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Review

A glance into the future of myositis therapy

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***Abstract*:** The idiopathic inflammatory myopathies are chronic diseases of the skeletal muscle that comprise various conditions, including dermatomyositis, polymyositis, immune-mediated necrotizing myopathy, and the antisynthetase syndrome. Although there are a number of distinguishing features, all these disorders are characterized by an immune and inflammatory response mainly directed against the muscle. Hence, therapy is geared toward curbing the autoimmune and inflammatory response. A quite wide range of medications are currently available to treat these disorders, but despite all therapeutic progress still a number of patients are unable to maintain a sustained remission. In this review article, we have marshaled a variety of potential therapeutic agents that may hold promise for the future treatment of the idiopathic inflammatory myopathies. It is to be expected that by increasing the therapeutic armamentarium with agents that have different mechanisms of action even challenging cases could be successfully managed, thus reducing disease burden and disability.

Keywords: dermatomyositis, glucocorticoids, immunosuppressants, myositis, polymyositis

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Search strategy

We searched the clinical trials database (clinicaltrials.gov) and included all treatments that were novel, repurposed for myositis, or else part of the established therapeutic armamentarium but investigated for aspects that had not been sufficiently documented in the published literature.

Introduction

Dermatomyositis (DM) and polymyositis (PM) are chronic idiopathic inflammatory myopathies (IIM), a range of diseases which also include immune-mediated necrotizing myopathy (IMNM) and the antisynthetase syndrome (ASS). While there are significant differences within the spectrum of the IIM, they all require immunosuppression with glucocorticoids and/or synthetic or biologic immunosuppressants.[1] The cornerstone of therapy of the IIM is still glucocorticoids, but synthetic or biologic immunosuppressive agents are frequently used, especially when patients do not have an adequate response to glucocorticoids, relapse upon glucocorticoid dose tapering or glucocorticoid withdrawal, or in the presence of organ involvement such as interstitial lung disease (ILD). However, despite a relatively large therapeutic armamentarium, recurrent flares and inability to induce remission of the IIM are not uncommon.[2] Therefore, there is an unmet need to explore new avenues in the treatment of the IIM. In this review article, we have looked at current therapeutic agents that might be repurposed for the treatment of the IIM as well as novel drugs that are currently in the pipeline. We have also considered agents already used to treat the IIM that are currently being investigated in ongoing clinical trials to better define their efficacy and safety profiles in patients with myositis.

Drugs already in current use for myositis

Rituximab

Rituximab (RTX) has been quite extensively investigated for the treatment of the IIM, including DM, PM, and the ASS.[3] A randomized controlled trial (RCT) (RIM, Rituximab In Myositis) failed to show superiority of delayed *versus* early RTX therapy, but the trial design has been subject to criticism because of the short time of

