Chapter

Novel Insights into the Use of Biologicals in Idiopathic Inflammatory Myopathies

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Abstract

Idiopathic inflammatory myopathies (IIMs) are a set of autoimmune disorders characterized by muscle inflammation and weakness, as well as a variety of extra-muscular presentations. IIMs are remarkably complex and difficult to treat, and glucocorticoid treatment and synthetic immunosuppressants are frequently ineffective. The pathophysiology of IIM has been linked to defects in both the innate and adaptive immune systems. Multiple prospective targets for biologic therapy have been studied because of a greater understanding of the main cytokines, as well as the cell-mediated and antibody effectors of disease. B-cell depletion with rituximab, as well as tumor necrosis factor inhibitors and other biologic treatments, is among the most extensively studied drug in IIM. There is currently no straightforward way to define all of the pharmaceuticals that are classified as biologics. This group of drugs has gained a lot of interest in the recent era for the treatment of various autoimmune and skeletal muscle disorders. This chapter shall address the mechanism of action, side effects, uses, and scope of biologics used in treatment of IIM.

Keywords: dermatomyositis, polymyositis, idiopathic inflammatory myopathy, biologics, rituximab

1. Introduction

The idiopathic inflammatory myopathies (IIMs)/myositis syndromes are a heterogeneous group of systemic autoimmune conditions that include polymyositis, dermatomyositis (DM), necrotizing myopathy, inclusion body myositis (IBM), anti-synthetase syndrome, and overlap syndromes with myositis. These have a significant influence on skeletal muscle, though they can also have extra-muscular consequences. They are linked to considerable disability as a result of progressive weakness, as well as an increased risk of mortality. These clinical signs, along with muscle biopsy data and specific serum autoantibodies, are used to make the diagnosis.

IIMs have always been difficult to treat. Glucocorticoids and traditional immunosuppressive or immunomodulatory drugs such as methotrexate, azathioprine, mycophenolate mofetil, tacrolimus, cyclosporine, and intravenous immunoglobulin are

examples of traditional treatment modalities. Some patients have recurrences of the disease during or after conventional therapy, while others do not respond completely, which can pose therapeutic challenges. A considerable number of patients have a partial response, necessitating long-term glucocorticoid therapy, which has its own set of adverse effects as well as the implications of incomplete disease control, such as persistent muscle deterioration. As a result, there has been an increasing interest in evaluating innovative and targeted therapeutics, such as biologics, that target specific pathways involved in IIM etiopathogenesis.

Biomarkers linked to IIM pathogenesis have been investigated utilizing a range of approaches, including cytokine/chemokine investigations, enhanced immunohistochemistry and flow cytometry, microarrays, and RNA-sequencing analysis. Multiple potential targets for biologic therapy have been identified because of growing knowledge of important cytokines as well as cell-mediated and antibody effectors of disease.

The introduction of biologic therapies has held promising potential for autoimmune diseases, allowing us to translate our knowledge of specific disease pathophysiology processes into medications that target certain autoimmune disorders. The aim of this chapter is to outline the pharmacologic profile of biologic treatment of myositis as per currently available literature.

2. Mechanism of action

2.1 Biological DMARDS – mechanisms of action

The complex pathogenesis of rheumatic and musculoskeletal disorders has gradually been pieced together, and this has led to the appreciation of the underlying cytokine networks underlying these disorders [1]. This has resulted in the development of targeted biological therapies with myriad mechanisms of action. For the purposes of understanding this broad and heterogeneous topic, the therapeutic agents will be classified, albeit arbitrarily based on the primary biological signaling pathways being targeted.

2.2 Biological targeting TNF-alpha signaling

Tumor necrosis factor-Alpha (TNF-Alpha) is produced by a wide variety of both immune and non-immune cells. It exists as a 26 kD transmembrane protein (tmTNF-Alpha), which is cleaved by the extracellular metalloproteinase, ADAM-17/TACE, which results in the release of a soluble form of TNF-Alpha (sTNF-Alpha). Both the transmembrane and soluble versions of TNF-Alpha are biologically active and signal via the two distinct TNF-Alpha receptors – TNFR1 and TNFR2 [2]. The receptors have partially redundant but distinct downstream signaling cascades, which result in differences in biological function, which have been highlighted in **Figure 1** [3]. TNFR1 signals via the canonical NF-κB pathway and may be pro-inflammatory, pro-survival, or pro-apoptotic in the given immunological context. TNFR2 signals via both the canonical and non-canonical NF-κB signaling cascades but lacks the pro-apoptotic signaling demonstrated by TNFR1. The biological outcomes of signaling via these two receptors are best exemplified by the effects they have on T-Regulatory (Treg) cell survival—TNFR1 enhances Treg cellular apoptosis while TNFR2 (as it lacks a death domain unlike TNFR1) enhances the expression of the Treg cell master transcription

