Recent clinical trials in idiopathic inflammatory myopathies

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Purpose of review
Idiopathic inflammatory myopathies (IIMs) are complex multisystemic autoimmune diseases. Glucocorticoids remain the cornerstone of treatment in IIM, and the benefit of additional immunosuppressors is still debated. A limited number of controlled clinical trials have been available to support treatment guidelines, but in the last year, several clinical trials have been published. In this review, the highlights of recently published and on-going clinical trials in IIM will be summarized and discussed.

Recent findings
Post hoc analyses of a large randomized controlled trial (RCT) suggested new predictive factors of response to rituximab in refractory IIM individuals. An international collaboration enabled the completion of a large RCT in early juvenile dermatomyositis that will orient first-line treatment in that population. New approaches are showing encouraging results in inclusion body myositis.

Summary
Recent advances in molecular mechanisms underlying IIM pathogenesis and the development of novel targeted therapies have influenced recent and on-going clinical research.

Keywords
clinical trials, dermatomyositis, inclusion body myositis, inflammatory muscle diseases, treatment

INTRODUCTION

Idiopathic inflammatory myopathies (IIMs) are autoimmune multisystemic diseases. The major subsets of IIM studied in clinical trials are dermatomyositis, polymyositis, juvenile dermatomyositis (JDM) and sporadic inclusion body myositis (sIBM). For decades, clinicians relied mainly on glucocorticoids often combined with immunosuppressors such as azathioprine, methotrexate, cyclosporine and mycophenolate mofetil to treat those chronic diseases. A Cochrane review on treatment of dermatomyositis and polymyositis failed to confirm the benefit of those additional immunosuppressors, because of the lack of evidence from randomized controlled trials (RCTs) [1]. In practice, these options are often not sufficient to induce prolonged clinical remission and long-term steroid exposition leads to unacceptable side-effects. Morbidity and mortality remain significant especially with specific extra-muscular organ involvement such as dysphagia or interstitial lung disease (ILD) [2,3].

In the last decades, successes of targeted therapies in various rheumatologic conditions and advances in understanding of pathophysiology have slowly modified the therapeutic landscape in IIM Figure 1. This review will present recently published as well as on-going clinical trials in IIM.

ADULT IDIOPATHIC INFLAMMATORY MYOPATHY

Traditional approach with conventional immunosuppressive treatment and intravenous immunoglobulin

Several published and on-going clinical trials in IIM focus mainly on refractory cases. A recent placebo-controlled factorial trial looked at the efficacy of

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KEY POINTS

- High interferon type 1 expression in skeletal muscle and serum at baseline, JDM subset, lower disease damage and certain autoantibody profiles such as anti-Jo1 were found to predict rituximab response in IIM.
- The results of a large RCT in JDM support the use of glucocorticoids in combination with methotrexate as the first-line treatment in that population.
- Alemtuzumab and follistatin gene therapy have shown some clinical benefit in sIBM.
- JAK inhibitors are under investigation in refractory dermatomyositis following positive results in case reports.

second-line immunosuppression in refractory IIM [4]. Fifty-eight individuals were randomized in four different groups: steroid alone, steroid and ciclosporine, steroid and methotrexate or a combination of steroids, ciclosporine and methotrexate. No added beneficial effect was found of combination therapy over glucocorticoid treatment alone. However, the number of patients in each arm was small and the IIM subsets were poorly defined in terms of autoantibody status or extra-muscular organ involvement. The PROMETHEUS trial, a randomized open-label assessor-blinded study, compared the efficacy and safety of a methotrexate and steroid combination to steroid alone in early dermatomyositis/polymyositis (NCT00651040). Their preliminary results on 31 individuals also showed no benefit of methotrexate combination therapy over glucocorticoids alone after 48 weeks of treatment [5]. These results further support the efficacy of glucocorticoids in IIM treatment, but controversy remains on the most appropriate glucocorticoid regimen to use. As an alternative to traditional glucocorticoids protocols and based on case report results [6], an open-label trial looked at the efficacy, safety and tolerability of adrenocorticotropic hormone gel (ACTH) 80 mg subcutaneously twice weekly for 6 months for treatment of active refractory dermatomyositis/polymyositis individuals (NCT01906372). At the time of writing, this trial was completed but no results were available. Intravenous immunoglobulins (IVIg) in refractory IIM are also a matter of debate among experts and important geographical variations exist in their use. There is evidence supporting IVIg efficacy in JDM, 3-hydroxy-3-methylglutaryl-coenzyme A reductase antibody-associated myopathy and for specific organ involvement such as dysphagia [7▪▪]. Subcutaneous immunoglobulins (SCIg) are an interesting and safe alternative that showed some efficacy in case reports [8] and retrospective [9▪] studies. An open-label

