

Precision and cellular therapies for adult idiopathic inflammatory myopathies: Recent advances

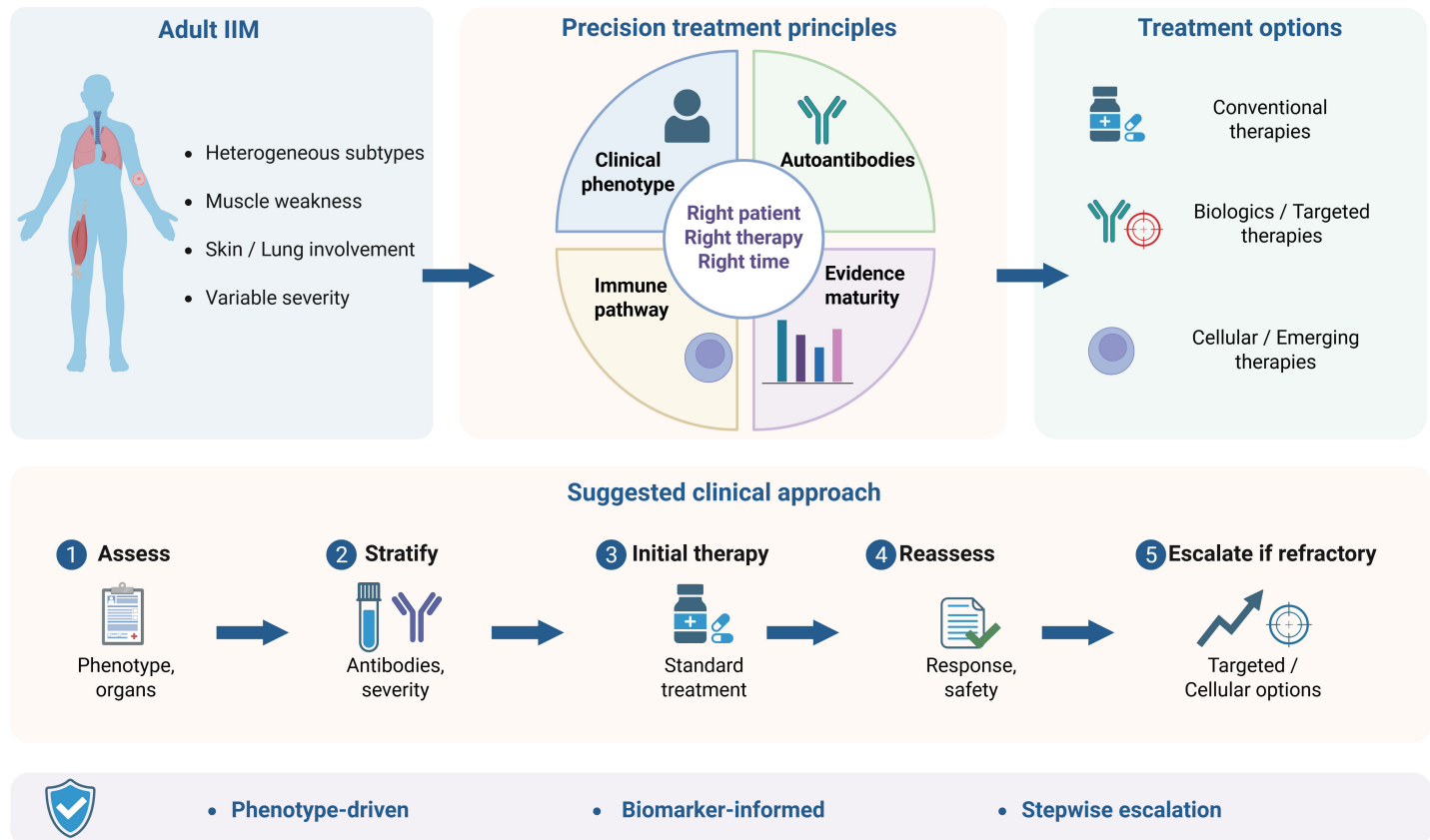
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GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Idiopathic inflammatory myopathies (IIMs) are rare autoimmune diseases affecting muscle and other organs.
- Biologics, targeted drugs, and cellular therapies expand options for adults with refractory IIMs.
- Phenotype, organ involvement, and biomarkers can guide more precise treatment choices.

Precision and cellular therapies for adult idiopathic inflammatory myopathies: Recent advances

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Idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of autoimmune diseases with variable extramuscular involvement and diverse treatment responses. Although glucocorticoids and conventional immunosuppressants remain the cornerstone of therapy, refractory disease and treatment intolerance are still common. Emerging biologic, pathway-based, and cellular therapies are expanding treatment options, particularly for selected patients with refractory disease, although the strength of evidence and current clinical applicability vary among approaches. Meanwhile, advances in single-cell and spatial omics are improving understanding of disease heterogeneity and facilitating more precise treatment stratification. This review summarizes current and emerging therapies for adult IIMs, with an emphasis on their clinical relevance, phenotype-specific application, and the evolving role of biomarker-informed precision medicine in refractory disease.

INTRODUCTION

Idiopathic inflammatory myopathies (IIMs) are a diverse group of rare, chronic autoimmune diseases. Meta-analyses indicate a broad incidence range of 1.16–19 cases per million person-years and a prevalence of 2.4–33.8 per 100,000 population.¹ Inflammation-induced muscle damage results in muscle weakness and is also associated with a wide range of extra-muscular manifestations, such as skin rashes, pulmonary involvement, and arthralgia. In adult clinical practice and research, four major phenotypes are most consistently evaluated—dermatomyositis (DM), polymyositis (PM), immune-mediated necrotizing myopathy (IMNM), and inclusion body myositis (IBM). Notably, randomized trials in IBM remain limited in number and scale, precluding definitive conclusions regarding therapeutic efficacy. Framing the therapeutic evidence according to these four adult phenotypes enhances the interpretability of trial data and facilitates translation to clinical decision-making. Clinically amyopathic dermatomyositis (CADM) most frequently occurs in association with anti-MDA5-positive DM (MDA5-DM), which is highlighted explicitly in this review when discussing disease heterogeneity and treatment evidence.

The disease burden of IIMs is substantial, encompassing not only progressive muscle weakness and disability but also frequent extramuscular involvement, particularly interstitial lung disease (ILD), which occurs in up to 40% of cases and is a major contributor to morbidity and mortality.^{2,3} Current treatment relies heavily on high-dose glucocorticoids and conventional immunosuppressants such as methotrexate, azathioprine, and mycophenolate mofetil. However, some patients experience incomplete or poor responses, especially in subtypes such as MDA5-DM and IBM, in which treatment resistance is common.^{4,5}

Over the past two decades, therapeutic goals in IIMs have evolved significantly, shifting beyond the mere suppression of inflammation toward a more holistic approach that includes restoration of muscle function, prevention of organ damage, and promotion of tissue regeneration.⁶ Historically, high-dose corticosteroids and broad-spectrum immunosuppressants were administered primarily to reduce inflammation and halt disease progression. However, emerging evidence suggests that resolution of inflammation does not necessarily correlate with meaningful functional recovery or long-term

quality of life, particularly in patients with refractory disease or chronic muscle damage.⁷ While no universally validated remission criteria have been adopted in routine adult IIMs practice, the International Myositis Assessment and Clinical Studies (IMACS) group has proposed preliminary consensus-based trial definitions—"complete clinical response" (≥6 months of no evidence of disease activity while on therapy) and "clinical remission" (≥6 months off therapy with no evidence of disease activity)—which still require prospective validation and are mainly used in research settings.⁸

