Review

Brepocitinib, a potent and selective TYK2/JAK1 inhibitor: scientific and clinical rationale for dermatomyositis

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Received on March 23, 2024; accepted in revised form on May 27, 2024.

Clin Exp Rheumatol 2025; 43(2): 354-363.

Key words: dermatomyositis, brepocitinib, JAK-STAT, TYK2/JAK1

Competing interests: see page 360.

ABSTRACT

Dermatomyositis (DM) is a rare and debilitating, systemic, autoimmune disease. While heterogenous in presentation and severity, DM is primarily characterised by a spectrum of skin and muscle disease, which may include proximal muscle weakness and recalcitrant cutaneous eruptions. DM may also be associated with joint pain and stiffness, inflammatory arthritis, dysphagia, fatigue, and calcinosis. The current standard of care for DM includes glucocorticoids, immunosuppressants, and intravenous immunoglobulin (IVIg). Unfortunately, these medications are not uniformly effective and can lead to adverse events, particularly with chronic use, necessitating discontinuation of therapy. Therefore, a substantial unmet need exists for more tailored and efficacious therapies that target DM pathogenesis.

Brepocitinib is an oral, once-daily, novel, and specific TYK2/JAK1 inhibitor. Brepocitinib's potent inhibition of TYK2 and JAK1 reduces the signalling of pro-inflammatory cytokines, including IFN-α/β, IL-12, IL-23, and IFNγ, that have been implicated in the pathogenesis of DM. Other JAK inhibitors have been used off-label in both case series and open-label clinical trials in patients with DM; and brepocitinib has demonstrated efficacy in phase 2 clinical trials of several other autoimmune diseases, including plaque psoriasis, psoriatic arthritis, Crohn's disease, hidradenitis suppurativa, and ulcerative colitis. Therefore, there is a strong scientific and clinical rationale for the utility and potential effectiveness of brepocitinib in the treatment of DM patients.

Currently, the safety, tolerability, and efficacy of brepocitinib is being evaluated in the largest (n=225) double-blind placebo-controlled phase 3 trial in DM patients to date (VALOR - NCT0543726).

Introduction

Overview of dermatomyositis

Dermatomyositis (DM) is a rare (1-3) and debilitating, systemic, immune-mediated, inflammatory disorder of the skin and muscles with significant unmet need and limited treatment options (4). DM is a heterogenous disease with regards to both clinical presentation and severity. The common features of classic adult DM include symmetric, proximal muscle weakness accompanied by characteristic erythematous to violaceous skin manifestations (including Gottron's sign, Gottron's papules, and heliotrope eruptions, amongst others). Muscle weakness and pain are the most common sources of morbidity, impairing even basic activities of daily life such as dressing, bathing, and walking up and down stairs (4). Notably, cutaneous disease in DM also results in substantial morbidity and has been shown to dramatically impact patients' quality of life, even more so than other severe skin diseases (5). Beyond skin and muscle, other systemic manifestations include interstitial lung disease (ILD), arthralgia or arthritis, dysphagia, cardiovascular disease (myocarditis, heart failure, arrythmias, etc.), and an increased risk of malignancy, which further contribute to disease-related morbidity and mortality (6-9).

A subset of DM patients, representing approximately 20% of the DM population, have the characteristic skin manifestations of DM but lack measurable muscle weakness (10). However, some patients originally thought to have amyopathic disease may go on to de-

velop muscle weakness as their disease progresses (11). Some patients with DM may become disabled by irreversible muscle damage and/or disfigured by cutaneous disease manifestations (12, 13).

Myositis-specific and myositis-associated antibodies have been characterised in patients with DM, including anti-TIF-1, one of the most common antibodies in DM patients and one associated with an increased risk of malignancy (14). Notably, these antibodies often correlate to specific phenotypes, allowing clinicians to better prognosticate and manage patients with DM (15). For example, some DM patients have high expression levels of anti-melanoma differentiation-associated gene 5 (MDA5) autoantibodies and are particularly prone to rapidly progressive interstitial lung disease (RP-ILD) (16). Calcinosis cutis, which is often associated with the presence of anti-NXP2 antibodies, is another serious manifestation of DM that can occur in up to 20% of adult DM patients (17). In a small subset of patients that present with DM-like symptoms, myositis can be attributed to anti-synthetase syndrome (ASS), which is characterised by the presence of serum autoantibodies directed against aminoacyl-tRNA synthetases. The severity of myositis symptoms is typically less in DM patients with ASS than without ASS (18). DM patients also have a significantly increased burden associated with their disease, including medication costs, loss of working hours due to disability, and hospital stays (19-21). Patients with an inpatient DM diagnosis have an increased length of hospital stay and a higher cost of care compared to inpatients without the disorder, likely due to a higher prevalence of comorbidities secondary to immune dysregulation (21). A cross-sectional, observational study characterising hospital readmission in the United States found the 30-day same cause and the calendar year same cause readmission rates for patients with dermatomyositis to be 18% and 31%, respectively, which represent the highest rates of readmissions for the 3.6 million dermatologic hospitalisations recorded from 2010 to 2014 (22). In aggregate, DM significantly affects the prognosis of patients, with reported five-year survival rates ranging from 60% to 90% (23).