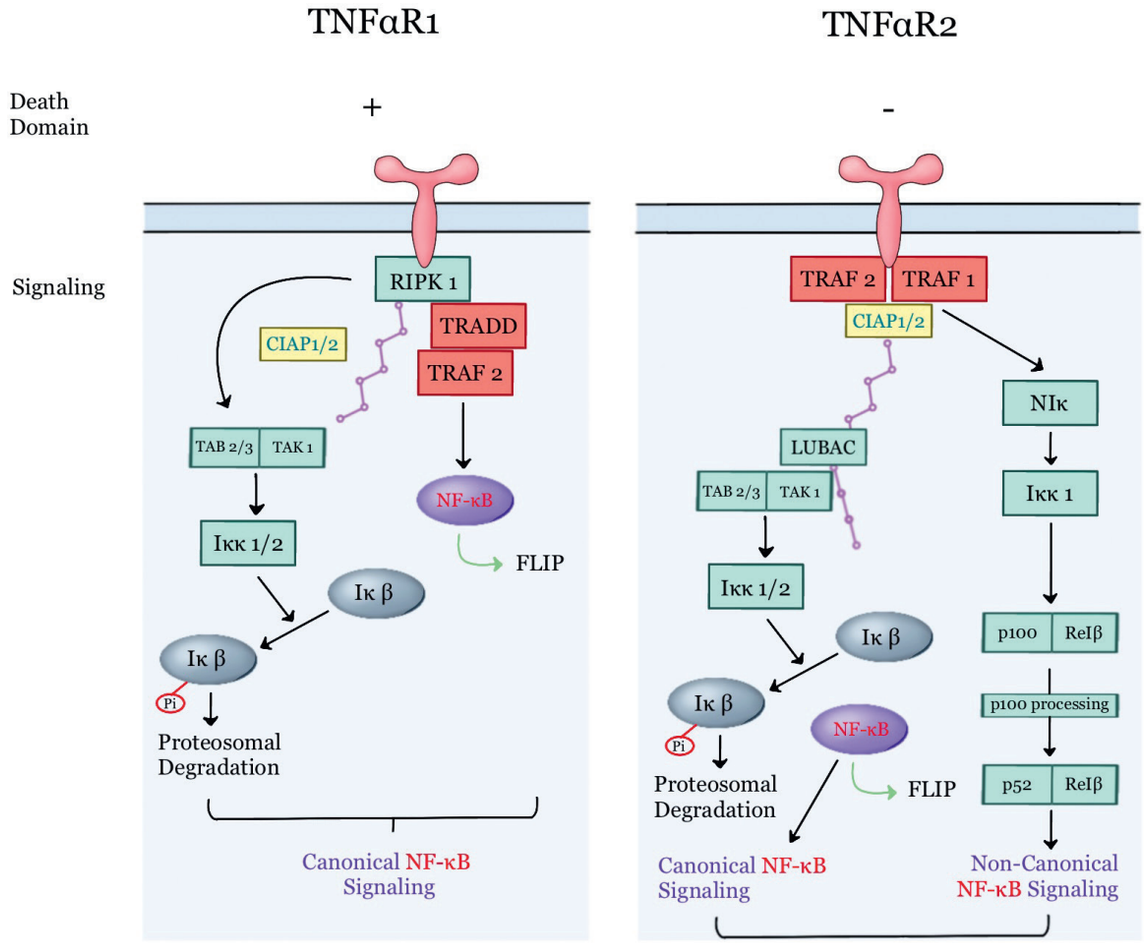

Figure 1.
Differences in biological functions of TNFR1 and TNFR2.

factor FOXP3, thus maintaining these regulatory cell populations. An additional difference between the two receptors of TNF-Alpha is that TNFR2 is able to interact with the tmTNF-Alpha, resulting in bidirectional signaling (both forward and backward), thus potentiating the immunoregulatory functions of TNFR2 signaling [4].

The therapeutic effects of anti-TNF-Alpha, although slightly variable based on the exact agent used, generally capitalize on the central role TNF-Alpha plays in determining pro vs. anti-inflammatory signaling. Overall biologicals targeting TNF-Alpha likely produce a clinical response as a result of the following effects:

1. Bind to sTNF-Alpha and counteract pro-inflammatory signaling via TNFR1.

2. Enhance apoptosis of pro-inflammatory cells- Possibly by blocking tmTNF-Alpha interactions with TNFR2 and/or enhancing the pro-apoptotic signaling downstream of TNFR1.

3. Direct antibody-dependent cellular cytotoxicity (ADCC) and complement-mediated cellular damage in cells expressing TNF-alpha [5].

A distinction must be made between etanercept and other anti-TNF-alpha agents in that is a fusion protein composed of the soluble portion of the TNFR2 and the constant region of the IgG1 molecule, while the latter are all monoclonal antibodies

directed against TNF-alpha. Thus etanercept acts as a decoy receptor and is effective in cases of TNF-alpha receptor associated auto-inflammatory syndrome patients with the T50M mutation (who have been reported to not respond to infliximab therapy in some cases) [6].

2.3 Biologicals targeting the IL-6 pathway

Interleukin-6 (IL-6) is a member of the IL-6 superfamily of interleukins, along with leukemia inhibitory factor and oncostatin M—all three signal via receptors that contain the common gp130 subunit. IL-6 (like IL-11, IL-13, and IL-27) signals using JAK1/2 and TYK-2, which then phosphorylate and cause the nuclear translocation of STAT3 and STAT6 [7]. IL-6 signaling plays a central role in activating the systemic inflammatory response inducing acute phase reactant production in the liver, inducing megakaryocytic differentiation, and resetting the hypothalamic set point to cause fever [8]. Additionally, IL-6 signaling plays a critical role in determining TH17 vs. Treg cell polarization—IL-6 signaling suppresses FoxP3 expression (decreasing Treg polarization) and in the presence of concomitant TGF-Beta signaling inducing ROR-GammaT expression (enhancing T17 polarization) [9]. Blocking IL-6 signaling using targeted biologicals is therefore therapeutically very useful given the critical contribution of excessive innate immune activation and TH17 polarized T cells to the pathogenesis of RMDs such as rheumatoid arthritis. This is achieved clinically by targeting either IL-6 itself (Siltuximab, Clazakizumab) or the IL-6 Receptor (Tocilizumab, Sarilumab).

2.4 Biologicals targeting the type 1 interferon pathway

An appreciation of the central role played by type 1 interferons in the pathogenesis of diseases such as SLE and type 1 interferonopathies has resulted in the development of biologicals targeting IFN signaling [10, 11]. Anifrolumab is an anti-interferon alpha R1 (IFNAR1) monoclonal antibody, which has shown promise in the management of SLE. It downregulates the expression of IFNAR1 on various cell types with a resultant decrease in the phosphorylation and nuclear translocation of STAT1 (**Figure 2**).

2.5 Biologicals targeting the IL-17/IL-23 axis

As detailed above in the section on biologicals targeting IL-6 signaling, IL-23 and IL-6 play central roles in determining TH17 vs. Treg T cell polarization. TH17 cells as the name suggests in turn produce IL-17 (along with other innate lymphocytes that also express the master transcription factor ROR-γT) [12, 13]. Excessive TH17 polarization has been shown to be crucial to the pathogenesis of seronegative spondyloarthropathies and psoriasis. Molecules that target IL-23 signaling may target the p40 subunit of the IL-23R such as ustekinumab and briakinumab, or they target the p19 subunit of the same receptor such as guselkinumab, rizankizumab, and tidrakizumab. Biologicals targeting IL-17 usually target IL-17A/F such as secukinumab and ixekinumab [14]. Brodalumab is, however, different in that it targets the IL17A receptor [15].