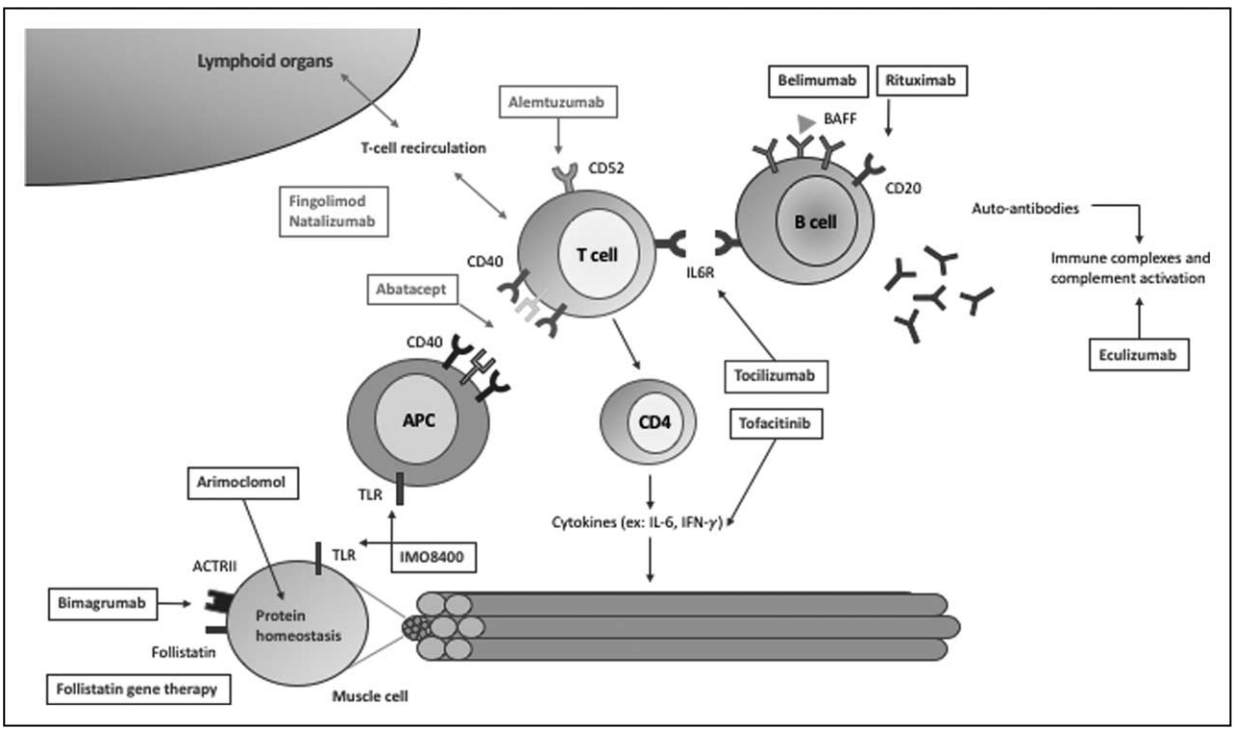

FIGURE 1. Overview of molecular mechanisms of action of different treatments studied in recent or on-going clinical trials in patients with idiopathic inflammatory myopathies. ACTRII, activin receptor; APC, antigen presenting cell; BAFF, B-cell activating factor; TLR, toll-like receptor.

study on SCIg efficacy in dermatomyositis is currently on-going (NCT02271165).