Pathogenesis of dermatomyositis

Overactivity of type I IFN signalling is a cardinal feature of DM pathogenesis (24-27). Type I IFN-inducible proteins (*i.e.* MxA, ISG15) are elevated in DM muscle, skin, and endothelium (28-32). Consistent with these observations, type I IFN gene transcription scores in blood correlate strongly with DM disease activity, decrease significantly with immunomodulatory therapy, and shift concordantly with major changes in disease activity (26, 31).

Multiple proinflammatory cytokines have been implicated in the pathogenesis of DM based on studies of serum (IL-12, IL-23, IL-6), muscle (IL-4, IL-22), or both serum and muscle (IFN-γ, IL-15, IL-21) from patients with DM (3, 33-40). Elevated levels of IFN-γ are associated with the high levels of MDA5 autoantibodies characteristic of patients with anti-MDA5 DM and RP-ILD (3, 27, 41). Increased IFN-γ signalling is also implicated in DM cutaneous lesions via upregulation of osteopontin expression and DM muscle weakness via inhibition of myoblast differentiation (41). IL-4 has previously been found to be associated with ILD and muscle damage (40). Elevated IL-6 and IL-12 levels have also been proposed as useful predictors of prognosis for CADM patients suffering from RP-ILD, with higher levels correlating with significantly increased mortality (37, 42). IL-15, IL-21, IL-22, and IL-23 were all found to be upregulated in muscle of DM patients, and their accumulation was implicated in the pathogenesis and clinical outcome of myositis (35, 40). IL-35 was recently described as being upregulated in DM and positively correlated with physicians' assessments of disease severity, creatine kinase levels, and pulmonary dysfunction in those DM patients also suffering from RP-ILD (43). Therefore, optimal treatment of DM may require a targeted therapy that inhibits a wide range of pro-inflammatory cytokines contributing to disease pathogenesis.

Current treatment paradigm and unmet need

Given that overactivation of multiple proinflammatory pathways is strongly associated with disease activity, immunomodulators and immunosuppressants are commonly used for the management of DM (44). Treatment is largely driven by the organ (*i.e.* skin, muscle, or lung) that is most active at diagnosis. Initial intervention for muscle inflammation includes high-dose glucocorticoids, followed by tapering to an appropriate maintenance dose based on symptom alleviation (45). However, high doses of prolonged glucocorticoids often lead to debilitating side-effects, further contributing to excessive morbidity in DM patients. Immunosuppressive agents (*i.e.* methotrexate, azathioprine, mycophenolate mofetil) are used in combination with glucocorticoids from the start of treatment for most patients (44, 45). In cases of insufficient efficacy or in the presence of side effects or contraindications, other drugs are also utilised (*i.e.* cyclosporine, tacrolimus, intravenous immunoglobulin (IVIg), and rituximab). Antimalarials (primarily hydroxychloroquine) are often utilised for cutaneous disease although they have been shown to have limited efficacy for this condition (46). Furthermore, topical glucocorticoids and tacrolimus are commonly used, but are considered largely ineffective for anything but mild disease.

There are currently no uniform treatment guidelines for DM. Glucocorticoids, repository corticotropin injection (47), azathioprine (48) (European Medicines Agency (EMA) only), and IVIg (49) are the only medications approved by the Food and Drug Administration (FDA) and/or the EMA for treatment of DM. Use of these therapies is often hampered by safety concerns and other challenges that may limit their use. As with other chronic autoimmune diseases, long-term treatment with glucocorticoids carries a substantial risk of adverse events and safety issues that include weight gain, osteoporosis, diabetes, hypertension, and opportunistic infections, amongst others. Additionally, calcinosis is one serious DM manifestation that usually

does not respond to any of the therapies currently used to treat DM (17). Thus, there remains a crucial unmet need for glucocorticoid-sparing, targeted treatments for DM. Important features for a novel therapeutic include a favourable benefit/risk profile, a rapid onset of action to limit duration of glucocorticoid use, greater patient convenience and tolerability, and a mechanism of action that is more specifically targeted to the molecular pathogenesis of DM.

Brepocitinib as a tyrosine kinase 2 (TYK2)/ Janus kinase 1 (JAK1) inhibitor

JAK/STAT signalling overview

Janus kinases (JAKs) are tyrosine kinases bound to cytoplasmic regions of cytokine receptors. Upon receptor activation with specific ligand-binding, JAKs recruit one or more of seven different Signal Transducer and Activator of Transcription proteins (STATs) for phosphorylation. Phosphorylated STATs then translocate to the nucleus and regulate the transcription of a large variety of target genes. Over 50 cytokines signal via the JAK/STAT pathway to regulate key cellular behaviours, including haematopoiesis, inflammation, and immune activation (50). There are 4 characterised JAK isoforms (JAK1, JAK2, JAK3, and TYK2), of which TYK2 was the first discovered (51). Distinct pairwise combinations of JAKs (including homo- and hetero-dimers) are required for fully competent cytokine signalling (Fig. 1).

Dysregulation and overactivation of the immune response through pro-inflammatory cytokine release has been implicated in numerous inflammatory and autoimmune diseases in addition to DM, including rheumatoid arthritis, ulcerative colitis, atopic dermatitis, and non-infectious uveitis (52-57). As these cytokines primarily signal through the JAK-STAT pathway, JAK-STAT inhibitors have received significant attention and development in recent years for autoimmune diseases. Several JAK inhibitors, with varying specificity and selectivity, are indicated for the treatment of a variety of inflammatory and autoimmune disorders, including rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, alopecia areata, Crohn's disease, and axial spondylarthritis, amongst others (*e.g.* tofacitinib, baricitinib, upadacitinib, filgotinib). More detailed information about the cytokine inhibition profiles of approved JAK inhibitors can be found in Bonelli *et al*. (58).