In this context, novel approaches targeting myogenic pathways are gaining increasing attention. For example, early-phase trials investigating agents that modulate myostatin signaling—such as bimagrumab, an anti-ActRIIB antibody—have demonstrated promising effects on lean body mass and muscle volume in IBM, although functional improvements remain modest.⁴ These findings underscore the need to redefine treatment success not only in terms of inflammation suppression but also restoration of strength, endurance, and quality of life. Accordingly, current research and clinical guidelines increasingly advocate for multi-dimensional therapeutic endpoints, including patient-reported outcomes and objective assessments of function and regeneration. Because randomized or endpoint-driven clinical trials specifically targeting anti-synthetase syndrome (ASyS) remain limited, this review synthesizes treatment evidence primarily across DM, PM, IMNM, and IBM, while addressing ILD-related management in a subtype-agnostic manner when appropriate. Beyond summarizing available therapies, this review aims to provide a clinically oriented framework for treatment selection in adult IIMs by integrating phenotype, organ involvement, refractoriness, and emerging biomarker-informed strategies. Unlike prior reviews that primarily summarize available agents, this review emphasizes how treatment selection in adult IIMs may be organized according to the intersection of clinical phenotype, organ involvement, dominant immune pathway, and evidence maturity.

CONVENTIONAL THERAPIES: STILL THE FIRST LINE

Non-pharmacological treatments

Conventional therapies remain the therapeutic foundation in adult IIMs; however, their clinical role is best understood as the baseline layer of a broader treatment framework in which escalation increasingly depends on phenotype, organ involvement, and refractoriness. Standard pharmacological and adjunctive therapies for IIMs, except for IBM, are shown in [Figure 1](#). [Figure 1](#) is intended as a pragmatic treatment-escalation framework rather than a rigid guideline, highlighting how baseline therapy may be modified according to phenotype, organ involvement, and refractory status. In the management of IIMs, exercise, dietary modification, and lifestyle interventions are important adjunctive therapies that contribute to symptom relief, recovery, and improved quality of life. Research has shown that moderate endurance exercise activates aerobic metabolic pathways, promotes muscle growth, and concurrently suppresses inflammatory responses.⁹ Moreover, consumption of high-quality protein and creatine supplementation has been reported to facilitate muscle repair in these patients.^{10,11} Initial interventions, such as strict photoprotection, are also essential to mitigate the exacerbating effects of ultraviolet light.¹² Conversely, unhealthy lifestyle choices may exacerbate systemic inflammation and thereby impede disease recovery. A 2024

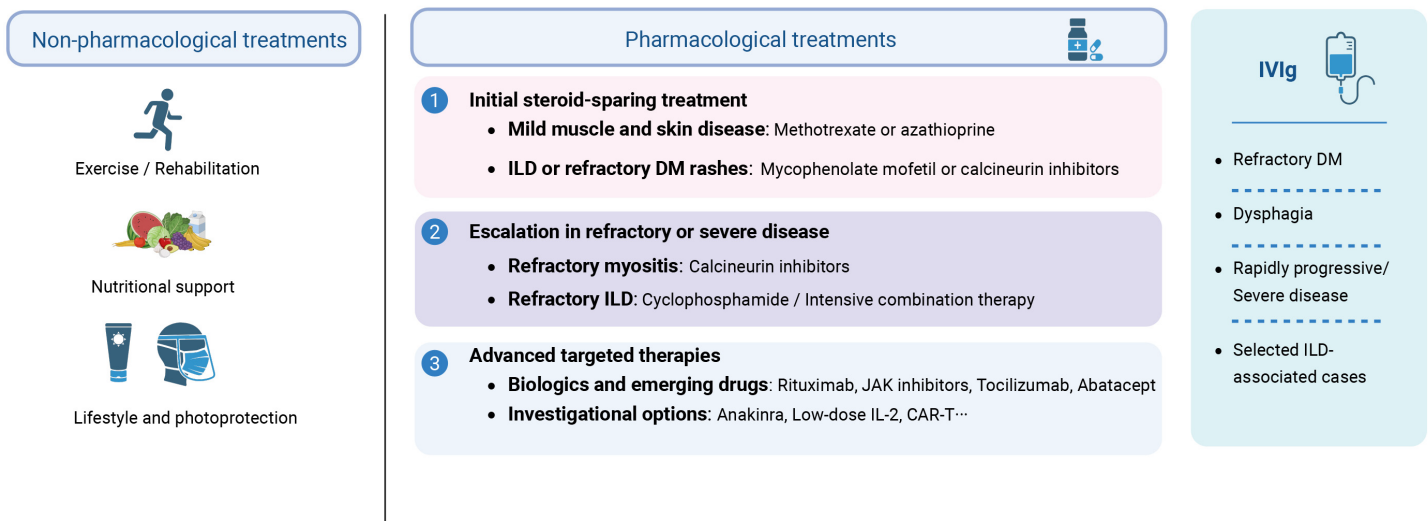


Figure 1. Stepwise treatment framework for adult IIMs excluding IBM Supportive non-pharmacological measures, including exercise/rehabilitation, nutritional support, and lifestyle interventions, should be maintained throughout treatment. Pharmacologic management begins with glucocorticoids plus phenotype-appropriate steroid-sparing therapy. Escalation is guided by disease severity, refractory status, organ involvement, and, where available, biomarker context. Advanced targeted and investigational therapies are mainly considered in refractory or phenotype-enriched settings. Notes: IIMs: idiopathic inflammatory myopathies. IBM: inclusion body myositis. ILD: interstitial lung disease. DM: dermatomyositis. IL: interleukin. CAR: chimeric antigen receptor.

study from Latin America also suggested potential benefits of spiritual involvement.¹³

Corticosteroids and optimization strategies for their use

Glucocorticoids remain the cornerstone of initial therapy for IIMs owing to their rapid anti-inflammatory effects. However, concerns regarding adverse effects have led to a shift in treatment paradigms toward early tapering and combination strategies aimed at minimizing glucocorticoid exposure while preserving efficacy.