delayed treatment, which could well have blurred the differences between the study arms.[4] All enrolled myositis (adult and pediatric) patients were refractory (failed glucocorticoids and at least one immunosuppressant). A total of 200 patients (76 PM, 76 DM, 48 juvenile DM) were randomized into two groups. Group A received placebo infusion at weeks 0–1 and RTX infusion (1 g) at weeks 8–9, whereas group B was treated with RTX infusion at weeks 0–1 and with placebo infusion at weeks 8–9. Patients were evaluated 14 times over 44 weeks. The glucocorticoid dosage was held constant until week 16; if patients met the definition of improvement (or experienced complications), a dosage reduction was begun at no more than 20% of the existing dose every 4 weeks. The primary end point was time to achieve improvement [in three of any six core set measures (CSM) of the International Myositis Assessment and Clinical Research (IMACS), with no more than two CSM worsening by ⩾25% excluding manual muscle testing (MMT) in two consecutive visits]. A total of 177 patients were analyzed (96 in group B, 81 in group A). The primary end point [time to achieve the definition of improvement (DOI) according to IMACS criteria] was 20.2 and 20.0 weeks in groups A and B, respectively. One hundred sixty-one of 195 (83%) randomized patients (78% PM, 82% DM, 83% juvenile DM) met the DOI during the course of the trial. Although in this RCT RTX failed to exhibit superiority over placebo, the trial design was such as to render difficult to show the effect of RTX, since the placebo group received RTX anyway a short time after the control group. Therefore, in our opinion, this RCT cannot be construed as proof of failure of RTX in the IIM. In fact, in a meta-analysis, 78% of RTX-treated (mostly refractory) patients with IIM had a satisfactory response to RTX.[5] An ongoing study (ClinicalTrials.gov Identifier: NCT00774462) is currently investigating the efficacy and safety of RTX in patients with the ASS and IMNM. Muscle strength improvement is the main outcome measure of this study. Twenty-four patients with primary IIM (12 with ASS, 12 with anti-SRP IMNM) and 12 with myasthenia gravis will be included in the study. If a success is observed in at least six patients, it will be possible to conclude that the response rate is above 25%. RTX is used not only to treat muscle disease strictly speaking, but also myositis-related ILD. An ongoing clinical trial is currently investigating the effects of RTX on myositis-associated ILD (Rituximab-Induced Pulmonary Function Changes, ClinicalTrials.gov Identifier NCT01632124), although the lack of radiographic data is likely to provide less than robust evidence in this regard. Yet another study is investigating in a comparative fashion the efficacy of RTX and cyclophosphamide (CYC) in ILD associated with connective tissue disease (CTD) including myositis (Rituximab Versus Cyclophosphamide in Connective Tissue Disease-ILD, ClinicalTrials.gov Identifier NCT01862926). An observational retrospective study has previously been conducted between 2003 and 2016 in three tertiary care centers on patients with ASS-related ILD who had been treated with CYC or RTX with at least 6 months of follow-up. This study showed similar pulmonary outcomes at 6 months, but superiority of RTX over CYC at 2 years.[6] An important limitation of this study was the fact that patients in the CYC group presented with more severe ILD compared with the RTX group. This difference could be related to the physician's preference to use CYC in more severe ILD, and may thus have biased the results in favor of RTX. Therefore, it will be useful to have more rigorous evidence on the comparative efficacy of RTX and CYC in myositis-related ILD.

Tacrolimus

T cells play a key role in the pathogenesis of myositis.[7] An RCT conducted in myositis patients has previously demonstrated the efficacy of ciclosporin, a calcineurin inhibitor which acts by selectively suppressing T cell activation.[8] Tacrolimus is another calcineurin inhibitor which is at least as effective as ciclosporin in curbing T cell activity. Tacrolimus has previously been shown to be effective in 78% of refractory patients with myositis and in 94% of those with refractory myositis-related ILD.[9] Two studies (Investigation in Myositis-Associated Pneumonitis of Prednisolone and Concomitant Tacrolimus, ClinicalTrials.gov Identifier NCT00504348; and Cyclophosphamide and Azathioprine vs Tacrolimus in Antisynthetase Syndrome-Related Interstitial Lung Disease, ClinicalTrials.gov Identifier NCT03770663) have been designed to investigate the efficacy and safety of tacrolimus in the treatment of ILD associated with myositis and with the ASS, respectively. In particular, it will be very useful to know whether tacrolimus can replace the age-honored therapeutic scheme of cyclophosphamide as induction followed by azathioprine maintenance treatment in ILD associated with CTD.[1] Because T cells are thought to play a key role in driving and maintaining not only muscle inflammation,

but also myositis-related ILD,[10] tacrolimus as a potent T cell inhibitor is particularly well poised to hold promise to replace the more toxic CYC as therapeutic agent of choice.

Drugs repurposed for use in myositis

Abatacept

Abatacept is a fusion protein composed of the Fc region of the immunoglobulin IgG1 fused to the extracellular domain of CTLA-4. Abatacept binds to the CD80 and CD86 molecules, which prevents the second signal required for T cell activation. Because T cells are involved in the pathogenesis of the IIM, there is a clear rationale for the use of abatacept in these disorders. In a randomized treatment delayed-start trial, 20 patients with IIM (DM and PM) received either immediate treatment with intravenous abatacept or a 3-month delayed start.[11] The primary end point was number of responders, defined by the IMACS DOI after 6 months of treatment. This trial provided evidence that after 3 months five (50%) patients were responders after immediate treatment compared with only one (11%) patient in the delayed treatment arm. There were no serious adverse events judged to be related to the study drug.