JAK inhibitors in dermatomyositis

Off-label treatment of DM using FDA-approved JAK inhibitors (tofacitinib, ruxolitinib, and baricitinib) in the context of case reports, case series, and investigator-initiated clinical studies have collectively shown promising efficacy of JAK inhibition in DM (59-62). Of 145 case reports documenting the use of JAK inhibitors in DM patients, 137 reported disease improvement with JAK inhibitor therapy (59). Sixty-two percent of the patients were treated with tofacitinib, and 88% of those were treated with tofacitinib 5 mg BID or equivalent. Clinically meaningful changes in validated metrics of DM disease activity (total improvement score [TIS], manual muscle testing in a subset of eight muscles [MMT-8], and Cutaneous Dermatomyositis Disease Area and Severity Index [CDASI]) were observed in most patients for whom these values were reported. Of the 61 adult patients with refractory skin disease, 16 adult patients with refractory muscle disease, and 33 adult patients with ILD, 100%, 100%, and 94% reported improvement in symptoms, respectively (59). While these JAK inhibitors each have distinct JAK selectivity profiles (tofacitinib: JAK1/JAK3; baricitinib: JAK1/JAK2; ruxolitinib: JAK1/JAK2), all exert some degree of anti-type I IFN signalling effects (63-65). Notably, in the five publications in which serum IFN levels and/or IFN-stimulated gene expression were assessed, a reduction in these metrics corresponded with disease activity reduction during JAK inhibitor treatment (59).

An open-label pilot study (STIR study) of 10 DM patients given daily 11 mg XR (equivalent to 5 mg twice daily) of tofacitinib showed consistent disease improvement after JAK inhibitor treatment (61). All 10 patients in the STIR study met the primary endpoint, the International Myositis Assessment and Clinical Studies Group Definition of Improvement (DOI), as defined by: 3 of any of the 6 core set measures (CSMs) improved by ≥20%, with no more than 2 CSMs worsening by ≥25%. Seventy percent of patients also improved from moderate/severe skin disease activity to mild skin disease activity as measured by CDASI (61). In the 96-week long-term extension to the STIR study, 86% of patients remaining in the study (6 out of 7) continued to meet the DOI, suggesting long-term benefit of JAK inhibition in DM (60). There are also several reports in which a JAK inhibitor had a positive effect on otherwise non-responding calcinosis (66, 67). Collectively, these data suggest that JAK inhibition may be an effective, rational treatment option for DM. Furthermore, a study genotyping single nucleotide polymorphisms (SNPs) in DM patients (n=523) identified TYK2 as a novel locus significantly associated with DM (68); hence, a potent TYK2/JAK1 inhibitor may provide further clinical benefit for the treatment of DM.

Brepocitinib

Brepocitinib is an oral, once-daily, novel, small molecule selective inhibitor of tyrosine kinase 2 (TYK2) and Janus kinase 1 (JAK1). The oral bioavailability for brepocitinib is approximately 75% and its primary route of elimination is renal excretion as metabolites (69). Treatment with brepocitinib leads to reductions in a range of pro-inflammatory cytokine signalling, including type I & II IFN, IL-6, and IL-12/IL-23 (Fig. 2).

Brepocitinib is a potent inhibitor of TYK2/JAK1 signalling cytokines

Brepocitinib is selective for TYK2/JAK1 over other human kinases; *in vitro* inhibition assays demonstrate IC_{50} (the concentration at which a drug exerts half of its maximal inhibitory effect) values of 22.7 nM and 16.8 nM for TYK2 and JAK1, respectively, *versus* 76.6 nM for JAK2 and 6490 nM for JAK3. The potency and selec-

tivity of brepocitinib's inhibition of cytokine signalling were evaluated in human peripheral blood mononuclear cells (PBMC) and whole blood assays. Brepocitinib most potently inhibited cytokine-induced phosphorylation of STATs that signal through TYK2/JAK1 (*e.g.* IFNa, IFNγ, IL-6, IL-10, IL-12, IL-13, and IL-23), with all IC_{50}s <300 nM. This demonstrates the potential utility of brepocitinib in the treatment of DM, a disease characterised by overexpression of these cytokines. Brepocitinib was less effective in inhibiting IL-4, IL-15, and IL-21 signalling due to their JAK1/JAK3 pairing. Brepocitinib demonstrated minimal inhibition (IC50 of >500 nM) of cytokines signalling through JAK2/JAK2. For example, brepocitinib is 19.2 times more selective for TYK2/JAK1 IFN-α induced STAT3 signalling than for JAK2/JAK2 EPO-induced STAT5 signalling, which supports a lack of off-target inhibition (70). Brepocitinib (1 μM) also demonstrated >50% inhibition of only one non-JAK kinase, TNK1, when tested against a panel of 157 kinases at the physiologically relevant concentration of 1 mM ATP (70).

