Biologics in Idiopathic Inflammatory Myopathies

9

Rudra Prosad Goswami and Uma Kumar

9.1 Introduction

Idiopathic inflammatory myopathies (IIMs) comprise diverse autoimmune systemic diseases characterised by chronic skeletal, muscular inflammation [1]. Treatable subtype of IIM include (juvenile) dermatomyositis ((j)DM), antisynthetase syndrome (ASS), immune-mediated necrotizing myopathy (IMNM) and overlap/non-specific myositis [OM/NSM, formerly called polymyositis (PM)]. Treatment of Idiopathic inflammatory myositis (IIMs), is not only long and often arduous but is also stymied by a general lack of guidelines or therapeutic algorithms available and updated readily and regularly as for other rheumatologic diseases such as rheumatoid arthritis or systemic lupus erythematosus. Corticosteroids have traditionally been used as the first-line agent along with other agents like methotrexate, cyclosporine, azathioprine, mycophenolate mofetil and rituximab [2, 3]. Often, either in case of non-responsive patients or in recurrent flares, biologics are employed. In this chapter, we will summarise the evidence and practices of the biologics already in use and those in the pipeline in the treatment of IIMs (not including inclusion body myositis, IBM).

Despite various completed and ongoing trials, issues regarding patient composition, sample sizes, heterogeneity with regards to inclusion and exclusion criteria and most important, outcome measures have hampered uniform interpretation of myositis clinical trials and other observational studies. The strongest evidence till date is for intravenous immunoglobulin (IVIg), rituximab, and abatacept. However, evidence is emerging for other drugs like sifalimumab and other anti-interferon therapies, Janus kinase (JAK) inhibitors and corticotropin injection.

R. P. Goswami · U. Kumar (✉)
Department of Rheumatology, AIIMS, New Delhi, India

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9.2 Rituximab (Anti-CD 20)

Mechanism of Action and Evidence

- Rituximab, a monoclonal antibody targeting the CD-20 molecule on B lymphocytes, depletes peripheral blood B cell lineage up to plasmablasts and not only depletes B cells and reduces total and autoimmune antibody levels but also affect antigen-presenting function of B cells. Other major mechanisms of action of rituximab are altered B cell signal transduction through interaction at the lipid raft level; apoptosis of B lymphocytes; complement-dependent and antibody-dependent cell-mediated cytotoxicity (ADCC) [4]. It is well known that plasma cells play a major role in the pathogenesis of IIMs, especially DM. Autoantibodies, though not ubiquitously, are well-recognised features of the disease process. Increased intramuscular perivascular localisation of B cells are observed in many patients with DM, along with evidence for B cell-driven upregulation of interferon production and signalling, as well as antibody production and antigen presentation to T cells [5–7]. Evidence of use of rituximab in IIMs comes from the RIM trial [3]. This was a double blind randomised placebo controlled delayed start trial. Trial population included both adult PM/DM and jDM patients. Patients with refractory myositis were included. Definition of refractory myositis was intolerance or partial response to glucocorticoids and at least another second immunosuppressant like methotrexate, mycophenolate, azathioprine, cyclophosphamide, cyclosporine, tacrolimus, intravenous immunoglobulin [IVIG], etc. "Adequate" glucocorticoid dose was either 60-mg/day prednisolone equivalent (adults) or 1-mg/kg/day prednisolone equivalent (jDM) for ≥1-month. The duration criterion for the second immunosuppressant was 3 months. A muscle weakness criterion was bilateral Manual Muscle Testing 8 (MMT-8) ≤125 for adults along with two other International Myositis Assessment and Clinical Studies Group (IMACS) core set measures. For jDM, weakness criteria were similar, except if MMT-8 was exactly 125, then a third core set measure was needed for inclusion. The other cores set measures were: (1) Global assessment of disease activity by visual-analogue-scale (VAS) ≥2 mm (patients' or parents'); (2) physician's global assessment VAS ≥2 mm; (3) Health Assessment Questionnaire (HAQ) or Childhood HAQ (C-HAQ) ≥0.25; (4) elevated muscle enzyme ≥1.3 upper limit of normal; (5) Global extramuscular disease (investigator's composite of skeletal, constitutional, gastrointestinal, cutaneous, pulmonary, and cardiac scores of the Myositis Disease Activity Assessment Tool [MDAAT]) activity score ≥1.0 cm. The two treatment arms were: the early group (rituximab at weeks 0 and 1) and the late group (rituximab given at weeks 8 and 9). The primary outcome measure was time to achieve the preliminary IMACS definition of improvement (DOI).
- Overall 195 IIM patients (75 with PM, 72 with DM, and 48 with jDM) refractory to steroids and an average of 2 other immunosupressive drugs were included in the trial. The median time to achieve a DOI in the early treatment arm was 20 weeks (n = 93) and in the late treatment arm was 20.2 weeks (n = 102). This represents no significant difference, and the trial did not meet its primary end