B-cell blockade

The largest RCT to date in IIM, the rituximab in myositis (RIM) trial, included 200 juvenile (JDM) and adult refractory polymyositis and dermatomyositis cases who were randomized in an early (weeks 0 and 1) or late rituximab treatment arm (weeks 8 and 9) [10]. The primary endpoint was comparison of time to achieve the International Myositis Assessment and Clinical Studies (IMACS) group definition of improvement (DOI) (Table 1) [11] and a secondary endpoint was comparison of response rates between the two groups at 8 weeks. Even if those endpoints were not achieved, 83% of the randomized individuals met the DOI by week 44 and a significant steroid-sparing effect was found. A post hoc analysis looked at cutaneous activity and damage scores of 120 patients included in the RIM trial to assess the efficacy of rituximab at improving refractory dermatomyositis rashes [12▪]. In adult individuals, there was a significant decreased frequency of any rash at week 36 (89–76%, $P = 0.047$), but no significant difference for more severe rashes (cutaneous ulceration, panniculitis or erythematous rashes with secondary changes). Interestingly, there was a significant decrease in the mean damage score. Similar declines were seen in JDM, but improvement in treatment-resistant cutaneous ulcerations was noted in this group. The clinical data of the RIM trial were also studied to identify possible predictors of treatment response. High interferon type 1 expression in skeletal muscle and serum at baseline, JDM subset, lower disease damage and certain autoantibody profiles (anti-Jo1, anti-TIF1γ and anti-Mi2) [13,14▪▪,15▪▪,16] were found to predict rituximab response. In line with those results, an open-label trial on rituximab efficacy in refractory antisynthetase syndrome reported increased muscle strength, decreased creatinine kinase levels and a steroid- sparing effect on 10 patients who completed the 12-month study [17]. Half of their individuals also showed ILD improvement on pulmonary function testing. Despite its small sample, this study remains one of the rare to focus on an autoantibody-defined IIM subset in a clinical trial. Another B-cell depleting agent, belimumab, is currently under study in refractory IIM (NCT02347891). This recombinant monoclonal antibody against B lymphocyte stimulator impairs B lymphocytes survival and is currently approved for systemic lupus erythematosus treatment.

Antifibrotic agents

ILD is an important cause of morbidity and mortality in antisynthetase syndrome and in clinically amyopathic dermatomyositis (CADM). When presenting with rapidly progressive ILD (RPILD) and antibodies against antimelanoma differentiation-associated gene 5, CADM individuals have a particularly high mortality rate [18]. A Chinese group administered pirfenidone, an antifibrotic agent recently approved for idiopathic pulmonary fibrosis, to 30 individuals with CADM and RPILD. This single center open-label trial with retrospective controls found decreased mortality in their subacute ILD subgroup ($n = 10$) at 1 year [19]. This might indicate a role for antifibrotic agents in slowing the progression of ILD in CADM with subacute ILD onset.

Table 1. Consensus on the minimum percentage change in the myositis core set of measures to classify a patient as clinically improved

Core set domain	Validated method of assessment	Percentage change, median (25th percentile, 75th percentile)	
		Adult specialists	Pediatric specialists
Physician's global activity assessment	Horizontal 10-cm VAS	20 (20,25)	20 (15,20)
Patient's/parent's global activity assessment	Horizontal 10-cm VAS	20 (20,25)	20 (15–24)
Muscle strength	MMT	15 (10,20)	18 (11,20)
Physical function	HAQ/C-HAQ; CMAS	15 (10,20)	15 (10,20)
Muscle-associated enzymes	At least two of CK, LDH, AST, ALT or aldolase	30† (20,50)	30† (20,30)
Extramuscular activity assessment	Extramuscular portion of the MDAAT	20 (20, 28)	20 (15,20)

Adapted from [11]. In the RIM trial, DOI was defined as three of any six core set measures improved by 20%, with no more than two worse by 25% which could not be MMT8.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; C-HAQ, Childhood HAQ; CK, creatinine kinase; CMAS, Childhood Myositis Assessment Scale; HAQ, Health Assessment Questionnaire; LDH, lactate dehydrogenase; MDAAT, myositis disease activity assessment tool; MMT, manual muscle testing; VAS, visual analog scale.