Recent management guidelines recommend initiating prednisone at 0.5–1 mg/kg/day (typically not exceeding 80 mg/day), followed by tapering over 6–12 months, in conjunction with a steroid-sparing immunosuppressant in patients with high disease activity.^{14,15} Multiple cohort studies have shown that early initiation of immunosuppressants facilitates more rapid glucocorticoid tapering without compromising disease control and is associated with a lower incidence of steroid-related adverse events.¹⁶

Moreover, high-dose intravenous methylprednisolone pulses (e.g., 500–1,000 mg/day for 3–5 days) are increasingly used in patients with severe organ involvement. However, optimal dosing and timing remain areas of active investigation, particularly in light of some study such as the JAMI cohort study in Japan, which is evaluating upfront intensive regimens for high-risk patients.¹⁷

Immunosuppressants

Methotrexate (MTX) and azathioprine (AZA) are widely used first-line immunosuppressants and are often combined with corticosteroids in newly diagnosed patients. Nevertheless, a significant proportion of patients exhibit an inadequate response, necessitating alternative immunosuppressive strategies. Mycophenolate mofetil (MMF) has been increasingly used, particularly in patients with IIMs-associated ILD. In a retrospective U.S. cohort, MMF maintained stable pulmonary function over 12 months in IIMs-ILD patients, although improvements were limited compared with calcineurin inhibitors.¹⁸ Moreover, a Cochrane systematic review of immunosuppressive and immunomodulatory treatments for adult dermatomyositis and polymyositis, which analyzed 10 randomized controlled trials (n = 258), found no clear superiority among commonly used steroid-sparing agents such as MTX, AZA, or ciclosporin (CsA), but confirmed their role as adjuncts to glucocorticoids and highlighted the limitations of the available trials (small sample sizes, heterogeneous outcomes, and risk of bias).¹⁹

Cyclophosphamide (CYC) and calcineurin inhibitors (e.g., CsA or tacrolimus) are typically used as second-line agents in refractory cases or in those with severe organ involvement. While CYC shows efficacy in patients

with life-threatening ILD, its toxicity profile limits long-term use.²⁰ In a recent U.S. study, tacrolimus was associated with improved forced vital capacity and reduced oxygen dependence in MDA5-ILD patients.¹⁸ In retrospective cohorts of refractory PM/DM, tacrolimus, either in combination with or as a substitute for steroids and other immunosuppressants, achieved partial or complete remission in approximately 72%–100% of patients, as evidenced by improvements in muscle strength, reductions in creatine kinase (CK) levels, and tapering of corticosteroid doses, with no serious adverse events reported.^{21,22} Current studies have also confirmed that a combined immunosuppressive regimen consisting of high-dose glucocorticoids, tacrolimus, and intravenous CYC is effective for MDA5-ILD.²³

Intravenous immunoglobulin

Intravenous immunoglobulin (IVIg) has established a role in specific clinical contexts, particularly in refractory DM, and has gained regulatory approval in recent years. The pivotal ProDERM trial provided high-quality evidence supporting the efficacy of IVIg in DM.²⁴ Based on these results, the U.S. FDA approved IVIg (Octagam 10%) for the treatment of adult DM in 2021. Beyond DM, observational studies have reported benefits of IVIg in IMNM and overlap myositis, particularly in cases complicated by dysphagia or ILD. Given the lack of clearly defined clinical trial endpoints specific to ASyS, we refrain from drawing ASyS-specific efficacy conclusions and instead discuss ILD-driven management in a subtype-agnostic framework.^{25,26} IVIg is also considered in patients with severe or rapidly progressive disease when other immunosuppressants are contraindicated.²⁷ In addition, a 2021 systematic review and meta-analysis that included 29 studies and 576 patients with IIM/ juvenile dermatomyositis (JDM) confirmed that both IVIg and subcutaneous immunoglobulin were associated with high partial response rates (approximately 88%) and meaningful steroid-sparing effects, while maintaining an acceptable safety profile, thereby supporting the use of Ig therapy as an evidence-based option in refractory or selected first-line settings.²⁷ Clinically, conventional therapy should be regarded as the foundational layer of adult IIMs management, whereas subsequent escalation should be individualized according to phenotype, organ-threatening manifestations, early treatment response, and evidence strength.

BIOLOGIC AGENTS: FROM EMPIRICAL USE TO TARGETED APPLICATIONS

Anti-B cell therapy in IIMs

Rituximab and CD20⁺ B-cell depletion. B cells have been increasingly recognized as key contributors to the pathogenesis of IIMs, particularly

through autoantibody production, antigen presentation, and cytokine secretion.²⁸ Rituximab, a chimeric monoclonal antibody targeting CD20⁺ B cells, has emerged as a promising therapeutic option in refractory IIMs, including DM and IMNM.

In a randomized, double-blind, placebo-phase-controlled study, rituximab was evaluated in patients with refractory myositis, including both adult and juvenile DM. The trial enrolled 195 patients who were randomized to receive rituximab either at week 0 or week 8 in a placebo-phase design. Overall, 83% of patients met the definition of improvement (DOI) by the end of the study, with no significant difference between early and delayed rituximab groups; nevertheless, substantial overall clinical improvement was observed across the cohort.²⁹ In a review of 34 refractory IMNM patients, rituximab led to significant improvement in muscle strength and normalization of CK levels in 61.8% of cases.³⁰

Despite encouraging overall outcomes with rituximab in refractory PM/DM, responses appear to be reduced in patients who are negative for myositis-specific antibodies (MSAs). Multiple analyses—including the RIM trial and real-world cohorts—have shown that absence of MSAs predicts a poor or absent therapeutic response, while MSA positivity, particularly anti-Jo-1 and anti-Mi-2 antibodies, correlates with favorable clinical outcomes.²⁹ Safety profiles across multiple studies have generally been acceptable, with infusion reactions and infections being the most commonly reported adverse events. Interpretation of these findings should take into account the placebo-phase design of the RIM trial, the heterogeneity of included myositis subtypes, and the reliance of other supportive evidence on retrospective case series, all of which limit precise estimation of treatment effect across phenotypes. In practice, rituximab currently has the strongest clinical rationale among B-cell-directed therapies, particularly in autoantibody-positive refractory disease.

BAFF-targeted therapy: belimumab. Belimumab, a monoclonal antibody targeting B cell activating factor (BAFF), has been investigated in refractory IIMs. A phase 2 randomized controlled trial showed numerically higher clinical improvement rates in the belimumab group compared with placebo, although the difference did not reach statistical significance.³¹ Additionally, a retrospective study in DM and JDM demonstrated significant reductions in disease activity and corticosteroid dose following belimumab treatment.³² However, the current evidence supporting belimumab in IIMs remains preliminary, as it is based on limited randomized data and small retrospective cohorts, and therefore does not yet support broad clinical adoption.

Dual BAFF/APRIL blockade: telitacept. Telitacept, a recombinant fusion protein targeting both BAFF and APRIL, represents a novel B cell-modulating therapy for refractory IIMs. By simultaneously inhibiting B cell maturation and long-lived plasma cell survival, telitacept may reduce pathogenic autoantibody production. A recent pilot study demonstrated that add-on telitacept therapy significantly improved muscle strength, lowered serum CK levels, and enabled substantial corticosteroid tapering in patients with refractory IIMs, particularly in those with IMNM.³³ These findings highlight telitacept as a promising treatment option for B cell-driven refractory myositis. However, as the currently available evidence is limited to an early pilot study, these findings should be interpreted as hypothesis-generating rather than practice-changing.

Targeting Type I interferon pathway: JAK/STAT inhibitors in the treatment of DM

Type I interferon (IFN) signaling is increasingly recognized as a central pathogenic driver in DM, contributing to both muscle and skin inflammation via upregulation of interferon-stimulated genes (ISGs). Janus kinase (JAK) inhibitors, by blocking JAK1/2-mediated downstream signaling of IFN- α/β receptors, have emerged as promising therapies for patients with refractory myositis.^{34,35} Furthermore, transcriptomic studies in some trials confirmed that responders showed down-regulation of IFN-regulated genes (e.g., MX1, IFIT1). This molecular change paralleled clinical improvement, suggesting that IFN-related signatures may serve as pharmacodynamic markers.^{36,37}

This mechanistic rationale has provided the basis for early clinical evaluation of JAK inhibitors in DM, particularly in refractory and interferon-enriched phenotypes.