2.6 Biologicals targeting immune checkpoint signaling

Abatacept is a fusion protein consisting of the extracellular domain of CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) and the constant region of IgG1. It

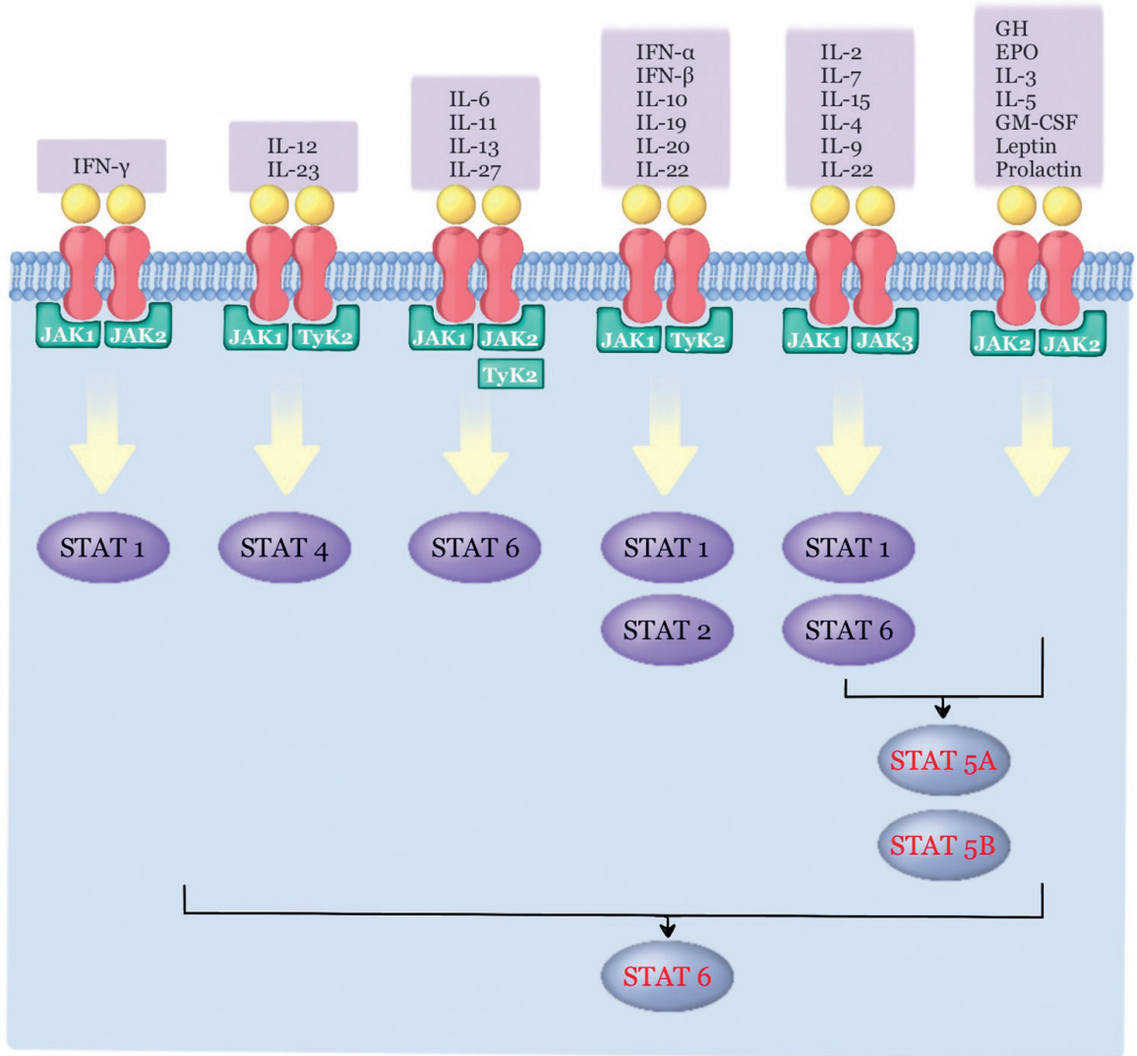

Figure 2.
Signaling pathways for various interferons. JAK – Janus kinase, TYK – tyrosine kinase, STAT – signal transducer and activator of transcription.

prevents a co-stimulatory signal by binding to CD80/86 and preventing its interactions with CD-28 from being delivered to T- cells during antigen presentation, thus preventing activation of naïve T-cells [16]. In the context of autoimmune disorders, this likely prevents aberrant activation of partially/completely self-reactive T cells. This strategy has been of particular use in the management of rheumatoid arthritis (**Figure 3**) [17].

2.7 Biologicals targeting specific cell types

The phenotypic heterogeneity of various immune cell types allows for the highly specific targeting of various cells that play crucial roles in immune responses, using molecules developed against specific cell surface targets. Examples of this approach include Anti-CD20 specific biologicals, such as rituximab, which are able to deplete B cell numbers reliably and thus are effective if diseases where B cells play a central role- B-cells act as important antigen-presenting cells in the RA joint, IgG4RD, and as sources of autoantibodies in AAVs. Similarly, recently the SLAMF7 and CD38 targeting elotuzumab and darutumumab, respectively, have shown promise in the management of SLE [18].