†In adult specialists, the median change was 25% for LDH. In pediatric specialists, the median change was 25% for aldolase.

T-cell blockade

T cells and their costimulatory molecules cytotoxic T lymphocyte associated antigen-4 (CTLA-4) and CD28 are playing an important role in IIM pathogenesis [20]. This explains T-cell blockade introduction as a possible new therapeutic approach in IIM. Abatacept, a CTLA-4 analog, blocks the interaction between antigen presenting cell and T cell, preventing costimulation. After positive results in case reports [21–24], the ARTEMIS trial, an open-label trial with delayed start design, was conducted in refractory dermatomyositis/polymyositis (NCT02971683). Preliminary results of this pilot study suggest improved muscle performance and health-related quality of life in refractory IIM cases treated with abatacept [25]. Fingolimod, a sphingosine 1-phosphate receptor modulator leading to T-cell trapping in lymphoid organs, has shown anti-inflammatory and possible neuroprotective effects in multiple sclerosis [26]. A trial of fingolimod in refractory dermatomyositis/polymyositis was completed (NCT02029274) with inconclusive preliminary results despite effective decrease (>75%) of absolute T lymphocytes counts as reported in an abstract [27].

JUVENILE DERMATOMYOSITIS

Traditional approach

In 2016, the first RCT on first-line treatment in early JDM was published [28▪▪]. The authors randomized 139 newly diagnosed untreated JDM patients to either prednisone monotherapy or combination treatment with either methotrexate or ciclosporine. Combination therapy, particularly methotrexate, showed shorter time to clinical remission, longer time to treatment failure, decreased treatment failure and a steroid-sparing effect. The methotrexate treated group also showed a better side effect profile. These results support the use of glucocorticoids in combination with methotrexate as the first-line treatment in JDM.

Exercise and creatine supplementation

Exercise has proven to be both safe and effective in the adult IIM population, but had never been studied in an RCT in the pediatric population [29▪▪]. Twenty-six JDM individuals were randomized to a 12-week home-based exercise programme ($n = 14$) or to a waiting control group ($n = 12$) starting the same exercise programme at week 12. Seventy-five percent of the participants completed the intervention without relapse or hospitalization. The intervention group showed increased muscle function and functional ability, which parallels the adult experience. The JDM individuals included in this study were clinically stable. The same intervention in an active population could generate different results, with possibly increased efficacy. Creatine supplementation was tested on 15 JDM patients, both with active and inactive disease, for 12 weeks [30▪]. The treatment was well tolerated, but the authors found no therapeutic effect. These results are contrasting with the improved functional performance found in an RCT on 37 IIM adult individuals [31]. The authors noted the lack of increase in intramuscular phosphocreatine content in their pediatric population, possibly explaining the lack of benefit observed in their study.

Sporadic inclusion body myositis

sIBM patients usually demonstrate a poor response to conventional treatment with consequent significant long-term impairment. There is still controversy on the pathogenesis of this disorder that displays both inflammatory and degenerative components.

Alemtuzumab

T-cell blockade has been tried with moderate success in sIBM in the uncontrolled proof-of-concept study CAMPATH-1 [32]. Thirteen sIBM individuals received alemtuzumab, a humanized monoclonal anti-CD52 antibody inducing a profound depletion of mature T cell and monocytes, at a dose of 0,3 mg/kg/day for 4 days. A slower muscle strength decline was noted 6 months after the treatment, but only five patients reported definite functional improvement. The biopsies before and after treatment were recently analyzed for inflammatory and degenerative markers [33▪]. A trend toward downregulation of the expression of certain inflammatory molecules was noted especially in responders. However, this trend was not seen for crucial markers of cell-stress and degeneration as B-amyloid or ubiquitin. Those results, even if modest, are still encouraging in a condition as refractory to treatment as sIBM.

Arimoclomol

Amplification of heat shock protein (HSP) expression was proposed as a novel treatment in sIBM. The HSPs form a family of ubiquitously expressed protein chaperones that prevents aberrant protein–protein interaction and promotes adequate protein folding. Arimoclomol is a drug that prolongs heat shock factor 1, the main transcription factor of HSP. An RCT proof-of-concept trial on 24 sIBM patients was well tolerated, but failed to show significant benefits in the treated group ($n = 16$) compared with

placebo ($n = 8$) [34]. The authors are now recruiting individuals for a larger RCT (NCT02753530).