Evidence from the STIR trial (tofacitinib). The STIR trial (Study of Tofacitinib in Refractory DM) was a single-arm, open-label study evaluating the

safety and preliminary efficacy of tofacitinib in adults with treatment-resistant DM. Among 10 patients enrolled, 70% achieved a ≥ 20 -point improvement in the Total Improvement Score (TIS) by week 12, with significant reduction in ISG expression and skin disease activity.³⁶ Notably, the treatment was well tolerated, and steroid-sparing effects were observed in most patients. Meta-analyses have suggested that efficacy appears consistent regardless of treatment initiation timing.³⁸ Additionally, multiple JAK inhibitors have demonstrated therapeutic benefit, suggesting a potential class effect.^{39,40} However, these findings should be interpreted cautiously, as the study was limited by its very small sample size, single-arm open-label design, and lack of a comparator group, thereby limiting the ability to distinguish true treatment effects from background variability or expectation bias.

Broader JAK inhibitor experience (baricitinib, ruxolitinib) and skin-dominant benefit. A recent open-label pilot study demonstrated promising results for the use of JAK inhibitors in adult patients with DM. The study included 12 patients treated with baricitinib and 4 treated with ruxolitinib. After 3 months of treatment, 90% of patients experienced improvements in skin symptoms, with a significant reduction in the mean Cutaneous Dermatomyositis Activity and Severity Index (CDASI) score. Although manual muscle testing (MMT-8) scores remained largely unchanged, the study also reported a reduction in prednisone dose to ≤ 5 mg/day in some patients and discontinuation of IVIg in others.⁴¹

These data support the growing rationale for JAK inhibitors as targeted immunomodulators in DM, especially for patients with skin-dominant or refractory disease. However, interpretation across JAK inhibitor studies remains limited by small sample sizes, predominantly non-randomized designs, and heterogeneity in outcome measures, with some studies emphasizing skin activity while others focus on muscle strength, steroid sparing, or interferon-related biomarkers. From a practical perspective, JAK inhibitors currently appear most relevant in refractory or skin-dominant DM, and potentially in interferon-enriched phenotypes.

Targeting the IL-6 pathway: tocilizumab in myositis-associated interstitial lung disease

Interleukin-6 (IL-6) is a key pro-inflammatory cytokine implicated in the pathogenesis of IIMs and their complications, particularly ILD. In a study of 168 MDA5-DM patients, serum IL-6 ≥ 13.41 pg/mL independently predicted 6-month mortality and the development of rapidly progressive ILD (RP-ILD). Moreover, immunohistochemical analysis demonstrated elevated IL-6 expression in lung tissue of RP-ILD patients, supporting the association of IL-6 levels in serum and bronchoalveolar lavage fluid with both disease activity and poor prognosis.⁴² Tocilizumab, a monoclonal antibody targeting the IL-6 receptor, has therefore emerged as a potential therapeutic agent for this severe disease phenotype.

A recent case series highlighted the potential of tocilizumab in managing refractory MDA5-ILD. Six patients who failed conventional immunosuppressive therapy showed significant improvement following tocilizumab treatment.⁴³ Another open-label pilot study further supported the efficacy of tocilizumab in refractory IMNM. In that study, 7 of 11 patients achieved clinically significant responses. Responders exhibited higher baseline serum IL-6 and muscle IL-6 mRNA levels, along with a greater proportion of CD56-positive muscle fibers.⁴⁴

In contrast, a phase 2b randomized, double-blind, placebo-controlled trial evaluating the efficacy and tolerability of tocilizumab in refractory adult PM/DM showed no significant difference ($P = 0.86$) in TIS over 24 weeks between the tocilizumab and placebo groups. Although the treatment was safe and well-tolerated, tocilizumab failed to meet the primary or secondary efficacy endpoints in refractory DM and PM.⁴⁵ These discrepant results likely reflect differences in study design (uncontrolled versus randomized), sample size, and patient selection, as well as heterogeneity in dominant clinical phenotype and study endpoints, thereby limiting direct comparison between ILD-predominant cohorts and broader refractory PM/DM populations.

Taken together, the currently available evidence does not support routine use of IL-6 blockade across unselected adult IIM populations. The discrepancy between encouraging case-based or open-label reports and the negative randomized trial is likely attributable to differences in evidence level, patient enrichment, and disease phenotype. At present, IL-6 inhibition may be

considered only in highly selected refractory cases, particularly those with IL-6 high or MDA5-associated ILD-predominant features, preferably within expert centers or clinical trials. Further biomarker-stratified studies are required before broader clinical recommendations can be established. Clinically, IL-6 blockade should therefore be reserved for highly selected refractory cases with a strong biological rationale rather than used as a routine escalation strategy.

Lessons from anti-TNF and IL-1 inhibitor therapies

Biological rationale and limited clinical translation. Although tumor necrosis factor- α (TNF- α) and interleukin-1 (IL-1) are pivotal cytokines in many autoimmune and autoinflammatory diseases, their role in IIMs appears more complex and less therapeutically promising. Multiple clinical studies have shown limited or even paradoxical outcomes with TNF or IL-1 blockade, reshaping our understanding of the immunopathogenesis of IIMs.

Anti-TNF agents: inconsistent efficacy and paradoxical myositis. Despite its efficacy in rheumatoid arthritis and ankylosing spondylitis, anti-TNF therapy has not demonstrated consistent benefit in IIMs. A randomized, double-blind, placebo-controlled trial investigated the safety and efficacy of infliximab in refractory PM/DM and showed no significant differences between infliximab and placebo groups in the primary or secondary endpoints.⁴⁶ Similarly, a case series of five patients with DM treated with etanercept reported variable clinical responses, with some patients experiencing disease exacerbation.⁴⁷

Moreover, case reports and cohort studies have described de novo or exacerbated myositis in patients receiving anti-TNF agents for other diseases, suggesting potential disease-triggering effects in genetically susceptible individuals.⁴⁸

IL-1 blockade and implications for IIMs pathogenesis. Similarly, IL-1 blockade with anakinra, a recombinant IL-1 receptor antagonist, showed limited clinical efficacy in a small open-label study involving DM patients with systemic features. A uncontrolled mechanistic study investigated the efficacy and safety of anakinra in refractory IIMs. The study included 15 patients with refractory myositis who were treated with anakinra for 12 months, of whom only 7 met the IMACS definition of clinical response.⁴⁹ These results suggested that, compared with JAK- or B-cell-directed approaches, the evidence base supporting IL-1 or TNF inhibition remains more limited and less generalizable.

Interpretation of these negative or inconsistent findings is further constrained by small sample sizes and, in some studies, non-uniform outcome definitions, making it difficult to determine whether the limited efficacy reflects true biological irrelevance or inadequate trial design. Taken together, the modest and inconsistent efficacy of TNF- and IL-1-directed therapies suggests that these pathways are unlikely to represent dominant and broadly actionable drivers across adult IIMs subtypes. Their relative lack of therapeutic success, compared with B-cell or JAK-directed approaches, also helps refine current understanding of pathogenic hierarchy in IIMs.