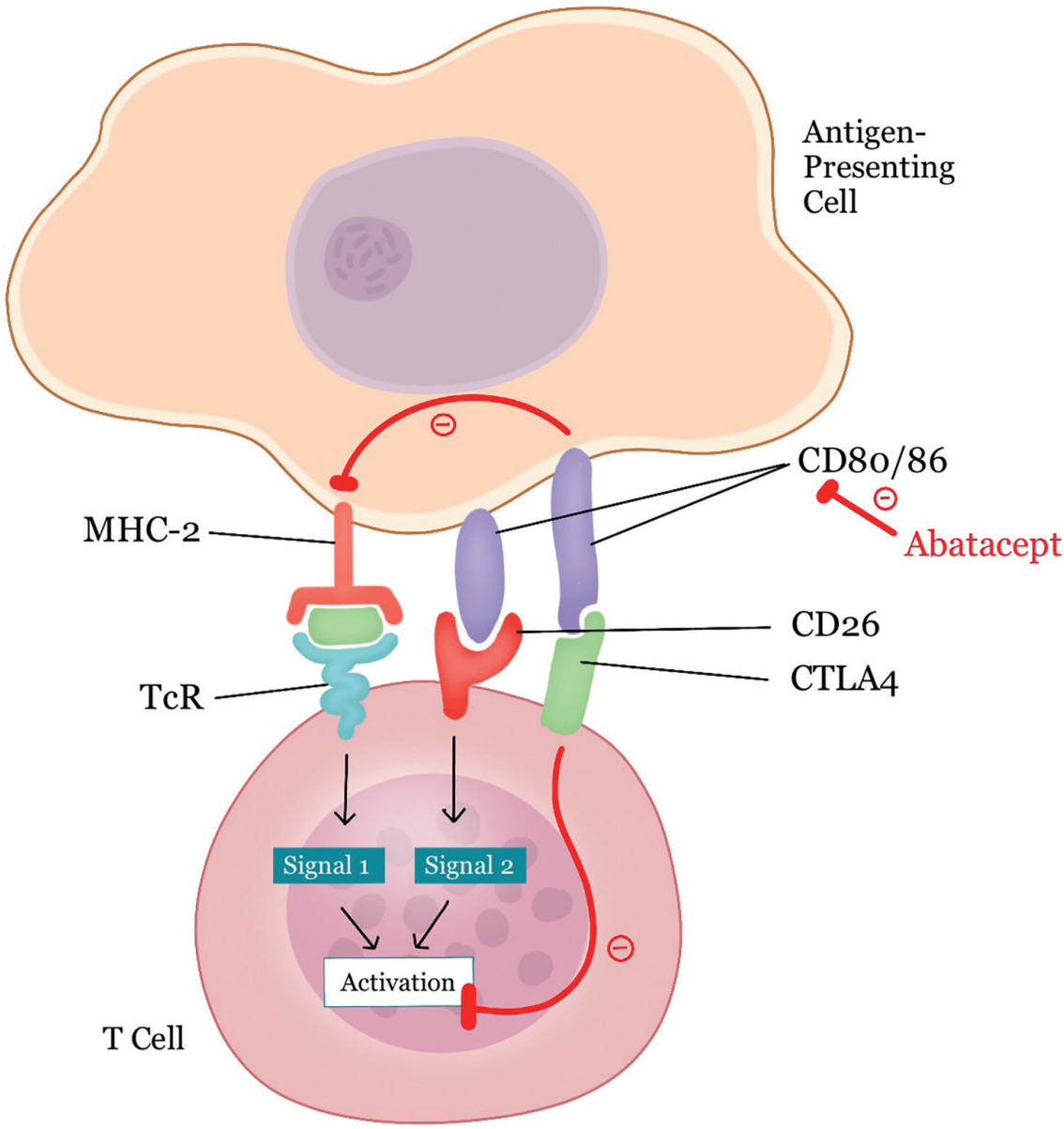

Figure 3.
Mechanism of action of abatacept. MHC-2 – major histocompatibility complex – 2, TcR – T cell receptor.

3. Pharmacology of biologics

The pharmacokinetics and pharmacodynamics of biological therapies, including monoclonal antibodies, are unique. Monoclonal antibodies have a distinct advantage over other drugs in that they can precisely bind and target certain antigen ligands with high affinity. These biologics, however, have some limitations in terms of pharmacological or pharmacokinetic features. They are absorbed, transported, and removed through completely distinct mechanisms, which poses significant challenges to how these drugs are delivered and can reach their pharmacological target [19–21].

Absorption: Because of the high molecular size of biologics and their breakdown in the gastrointestinal tract, most biologics are taken by the parenteral route, which includes intravenous (IV), subcutaneous (SC), and intramuscular (IM) injection [19, 20]. Bioavailability after SC and IM treatment might be variable, ranging from 20% to 95%.

Absorption following these routes of administration can be extremely slow (peak plasma concentrations reported 1–8 days after the dosage) and occurs mostly through the lymphatic system.

Distribution: In terms of distribution and tissue infiltration, biologicals can readily travel from the SC space by diffusion and/or convection through lymphatic capillaries. Pinocytosis or receptor-mediated endocytosis can allow them to reach intracellular destinations beyond systemic circulation [22]. The distribution of monoclonal antibodies (mAbs) in the vascular and interstitial fluids is explained by their large size and physicochemical features (charge and hydrophobicity). Tissue distribution accounts for 5–15% of the overall quantity of mAb, and distribution into the brain is quite limited (0.1%) [23]. If mAb-tissue target binding occurs with high affinity, a large proportion of mAb may be detected in the body.

As a result, mAbs might have high apparent volumes of distribution in steady state (Vss) [20].

Metabolism and Elimination: In mAb disposal, two metabolic routes, specific and nonspecific, are implicated, and their influence varies over time depending on the amount of free mAb in the plasma and the dosage provided. Metabolism through the reticuloendothelial system by pinocytosis/proteolysis reflects the linear and nonspecific clearance, which may be significant at certain dosage levels because of the higher endothelial surface area in the stomach, muscle, and skin [24]. The specific pathway begins once the receptor–drug combination is internalized, allowing the drug to enter the cell and be inactivated by cytoplasmic endosomes. FcRn, on the other hand, may bind IgG and mAbs at the acidic pH of the lysosome, avoid proteolysis, and return to the cell membrane [25–27].

3.1 Anti-TNF α

3.1.1 Etanercept

• Pharmacodynamics

Etanercept is a fully humanized, dimeric fusion protein made up of two copies of the extracellular ligand-binding region of the human TNF p75 receptor coupled to a part of immunoglobulin G1. It binds to TNF, preventing it from binding to cell surface receptors and inhibiting its pro-inflammatory effects [28].

• Pharmacokinetics

Absorption: Population pharmacokinetic modeling in adults with RA, AS, or who were healthy showed a subcutaneous bioavailability of 56.9% with a Ka of 0.0223/h [28].

Distribution: In adults with RA, population pharmacokinetic modeling predicts a total Vd of 5.49 L with a peripheral compartment of 1.24 L and an apparent Vd of 7.88 L after subcutaneous dosing in pediatric patients with JIA [28, 29].

Metabolism and Excretion: As etanercept is a fusion protein antibody, it is assumed to be metabolized and degraded via proteinases similarly to endogenous proteins.

Half-Life: 102 hours [30].

Clearance: 160 mL/h [30].

- Adverse Effects:
  - Infection (including bacterial infection, fungal infection, serious infection, viral infection: 50–81%)
  - Respiratory tract infection (21–54%), upper respiratory tract infection (38–65%)
  - Injection site reaction (adults: 15–43%; children: 7%; mild to moderate; usually decreases with subsequent injections)
  - Antibody development (non-neutralizing; 4–16%).
  - Diarrhea (3–16%).
  - Skin rash (3–13%).

3.1.2 Infliximab

- Pharmacodynamics

Infliximab inhibits the activation of the pro-inflammatory signaling cascade. Infliximab has been reported to prevent inflammatory cell infiltration into inflammatory areas. It also suppresses the expression of molecules involved in cellular adhesion, such as E-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), chemoattraction (IL-8 and monocyte chemotactic protein (MCP-1)), and tissue degradation (matrix metalloproteinase (MMP) 1 and 3).

- Pharmacokinetics

Absorption: Infliximab absorption follows a linear relationship between the dose given and the maximal serum concentration after a single intravenous infusion.

Distribution: The distribution at steady state was independent of dose in adult patients' pharmacokinetic investigation, indicating that infliximab was distributed largely within the vascular compartment.

Half-life: 7–12 days [31].

Clearance:11–15 mL/hour [31].

- Adverse Effect:
  - Infection (27–74%), serious infection (3–60%)
  - Antibody development (10–52%), increased ANA titer (~50%)
  - Abdominal pain (12–26%)
  - Nausea (21%)
  - Infusion-related reaction (≤20%)

- Headache (18%)
- Abscess (≤15%)
- Anemia (≤11%)

3.1.3 Adalimumab

• Pharmacodynamics

After treatment with adalimumab, a decrease in levels of acute-phase reactant proteins of inflammation (C reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) and serum cytokines (IL-6) was measured compared with baseline in patients diagnosed with rheumatoid arthritis. CRP levels were also shown to be lower in Crohn's disease patients. After treatment with adalimumab, serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that cause tissue remodeling and cartilage degradation were found to be lower [32]. In adult and pediatric patients with diverse inflammatory disorders, a reduction in disease signs and symptoms, induction of clinical response, suppression of structural damage, and improvements in physical function have been documented [33, 34].