There is an ongoing trial to evaluate the efficacy and safety of abatacept in combination with standard therapy compared with standard therapy alone in improving disease activity in adults with active IIM (ClinicalTrials.gov Identifier NCT02971683). This study will provide in a more rigorous fashion the benefit conferred by abatacept in a population of myositis patients. Importantly, abatacept will be used in this trial as add-on rather than stand-alone therapy. This is reflective of current clinical practice, where many patients show some degree of response to conventional therapy, but may not exhibit full remission.

An ongoing trial (ClinicalTrials.gov Identifier: NCT03215927) is also evaluating the efficacy and safety of abatacept in the setting of ASS-related ILD. Subcutaneous injection of abatacept 125 mg (or placebo) will be administered weekly for 24 weeks. The primary outcome criteria for efficacy will be the FVC% change from the baseline visit to week 24 between the two treatment arms. This study will provide useful information on the role of abatacept on ILD associated with the ASS. Because T cells are involved in the pathogenesis not only of ASS-related myositis, but also of ILD, it is to be expected that abatacept will also be useful in this setting.

Anakinra

Data on Anakinra, an interleukin-1 (IL-1) inhibitor, in myositis is scanty, although there is a rationale for using Anakinra in the IIM, since IL-1 is expressed in the inflamed muscles.[12] An open-label study investigated the effects of Anakinra in a population of 15 patients with refractory myositis (both DM and PM).[13] All patients were on stable concomitant treatment (glucocorticoids, immunosuppressants, or both). Patients were treated for a duration of 12 months. Response to the study drug was assessed by the six core items of the IMACS criteria. In addition, to help to elucidate the mechanisms involved in the response, muscle biopsy findings were analyzed before and after Anakinra therapy. Seven patients had a significant clinical response, while only three worsened; although the numbers were small, no difference was evidenced between DM and PM patients. Adverse events included rash at injection site (6 patients) as well as various (respiratory tract, urinary tract, and tooth) infections. Comparative (pre- and post-treatment) analysis of muscle biopsies showed unchanged CD3+ lymphocytes and both IL-1 and HLA-I molecule expression. In contrast, there was an inverse correlation between IL-1alpha expression and muscle strength, while a shift from in T cell differentiation from Th17 to Th1 was observed. A major limitation of this study is not only the small population, but also its heterogeneity including the various previous and concomitant treatments, which render difficult to tease out the effects attributable to Anakinra. Therefore, a more rigorous trial investigating the efficacy and safety of Anakinra in the IIM is required.

Apremilast

Apremilast is a phosphodiesterase-4 (PDE-4) inhibitor that has been licensed for the treatment of psoriatic arthritis, but has also proved useful for the management of mucocutaneous manifestations of Adamantiades-Behçet's disease. Although the mechanism of action of apremilast is not fully elucidated, it is thought that the key pathway of apremilast action is related to increasing cyclic adenosine monophosphate levels; in turn, this leads to decreased expression of proinflammatory cytokines and a reduced Th1 response.[14]

Apremilast (30 mg orally twice daily) has been shown to be effective for cutaneous features of DM in three refractory cases; in one case, muscle symptoms also improved after 9 months.[15] However, this study was retrospective in design and the number of patients reported very limited.

A clinical trial, evaluating safety and efficacy of apremilast in the treatment of cutaneous disease in patients with recalcitrant DM (ClinicalTrials.gov Identifier NCT03529955), has recently been conducted. The results, however, are still awaited.

Basiliximab

Basiliximab is a monoclonal antibody targeting activated T cells, which express the CD25 (high-affinity IL-2) receptor. Basiliximab has previously been demonstrated to be effective as adjunctive therapy in addition to GC and IS in ¾ patients with anti-MDA5 ILD resistant to GC and ciclosporin.[16] On the other hand, we have previously reported a patient with PM (with negative myositis-specific antibodies) in whom basiliximab did not improve, and possibly worsened muscle disease manifestations.[17] T cell mediated tissue damage is related to the balance between effector and regulatory T cells, which both express the CD25 receptor. Therefore, basiliximab could act as a 'double-edged sword', in that it curbs the activity of pathogenic T cells, but also of regulatory T cells, which inhibit effector T cell action. How the action of basiliximab plays out in the context of inflamed muscle and lung in myositis therefore needs to be established. An ongoing trial (ClinicalTrials.gov Identifier NCT03192657) is currently investigating the efficacy and safety of basiliximab in the treatment of interstitial pneumonia of clinically amyopathic DM (CADM).