Overall, these biologic therapies should not be viewed as interchangeable escalation options, but rather as pathway-selective interventions whose clinical relevance may differ according to autoantibody profile, dominant organ involvement, inflammatory program, and the strength of supporting evidence.

NOVEL TARGETED THERAPIES AND PATHWAY-BASED INTERVENTIONS

Interferon-stimulated genes (ISGs) as predictive biomarkers in IIMs

IFN-I signatures and biomarker candidates in IIMs. IFN-I signaling plays a pivotal role in the pathogenesis of IIMs, particularly DM. ISGs, such as MX1 and ISG15, are consistently overexpressed in muscle and skin tissues from IIMs patients, making them attractive candidates as biomarkers for disease activity and therapeutic response.⁵⁰

In a large transcriptomic analysis, distinct IFN signatures were observed across IIMs subtypes: DM exhibited a dominant type I IFN signature with upregulation of ISG15 in muscle tissue, while ASyS and IBM demonstrated a stronger type II IFN profile.⁵¹

A study showed that Siglec-1, a type I interferon biomarker, is elevated in treatment-naïve IIMs patients and tends to decline following IVIg monotherapy. The study further demonstrated correlations between Siglec-1 expression and clinical measures of disease activity. Moreover, longitudinal changes

in Siglec-1 levels were associated with treatment response in DM, suggesting its potential utility as a biomarker for disease activity and treatment response in IIMs, particularly DM.⁵²

At present, however, these biomarkers are best regarded as tools for biological enrichment and disease monitoring in research-oriented or specialist settings, as standardized thresholds, assay accessibility, and therapy-directing algorithms for routine clinical use remain insufficiently established.

Clinical blockade of IFN-I: Sifalimumab. A phase 1b clinical trial evaluated sifalimumab, an anti-IFN- α monoclonal antibody, for the treatment of DM/PM. The study found that sifalimumab effectively suppressed the type I interferon gene signature (IFNGS) in both blood and muscle tissue of myositis patients, with a median suppression of 53-66% in blood and 47% in muscle specimens. The suppression of IFNGS was associated with a positive trend in clinical improvement, particularly in patients showing a 15% or greater improvement in MMT-8 scores. Sifalimumab also significantly reduced IFN-inducible transcripts and proteins, and its effects correlated with changes in pathways related to leucocyte infiltration, antigen presentation, and immunoglobulin responses.⁵³

Next-generation IFN-I targeting: Dazukibart. Dazukibart, an anti-IFN β monoclonal antibody, showed significant efficacy in the treatment of DM in a phase 2 trial. The therapy rapidly reduced disease activity in both skin-predominant and muscle-predominant patients, with notable improvements in CDASI-A scores and muscle function outcomes. Dazukibart was also well tolerated, highlighting its potential as a promising therapeutic option for DM.⁵⁴

Overall, IFN-related biomarkers currently appear most useful for biological enrichment, phenotype recognition, and treatment-response monitoring in specialist settings, rather than as standalone tools for routine treatment selection.

Complement system blockade

Complement activation has long been recognized as a key immunopathogenic feature of DM, characterized by membrane attack complex (MAC, C5b-9) deposition on endomysial capillaries and perifascicular atrophy, representing a complement-mediated microangiopathy. Similarly, in IMNM, complement activation, evidenced by C5b-9 deposits on necrotic muscle fibers, has been observed, supporting a potential role for complement blockade in its treatment.⁵⁵

Eculizumab, a monoclonal antibody targeting complement component 5 (C5) to prevent MAC formation, has shown therapeutic potential in IIMs. A case report described a 19-year-old patient with severe, life-threatening DM that was resistant to steroids, IVIg, and plasma exchange but improved markedly after eculizumab induction.⁵⁶ With respect to ravulizumab, to the best of our knowledge and at the time of revision, there are no completed clinical studies evaluating its efficacy in inflammatory myopathies; therefore, no firm conclusions can be drawn for MDA5-DM or other adult IIMs phenotypes.

Therapeutic potential of AMPK and mTOR modulators

AMPK serves as a cellular energy sensor and exerts anti-inflammatory effects through multiple mechanisms, including inhibition of mTOR. In recent studies, AMPK activation (e.g., via metformin or AICAR) suppressed inflammation and promoted autophagy by downregulating mTOR phosphorylation.⁵⁷

The study by Ching et al. in 2013 demonstrated that mTOR dysfunction contributes to the vacuolar pathology and weakness in valosin-containing protein-associated inclusion body myopathy (VCP-IBM), highlighting the role of mTOR in muscle autophagy and pathology.⁵⁸ Another study showed that iron promotes glucose metabolism in CD4⁺ T-cells from patients with autoimmune myopathy by upregulating PFKFB4 through AKT-mTOR signaling, indicating the involvement of mTOR in the pathogenicity of T helper cells.⁵⁹ Additionally, Geng et al. in 2017 identified palmitoleic acid, regulated by mTOR signaling, suggesting the potential of mTOR in the detection and therapy of polymyositis.⁶⁰ These studies collectively underscore the potential of AMPK/mTOR signaling as a therapeutic target in myositis, where mTOR inhibitors like sirolimus have shown clinical improvement in patients with IBM.⁶¹ The mTOR pathway's regulatory role in inflammation and metabolism

positions it as a key player in the pathogenesis and treatment of various myositis subtypes.

Taken together, these mechanistic observations suggest that AMPK-mTOR-directed approaches are most likely to benefit IIMs patients in whom overt inflammation has been partially controlled but muscle weakness, atrophy, or autophagy defects persist (e.g., IBM, chronic PM/DM, or IMNM with degenerative features). In such phenotypes, pathway modulation would act as an adjunct to, rather than a replacement for, immunosuppressive therapy by promoting myofiber repair, improving metabolic fitness, and potentially slowing functional decline. Because the current clinical evidence for mTOR inhibition (e.g., sirolimus in IBM) comes from small and heterogeneous cohorts, future trials should stratify by IIMs subtype and baseline functional status and should incorporate muscle performance/endurance and patient-reported outcomes, not only biochemical markers, to determine which patients translate pathway correction into meaningful clinical improvement.

Other emerging experimental targets

Abatacept, a fusion protein that selectively inhibits the interaction between antigen-presenting cells (APCs) and T-lymphocytes by binding to CD80 and CD86 receptors on APCs, has shown promising results in a phase IIb clinical trial for patients with refractory DM and PM.⁶² Mechanistically, Cytotoxic T lymphocyte-associated antigen 4 (CTLA4)-Ig (abatacept) has been associated with an increase of intramuscular Foxp3⁺ regulatory T cells in DM/PM, as demonstrated in muscle biopsies, supporting a tolerance-restoring mode of action.⁶² These findings prompted a phase III study; however, that study failed to meet its primary objective.⁶³

Basiliximab is a monoclonal antibody targeting the IL-2 receptor, which is expressed on activated T and B cells. Evidence suggests that IL-2 receptor levels correlate with disease activity in active DM.⁶⁴ In a case series of four adult patients with RP-ILD associated with MDA5-DM, three patients showed clinical improvement following basiliximab treatment.⁶⁵ The role of low-dose IL-2 in autoimmune diseases is emerging, with implications for IIMs treatment.^{66,67} Immunological mechanisms of emerging treatment regimens for IIMs are shown in Figure 2.