Brepocitinib's unique mechanism of action (MOA) may be suited to improve skin manifestations in DM, which are often more recalcitrant to currently available therapies than muscle disease, and thus pose a significant unmet need for many patients (71). Serum levels of IFN-β, IL-6, and IL-10 are correlated with cutaneous disease activity in DM (72). Brepocitinib, which inhibits both TYK2 and JAK1, may improve skin manifestations in DM, as IL-6 is regulated by JAK1 and IFN-β and IL-10 are regulated by JAK1/TYK2. In addition, IL-6, IL-12, and IFN-γ expression is correlated with RP-ILD in CADM, (27, 37, 39, 42) and brepocitinib's MOA inhibits all 3 of these ILD-related cytokines (Fig. 2). This unique JAK inhibition profile allows for significant inhibition of type I interferons and other DM-relevant cytokines, such as IL-12 and IL-23, while reducing off-target JAK inhibition, such as that impacting erythropoietin signalling, lending to a potentially favourable benefit-to-risk ratio for brepocitinib. Finally, in cross-study descriptive comparisons, clinical doses of oral brepocitinib 30 mg or 15 mg once daily (QD) inhibited DM-relevant cytokines to a greater or similar extent, respectively, than oral tofacitinib 5 mg twice daily (BID), the tofacitinib dose most commonly used off-label to successfully treat DM patients (60,61) (Fig. 2).

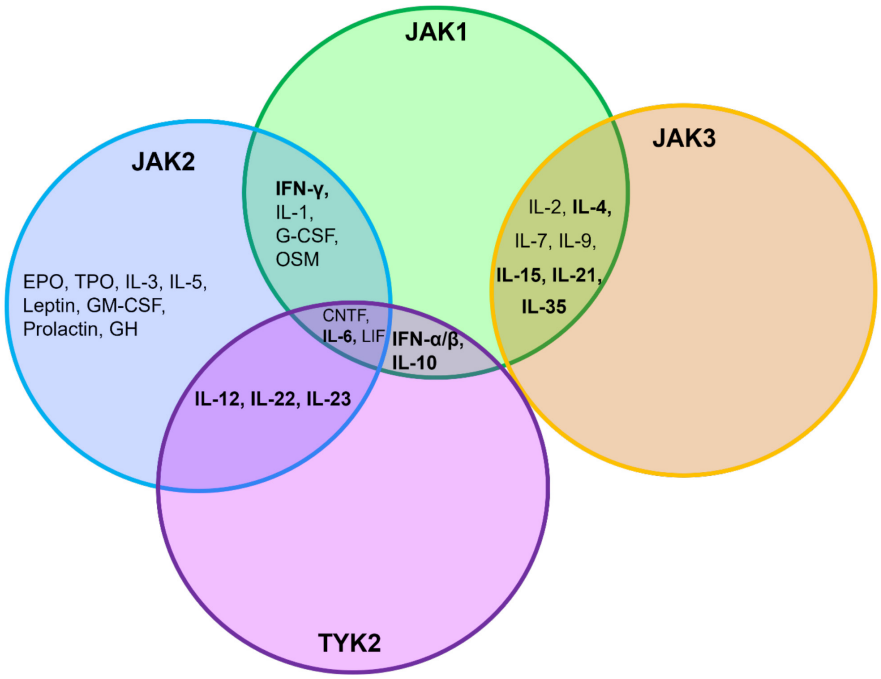

Fig. 1. JAK combinations required for various cytokines. Cytokines that appear in one circle only require a homodimer of the JAK. Cytokines that appear in between two circles require a heterodimer of the respective JAKs. Cytokines that appear in between three circles may signal with heterodimers of any two or three JAKs represented. Cytokines in bolded text are involved in DM pathogenesis. All DM-related cytokines require JAK1 and/or TYK2 to signal.

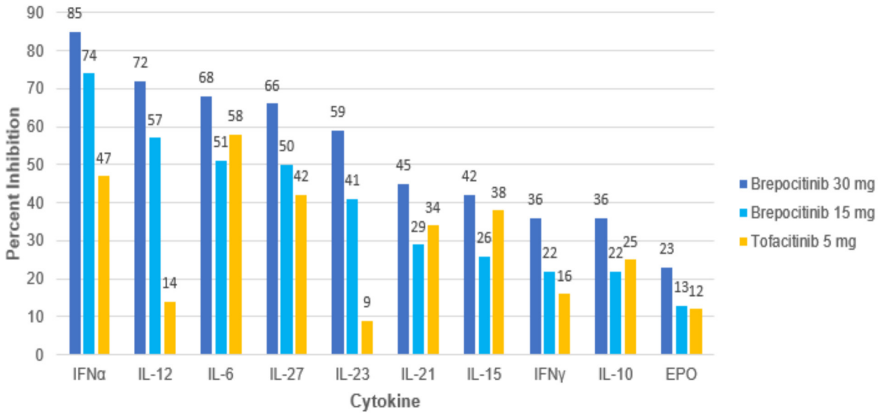

Fig. 2. Brepocitinib is a potent inhibitor of type I interferons and other DM-relevant cytokines. The percent inhibition values are from separate studies, not direct head-to-head comparisons. The percent inhibition was calculated from unbound IC_{50} and unbound C_{avg} values for each compound using the following formula: $(C_{avg} * 100) / (C_{avg} + IC_{50})$. The tofacitinib C_{avg} value was obtained from its FDA-approved label and the IC_{50} values for each cytokine as well as the tofacitinib unbound fraction were obtained from Dowty *et al.* (64).