Belimumab

In the pathogenesis of PM and DM B cells are thought to play a key role, not only because of the presence of autoantibodies, but also because of the presence of B cells and plasma cells both in muscle tissue and in peripheral blood. B cell activating factor (BAFF) has been identified at high levels in the serum of patients with anti-Jo-1 antibodies and patients affected by DM.[18] B cells' role in the pathogenesis of the IIM is also indirectly borne out by the favorable response to RTX, as we have already alluded to herein. In view of the important role that B cells have in the pathogenesis of the IIM, anti-BAFF therapy could therefore be an appropriate treatment that merits further investigation.[19]

In this regard, a 40-week multicenter randomized, double-blind, placebo-controlled clinical trial has been conducted, with a 24-week open-label extension of intravenous belimumab for adult patients with refractory IIM.[20] 16 patients were randomized; patients had to receive at least 4 doses of belimumab or placebo to be included in the analysis. 15 patients received 4 doses, 9 belimumab and 6 placebo. Patients were on standard-of-care therapy and were randomized 1:1 to intravenous belimumab 10mg/kg or placebo for 40 weeks, followed by an open-label phase of 24 weeks' duration. Primary outcome included the proportion of patients reaching the DOI at week 40 in Belimumab arm *versus* standard-of-care alone arm. There was a significantly higher proportion of patients reaching DOI by week 40 in the belimumab arm (belimumab 37.5% *versus* standard-of-care 16.7%). In addition, 42.9% of patients in the belimumab arm achieved DOI at week 64, while none of standard-of-care arm did. There were no differences in the occurrence of infections between the two groups. These results may suggest that belimumab may have a role in the IIM, similarly to what has been shown for systemic lupus.[21] However, it has to be underlined that the reported between-group differences were not statistically significant, probably due to the sample small size of the study arms. Therefore, there is a need for a large RCT of belimumab in the IIM.

Eculizumab

Eculizumab is a monoclonal antibody that blocks complement cascade progression by binding C5 complement molecule and preventing the formation of C5a anaphylatoxin and MAC complex (C5b-9), which are involved in the pathogenesis of thrombotic microangiopathy.[22] Eculizumab is the long acting, humanized version of the anti-C5 antibody (h5G1.1). In a retrospective study, 7 patients affected by IIM presenting with thrombotic microangiopathy were treated with eculizumab added at the standard of care therapy at a dosage of 900 mg once weekly for 4 weeks, then followed by 1200 mg bimonthly. Eculizumab was maintained until thrombotic microangiopathy remission and for a minimal length of time of four weeks. After eculizumab administration hematological parameter normalized. Of interest is that in this study the first year survival of IIM-TMA

was 72%, compared to other cohort survival in PM/DM-TMA (19%).[23] The results of this study may suggest a role of add-on eculizumab that for management of thrombotic microangiopathy in the setting of IIM.

Janus kinases inhibitors

Janus kinases (JAK) inhibitors are so-called because they suppress the JAK, which are cytoplasmic protein tyrosine kinases that mediate key nuclear signal transduction and downstream activation of inflammatory / interferon pathways. JAK inhibitors that are currently available are tofacitinib and baricitinib. There is a rationale for the use of JAK inhibitors in patients with myositis (particularly in DM) because JAK inhibitors have been demonstrated to mitigate type I IFN signaling including inducible transcripts and proteins, which are elevated in DM muscle and skin.[24]