At the same time, interpretation of the therapeutic literature in adult IIMs remains complicated by methodological heterogeneity across studies, including small cohorts, inconsistent endpoint selection, and limited availability of randomized controlled data for many emerging therapies.

CELLULAR THERAPIES AND REGENERATIVE STRATEGIES

Stem cell-based therapies for severe or refractory IIMs

Hematopoietic/immune reconstitution approaches (SCT/HSCT). SCT has emerged as a potential therapy for refractory autoimmune rheumatic disorders, including IIMs. Early-phase studies indicated that SCT could induce clinically significant responses in various autoimmune diseases, though with notable morbidity and mortality.⁶⁸ A 2012 review by Mascarenhas et al. highlighted that SCT might reset the immune system, offering benefits in conditions like PM and DM.⁶⁹ However, the number of patients studied was small, and transplant-related mortality remained a concern. Recent studies have reported some success in using allogeneic mesenchymal stem cell transplantation to improve muscle strength and reduce inflammation in PM/DM patients, but larger, randomized controlled trials are still needed to better define the efficacy and safety of SCT in these conditions. Overall, while SCT shows promise for treating severe, refractory myositis, it should be reserved for patients with life-threatening disease refractory to conventional therapies, and further research is necessary to optimize patient selection and transplantation protocols.

Mesenchymal stem cell transplantation (MSCT) and immunomodulation. Mesenchymal stem cells (MSCs) exert broad immunomodulatory effects via both direct cell-cell interactions and secretion of paracrine factors. They can suppress pro-inflammatory cytokines such as TNF- α and IL-6 while promoting anti-inflammatory mediators like IL-10 and TGF- β . Furthermore, MSCs induce the differentiation of regulatory T cells (Tregs), inhibit Th1 and Th17 responses, and promote the apoptosis or functional inhibition of activated macrophages and B cells.⁷⁰ A small-scale pilot study assessed the safety and clinical efficacy of allogeneic MSCT in 10 patients with drug-resistant PM or DM. This single-arm trial included patients who were either refrac-

tory to standard treatment or had severe systemic involvement. All patients provided consent and underwent allogeneic MSCT, with clinical and laboratory manifestations compared before and after the procedure. Notable improvements were observed in serum CK, patient global assessment by visual analogue scale, muscle strength by manual muscle test, and interstitial lung disease in selected patients. One patient also experienced improvement in chronic non-healing skin ulcers. Additionally, clinical responses were noted in patients undergoing a second MSCT for disease recurrence. The study concluded that MSCT appears to be safe and effective for drug-resistant DM/PM patients, although current evidence remains limited to small uncontrolled cohorts.⁷¹

Mitochondrial transplantation from MSCs (PN-101). While exploring the role of mesenchymal stem cells in myositis therapy, mitochondrial transplantation, an emerging therapeutic strategy, also deserves attention. A recent study demonstrated that mitochondria isolated from human umbilical cord mesenchymal stem cells (PN-101) can enhance muscle differentiation and mitochondrial function in myoblasts from patients with IIMs and in vivo models. In vitro experiments showed that PN-101 restored myosin heavy chain expression and mitochondrial protein levels in myoblasts treated with inflammatory cytokines, and improved oxygen consumption rates. In the C-protein-induced myositis (CIM) mouse model, PN-101 reduced myositis severity by decreasing inflammatory cell infiltration, suppressing pro-inflammatory cytokine expression, and reversing metabolic shifts. A phase 1/2a clinical trial in nine adults with refractory polymyositis or dermatomyositis indicated that PN-101 was safe and well-tolerated, with improvements observed in the Total Improvement Scores. These findings support further evaluation of mitochondrial transplantation as a therapeutic strategy for IIMs.⁷² Although these early findings are encouraging, the current evidence is still based on very limited phase 1/2a experience and requires cautious interpretation.

CAR-T cell therapy: An immune reset strategy in IIMs

Chimeric antigen receptor (CAR) T cell therapy has emerged as a promising therapeutic approach for refractory autoimmune diseases, including IIMs. Recent studies have demonstrated the potential of CD19-targeted CAR T cells in inducing deep and sustained remission in patients with severe autoimmune conditions such as IIMs, systemic lupus erythematosus, and systemic sclerosis. For instance, Wang et al. reported the successful application of allogeneic CD19-targeted CAR-T therapy in patients with severe IIMs and systemic sclerosis, highlighting the potential of off-the-shelf CAR-T therapy in advancing clinical management of severe refractory autoimmune diseases.⁷³ Similarly, Muller et al.⁷⁴ and Volkov et al.⁷⁵ provided evidence for the feasibility, safety, and efficacy of CD19 CAR-T cell therapy in inducing remission in patients with IIMs, including those with the IMNM subtype. However, challenges such as disease relapse after initial CAR-T cell therapy and the need for alternative targets or products have been identified. A case reported by Muller et al.⁷⁶ illustrated the potential of switching to B-cell maturation antigen (BCMA) CAR T cell therapy to restore drug-free remission after relapse of IIMs following CD19 CAR-T cell treatment. A related report by He et al. described CD19 CAR T-cell therapy in pediatric refractory systemic lupus erythematosus, supporting broader translation across severe autoimmune diseases.⁷⁷

Overall, currently available reports suggest that CD19-directed CAR-T therapy may have potential in a very limited number of highly selected patients with refractory IIMs; however, the evidence remains preliminary, the risks are non-negligible, and its role should currently be regarded as investigational rather than established clinical practice.

While CAR-T cell therapy offers a promising immune-reset approach for refractory IIMs, several important limitations must be acknowledged. First, the currently available data come from very small, highly selected cohorts or single-case experiences, often in patients with multi-refractory, B-/plasma-cell-driven disease; as such, the generalizability of these responses to unselected adult IIM populations is unknown. Second, clinical relapse after an initial CD19-CAR-T infusion has been reported, sometimes driven by anti-CAR immune responses or insufficient CAR-T expansion, which may preclude simple redosing and has prompted exploratory switches to alternative targets such as BCMA.⁷⁶ Third, hematologic and infectious toxicities-