point. But the most important statistic available from the RIM is that 161/195 (83%) of the entire study population achieved the DOI by 44 weeks. Interestingly the authors provided data for retreatment in some patients. Nine patients were retreated with rituximab out potential 17. The time to relapse was 16.5 weeks on average. Eight of the relapsed patients achieved repeat DOI after a mean of 19.9 weeks. This was the first and currently, the only randomised controlled trial (RCT) providing evidence of rituximab in the treatment of refractory IIMs and jDM. Several sub-studies were later published. The authors showed that patients with baseline higher interferon expression and positive Mi-2 autoantibody expression had a better clinical response [8]. In another analysis, and particularly in the absence of the interferon chemokine score, which is still a research tool, presence of anti-Jo-1 (hazard ratio (HR): 3.08), anti-Mi-2 (HR 2.5), jDM (HR 2.45) and lower damage score (HR 2.32) predicted a favourable outcome [9]. For cutaneous disease in DM, significant improvements were noted in both arms of rituximab regimens, but faster resolution was noted in the early treatment arm [9].

Dose children with a BSA $\leq$ 1.5 m^2: 575 mg/m^2 (0, 1 week); adults and children with a BSA > 1.5 m^2: 750 mg/m^2 (0, 1 week); max dose 1 g per infusion

Mode of Administration IV infusion

Frequency weeks 0, 1; repeat courses as per clinical guidance (generally not before 4–6 months)

Duration Evidence available for up to 1 year

Indication Refractory myositis

Can Be Used in JDM Yes

Adverse Effects Common: Infusion reaction; Infections (urinary tract, upper and lower respiratory tract, skin and soft tissue, herpes zoster); Less common: Hypogammaglobulinemia; Leucopenia; Fungal infections

9.3 Abatacept (CTLA-4 Agonist)

Mechanism of Action and Evidence

- Activated cytotoxic and helper T cells occupy a central role in the pathology and pathogenesis of IIMs. Abatacept acts by engaging co-receptor molecules expressed on effector T cells (CD80/86) and downregulating these and thereby suppressing T-cell activation, proliferation, and effector function [10]. Apart from this, abatacept also decreases the antigen-presenting capability of myocytes, inhibits macrophage migration and function, and decreases pro-inflammatory cytokines expression especially, interleukins (IL-) 6, and TNF-alpha [11].

- A phase 2b randomised, multicentre, delayed start trial has recently been published [12]. This trial included 20 patients with refractory IIM (9 patients with DM, the rest 11 with PM). The definition of refractory disease in this trial was the presence of active disease (Manual Muscle Test (MMT-8) <150) or low endurance (Functional Index for myositis (FI-2) <20% of upper limit), with elevated enzymes, recent biopsy evidence of active inflammation or MRI findings consistent with inflammation, or active extramuscular disease, while on ongoing treatment with glucocorticoids (≥0.5-mg/kg/day prednisolone equivalent for more than a month) and a second immunosuppressant (either methotrexate (≥15 mg/week) or azathioprine (≥100 mg/day) for more than 3 months). Patients were randomised to receive either immediate treatment or delayed start, i.e. after 3 months. The primary outcome measure was IMACS DOI at 6 months which was achieved by eight patients. The authors also observed a parallel increase in regulatory T cells in repeat muscle biopsy samples concomitant with clinical improvement. Certain parameters, like the global physician health, muscle enzyme and cardiovascular disease activity, fared better in the active early treatment arm. The drug was well tolerated.
- Similar results were reported from a sub-study of the ongoing ARTEMIS trial, with similar inclusion criteria and the authors reported that 7/12 patients had DOI at 6 months. The authors also suggested that CD4/CD8 ratio in blood sample may be a biomarker of treatment efficacy.