Clinical data on the effects of JAK inhibitors in myositis is scanty. Tofacitinib has been more extensively studied than baricitinib, and has been shown to have efficacy especially on the skin manifestations of DM and possibly on arthritis and muscle involvement,[25,26] while a Japanese study suggested its utility as add-on therapy in severe ILD in patients with anti-MDA5+ DM.[27] In our experience, tofacitinib has proved useful in significantly ameliorating skin DM manifestations, including calcifications,[28] in patients that had been resistant to other drugs. This beneficial effect of tofacitinib on the skin in DM is in agreement with published data; particularly its efficacy in preventing calcifications is of great interest, because this may be a resistant sign in DM even in otherwise well-controlled patients. More limited data (again both from the literature and from our experience) also point to the efficacy of tofacitinib in myositis-associated arthritis. In contrast, the evidence on the usefulness of tofacitinib on muscle and lung disease is not well established. It is likely that the effects of tofacitinib will as be shared by baricitinib, for which the evidence is currently more limited[29] as they pertain to the specific mechanisms of these drugs ('class effect'). Likewise, adverse events (especially infections) are likely to be encountered in the treatment with both drugs. There is an ongoing phase IIa trial of baricitinib, in the treatment of adult myositis (ClinicalTrials.gov Identifier NCT04208464), a study on baricitinib in patients with relapsing or naïve DM (ClinicalTrials.gov Identifier NCT04208464 NCT04972760), a study assessing the efficacy and safety of JAK inhibitor in the treatment of anti-MDA5 antibody-positive DM patients (ClinicalTrials.gov Identifier NCT04966884) and a study of tofacitinib in refractory DM (ClinicalTrials.gov Identifier NCT03002649). These trials will be very useful in clarifying in more rigorous settings the role of JAK inhibitors in DM, in particular, whether – and to what extent – they may ameliorate not only skin and joint, but also muscle and lung involvement related to DM.

Pirfenidone

Pirfenidone is an antifibrotic agent currently used in the treatment of idiopathic pulmonary fibrosis, where it acts by slowing down interstitial fibrosis progression and loss of pulmonary function, despite the fact that its mechanism of action is not fully clear. A recent meta-analysis has indeed shown that pirfenidone in this patients' group significantly prolongs pulmonary progression-free survival and reduces mortality.[30]

A role for pirfenidone has also been proposed for CTD-related ILD, even though there is no firm evidence of efficacy in this regard as yet. Pirfenidone has been investigated in patients affected by rapidly progressive interstitial lung disease (RPILD) related to CADM.[31] Thirty patients diagnosed with CADM-RPILD with a disease duration <6 months were prospectively enrolled and treated with pirfenidone, at a target dose of 1800 mg/die in addition to standard-of-care therapy. Patients were stratified according to disease duration, in particular distinguishing acute ILD (<3 months) from subacute ILD (3-6 months). The results of this trial showed that while for acute ILD there was no difference in survival between pirfenidone patients and control patients, the outcome was significantly different for subacute ILD patients treated with pirfenidone, who showed a better prognosis and improvement in ILD by lung computerized tomography criteria. These data thus suggest that pirfenidone could have a beneficial effect in subacute to chronic IIM-related ILD, while it does not appear to confer a benefit in acute ILD, possibly because of a slow onset of action. An ongoing trial (ClinicalTrial.gov NCT04928586) is now enrolling (target: 200 cases) patients with CTD-related ILD, including those with IIM. According to the patients' condition, the participants will be treated with different immunosuppressive agents with or without the addition of

pirfenidone. The results of this trial will no doubt help clarify the role of pirfenidone in this patients' population.

PN-101: human umbilical cord mesenchymal stem cell (UC-MSC) derived allogeneic mitochondria

An ongoing clinical trial (ClinicalTrials.gov Identifier: NCT04976140) is evaluating the maximum tolerated dose of PN-101 and the efficacy after single-dose administration, by IMACS outcome measures at 12 weeks, in patients affected by refractory DM or PM. PN-101 consists in umbilical cord mesenchymal stem cell derived allogeneic mitochondria. Human stem cells therapy has been tried with some benefit in systemic sclerosis,[32] but on the whole its use has been limited to isolated cases. Given the nature of this therapy, it is likely that it will remain – at best – a niche treatment.

Sodium thiosulfate

An ongoing prospective open controlled phase II trial (ClinicalTrial.gov NCT03582800) is evaluating the use of sodium thiosulfate (STS) to treat calcifications in patients affected by systemic sclerosis, DM and ectopic ossifications secondary to pseudo-hypoparathyroidism 1a type (PHP1A/iPPSD2) (inactivating PTH/PTHrP signaling disorder 2 [iPPSD2]).