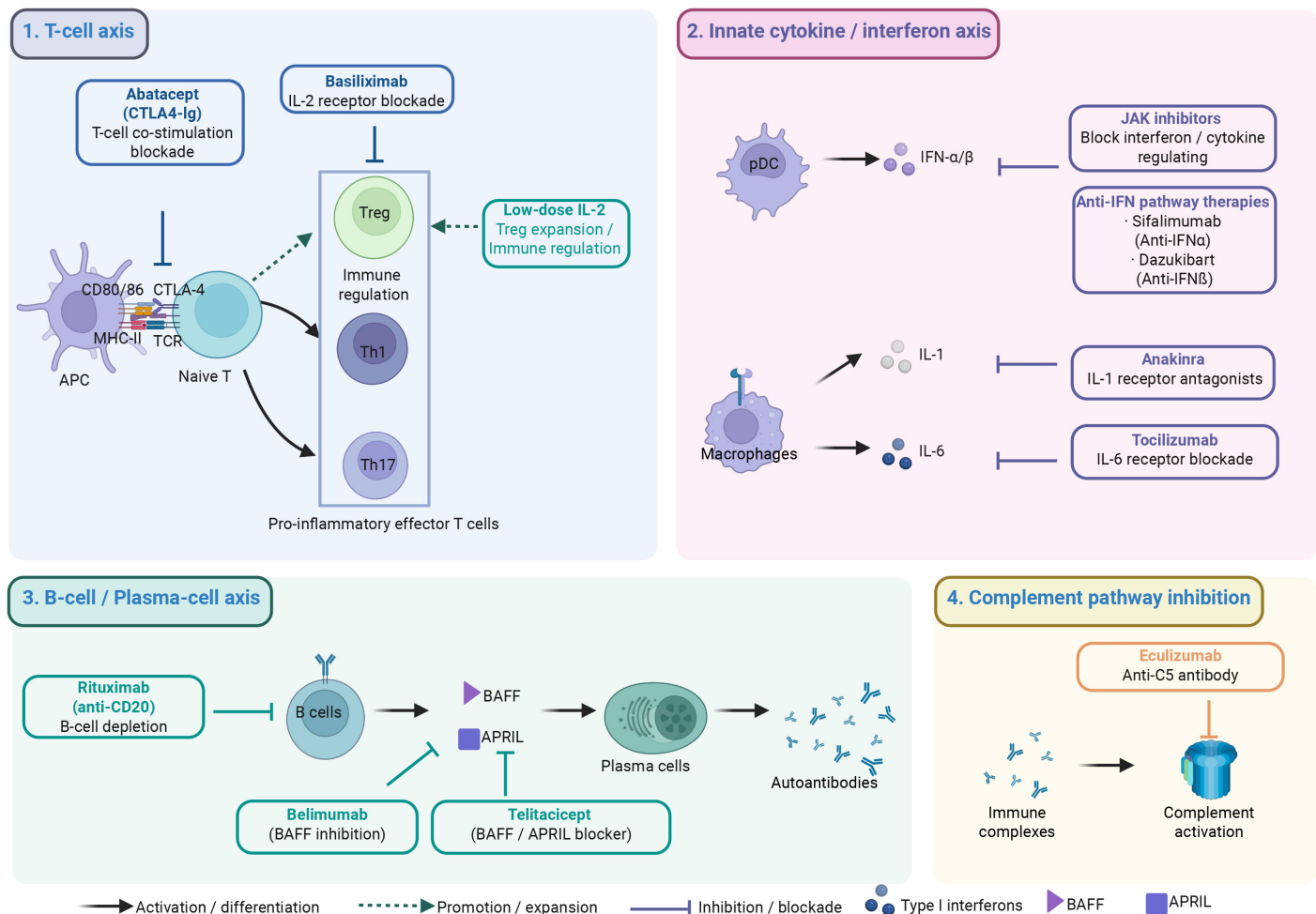


Figure 2. Immunological mechanisms of emerging treatment regimens for IIMs Notes: CTLA4: cytotoxic T lymphocyte-associated antigen 4. IL-2: Interleukin-2. MHC: major histocompatibility complex. TCR: T-cell receptor. Treg: regulatory T cell. Th: T helper cells. pDC: plasmacytoid dendritic cells. IFN: interferon. IL-6: Interleukin-6. IL-1: Interleukin-1. JAK: Janus kinase. BAFF: B cell-activating factor. APRIL: a proliferation-inducing ligand. C5: Complement Component 5.

including prolonged neutropenia, cytopenias, and hypogammaglobulinemia have been observed in autoimmune indications, underscoring the need for close monitoring and center experience.⁷⁸ In addition, logistical, manufacturing, and regulatory constraints currently limit large-scale or routine deployment. Therefore, CAR-T therapy should not currently be viewed as a broadly applicable option for refractory IIMs, but rather as a highly experimental strategy reserved for exceptional, life-threatening, multi-refractory cases, and only within clinical trials or specialized centers (Figure 3).

Taken together, cellular and regenerative strategies in IIMs remain promising but early-stage approaches, with current evidence derived largely from small, highly selected, or non-randomized studies, and they should therefore be interpreted as investigational rather than near-term standard-of-care options. Accordingly, the current role of CAR-T in adult IIMs is not one of routine therapeutic escalation, but of exceptional consideration in life-threatening, multi-refractory, B-/plasma-cell-driven disease after exhaustion of more established treatment options.

PRECISION MEDICINE AND BIOMARKER-DRIVEN THERAPY

Single-cell landscape of IIMs

From a clinical perspective, the value of emerging biomarkers in adult IIMs currently lies more in phenotype definition, risk stratification, and monitoring of dominant inflammatory programs than in directly dictating a specific therapy in routine practice. Recent advancements in multi-omics technologies have significantly enhanced our understanding of IIMs, facilitating the identification of therapeutic targets and the development of stratified treatment approaches. Key methodologies such as transcriptomics, single-cell

sequencing, and proteomics have been instrumental in these developments. Low-input sequencing technologies and their medical applications have also been reviewed by Li et al.⁷⁹

Single-nucleus RNA sequencing (snRNA-seq) and spatial transcriptomics applied to quadriceps muscle biopsies from IBM patients revealed an enrichment of cytotoxic T lymphocytes (CTLs) and conventional dendritic cells type 1 (cDC1), along with a depletion of homeostatic macrophages. Notably, there was selective loss of type 2 myonuclei and upregulation of stress-response pathways involving GADD45A and the lncRNA NORAD, suggesting subtype-specific muscle fiber susceptibility and functional denervation. These insights may guide future therapeutic interventions.⁸⁰

Single-cell RNA sequencing (scRNA-seq) of peripheral blood mononuclear cells (PBMCs) from ASyS patients demonstrated heightened type I interferon responses across natural killer cells, monocytes, and T cells. A notable increase in the ratio of effector memory CD8⁺ T cells to naïve CD8⁺ T cells was observed, indicating immune activation. Moreover, upregulation of transcription factors BATF2 and SOCS3 in monocytes was identified, providing candidate biomarkers for disease activity.⁸¹

In MDA5-DM, scRNA-seq analyses of peripheral blood T and B cells revealed enhanced plasmablast activity and CD8⁺ T cell responses, alongside overactivation of type I interferon signaling. T cell receptor (TCR) repertoire analysis identified clonally expanded CD8⁺ T cells, suggesting their pathogenic relevance. Moreover, immunological profiling of lung tissue highlighted crosstalk between infiltrating immune cells and fibroblasts, potentially contributing to ILD.⁸²