• Pharmacokinetics

Absorption: Following a single 40 mg subcutaneous injection of adalimumab to healthy adult volunteers, the maximum serum concentration (Cmax) and time to achieve the maximum concentration (Tmax) were 4.7 ± 1.6 g/mL and 131 ± 56 hours, respectively. The average absolute bioavailability of adalimumab after a single 40 mg subcutaneous dose was 64%, according to three clinical investigations.

Distribution: The distribution volume (Vss) ranges from 4.7 to 6.0 L.

Half-life: The average terminal half-life was 2 weeks, ranging from 10 to 20 days in different trials.

Clearance: 12 mL/hr. [RA patients with dose 0.25–10 mg/kg].

• Adverse Effect:

- Injection site reaction (5–20%)
- Antibody development (3–26%)
- Upper respiratory tract infection (17%)
- Increased creatine phosphokinase in blood specimen (children and adolescents: 15%)
- Positive ANA titer (12%)
- Skin rash (12%)
- Headache (12%)
- Sinusitis (11%)

3.2 IL-1 Inhibitors

3.2.1 Anakinra

- Pharmacodynamics

Anakinra is a recombinant human interleukin-1 receptor antagonist (IL-1Ra) that inhibits capacity of interleukin-1 (IL-1) to bind to the IL-1 type I receptor (IL-1RI), therefore blocking its biologic function [35].

- Pharmacokinetics

Absorption: The bioavailability of anakinra is 95% in healthy subjects administered a 70 mg subcutaneous bolus injection.

Distribution: In adult subjects with rheumatoid arthritis (RA) treated with anakinra (n = 35), the volume of distribution averaged 18.5 L [36].

Elimination: Elimination is largely through the kidney, thus persons with compromised renal function are at risk to toxicity.

Half-life: In patients with rheumatoid arthritis (RA), the terminal half-life of anakinra ranged from 4 to 6 hours.

Clearance: Clearance is varied and rises with increasing creatinine clearance and body weight rise. The mean plasma clearance of anakinra was 16% and 50% lower in individuals with mild (creatinine clearance 50–80 mL/min) and moderate (creatinine clearance 30–49 mL/min) renal impairment, respectively. The mean plasma clearance of anakinra was 70% and 75% lower in patients with severe renal insufficiency and end-stage renal disease, respectively.

- Adverse Effect:
  - Injection site reaction (adults: 71%; infants, children, and adolescents: 16%)
  - Antibody development (49%)
  - Infection (39%)
  - Vomiting (14%)
  - Headache (12–14%)
  - Arthralgia (12%)

3.3 IL-6 Inhibitors

3.3.1 Tocilizumab

- Pharmacodynamics

Tocilizumab binds soluble and membrane-bound IL-6 receptors, preventing IL-6-mediated inflammation [37].

- Pharmacokinetics

Absorption: A 162 mg subcutaneous dose given weekly has a Cmax of 51.3 ± 23.2 μg/mL and an AUC of 8254 ± 3833 μg*h/mL [38].

Distribution: Tocilizumab is eliminated from the circulation in two phases after intravenous administration. The core volume of distribution was 3.5 L, and the peripheral volume of distribution was 2.9 L in rheumatoid arthritis patients, resulting in a volume of distribution of 6.4 L in steady state.

Half-life: Tocilizumab has a concentration-dependent half-life. In rheumatoid arthritis sufferers, the terminal half-life is 21.5 days.

Clearance: Clearance is dose-dependent, changing from nonlinear to linear at higher doses.

- Adverse Effect:
  - Injection site reaction (SubQ: children and adolescents: 15–44%; adults: 7–10%)
  - Increased serum alanine aminotransferase (≤36%), serum aspartate aminotransferase (≤22%)
  - Neutropenia (26–4%)
  - Increased serum cholesterol (19–20%)
  - Infusion-related reaction (4–20%)
  - Constipation (6–13%)
  - Arthralgia (12%)

3.4 IL-17 Inhibitors

3.4.1 Secukinumab

- Pharmacokinetics

Dosing: Secukinumab is administered by monthly subcutaneous injection after several loading doses [39].

Onset of action: Psoriasis: After 12 weeks, the optimal response can be established. (AAD-NPF [Menter 2019]).

Distribution: Vd: 7.1–8.6 L.

With increasing body weight, clearance and volume of distribution also increase.

Metabolism: Expected to be degraded into small peptides and amino acids via catabolic pathways similar to that which is seen with endogenous IgG.

Bioavailability: 55–77%.

Half-life elimination: 22–31 days.

Time to peak: ~6 days.

- Adverse Effect:
  - Infection (29–48%, serious infection, ≤1%).
  - Nasopharyngitis (11–12%).
  - Urticaria.
  - Hypercholesterolemia.
  - Diarrhea.

3.4.2 Ixekizumab

- Pharmacokinetics

Onset of action: Psoriasis: After 12 weeks, the optimal response can be established. (AAD-NPF [Menter 2019]).
Distribution: Vdss: 7.1 L. With increasing body weight, clearance and volume of distribution also increase.
Metabolism: Broken into tiny peptides and amino acids by catabolic processes similar to endogenous IgG.
Bioavailability: 60–81%.
Half-life elimination: 13 days.
Time to peak: ~4 days.

- Adverse Effect:
  - Neutropenia (11%, grades ≥3, <1%).
  - Antibody development (5–22%, neutralizing antibodies associated with decreased drug concentration and loss of efficacy, 2%).
  - URTI.
  - Conjunctivitis.

3.5 IL-12/23 Inhibitors

3.5.1 Ustekinumab

- Pharmacokinetics

Onset of action: Psoriasis: After 12 weeks, the optimal response can be established. (AAD-NPF [Menter 2019]).
Half-life elimination: SubQ: 14.9 ± 4.6 to 45.6 ± 80.2 days.
Time to peak: Psoriasis: SubQ: 45 mg: 13.5 days; 90 mg: 7 days.

- Adverse Effect:
  - Antibody development,

- Infections
- Nasopharyngitis

3.5.2 Guselkumab

• Pharmacokinetics

Onset of action: Psoriasis: After 12 weeks, the optimal response can be established. (AAD-NPF [Menter 2019]).
Distribution: Vd: 13.5 L.
Metabolism: Degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.
Bioavailability: Subcutaneous: ~49%.
Half-life elimination: 15–18 days.
Time to peak: 5.5 days.