Brepocitinib prevents type I interferon induced damage in cultured myocytes and endothelial cells

The ability of brepocitinib to inhibit type I IFN induced muscle damage was investigated *in vitro* in human muscle myoblast and microvascular endothelial cell models (73). Briefly, human skeletal muscle myoblasts were cultured until most of the myoblast cells

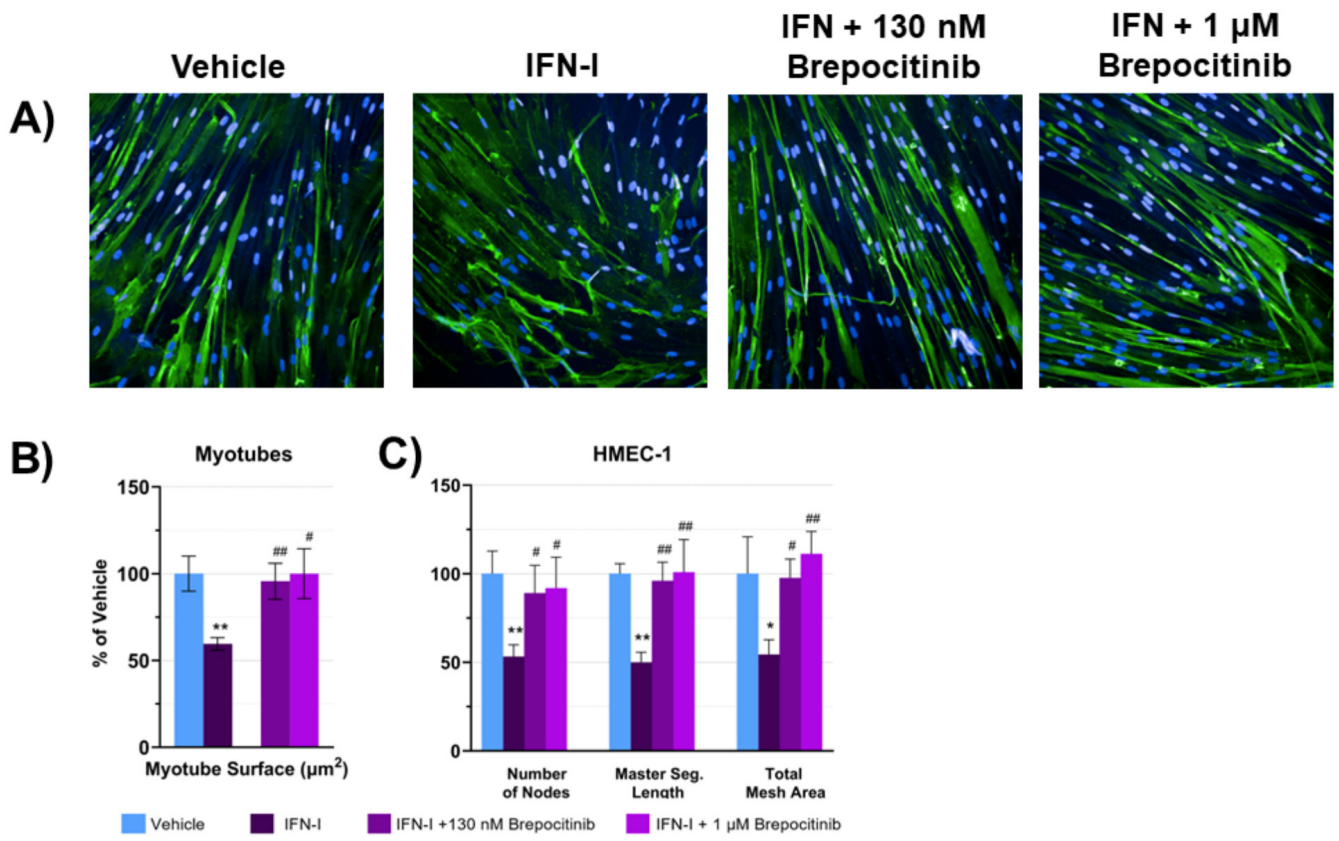

Fig. 3. Brepocitinib prevents type-I interferon-induced damaged of human myotubes and dermal microvascular endothelial cells. Myotubes and HMEC-1 cells were pre-treated with 130 nM (clinically relevant concentration equivalent to 30 mg QD) or 1 µM of brepocitinib before stimulation with 5000 units/mL of IFN-I.

A: Representative images of myotubes ± IFN-I and brepocitinib treatment. Blue: Nuclei (Hoechst), green: myosin 4. **B**: Quantification of myotube service area compared to vehicle (DMSO) control. **C**: Quantification of the number of nodes, master segment length and total mesh area of HMEC's compared to vehicle control.

*p<0.001 relative to vehicle; **p<0.0001 relative to vehicle; #p<0.001 relative to IFN-1; ##p<0.0001 relative to IFN-1. N: 3 experiments with 3 technical replicates each.

differentiated into multinucleated myotubes. The myotubes were then preincubated with vehicle or brepocitinib prior to type I interferon exposure at concentrations detailed in Figure 3. After 48 hours of treatment, cells were fixed and stained with Myosin 4 Monoclonal antibody and Hoechst for nuclei visualisation. The effect on total myotube surface area was evaluated via fluorescent image analysis. Similarly, human dermal microvascular endothelial cells (HMEC) were cultured and allowed to form vascular networks. Subsequently, the HMEC's were pretreated with brepocitinib prior to type I IFN exposure at the same concentrations as for myotubes. The effect of type I IFN exposure ± brepocitinib treatment on the number of nodes, master segment length, and total mesh area was evaluated by taking bright-field images every 16 hours.