Bimagrumab

Another approach proposed to address the degenerative aspect of sIBM was to block the myostatin pathway. Myostatin binds the activin receptors (ActRII) which, when activated, inhibit skeletal muscle differentiation and growth. Bimagrumab, a human monoclonal antibody against ActRII, was tested in an RCT on 14 sIBM individuals. Eleven individuals received one single intravenous infusion of bimagrumab and three individuals a placebo dose [35]. Even if this proof-of-concept study showed some increase in the thigh volume at 8 weeks correlating with improvement on the 6-min walk test (6MWT), a phase IIb/III (NCT01925209) failed to meet its primary endpoint (Novartis April 21, 2016).

Follistatin gene therapy

A novel therapeutic approach to myostatin inhibition is through follistatin gene therapy [36▪▪]. On the basis of mouse models and positive results in Becker muscular dystrophy [37], six sIBM patients received follistatin gene transfer in the quadriceps muscles of both legs. To prevent immune response to the gene delivery, they also received high-dose prednisone for at least 2 months and were encouraged to exercise. The treatment was well tolerated and treated individuals ($n = 6$) improved their 6MWT by 56 m/year, whereas untreated patients ($n = 8$) decreased their walking distance by 25,8 m/year. On comparison of muscle biopsies obtained at baseline and 6 months after gene transfer, treated patients showed decreased fibrosis and improved regeneration. These positive results are encouraging and future studies will show if those benefits can be maintained and reproduced in a larger trial.

New perspectives

The aim of this review was to present the findings of recent clinical trials. However, novel therapies currently under study are listed in Table 2 [25,27,5,38] and some will be reviewed in this section.

Janus kinase inhibitors

Janus kinase (JAK) inhibitors, recently approved for the treatment of rheumatoid arthritis, showed

Table 2. Completed, on-going or terminated clinical trials in idiopathic inflammatory myopathy

Drug	Mechanism of action	Population
Completed but not yet published		
Abatacept [25], NCT02971683	T-cell activation inhibitor	Refractory DM/PM
ACTH, NCT01906372	Adrenocorticotropic hormone	Refractory DM/PM
Eculizumab, NCT00005571	Anti-C5 antibody	Refractory DM
Fingolimod [27], NCT02029274	Sphingosine 1-phosphate modulator	Refractory DM/PM
GC vs. GC + MTX [5], NCT00651040	Antifolate agent	Early DM/PM
On-going		
Arimoclomol, NCT02753530	Amplification of HSP expression	sIBM
Belimumab, NCT02347891	B-cell activation inhibitor	Refractory IIM
Hizentra, NCT02271165	Subcutaneous immunoglobulins	DM
Natalizumab [38], NCT02483845	Anti-α-4 integrin	sIBM
Rapamycin, NCT02481453	mTOR complex 1 inhibitor	sIBM
RTX vs. CYC, NCT01862926	Chimeric anti-CD20 antibody	Scleroderma, IIM and MCTD
Tocilizumab, NCT02043548	Anti-IL6 receptor antibody	Refractory DM/PM
Tofacitinib, NCT03002649	JAK1/3 inhibitor	Refractory DM
IMO8400, NCT02612857	Anti-TLR	Refractory DM
Terminated		
Autologous stem-cell transplant (NCT00278564)		
Fingolimod (NCT01148810, NCT01801917)		
Gevokizumab (EudraCT 2012–005772–34)		

ACTH, adrenocorticotropic hormone; CYCs, cyclophosphamide; DM, dermatomyositis; GCs, glucocorticoids; HSP, heat shock protein; IIM, idiopathic inflammatory myopathy; IL6, interleukin 6; JAK, janus kinase; MCTD, mixed connective tissue disease; mTOR, mammalian target of rapamycin; MTX, methotrexate; PM, polymyositis; RTX, rituximab; sIBM, sporadic inclusion body myositis; TLR, toll-like receptor;
Data compiled from ClinicalTrials.gov and other sources.