• Adverse Effect:

- Antibody development
- Infections
- Nasopharyngitis

3.6 Costimulation blockade

3.6.1 Abatacept

• Pharmacodynamics

CTLA-4 with the Fc component of immunoglobulin G1 (IgG1) forms Abatacept, a soluble fusion protein (CTLA4-Ig). It can be used in the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, and psoriatic arthritis. Following numerous loading doses, abatacept can be given either as a weekly subcutaneous injection or as a monthly intravenous infusion.

• Pharmacokinetics

Distribution: IV: 0.07 L/kg (range: 0.02–0.13 L/kg).
Bioavailability: Subcutaneous: 78.6% (relative to IV administration).
Half-life: IV: 13.1 days (range: 8–25 days).
Clearance: Increases with increasing body weight.

3.7 Anti B-cell depletion and inhibition

3.7.1 Rituximab

• Pharmacokinetics

Onset of action: Within 2 weeks.
Duration: Depletion of B cells lasts at least 6 months.
Distribution: 3.1 L.
Half-life elimination: 18 days (range:5–78 days).
Clearance: 0.335 L/day.

- Adverse Effect:
  - Fatal infusion-related reactions.
  - Mucocutaneous reactions.
  - Hepatitis B virus (HBV) reactivation.
  - Progressive multifocal leukoencephalopathy (PML) (**Table 1**).

Drug	Bio-availability	Volume of Distribution (L/kg)	Half-life (units shown)	Clearance (mL/hour)	Adverse Effects
TNF-α Inhibitors					
Etarnecept	56.9%	5.49–7.88	102 hours	160	Infection, Injection site reaction, Antibody development, Diarrhea, Skin Rash
Infliximab	N.R.	N.R.	7–12 days	11–15	Infection, Antibody development, Abdominal pain, Nausea, Infusion-related reaction, Headache, Abscess, Anemia
Adalimumab	64%	4.7–6.0	10–20 days	12	Injection site reaction, Antibody development, Upper respiratory tract infection, Increased creatine phosphokinase in a blood specimen, Positive ANA titer, Skin rash, Headache, Sinusitis
IL-1 Inhibitors					
Anakinra	95%	18.5	4–6 hours	N.R.	Injection site reaction, Antibody development, Infection, Vomiting, Headache, Arthralgia
IL-6 Inhibitors					
Toculizumab	N.R.	6.4	21.5 days	N.R.	Injection site reaction, Increased S. ALT, S. AST, Neutropenia, Increased S. Cholesterol, Infusion-related reaction, Constipation

Drug	Bio-availability	Volume of Distribution (L/kg)	Half-life (units shown)	Clearance (mL/hour)	Adverse Effects
IL-17 Inhibitors					
Secukinumab	55%–77%	7.1–8.6	22–31 days	N.R.	Infection, Nasopharyngitis, Urticaria, Hypercholesterolemia Diarrhea
Ixekizumab	60%–81%	7.1	13 days	16.5	Neutropenia, Antibody development, URTI, Conjunctivitis
IL-12/23 Inhibitors					
Ustekinumab	57.2%	0.076–0.161	14.9 to 45.6 days	7.91	Antibody development, Infections, Nasopharyngitis
Guselkumab	49%	13.5	15 to 18 days	21.5.	Antibody development, Infections, Nasopharyngitis
Costimulation blockade					
Abatacept	78.6%	0.07	8 to 25 days	Adults: 0.22 mL/hr/kg Children: 0.4 mL/hr/kg	Hypertension Nausea Anemia Antibody development
Anti B-cell depletion and inhibition					
Rituximab	N.R.	3.1	5 to 78 days	0.335 (L/day)	Fatal infusion-related reactions, Mucocutaneous reactions, hepatitis B virus (HBV) reactivation, Progressive multifocal leukoencephalopathy (PML)

Table 1.
Pharmacokinetics parameters of biologicals.

4. Clinical uses

4.1 Rituximab

Rituximab is a chimeric monoclonal antibody that targets the CD20 antigen on the surface of B cells, causing them to be depleted in the bloodstream. Several case reports, case series, and open-label trials have demonstrated that rituximab can benefit refractory myositis patients [40]. The rituximab in myositis (RIM) trial, which included 195 subjects who were refractory to glucocorticoids and at least one immunosuppressive agent, is the largest randomized, double-blind, placebo-controlled trial on the efficacy of rituximab in adult and juvenile myositis to date [41]. Despite the fact that the primary goal was not met, the majority of patients (83%) experienced

clinical improvement and steroid-sparing during the trial. The rituximab treatment was generally well tolerated, with infections being the most common side effect. Anti-Jo1 and anti-Mi-2 antibodies were found to be predictive of a successful response to rituximab in a post-hoc analysis of the RIM trial [42]. After B-cell depletion, both antibody levels dropped, and this was linked to changes in disease activity [43]. In a registry-based research of 43 individuals with ASS, the efficacy of rituximab was further assessed by comparing the clinical response after numerous rituximab cycles in antisynthetase antibody-positive and -negative patients [44]. Only the antibody-positive group demonstrated a significant steroid-sparing impact, though both groups showed clinical improvement regardless of antibody status.

A recent retrospective cohort analysis of 43 patients with refractory myositis found that rituximab is effective, with 75% of patients showing clinical and laboratory improvement after 1 year, as well as a considerable reduction/discontinuation of glucocorticoids [45].

Although the role of B lymphocytes in the development of myositis is not fully known, the present literature supports the use of rituximab in patients with refractory myositis. Infusion responses, potential cardiotoxic effects, and serious infections are all common side effects of rituximab treatment.

4.2 Anakinra

Anakinra, an IL-1 receptor antagonist, was explored in 15 individuals with refractory myositis in a small case study [46]. Seven patients responded clinically to the core set of disease activity measures used by the International Myositis Assessment and Clinical Studies (IMACS), and four of them improved their functional index scores. Randomized controlled research is still required to corroborate the findings.

4.3 Anti-TNFα therapies

Monoclonal antibodies, such as infliximab, and circulating receptor fusion proteins, such as etanercept, are examples of TNFα inhibitors. The present evidence in the literature for anti-TNFα therapy in myositis is mixed, with some studies and trials indicating a positive benefit in myositis patients, while others indicate no efficacy or even worsening symptoms following TNFα inhibitor treatment [47]. Only four out of 12 patients responded to therapy with infliximab in a recent randomized, double-blind, placebo-controlled trial investigating the efficacy of infliximab in refractory PM and DM [48]. However, two individuals who looked to respond to infliximab had their myositis worsen, and restarting the drug was linked to anaphylaxis and the formation of anti-dsDNA antibodies [49]. Infliximab usage was related to better muscle strength and fatigue but only a partial decline in blood CK levels in a larger retrospective study of eight patients with refractory dermatomyositis or polymyositis [50]. Infliximab therapy (four infusions of 5 mg/kg body weight over 14 weeks) proved ineffective in a more recent pilot study of 13 individuals with refractory IIM [51]. A multicenter, open-label, controlled trial of infliximab in combination with weekly methotrexate in patients with polymyositis or dermatomyositis was prematurely terminated due to a low inclusion rate and a high drop-out rate due to disease progression and infusion reactions [52]. TNFα inhibitors may also cause myositis, according to some reports [53]. Therefore, the use of TNFα inhibitors in the treatment of myositis cannot be supported at present.