Type I IFN induced damage was almost completely prevented by brepocitinib preincubation in both myotubes and endothelial cells at a clinically relevant concentration equivalent to the average unbound plasma concentration after 30 mg QD (Fig. 3). These biological studies are supportive of the potential of a JAK1/TYK2 inhibitor to treat both skin and muscle inflammation in DM.

Brepocitinib in autoimmune disorders

Brepocitinib clinical development history

As part of the clinical development programme for oral brepocitinib, ten Phase 1 and eight Phase 2 studies have been completed. Eight Phase 2 studies evaluated the safety, tolerability, and efficacy across a wide range of brepocitinib doses for the treatment of plaque psoriasis, psoriatic arthritis, alopecia areata, Crohn's disease, ulcerative colitis, hidradenitis suppurativa, systemic lupus erythematous (SLE), and non-segmental vitiligo, all but one of which have demonstrated statistically significant and/or clinically relevant efficacy (Table I). The multiple autoimmune diseases for which there is observed clinical efficacy data for brepocitinib have mechanistic pathway similarities to DM, as shown in Table I. For example, psoriasis is driven by IL-17, which is downstream of IL-12 and IL-23 signalling via TYK2 and/or JAK1 (74), and alopecia areata is characterised by excessive activity of IFN-γ, a type II interferon which also signals via JAK1 (75). Of note, dose dependent reductions in IP-10 (CXCL10), an IFN-γ inducible gene (76), have been observed in brepocitinib clinical studies, separating from placebo at doses ≥10 mg QD. Importantly, in these phase 2 studies, clinical response with

Table I. Results, statistical significance of endpoints, and key overlapping cytokines in positive, completed phase 2 studies with brepocitinib 30 mg QD or greater.

Study identifier	Disease/patient population	Treatment dose and duration	Endpoint/result	Statistical significance	Key cytokines involved in disease pathogenesis that overlap with DM
NCT02969018	Moderate to severe plaque psoriasis (80)	30 mg QD; 12-week primary endpoint	CFB in PASI Score Placebo: -7.21 Brepocitinib: -17.28	$p<0.0001$	Type I Interferon (IFNα, IFNβ) Type II Interferon (IFNγ) IL-12, IL-23 (85)
NCT02974868	Moderate to severe alopecia areata (86)	30 mg QD; 24-week primary endpoint	%CFB in SALT score Placebo: 1.41 Brepocitinib: 50.59	$p<0.0001$	Type II Interferon (IFNγ) IL-23 (87)
NCT03963401	Active psoriatic arthritis (77)	30 mg and 60 mg QD; 16-week primary endpoint	ACR 20 Response Rate Placebo: 43.28% 30 mg brepocitinib: 66.67% 60 mg brepocitinib: 74.58%	$p=0.0197$ $p=0.0006$	Type I Interferon (IFNα, IFNβ) Type II Interferon (IFNγ) IL-12, IL-23 (88)
NCT02958865	Moderate to severe ulcerative colitis (82)	30 mg and 60 mg QD; 8-week primary endpoint	Difference to placebo in total mayo score 30 mg brepocitinib: -2.28 60 mg brepocitinib: -3.21	$p=0.0005$ $p<0.0001$	Type II Interferon (IFNγ) IL-12, IL-23 (89)
NCT04092452	Moderate to severe hidradenitis suppurativa (90)	45 mg QD; 16-week primary endpoint	HiSCR Response Rate Placebo: 33.3% Brepocitinib: 51.9%	$p=0.0298$	Type II Interferon (IFNγ) IL-12, IL-23 (91)
NCT03715829	Moderate to severe active, non-segmental vitiligo (92)	60 mg QD 4-week induction, 30 mg-QD 12-week maintenance in an unblinded OLE	%CFB in F-VASI at week 16 Brepocitinib: -32.27%	NA	Type II Interferon (IFNγ) (93)
NCT03395184	Moderate to severe Crohn's disease (94)	60 mg QD; 12-week primary endpoint	SES-CD 50 Response Rate Placebo: 12.8% Brepocitinib: 33.8%	$p=0.0012$	Type II Interferon (IFNγ) IL-23 (95, 96)

ACR: American College of Rheumatology; CFB: change from baseline; F-VASI: facial-vitiligo area scoring index; HiSCR: hidradenitis suppurativa scoring area; OLE: open-label extension; PASI: Psoriasis Area and Severity Index; QD: once-daily; SALT: severity of alopecia score; SES-CD 50: simple endoscopic score for Crohn's disease 50% decrease.

