treatment effects in investigational studies that include the full spectrum of DM patients.

Novel treatments in cutaneous dermatomyositis

Management of cutaneous DM is individualised for each patient, as skin disease can often respond differently than muscle disease. The first-line approach encompasses photoprotection, topical corticosteroids and calcineurin inhibitors, although systemic treatments are required in most cases (110, 111). The systemic options include antimalarials (hydroxychloroquine, chloroquine, quinacrine), favoured for mild disease, and immunosuppressants such methotrexate or mycophenolate mofetil (MMF) in severe or recalcitrant cases. Antimalarial monotherapy permits control in only 11-15% of patients, and 20–33% of DM patients have an adverse cutaneous response or DM flare, and one study suggested this might be particularly common in the anti-SAE autoantibody subgroup (112-114). A recent study showed no significant difference between methotrexate and MMF efficacy, with the interesting finding that responders continued to improve over months whereas non-responders showed little improvement at first follow-up (115). Non-responders to one immunosuppressive may respond to another (115). Multiple therapies are frequently required before achieving control (114). Development of new treatments for cutaneous DM is paramount given its resistance to standard-of-care management while impacting QoL (8, 9).

Intravenous immunoglobulin (IVIG)

IVIG possesses immunomodulatory effects including clearing of autoantibodies through blockade of the FcRN receptor, inhibition of immune complexes, cytokines and B-cells, binding of complement and activation of regulatory cells (116). Several studies underscore its usefulness in cutaneous DM. Cost and the need for repeat infusions can limit IVIG. In 1993, a RCT evaluating 15 CDM demonstrated IVIG's efficacy in myositis and mentioned marked skin disease clearance among 8 patients without details (117). In another study, the use of IVIG led to an improvement in 13 refractory cutaneous DM patients with 8 complete responses. All immunosuppressants were discontinued except in 3 patients who needed continued use for extracutaneous features (118). A group from Cleveland reviewed 42 cutaneous DM patients treated with IVIG: 83% improved after 1.82 cycles and systemic glucocorticoids were decreased or discontinued in 80% (119). In a French study, 70% of skin-predominant severe DM patients exhibited a major response (PGA) (120). Among complete or almost complete responders, 53% relapsed 6.2 months following the last IVIG course, but responded to a second course, indicating requirement for maintenance therapy.

Recently, a RCT demonstrated IVIG's efficacy in 95 CDM patients where a significant difference was noted between the treatment and placebo groups achieving a TIS of ≥20 at week 16 (79% *vs*. 44%; $p<0.001$) (121). A significant CDASI change of -9.4 in IVIG group versus -1.2 in placebo group was observed. This study led the Food and Drug Administration's approval of IVIG in DM, but the absence of CADM patients in the study may make this therapy less accessible for this group, highlighting the need for inclusion criteria and outcomes relevant to skin-predominant DM. A trial of subcutaneous immunoglobulins in DM is ongoing (NCT04044690).

Janus Kinase (JAK) inhibitors

JAK inhibitors impair signaling through multiple signalling receptors, and it is thought that inhibition of IFN signaling is an important mechanism for efficacy in DM (122). Tofacitinib, a JAK-1/3 inhibitor, was associated with a meaningful improvement of 17.8 in the CDASI-A score among 11 refractory cutaneous DM patients in a retrospective case series (123, 124). 91% discontinued or tapered other systemic medications. In a prospective, open-label pilot study of 10 refractory DM patients, 11 mg daily of extended-release tofacitinib was associated with a mean decrease in CDASI-A from 28 to 9.5 (-66%; $p=0.0005$) after 12 weeks of treatment (125). A marked decrease in STAT1 signalling in skin biopsies was also demonstrated.

Ruxolinitib, a JAK-1/2 inhibitor, has also been associated with some efficacy in DM (126). A CDM patient (CDASI 30) with myelofibrosis experienced complete resolution of the DM

rash on ruxolitinib, with strength gain and discontinuation of previous glucocorticoids, MMF and IVIG (126). A proof-of-concept study demonstrated that type I IFN-induced pathogenic effects *in vitro* were abolished by ruxolitinib (127). This was accompanied by skin and muscle improvement in 4 refractory DM patients whose serum type I IFN-inducible genes scores were reduced. Another study of 12 patients treated with ruxolitinib (n=6) and baricitinib (n=6) found that the CDASI-A significantly improved from 31 to 8 (p<0.0001) after 11.6 months (128). Thrombo-embolism requiring hospitalisation was reported in 1 patient.

In an open-label study among 12 cutaneous DM receiving baricitinib, a JAK-1/2 inhibitor, 75% achieved a 40%-decrease in the CDASI-A. Pruritus (VAS itch score) resolved in all 7 affected patients (129). Remarkable visual skin improvement was reported in one CDM patient resistant to 6 previous therapies (130). An upcoming trial for cutaneous DM (NCT05361109) and an ongoing trial for DM (NCT05524311) assessing skin activity with the CDASI will provide further data.