Dose <60 kg: 500 mg, 60–100 kg: 750 mg; >100 kg: 1000 mg

Mode of administration IV infusion

Frequency weeks 0, 2, 4, 8, 12, 16, 20, 24.

Duration Evidence available for up to 6 months

Indication Refractory myositis

Can Be Used in JDM Trial data not available, anecdotal evidence available

Adverse Effects Generally considered to be one of the safest biologics in terms of infections: pneumonia, skin and soft tissue infections and urinary tract infection and some reports on opportunistic infections like *Mycobacterium tuberculosis*, Aspergillosis, blastomycosis, and systemic candida infections are available from non-IIM studies; (0.01); Common: infusion reaction, headache; Uncommon: induction of autoimmune reactions: mostly mild to moderate, psoriasis being the most common; worsening of chronic obstructive pulmonary disease

9.4 Intravenous or Subcutaneous Immunoglobulin (IVIg/SCIg)

Mechanism of Action and Summary of Evidence

- Intravenous (and more recently subcutaneous) immunoglobulin preparations (IVIg/ScIg) work in various immunological diseases through multiple and often poorly defined mechanisms such as blocking cellular receptors, neutralisation of cytokines, complements, and autoantibodies (Fab dependent mechanisms) and blockage of activating Fcγ receptors and modulation of activation of activating versus inhibiting Fcγ receptors and selective upregulation of inhibiting Fcγ receptor FcγRIIB (Fc portion dependent mechanisms), etc. [13] There are multiple other mechanistic evidences which are closer at home when talking about idiopathic inflammatory myositis like decreasing deposition of complements and membrane attack complexes on capillaries as well as muscle fibres [14], downregulation of transforming growth factor (TGF-B) expression on muscle fibres [15], and downregulation of expression of adhesion molecules on myocytes and capillaries [16].
- The major study of any drug other than glucocorticoids shown to be effective in IIMs was on IVIg. This was shown in the pivotal trial by Dalakas et al. back in 1993 on 15 patients with refractory dermatomyositis (many of which would actually be classified as jDM nowadays) who were given IVIg (2-g/kg-bodyweight) or placebo monthly for 3 consecutive months in a randomised manner. Inclusion criteria were clinical active disease, active rash and positive biopsy. Patients needed to have at least 4–6 months of exposure to non-glucocorticoid immunosuppressive drugs like methotrexate, azathioprine, or cyclophosphamide and needed to have either poor response or poor tolerance to these agents to be eligible. Response was gauged clinically. The Medical Research Council (MRC) muscle strength score improved from 76.6 to 84.6 in the IVIg group (n = 8) and remained the same at 76.6 in the placebo group (n = 7). There was a cross—over portion of the trial after the initial 3 months, thereby increasing the number of patients in IVIg to 12, of whom 9 with severe disabilities experienced major improvements. The MRC scores improved from 74.5 to 84.7, an improvement hitherto almost unattainable in the field of IIM. Among the 11 patients treated with placebo, none had a major improvement, and 5 patients worsened with stable disease or mild improvement in the rest. This was the first trial that showed a marked response of refractory patients with DM to this drug. There were several later prospective cohorts and one RCT, some of which reproduced this result, and others provided data to the contrary. Several points need mentioned, like the continuous use of moderate to high dose steroids in the Dalakas trial, a trend which was not followed in later studies, patient population heterogeneity and most importantly, the point in which this drug is introduced and whether the "Goldilocks period" was lost or not in later studies [17–19]. One RCT later unsuccessfully used IVIg as first-line therapy in IIM [17].
- A 2012 systematic literature review of adult patients with PM/DM compiled data from 1985 to 2011 and concluded that given at a dose of 2 g/kg, divided into 2–5

individual daily doses, once monthly for 3–6 months, beneficial effects were notable in refractory, flare-up, rapidly progressive, or severe PM/DM and most therapeutic benefit are noted among patients with lung involvement and oesophageal involvement. Some steroid-sparing effect was also observed by the authors [2]. Despite this, the present authors warn the reader that the majority of the benefit of IVIg are seen in cases of DM, and there is a dearth of evidence in favour of its use in OM/NSM/PM are scanty [10]. One Cochrane review summarised evidence of various drugs in DM and found only one eligible study, discussed above on IVIg. The authors showed a non-significant relative risk of 4.44 of muscle power improvement with IVIg use [20].