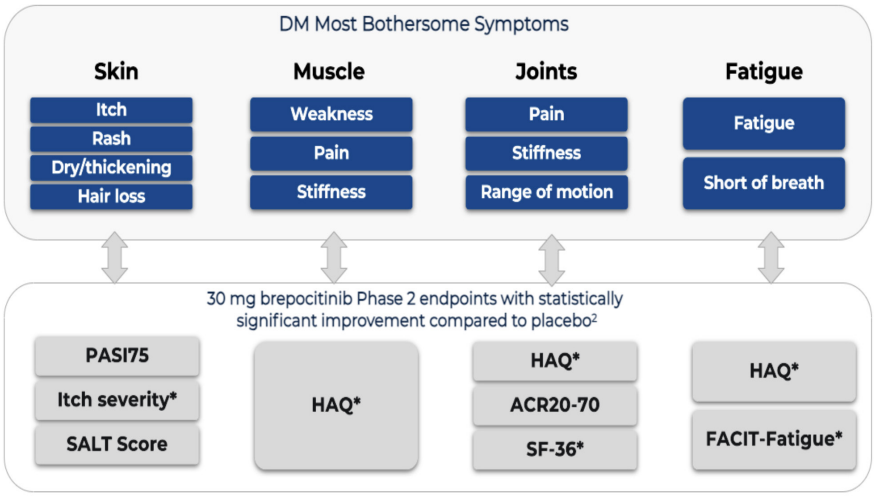

Fig. 4. Bothersome DM symptoms that overlap with phase 2 endpoint results observed with 30 mg brepocitinib in other autoimmune diseases. The DM most bothersome symptoms were obtained from an online survey to explore the patient experience of DM (97).
*Endpoints based on phase 2 studies in alopecia areata (NCT02974868), plaque psoriasis (NCT02969018), and psoriatic arthritis (NCT03963401). HAQ refers to the Health Assessment Questionnaire Disability Index.

brepocitinib treatment rapidly separates from placebo. For example, in the phase 2 study assessing brepocitinib's efficacy in psoriatic arthritis (77), brepocitinib 30 mg achieved a 52% ACR20 response rate after 4 weeks compared to a 19% response rate in placebo patients. This suggests brepocitinib has a rapid onset of action that may begin alleviating patient symptoms quickly.

The challenging disease manifestations experienced by patients with DM (across skin, muscle, joints, and fatigue domains) also overlap with those in previously studied populations treated with brepocitinib (Fig. 4). Statistically significant and clinically relevant improvements across each of these domains (Table I) have been demonstrated with brepocitinib. Additionally, cross-trial comparisons between tofacitinib 5 and 10 mg BID and brepocitinib 30 mg QD in psoriatic arthritis (77, 78), plaque psoriasis (79, 80), and ulcerative colitis (81,82) suggest that brepocitinib 30 mg QD compares favourably when treating other autoimmune diseases, although caution should be taken in interpreting cross-trial comparisons (Fig. 5).

Brepocitinib has been generally well-tolerated in studies to date. The most common treatment emergent adverse events affecting patients exposed to at least one dose of brepocitinib in completed phase 2 studies are nasopharyngitis, headache, and upper respiratory

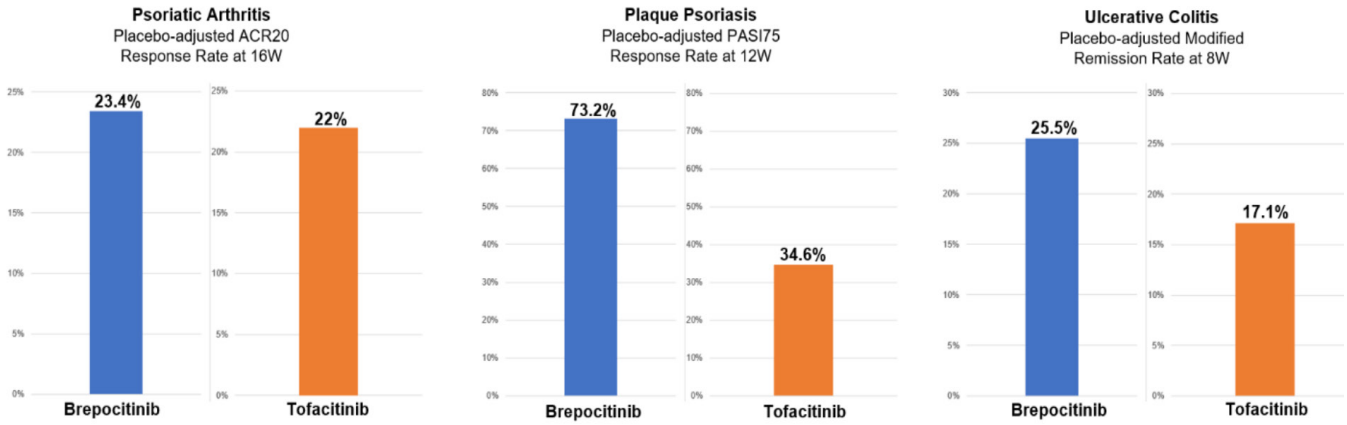

Fig. 5. Brepocitinib 30 mg QD appears to have equal or greater efficacy than tofacitinib in treating patients with psoriatic arthritis, plaque psoriasis, and ulcerative colitis based on cross-trial comparisons.
The comparisons are from separate clinical trials, not direct head-to-head comparisons of the two compounds. All 3 trials featured brepocitinib 30 mg QD, and within indications had similar study designs and inclusions/exclusion criteria. Psoriatic arthritis and plaque psoriasis evaluated tofacitinib 5 mg BID while ulcerative colitis evaluated tofacitinib 10 mg BID.