Brepocitinib is a TYK2/JAK-1 inhibitor is being studied in a phase 3 multicenter RCT recruiting DM patients (NCT05437263).

Rituximab

Rituximab is a monoclonal antibody targeting CD20 antigen on B-cells. Conflicting results have been reported for cutaneous DM responsiveness. In an open-label pilot trial evaluating 7 DM patients, improvement of rash in all patients was seen, with hair regrowth in 2 patients, although there was no objective skin activity measure (131). Another open-label trial of 8 DM patients did not show a significant change in DSSI from baseline at week 24 (9.5%; p=0.42) despite depletion of peripheral B-cells (132). A placebo-phase-controlled trial assessed the use of rituximab in 72 adult DM receiving 2 infusions one week apart, given either early (week 0/1) or late (week 8/9) (133). Overall, a significant change in cutaneous disease activity was observed: VAS went from 3.22 to 1.72 at week 16 (p=0.0002). Cutaneous response was faster in the early-drug group. Further investigations are needed to better evaluate rituximab's efficacy in cutaneous DM.

Lenabasum

Lenabasum is a non-immunosuppressive selective agonist for cannabinoid receptor type 2 (CB2), mainly expressed on activated immune cells with highest expression on DCs and B cells within DM skin (134, 135). It is postulated to have anti-inflammatory properties and be associated with resolution of immune responses (136-138). A placebo-controlled phase 2 trial evaluated its use among 22 resistant moderate-to-severe skin-predominant DM patients. On day 113 (4 weeks after lenabasum discontinuation), the mean difference in CDASI-A change from baseline between the 2 groups was -6.5 (p=0.038), suggesting prolonged effects of lenabasum on inflammation modulation. Lenabasum reduced cutaneous IFN-β and IFN-γ protein and mRNA gene expression levels, and lesional IL-31 levels among itch responders (135, 139). A multicentre phase 3 trial did not meet the primary endpoint at week 28 (TIS 28.3 *vs*. 27.2) (140). When restricting analysis to subjects without myositis, improvement in CDASI-A was superior in the lenabasum 20 mg BID than placebo group at week 28 (p=0.0461) and 52 (p=0.0059). The TIS became significant only at 52 weeks in skin-predominant DM patients, suggesting that it is less sensitive than the CDASI in capturing improvement in skin activity.

Other treatments

Apremilast is a phosphodiesterase-4 inhibitor downregulating proinflammatory cytokines. In a phase 2a, open-label, single-arm trial, 7/8 recalcitrant skin-predominant DM patients achieved a 4-point CDASI decrease from baseline at 3 months (-56.7%; p<0.001) (141). Downregulation of JAK/STAT, IL-4/6/12/23, IFN-γ/α and TNF-α was demonstrated in skin biopsies. A phase 1b single-arm trial reported a 39.4% CDASI reduction from baseline among 3 refractory skin-predominant DM patients at 3 months (142). Favourable responses were also described in case reports (143, 144).

Abatacept is a CTLA-4 inhibitor which effect on myositis was studied in a phase 2b trial among 9 DM and 11 polymyositis (145). Cutaneous improvement did not reach statistical significance using a VAS scale. The phase 3 RCT evaluating abatacept among 148 IIMs showed a lack of efficacy in DM (146). Abatacept led however to noteworthy improvement of extensive calcinoses with secondary cutaneous ulcerations in 2 juvenile DM (147, 148).

The following treatments have been mentioned in case reports of improvement in DM: ustekinumab (anti-IL-12/23 antagonist), tocilizumab (anti-IL-6 antagonist) and anakinra (anti-IL-1 antagonist) (149-154). Both ustekinumab (NCT03981744) and tocilizumab did not meet primary outcomes in trials assessing myositis (155).

Pharmacodynamic effects of sifalimumab, an anti-IFN-α antibody, showed suppression of type 1 IFN gene signature in blood and muscle of DM and polymyositis patients in a phase 1b trial (156). An anti-IFN-β therapy is currently evaluated in a phase 2 trial (NCT05192200). A phase 2 RCT is studying nipocalimab, a FcRn-targeted antibody, among IIMs (NCT05379634). The latter two include CDASI as secondary outcomes.

Conclusion

In recent years, skin-predominant DM has been increasingly recognised as a distinct entity that has clinical importance since the disease has shown to significantly impact QoL, is associated with malignancy, ILD or arthritis, and often does not respond to traditional treatments. Use of classification criteria and validated measures relevant to skin-predominant DM are crucial to allow their inclusion in clinical trials and accurately evaluate much-needed new therapies.

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