- More recently, subcutaneous immunoglobulin preparation (ScIg) has been tested in several prospective studies [21, 22]. There are several advantages like home usage, lack of need for vascular access and subsequent reduction of infection risk, lesser hyperviscosity-related side effects like headache and visual disturbance and lower cost [10].

Dose 2 g/kg body weight

Mode of Administration IV infusion/SC infusion

Frequency Monthly

Duration Up to 6 months

Indication refractory myositis/Pharyngeal muscle weakness/Respiratory muscle weakness/Concomitant infection

Can Be Used in JDM Yes

Adverse Effects One of the safest if not the safest agent to use in terms of infectious side effects and often is used in patients with a concomitant active systemic infection where high doses of glucocorticoids or other biologics cannot be used; Common: infusion reactions like headache, fever, or asymptomatic laboratory changes like increased liver enzymes, dizziness, hypertension (generally mild, but may be severe, especially with older preparation which was rich with immunoglobulin A (IgA) given in patients with IgA deficiency, a problem which had largely been unnoticed with newer IgA poor preparations; these reactions, when occur could be resolved by reducing the infusion rate or with symptomatic therapy); Uncommon: aseptic meningitis; thromboembolic complications; hyperviscosity

9.5 Sifalimumab

Mechanism of Action and Evidence

- Sifalimumab is an anti-interferon alpha (IFN-α) monoclonal antibody. Increased interferon response and interferon gene signature, both systematic and localised

to muscular tissue, has been described from yesteryears' studies back in 1980s to the most recent exponents [23, 24]. Interestingly, both jDM and DM have several mechanistic pathways common to lupus-like complement activation and vascular wall deposition of membrane attack complex, lymphocytic infiltration of target organ, plasmacytoid dendritic cell expression at the target site of inflammation and consequent type I interferon expression [25]. Recently, a fairly good number of studies on interferon blocking agents came in lupus, some failed like rontalizumab, but others succeeded like sifalimumab and anifrolumab. Recently a trial on sifalimumab came in the field of IIM [26].

- This was a pharmacodynamic study (phase Ib) in which neutralisation of a type I IFN gene signature (IFNGS) at blood and muscle level was assessed following drug exposure. At baseline, 72% of all patients had positive IFNGS. The IFNGS was suppressed by 53–66% on the various time points of measurements (4, 8, and 14 weeks) in the blood ($p = 0.019$) and by 47% (98th day) in muscle. Patients with 15% or greater improvement in manual muscle testing at day 98 from baseline showed greater neutralisation of the IFNGS. However, only 8 out of 24 patients experienced such clinical improvement. However, regarding the pharmacodynamic parameters, which were the primary outcome measure analysed in this study, this RCT reached its goals and is considered a success. In a subsequent sub-study, treated patients showed a significant reduction of several T-cell associated proteins, especially soluble interleukin-2 receptor chain alpha (IL-2RA) levels, which, apart from being of pathological importance, and the reader is drawn to its parallels with lupus, may also serve as a biomarker for response to therapy [27]. Unfortunately, further development of sifalimumab was blocked during a later trial on lupus due to an adverse event profile (NCT00979654). Recent report of a positive trial of anifrolumab in lupus has again rekindled hopes of targeting the interferon pathways [28], and trials on interferon pathways are ongoing, either in the developmental phase or recruitment phase (NCT02980198; NCT03181893).

Dose; Mode of administration; Frequency; Duration; Indication No extant drug available

Adverse Effects Primarily infections, especially herpes zoster infections, pharyngitis, and other viral infections (mostly available from trials on systemic lupus erythematosus rather than myositis trials)

9.6 Other Biologics

Several other biologics and targeted molecules have been tried PM/DM and are tabulated in Table 9.1 [29–36]. Of these, only tofacitinib and repository corticotropin injection have some potential and are being actively researched. TNF inhibitors may have some role, especially in jDM, however paradoxical worsening of myositis activity, especially dermatomyositis skin rash, is sometimes noticeable.