tract infection. Overall, brepocitinib's safety profile to date appears similar to other approved JAK inhibitors including observations of class effects for major adverse cardiovascular events, serious infection, malignancies, and thromboembolism, as stated in other JAK inhibitor prescribing information. Overall, there are eight completed phase 2 safety and efficacy studies to date for brepocitinib in autoimmune diseases that share some pathophysiologic and clinical features in common with DM.Currently, brepocitinib is being evaluated in a double-blind, randomised, placebo-controlled Phase 3 study in DM (NCT0543726; VALOR Study). With a planned enrolment of 225 subjects, the VALOR Study is the largest well-controlled trial in DM to date. Adult patients with definite or probable idiopathic inflammatory myopathy (IIM), who meet the subclassification criteria for DM, have both muscle and skin disease involvement (classic DM), and are receiving (or are not responsive to or are intolerant to) corticosteroids and/or immunomodulatory/ immunosuppressive therapies are eligible to enrol. The primary endpoint is the total improvement score (TIS) at week 52. The TIS is a composite endpoint based on the following six CSM scores: the Physician Global Disease Activity, the Patient Global Disease Activity, the Health Assessment Questionnaire, MMT-8, Extra-muscular Disease Activity, and muscle enzymes. To evaluate the steroid-sparing effect of brepocitinib, participants using glucocorticoids at baseline must taper to an oral glucocorticoid dose of prednisone ≤ 5 mg/day (or equivalent) by week 36. Participants who complete the full week 52 trial are eligible to participate in an open-label extension. Topline results for the VALOR Study are expected in 2025. In sum, clinical and molecular data support the use of brepocitinib, an oral TYK2/JAK1 inhibitor, as a rational and targeted approach for the treatment of DM, with an ongoing double-blind, randomised, placebo-controlled Phase 3 trial to confirm this hypothesis.

Previous studies detailing the significant improvement DM patients' have experienced with off-label JAK inhibitor use (59, 61) stress the unmet need for and importance of evaluating the safety and efficacy of brepocitinib in a registration study in DM patients where little approved therapies currently exist.

Conclusions

Dermatomyositis is a systemic, clinically heterogenous disease with diverse presentations and severity of symptoms (83, 84). Despite available medication options for DM, many patients have ongoing disease activity and progressive disease damage. Additional steroid-sparing therapies with a more targeted and rapid onset of action are highly desirable.

The clinical and scientific rationale for brepocitinib treatment in patients with DM is based on: 1) brepocitinib is a potent TYK2/JAK1 inhibitor that abrogates signalling of key cytokines implicated in DM pathogenesis; 2) brepocitinib has demonstrated clinical effectiveness in randomised, double-blind, placebo-controlled phase 2 trials in autoimmune diseases that share some aspects of disease pathogenesis and manifestations with DM; 3) JAK inhibitors have recently been used off-label and in open-label studies to treat DM patients (59); and 4) in cross-study comparisons, brepocitinib 30 mg exhibits favourable cytokine inhibition and clinical efficacy across multiple autoimmune disease compared to tofacitinib 5 mg BID, the JAK inhibitor with the most supportive clinical data (open-label studies and off-label use) in patients with DM (59).

Brepocitinib is a promising investigational treatment to address the high unmet need for patients with DM. The clinical benefit/risk profile of brepocitinib in patients with DM is being evaluated in the ongoing randomised, double-blind, placebo-controlled Phase 3 study (NCT0543726; VALOR), the largest well-controlled DM trial conducted to date.

Competing interests

J.J. Paik has received research support from ArgenX, Corbus Pharmaceuticals, Kezar Life Sciences, and Pfizer Inc.; consulting fees and/or honoraria from ArgenX, Alexion, EMD Serono, Guide-

point Consulting, Pfizer Inc., and Roivant Sciences, and is supported by grant no. K23AR073927 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS).

J. Vencovský has received honoraria and/or consulting fees from Argenx, Galapagos, Horizon, Sobi, and UCB; and has participated in company sponsored speaker's bureau of Abbvie, Biogen, Eli Lilly, Fresenius, MSD, Octapharma, Pfizer, and Takeda.

C. Charles-Schoeman has received grant support from Alexion, Priovant, CSL Behring, Janssen, grant support and/or consultancy fees from Octapharma, Pfizer, Abbvie, Bristol Myers Squibb, and consultancy fees from Boehringer Ingelheim, Recludix, Galapagos.

G.C. Wright has received consulting fees and/or honoraria from Abbvie, AstraZeneca, Bristol Myers Squibb, Lilly, Novartis, Pfizer, UCB. She serves on the Board of Directors of the Association of Women in Rheumatology and the Medical Policy Committee of United Rheumatology (Specialty Network).

R.A. Vleugels has received consulting fees and/or honoraria from AstraZeneca, Abbvie, Lilly, Priovant Therapeutics, and Roivant Sciences, and research support from Pfizer Inc.

R. Aggarwal has received consulting fees from Alexion, ANI Pharmaceutical, Argenx, Artasome, AstraZeneca, Boehringer Ingelheim, Bristol Myers-Squibb, CabalettaBio, Capella, Capstan, Corbus, CSL Behring, EMD Serono, Galapagos, Horizontal Therapeutics, I-Cell, Immunovant, Janssen, Kezar, Kyverna, Manta Medicines Corporation, Merck, Novartis, Nuvig Therapeutic, Octapharma, Pfizer, Priovant Therapeutics, Roivant, Sanofi, and Teva; and has received research grants from Boehringer Ingelheim, Bristol-Myers Squibb, EMD Serono, Janssen, Mallinckrodt, Pfizer, and Q32.

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