their efficacy at treating different inflammatory conditions including skin autoimmune diseases. The first generation of JAK inhibitors, including tofacitinib, ruxolitinib and baricitinib, are blocking more than one of the four JAKs (JAK1, JAK2, JAK3 and TYK2). These molecules have a suppressing effect on interferon signaling, which is suggested to be dysregulated in IIM [39]. The first case published of JAK inhibition in IIM presented the case of a patient with post–polycythemia vera myelofibrosis treated with ruloxitinib that improved both her hematological condition and dermatomyositis rash [40]. This was followed by a case series of refractory dermatomyositis reporting clinical improvement in three patients treated for 4 weeks with tofacitinib, mainly a JAK1 and JAK3 inhibitor [41▪▪]. These results suggest some efficacy of JAK inhibition in treating refractory dermatomyositis cutaneous manifestations, and a clinical trial on tofacitinib is currently recruiting refractory dermatomyositis individuals (NCT03002649).

Inhibitors of toll-like receptors

Evidence is suggesting that toll-like receptors (TLRs) are involved in IIM pathogenesis. These transmembrane receptors are expressed on a variety of immune and nonimmune cells and are known as key players of the innate arm of the immune system. They recognize certain molecular patterns displayed by invading organisms or damage-associated molecules. Upon recognition, they trigger an immune response and the release of cytokines. Muscle biopsies of IIM individuals have shown increased expression of TLR-2, TLR-3, TLR-4 and TLR-9 [39]. The protein histidyl-tRNA-synthetase, the antigen against which certain IIM patients produce a myositis-specific autoantibody (anti-Jo1), and the high-motility group box protein 1 have been proposed as certain damage-associated molecular patterns in IIM. TLR antagonism was previously studied in a small RCT in psoriasis with modest results, but overall good tolerance [42]. On the basis of this evidence, a double-blind, placebo-controlled trial with an investigational oligonucleotide-based antagonist of TLR-7, 8 and 9 has been initiated in dermatomyositis (NCT02612857) [43].

Stem-cell transplantation

Another therapy gaining attention in severe refractory IIM is stem-cell transplantation. The rationale of this treatment is to administer lymphotoxic chemotherapy (e.g. cyclophosphamide and antithymocyte globulins) with subsequent restauration of immunological tolerance. Autologous hematopoietic stem-cell transplantation has been used for two decades for the treatment of severe cases of various autoimmune diseases. To date, only a few case reports have been published on dermatomyositis, JDM and polymyositis cases [44–46]. The largest case series of 10 dermatomyositis/polymyositis patients treated with allogeneic mesenchymal stem-cell transplantation showed improved creatinine kinase levels, patient assessment scores and muscle strength [45]. Of note, some of these patients even had ILD improvement. A positive clinical response in two JDM patients was also reported in another recent case series [46]. These encouraging results led to an open-label trial of autologous stem-cell transplantation in refractory dermatomyositis and polymyositis that was, however, terminated because of the high-relapse rate in treated individuals (NCT00278564).

CONCLUSION

Conducting clinical trials in IIM is challenging. Recruiting large numbers of patients requires international multicenter collaboration as shown in the largest trials reviewed in this article [10,28▪▪]. This will become critical as we are now approaching subsetting based on clinical, pathological and, more importantly, autoantibody status. An individualized approach in IIM calls for well-defined subsets and a clear understanding of underlying pathologic mechanisms. In this regard, using to its full extent the material gathered in clinical trials is essential in understanding response predictors and molecular mechanisms. With the advent of targeted therapies and improved outcomes in IIM, also comes the question of ‘treating to target’. In a population as heterogeneous as IIM, this is not straightforward. The meaning of satisfactory treatment response might differ depending on individual perspective, clinical phenotypes and underlying comorbidities. New clinical response criteria from IMACS and paediatric rheumatology international trials organisation, endorsed by the american college of rheumatology/european league against rheumatism, were recently published and address some of these issues [47,48]. Clinicians might, however, find these criteria difficult to transpose on an individual level particularly when extra-muscular features are dominating the clinical picture. Yet, we believe that international multidisciplinary collaboration is a key to future success in the development of new therapies for patients with IIM.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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