4.4 Tocilizumab

Tocilizumab, an interleukin 6 (IL-6) receptor antagonist, has only been used in a few case reports so far; the first involved two patients with refractory Jo-1-positive PM who showed a reduction in serum CK levels and resolution of inflammatory signs in muscle magnetic resonance imaging (MRI) after tocilizumab treatment [54]. Another study revealed that tocilizumab treatment improved clinical and laboratory markers in a patient with an overlap syndrome comprising DM and systemic sclerosis who had been resistant to multiple therapies [55]. After continued treatment with tocilizumab, a patient with anti-Jo1- and Ro52-antibodies who suffered from recurring flares of myositis and arthritis with insufficient response to numerous medications showed clinical improvement and normalization of C-reactive protein and CK levels [56]. Tocilizumab did not fulfill the primary or secondary effectiveness outcomes in refractory DM and PM when studied in a randomized, double-blind, controlled phase II trial testing its efficacy in myositis patients [57].

4.5 Abatacept

Abatacept is a human fusion protein that inhibits T-cell costimulation by combining CTLA4 and the fragment-crystallizable region of IgG1. A recently published randomized, open-label, delayed-start trial in 20 individuals with refractory DM or PM indicated that abatacept therapy is effective [58]. The trial showed a significant improvement in muscle strength and health-related quality of life in half of the patients after treatment with i.v. abatacept for 6 months. The therapy was generally well tolerated. These positive results led to an ongoing phase III, randomized, double-blind trial evaluating the efficacy and safety of abatacept in myositis in which the primary endpoint was met in 56% of patients, but the p-value was denoted 0.08 [ClinicalTrials. gov identifier: NCT02971683].

4.6 Bimagrumab

The myostatin/activating type II receptor pathway controls muscle mass. In mouse studies, employing anti-ActRII antibodies causes muscular hypertrophy. The human anti-ActRII antibody is known as bimagrumab [59]. Bimagrumab was studied in 14 patients with IBM. Bimagrumab treatment resulted in an increase in muscle mass and body volume in the patients. In comparison to the placebo group, they improved their 6-minute walking distance [60]. However, in a recent double-blind multicenter trial, the primary endpoint (increasing muscle strength and 6-minute walking distance) was not, despite a favorable safety profile of the drug [61].

4.7 Sifalimumab

Overexpression of IFN-induced genes and IFN-regulated cytokines in blood samples from DM and PM suggests an essential involvement of interferon (IFN)/–mediated immunity in the pathogenesis of myositis [62, 63]. Sifalimumab is an anti-IFN monoclonal antibody whose effects in PM and DM were studied in a phase Ib randomized, double-blind, controlled clinical trial [64]. The suppression of the IFN signature in blood and muscle tissue in myositis patients treated with sifalimumab was linked to clinical improvement. Patients at baseline were identified as having IFN high vs. low gene expression profiles based on 13 type1 interferon-inducible genes.

Sifalimumab suppressed type I IFN expression by 66% in the blood and 47% in the muscle at day 98. Additionally, the levels of multiple dysregulated proteins (type 1 interferon-dependent and -independent) were measured in these patients and were found to be elevated in interferon high but not interferon low groups and correlated with MMT-8 scores. Patients with ≥15% MMT improvement showed greater neutralization of IFN signature than those with <15% improvement in both blood and muscle. Moreover, a reduced level of multiple T cell-associated proteins after sifalimumab but not placebo suggests a suppressive effect of blocking type I IFN signaling on T cell activation and chemoattraction that may lead to a reduction of T cell infiltration in the muscle of myositis patients.

4.8 JAK inhibitors

Ruxolitinib, a Janus kinase inhibitor, was recently shown to be successful in treating refractory dermatomyositis [65]. Ruxolitinib monotherapy led to rapid and significant improvement of dermatomyositis symptoms as the dermatomyositis was in remission by 12 months. Further case reports in juvenile dermatomyositis suggested the beneficial effect of JAK1/2 inhibitors, owing to primary role of constitutive type I IFN activation in the pathogenesis of the condition [66–68]. The use of another JAK inhibitor tofacitinib (a JAK 1/3 inhibitor) has been shown in a few case reports, comprising nine adult patients with refractory DM in total, with the majority improving clinically. Recently, preliminary results of an open-label pilot study evaluating tofacitinib in nine adult patients with refractory DM were presented. All nine patients showed minimal to moderate improvement after 12 weeks of treatment, with no reported serious adverse events. Further randomized controlled trials are expected to evaluate the efficacy and safety of JAK inhibitors.

4.9 Basiliximab

Basiliximab is an interleukin-2 receptor (IL-2R; CD25) chimeric monoclonal antibody that binds to IL-2 receptor on the activated T cells. The expression of interleukin – 2 receptor-α (IL-2Rα, or CD25) is especially upregulated on activated T and B cells. A small amount of IL-2Rα is also present in ordinary healthy people on inactive T and B cells and serum as soluble IL-2 receptor (sIL-2R). The increase in the expression of IL-2Rα, as well as sIL-2R, occurs in autoimmune diseases. One rationale for basiliximab use in myositis is that sIL-2R is correlated with disease activity in some DM/JDM patients.

Jing Zou et al. reported a case series of four adult amyopathic DM patients (positive anti-MDA5 antibody) who had failed conventional therapy. Three of four patients with rapidly progressing ILD demonstrated improved survival, reduction in ferritin levels, and improved lung functions with the use of two doses of 20 mg IV basiliximab 7 days apart. Subsequent trials are awaited.

4.10 Belimumab

Belimumab is a recombinant, fully human, monoclonal antibody directed against the cytokine BLyS, also known as B-cell activating factor (BAFF). It belongs to the tumor necrosis factor (TNF) superfamily and plays a central role in B-cell survival and function. A 40-week multicenter randomized, double-blind placebo-controlled trial with a 24-week open-label phase was conducted to assess the safety and efficacy

of belimumab for IIM patients [69]. All patients met Peter and Bohan criteria and ACR 2017 classification criteria of polymyositis/dermatomyositis (PM/DM) with PM diagnosis adjudication. Refractory IIM was defined as inadequate response/intolerance to 3 months of glucocorticoids and/or at least one immunosuppressive agent (IS). Standard Core Set Measures (CSM) with MMT8 < 125/150 were used to define active disease. Patients on standard of care (SoC) therapy were randomized 1:1 to IV belimumab 10 mg/kg or placebo for 40 weeks followed by 24 weeks of belimumab 10 mg/kg in open-label phase. The study reported a numerically higher proportion of patients on belimumab reaching definition of improvement (DOI) vs. on standard of care (SoC) only arm. A higher proportion of patients on Belimumab achieved sustained moderate or major total improvement score (TIS) at 40 and 64 weeks compared with SoC. Detected differences were not statistically significant; however, the sample size was small.