In another ongoing trial, participants at a single center into a single-arm, open-label study will be enrolled, with the overall objective of evaluating the efficacy and safety of intravenous sodium thiosulfate in patients with moderate to severe extensive calcinosis associated with juvenile and adult DM (Sodium Thiosulfate for Treatment of Calcinosis Associated With Juvenile and Adult Dermatomyositis, ClinicalTrials.gov Identifier NCT03267277). These studies are being carried out against the background of some efficacy of STS when given intralesionally,[33] presumably because of its role as a calcium-chelating agent, which binds to Ca2+ and increases its solubility.[34] Whether STS may also be effective when given intravenously is a matter of debate.

Tocilizumab

Tocilizumab (TCZ), an IL-6 inhibitor, had raised hopes as a promising treatment for myositis, because IL-6 has been shown to be involved in animal models of myositis and because myoblasts are able to synthesize themselves IL-6 in inflamed muscles. Preliminary reports had indeed suggested efficacy of TCZ in the context of myositis, including amelioration of muscle and joint manifestations. To establish the role of TCZ in myositis in a rigorous fashion, a multicentric RCT has been performed (ClinicalTrials.gov Identifier NCT02043548) in patients with refractory DM and PM. Adult patients with refractory DM and PM were enrolled in a phase IIb double-blind, placebo-controlled, clinical trial randomized 1:1 for active drug: placebo for 6 months. Subjects were randomized to receive either six doses of TCZ (8 mg/kg IV) or placebo every 4 weeks for 24 weeks. The primary end point compared the Total Improvement Score (TIS; 2016 ACR/EULAR Criteria) between both arms at weeks 4–24. Thirty-six subjects (23 DM, 13 PM) were randomized (18 in each arm). All but four (two TCZ/2 placebo) completed 24 weeks of treatment. There was no significant difference in the primary outcome over 24 weeks between TCZ and placebo in the entire cohort or by subgroup. Changes in myositis core set measures and GC dose also did not significantly differ between groups. TCZ was safe and well tolerated.[35] The results of this RCT have thus ruled out a significant role for TCZ in the treatment of myositis.

Ustekinumab

Ustekinumab is a IL-12/IL-23 inhibitor licensed for the treatment of active psoriatic arthritis. The importance of the IL-12/IL-23 axis in myositis is borne out by the evidence that serum IL-23 is raised and that IL-23 is expressed by macrophages and dendritic cells in inflamed muscles of patients with myositis. IL-23 is also essential for the development of murine C protein induced-myositis (CIM); conversely, administration of anti-IL-23R antibodies after the onset of the myositis is able to ameliorate CIM.[36] Therefore, IL-12/IL-23 inhibition holds promise as a useful treatment of myositis. However, currently clinical data on the use of ustekinumab in myositis is very scanty. In a previous report, ustekinumab proved effective on mechanic hands in a patient with ASS who was on GC and MMF.[37] There is now an ongoing study of ustekinumab in participants with active DM and PM who have not adequately responded to one or more standard-of-care treatments (ClinicalTrials.gov Identifier NCT03981744).

Novel treatments

KZR-616

KZR-616 is a selective inhibitor of the immunoproteasome. KZR-616 was analyzed in a study[38] conducted in C protein-induced myositis in mouse model that resembles PM in human. After the induction of myopathy in mice, animals were treated with KZR-616 10 mg/kg, ONX 0914 (a KZR-616 structural analogue), or vehicle three times per week until day 28. End points comprehended muscle strength assessment, serum creatine kinase activity, immunohistology, and immunohistochemistry evaluation.

KZR-616 or ONX 0914 administered after the induction of myopathy in mice blocked the loss of grip strength, whereas mice treated with vehicle only exhibited progressive muscle weakness. Moreover, immunoproteasome inhibitor reduced myopathy-associated leukocyte infiltration in muscle biopsy and prevented serum creatine kinase increase.