Table 9.1 Summary of evidence on various biologics in idiopathic inflammatory myopathies (IIMs)

Agent	Study design	Population	Summary of results	Current status
Infliximab	RCT	Adult polymyositis and dermatomyositis (n = 13)	• Nine patients completed the trial (three discontinued due to adverse effects and one due to a discovered malignancy) • Three of the completers improved by ≥20% in ≥3 core sets • Six remained unchanged or worsened • No patient improved in muscle strength by manual muscle test.	Not in contention in adult IIM
	Retrospective study	JDM (n = 39)	• Global disease activity increased at both 6 and 12 month time points • Muscle power also commensurately increased • 50% of patients had a reduction in the number and/or size of calcinosis lesions. • 25% switched from infliximab to adalimumab	Still a contender for JDM
Etanercept	RCT	Adult dermatomyositis (n = 16)	• Sixteen subjects were randomized, 11 to etanercept • Primary outcome was adverse effects • Five etanercept-treated and one placebo-treated subject developed the worsening rash. • All five subjects receiving placebo were treatment failures • Five were successfully weaned off prednisone	Generated some hope for a TNF inhibitor in DM
	Clinical Trial	JDM (n = 9)	• At the 12th week, seven patients had a mild decrease in disease activity, one remained stable, and one worsened • At the 24th week, one patient remained stable, two worsened, and three improved • There was no appreciable change in serum muscle enzymes or CMAS throughout the study.	Overall a negative study; found the TNF alpha 308 alleles to be associated with worsening DM skin rash

Table 9.1 (continued)

Agent	Study design	Population	Summary of results	Current status
Tocilizumab	RCT	Adult IIM (n = 40)	Ongoing	No results posted
Anakinra	Prospective study	Adult polymyositis, dermatomyositis and IBM (n = 15)	• Clinical response in 7/15 • Concomitant changes noted in repeat muscle biopsy	Still investigational
Tofacitinib	Prospective study	anti-MDA5 Ab+ DM-ILD (n = 5)	• Aggressive ILD with poor prognostic factor patients treated with triple therapy with high dose glucocorticoids, CSA and CYC were given additional TOF (10 mg/day). • Three survived, and two died. • The survival rate of patients who received TOF was significantly better than that of the historical controls.	Has definite potential both in cutaneous disease and lung disease
	Retrospective study	Multidrug-resistant cutaneous dermatomyositis (n = 3)	• Clinical response was observed after 4 weeks, and the mean treatment period was 9.6 months. • Clinical activity scores decreased in all three patients • No adverse events occurred • Tofacitinib was given as monotherapy in two patients, and one patient continued using hydroxychloroquine	

(continued)

Table 9.1 (continued)

Agent	Study design	Population	Summary of results	Current status
Repository Corticotropin Injection	Clinical trial	PM (n = 4)/DM (n = 6)	• 10/11 completed the study • 7/10 patients met primary end point at 8 weeks (IMACS definition of improvement) • Significant decrease in prednisolone dose from 18.5 mg/day to 2.3-mg/day • RCI was considered safe and tolerable. • No patient developed significant weight gain or an increase of haemoglobin A1c or cushingoid features.	Has definite potential, especially in cutaneous disease
	Clinical trial	DM patients with active cutaneous disease (n = 9)	• At 3 months, 7/9 patients had improved clinical cutaneous score and 8/9 improved global activity score • At 6 months, 7/7 patients had improved cutaneous score and global disease activity score	

Abbreviations used: *Ab* antibody, *CMAS* childhood myositis assessment scale, *CSA* cyclosporine, *CYC* cyclophosphamide, *DM* dermatomyositis, *IBM* inclusion body myositis, *IIM* idiopathic inflammatory myopathy, *ILD* interstitial lung disease, *IMACS* International Myositis Assessment and Clinical Studies, *JDM* juvenile dermatomyositis, *MDA* melanoma differentiation-associated protein, *PM* polymyositis, *RCI* repository corticotropin injection, *RCT* randomised controlled trial, *TNF* tumor necrosis factor, *TOF* tofacitinib

9.7 Conclusion

The niche of biologics in the treatment of adult PM/DM and jDM is restricted to mostly refractory patients who are either intolerant to conventional immunosuppressive drugs or are non-responsive or develop frequent flares, especially with glucocorticoid tapering. Exceptions to these exist in severe initial disease, especially with severe pharyngeal muscle weakness or respiratory muscle weakness where a definite role of IVIg is well known and practiced. In other cases, rituximab is till now the drug with the most promising evidence. The other especially promising drug is abatacept, but unfortunately, it is no more available in India. Tofacitinib and repository corticotropin injection are the two most "new kids in the block" which might prove to be game changers in the near future.

Conflict of interest None to declare

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