	Trial	Results
Rituximab	1. **Rituximab in Myositis (RIM) trial**: 195 patients were randomized, double-blind, and placebo-controlled in this study (75 with PM,72 with DM, and 48 with JDM; all refractory to glucocorticoid therapy and at least one immunosuppressive drug) RIM trial-related research 2. **Efficacy of Rituximab in ASS trial**: Registry-based study of 43 patients evaluating the clinical response to many rituximab cycles in individuals with and without antisynthetase antibodies	83% of patients satisfied the definition of improvement. The steroid-sparing effect of rituximab was statistically significant. The most prevalent side effects of rituximab were infections. • Antisynthetase and anti-Mi-2 autoantibodies, as well as the juvenile DM subgroup and reduced disease damage, were all strong predictors of clinical improvement and rituximab response. • In adult DM and JDM patients, the addition of rituximab to conventional treatment resulted in significant improvements in cutaneous disease activity. Only the antibody-positive group demonstrated a substantial steroid-sparing effect, while both groups improved clinically independent of antibody status.
Anakinra	Case study based on 15 individuals with refractory myositis	Seven individuals had a clinical response to the International Myositis Assessment and Clinical Studies' core set of disease activity markers (IMACS), and functional index scores of four of them improved.
Infliximab	1. Randomized, double-blind, placebo-controlled trial investigating the efficacy of infliximab in refractory PM and DM. 2. Retrospective study of eight patients with refractory dermatomyositis or polymyositis. 3. Pilot study of 13 individuals with refractory IIM.	• Infliximab was effective in four out of twelve individuals. • However, myositis worsened in two people who appeared to respond to infliximab, and resuming the treatment was connected to anaphylaxis and the production of anti-dsDNA antibodies. The use of infliximab was associated with enhanced muscular strength and fatigue, but only a partial reduction in blood CK levels. Treatment with infliximab (four 5 mg/kg body weight infusions over 14 weeks) was found to be ineffective.

	Trial	Results
Tocilizumab	1. Case report of two patients with refractory Jo-1-positive PM 2. Case study of a patient with an overlap syndrome comprising DM and systemic sclerosis who had been resistant to multiple therapies. 3. Case study of a patient with anti-Jo1- and R052-antibodies who suffered from recurring flares of myositis and arthritis with insufficient response to numerous medications 4. Randomized, double-blind, controlled phase-II trial testing its efficacy in myositis patients.	Tocilizumab therapy resulted in a decrease in blood CK levels and the remission of inflammatory signals in muscle magnetic resonance imaging (MRI). Improved clinical and laboratory markers on treatment with tocilizumab. Following continued tocilizumab treatment, the patient's clinical condition improved, and his C-reactive protein and creatine kinase values returned to normal. In refractory DM and PM, tocilizumab did not meet the primary or secondary effectiveness outcomes.
Abatacept	Randomized, open-label, delayed-start trial in 20 individuals with refractory DM or PM	After 6 months of therapy with i.v. abatacept, half of the patients had a significant improvement in muscular strength and health-related quality of life.
Bimagrumab	1. Clinical trial in 14 patients with IBM 2. Double-blind multicenter trial	• Patients who received bimagrumab experienced an increase in muscle mass and body volume. • They improved their 6-minute walking distance when compared to the placebo group. Despite the drug's favorable safety profile, the primary goal (increased muscular strength and 6-minute walking distance) was not fulfilled.
Sifalimumab	Phase-Ib randomized, double-blind, controlled clinical trial.	• Clinical improvement was associated with the reduction of the IFN signature in blood and muscle tissue in myositis patients treated with sifalimumab. • Patients with ≥15% MMT improvement showed greater neutralization of IFN signature than those with <15% improvement in both blood and muscle. • A reduced level of multiple T cell-associated proteins after sifalimumab but not placebo, suggests a suppressive effect of blocking type I IFN signaling on T cell activation and chemoattraction that may lead to a reduction of T cell infiltration in the muscle of myositis patients
Ruxolitinib	Case reports (nine adult patients with refractory DM)	• Majority improved clinically with Ruxolitinib treatment. • After 12 weeks of therapy, all nine patients demonstrated modest to moderate improvement, with no significant side effects noted.

	Trial	Results
Basiliximab	Jing Zou et al. case series of four adult amyopathic DM patients (positive anti-MDA5 antibody) who had failed conventional therapy.	With two doses of 20 mg IV basiliximab given 7 days apart, three of four patients with rapidly progressing ILD showed better survival, reduced ferritin levels, and improved lung function.
Belimumab	40-week multi-center randomized, double-blind placebo-controlled trial with 24 weeks open-label phase in IIM patients.	• Higher proportion of patients on belimumab reaching definition of improvement (DOI) vs. on standard of care (SoC) only arm. • When compared to SOC, a larger percentage of patients on Belimumab had a sustained moderate or substantial total improvement score (TIS) at 40 and 64 weeks.

5. Conclusion

The introduction of biologic therapies has held considerable promise for autoimmune diseases, allowing us to translate our knowledge of specific disease pathophysiology processes into treatments that target certain autoimmune disorders. One challenge in examining prospective biologic and other treatments for IIM in the future is the scarcity of information. There is mounting evidence that biologic therapy in IIM can help patients with refractory disease by improving muscle strength, lowering biochemical markers of muscle inflammation, and weaning them off of glucocorticoids. The fact that IIMs are rare diseases poses a substantial hurdle, as it limits the number of people who can participate in clinical studies. Furthermore, while substantial progress has been made in understanding the etiology of IIM, much remains unknown about the immunological systems that underpin these disorders. Rituximab has been the most thoroughly studied of the biologic medicines, and it appears to be successful in people with PM, DM, and JDM. Other agents are constrained by a lack of trial data and small sample sizes, notwithstanding their promise. Because of the significant basic research evidence that interferon is essential to the etiopathogenesis of IIM disease, sifalimumab must currently be considered the biologic with the most potential in the future. The biologic rationales for the medicines may be discussed in-depth, and the enthusiasm for the future is genuine. However, most of these treatments are likely to be 3–5 years, if not more, away from the clinician's repertoire and patient therapy. It's anyone's guess what the future holds and how much the drugs will cost.

Conflict of interest

The authors declare no conflict of interest.

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