From these results, a further investigation is ongoing with a phase II placebo-controlled, crossover study (PRESIDIO; KRZ-616-003, NCT: NCT04033926) analyzing the application of KZR-616 in patients affected by PM and DM to evaluate safety, tolerability, and efficacy in terms of muscle function and disease activity over a period of 32 weeks of treatment. Patients are divided into two arms: A arm of the study receiving subcutaneous KZR-616 30 mg weekly for 2 weeks, then 45 mg weekly for 14 weeks, followed by subcutaneous placebo administration weekly for 16 weeks, B arm receiving Placebo at firs for 16 weeks, followed by subcutaneous KZR-616 30 mg weekly for 2 weeks, then 45 mg weekly for 14 weeks. Primary outcome measure is the mean change from start to end of KZR-616 treatment in the TIS.

Lenabasum

Lenabasum (JBT-101) is a preferential cannabinoid receptor type 2 (CB2) agonist. Lenabasum binding CB2 promotes arachidonic acid production, cyclooxygenase-2, prostaglandin D synthetase and lipoxin A4 that lead to inflammation resolution.[39] A 16-week double-blinded, randomized, placebo-controlled phase II (NCT02466243) in classic or amyopathic DM recruited subjects with refractory skin disease and minimal or no active muscle involvement at the time of enrollment followed by a an open-label extension. Lenabasum was used as add-on treatment in 85% of subjects enrolled. A significant improvement was observed in skin disease extent and severity by objective and subjective criteria, while no major safety signals emerged. A phase III (DETERMINE) study of lenabasum in DM confirmed a significant efficacy of lenabasum on the skin manifestations of DM, while the total improvement score (which heavily reflects muscle involvement) was unaffected [https://www.globenewswire.com/news-release/2021/06/24/2252567/0/en/Corbus-Pharmaceuticals-Announces-Topline-Results-from-DETERMINE-Phase-3-Study-of-Lenabasum-for-Treatment-of-Dermatomyositis.html]. Because some patients with DM have disease activity limited to the skin, lenabasum could thus have a role to treat this manifestation.

Low-dose IL-2 adjunctive therapy

A study (Low-dose Interleukin-2 in Combination With Standard Therapy on Idiopathic Inflammatory Myopathy, clinicaltrials.gov identifier NCT04237987) is currently investigating the efficacy and safety of adjunct low-dose IL-2 therapy in the IIM. The rationale behind this study is that low-dose IL-2 has been shown to enhance regulatory Treg cell while inhibiting T helper 17 cell activity. In systemic lupus erythematosus (SLE), adjunctive low-dose IL-2 therapy (1 million IU subcutaneously every other day for 2 weeks) administered together with standard treatment proved superior to placebo plus standard treatment in achieving a composite outcome measure, the SLE Responder Index-4 at week 12 (response rates 55% and 30% for IL-2 and placebo, respectively).[40] Because a Treg/Th17 imbalance is also a feature of the IIM, it is to be expected that IL-2 therapy might be of benefit in these disorders as well.[7]

Sifalimumab

Type 1 interferon-alpha signature has been shown to play a key role in the pathogenesis of interfacies dermatitis, which is a feature of both DM and systemic lupus erythematosus. In addition, type 1 interferon-alpha signature has also been linked to the so-called 'perifascicular atrophy', the pathognomonic (albeit not obligatory) pathological finding of muscle disease in DM. Finally, activation of the type 1 interferon-alpha signature pathway has also been demonstrated in PM, although

probably to a lesser degree than in DM.[41] Conversely, use of anti-TNF agents, which enhance this pathway, leads to disease flare in DM patients.[42] Therefore, there is a rationale for trying to inhibit this pathway in DM. There is preliminary data to support the concept that such inhibition may indeed be of benefit in DM. In this regard, sifalimumab, an anti-interferon-α monoclonal antibody has been investigated at various dosages in a pilot study in 51 patients with DM and PM *versus* 12 placebo-treated patients. Overall, sifalimumab proved able to significantly inhibit IFN-induced transcripts and proteins. Patients with 15% or greater improvement from baseline MMT scores showed greater neutralization of the INF-alpha signature markers in both blood and muscle. Adverse events were usually mild, with headache being the most common side effect. The main limitation of this study is that it was not designed to prove (or disprove) clinically significant efficacy of sifalimumab in myositis.[43] Therefore, adequate clinical trials are required before sifalimumab could be considered for the treatments of myositis. In this regard, two studies are ongoing: one is a phase II open-label study to evaluate the long-term safety of sifalimumab in adult subjects with systemic lupus erythematosus or myositis (ClinicalTrials.gov Identifier: NCT00979654), while the other is a phase Ib study with a dose-finding design (a study to evaluate safety of multi-dose MEDI-545 [sifalimumab] in adult patients with DM or PM, ClinicalTrials.gov Identifier NCT00533091).

Siponimod

BAF 312 (siponimod) is an oral sphingosine-1-phosphate 1/5 modulator that inhibits lymphocyte trafficking from secondary lymphoid organs to the target tissue. This pathway has been recognized as being of importance in myositis. BAF 312 efficacy and tolerability has been evaluated in patients affected by PM/DM in a randomized double-blind, placebo-controlled, multicentric, partial crossover, phase IIa, proof of concepts study.[44] Eighteen patients with clinically active PM/DM who had responded inadequately to conventional treatment were randomized to receive 10 mg BAF312 or matching placebo once daily for 12 weeks. Following the placebo-controlled phase, all patients received 10 mg BAF312 for an additional 12 weeks. Only glucocorticoids were allowed as concomitant medication. IMACS core set measure of myositis was used to evaluate the clinical response. Clinical response was defined by an improvement in the IMACS core set measure of myositis disease global activity by greater than 30% and improvement in MMT by 1–15%; or an improvement in MMT greater that 15% and myositis disease global activity greater than 10%; and in either case with no more than 2 IMACS measures worsening by 25%. BAF 312 appeared to be safe and well tolerated. According to IMACS definition, responder rates at week 12 were 4/7 (57%) for BAF312 and 1/7 (14%) for placebo. On the other hand, a study investigating the dose response relationship for the efficacy and safety of BAF312 compared with placebo in active DM patients (ClinicalTrials.gov Identifier: NCT02029274) was terminated prematurely after an interim analysis for futility.

Toll like receptor 7/8/9 antagonist

The rationale for Toll Like Receptor 7/8/9 Antagonist (IMO-8400) use in DM is the activation of the TLR 7/8/9 pathway, leading to increased interferon signaling.[7] A double-blind, randomized, placebo-controlled, 24-week trial of IMO-8400 has been conducted,[45] which included 30 patients with probable or definite diagnosis of DM. Primary end point was the change in Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) activity score after 24 weeks of treatment. Blood and skin samples were collected to measure changes in type I IFN signaling. IMO-8400 was neither effective in reducing cutaneous DM disease activity, nor in decreasing type 1 IFN signature in skin or blood. Thus, the current data do not let envision a role for this agent in the treatment of DM.

Zilucoplan

Zilucoplan is a small, subcutaneously administered, macrocyclic peptide that inhibits cleavage of complement component C5 and the subsequent formation of the membrane attack complex,[46] a pathway involved in the pathogenesis of DM. In a randomized, double-blind, placebo-controlled, phase II clinical trial, zilucoplan demonstrated clinically meaningful complement inhibition in patients with acetylcholine receptor-positive myasthenia gravis.[46] Like DM and myasthenia gravis, humoral immune response is thought to play a pathogenic role.[47] A small, pilot study (NCT04025632) has evaluated the safety and efficacy of zilucoplan in patients with IMNM; however, no relevant clinical effects were identified. The results of this study suggest that complement activation is less relevant in the disease biology of IMNM than hypothesized.

Conclusion

Currently, various therapeutic agents are available to treat the IIM, but there is still a sizable proportion of patients who are unable to maintain a sustained remission. A fairly large number of novel or repurposed agents are under investigation to determine their efficacy and safety in the IIM. While the IIM all share features of an active immune and inflammatory response mainly directed against the skeletal muscle, there is ample evidence to suggest that different pathways are operative within the IIM and between different patients. Therefore, it is to be expected that agents that have different mechanisms of action may succeed in controlling resistant disease, thus reducing IIM-related burden and disability.

Author contribution(s)

Ilaria Chiapparoli: Writing – original draft.

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