Practically, biomarker-informed care in adult IIMs should currently be

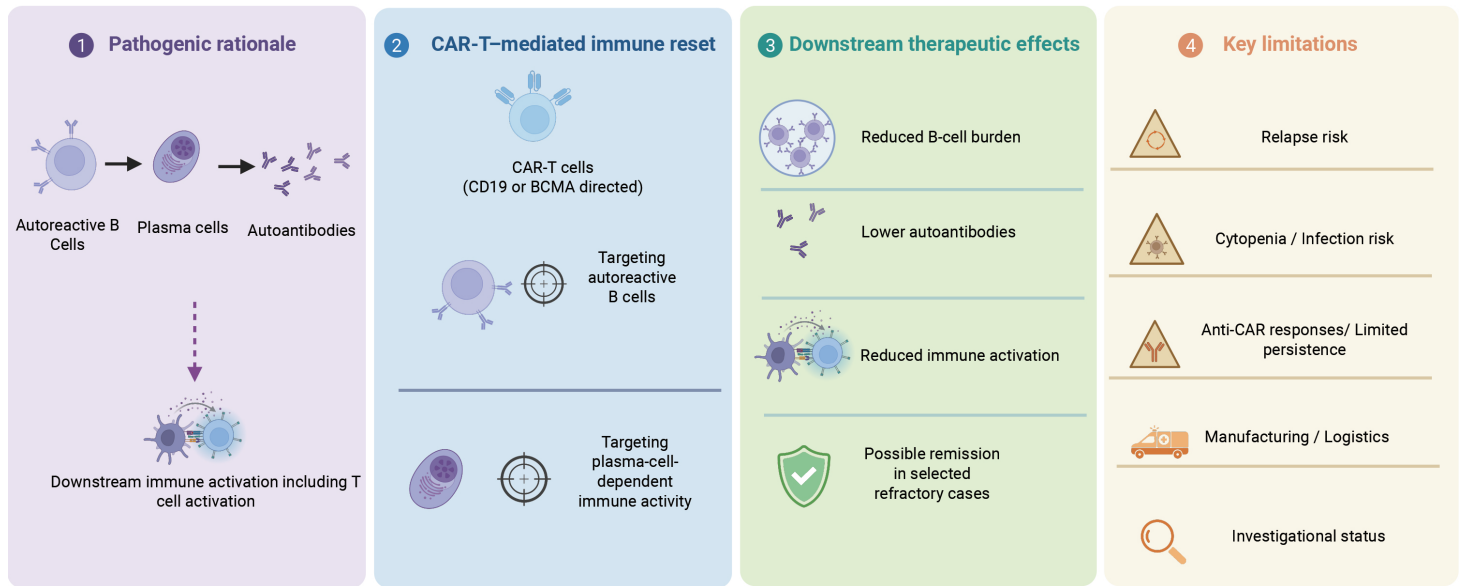


Figure 3. CAR-T therapy in refractory IIMs: immune reset rationale, effects, and limitations This schematic emphasizes the core therapeutic logic of CAR-T therapy in IIMs rather than a comprehensive map of all possible immune interactions. CAR-T cells directed against CD19 or BCMA aim to reduce autoreactive B-cell and plasma-cell-dependent immune activity, thereby lowering autoantibody burden and attenuating downstream immune activation. These effects may contribute to clinical remission in selected refractory cases. The figure also highlights major limitations, including relapse, cytopenia/infections, immune-mediated loss of CAR-T persistence, manufacturing barriers, and the still investigational status of this strategy. Notes: IIMs: idiopathic inflammatory myopathies. CAR: Chimeric antigen receptor. BCMA: B-cell maturation antigen.

implemented as a complement to, rather than a replacement for, conventional clinical assessment; biomarkers may refine subgroup recognition and support treatment prioritization, but they rarely function as standalone decision tools in routine practice.

Artificial intelligence and machine learning

Recent advancements in artificial intelligence (AI) and machine learning (ML) have significantly contributed to the development of predictive models and personalized treatment strategies for IIMs. Cao et al. have also reviewed AI and ML approaches for advancing precision medicine in autoimmune diseases.⁸³

Danieli et al. (2023) applied various supervised ML algorithms, including classification and regression trees (CART), to analyze clinical parameters such as MMT-8, disease activity (MITAX), and damage indices (MDI, HAQ-DI) in IIMs patients. Their findings demonstrated that ML models could effectively predict long-term outcomes, with CART models showing strong predictive capabilities for MMT-8 scores at follow-up. Additionally, the presence of RP-ILD and skin involvement were significant predictors of disease activity.⁸⁴

Qiang et al. (2024) developed a logistic regression model combining quantitative computed tomography (QCT) features from high-resolution CT scans with clinical variables to predict the risk of RP-ILD in IIMs patients. The model achieved an area under the curve (AUC) of 0.882 in the validation cohort, outperforming models based solely on imaging or clinical data. Key predictive features included pulmonary function parameters (FEV₁%, DLCO%), oxygenation index, and imaging markers such as ground-glass opacities and pulmonary vascular alterations.⁸⁵

In this context, precision medicine in IIMs should be viewed not merely as the addition of biomarkers to existing practice, but as a reorganization of therapeutic choice around clinically and molecularly defined subgroups.

RECENT THERAPEUTIC ADVANCES IN IBM

IBM remains challenging due to its resistance to conventional immunosuppressive therapies and progressive nature. Treatment with IVIg may provide at most modest benefit in selected IBM patients, mainly as symptomatic or stabilizing therapy rather than a clearly disease-modifying approach.⁸⁶ Recent clinical trials have explored promising novel therapeutic strategies. Sirolimus (rapamycin), an mTOR inhibitor, demonstrated beneficial effects in a randomized phase IIb trial, showing improvements in 6-minute walk distance, respiratory function, thigh muscle fat fraction (assessed by MRI), and HAQ-DI scores compared to placebo, thus highlight-

ing its potential in stabilizing disease progression.^{87,88} A large, international phase IIb/III trial is currently underway to confirm these findings.⁸⁷ Meanwhile, bimagrumab-despite increasing lean body mass in earlier studies-did not yield clinically meaningful functional improvement in randomized studies and did not meet primary functional endpoints; accordingly, we do not consider bimagrumab an effective disease-modifying option for IBM at present.⁸⁹

CHALLENGES AND FUTURE DIRECTIONS

In practical terms, treatment escalation in adult IIMs should follow a stratified rather than purely sequential logic, with priority given to disease tempo, organ-threatening involvement, serological context, and early response to standard therapy. Clinical trials in myositis-associated ILD (MA-ILD) face significant heterogeneity, which hampers the generalizability of findings and the development of tailored therapies. Patients exhibit diverse clinical sub-phenotypes-driven by MSAs, variable ILD patterns such as non-specific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP), and mixed disease courses ranging from chronic to rapidly progressive forms-resulting in inconsistent pulmonary function trajectories and variable responses to immunosuppression.⁹⁰ The INBUILD trial and its subgroup analyses indicated that nintedanib reduces forced vital capacity (FVC) decline across connective-tissue disease-associated ILD, but it was not powered to assess effects in MA-ILD specifically, with only two PM or ASyS patients included, limiting disease-specific conclusions.⁹¹ Retrospective IIMs-ILD studies similarly suffer from small sample sizes, concomitant immunosuppressive therapies, and heterogeneous patient selection, complicating efficacy assessments of antifibrotic add-on treatment. Moreover, diagnostic and inclusion criteria vary widely-autoantibody profiles, imaging patterns, and functional criteria differ substantially across studies-making patient cohorts poorly comparable. To overcome these limitations, future trials such as the MINT study are adopting hybrid designs, remote monitoring, and stratification based on autoantibody status and immunosuppression to enhance precision, reduce bias, and address biological and clinical heterogeneity.⁹² In this context, adult IIMs still lack universally validated, practice-wide remission criteria; accordingly, studies often rely on IMACS preliminary trial constructs and on improvement/response instruments rather than remission endpoints.

Despite advancements, clinical research in MA-ILD remains constrained by inadequate long-term follow-up and inconsistent efficacy evaluation frameworks. Most cohort studies emphasize short-term outcomes, with long-term data sparse and heterogeneous-only a minority reach 5 to 10-year monitor-

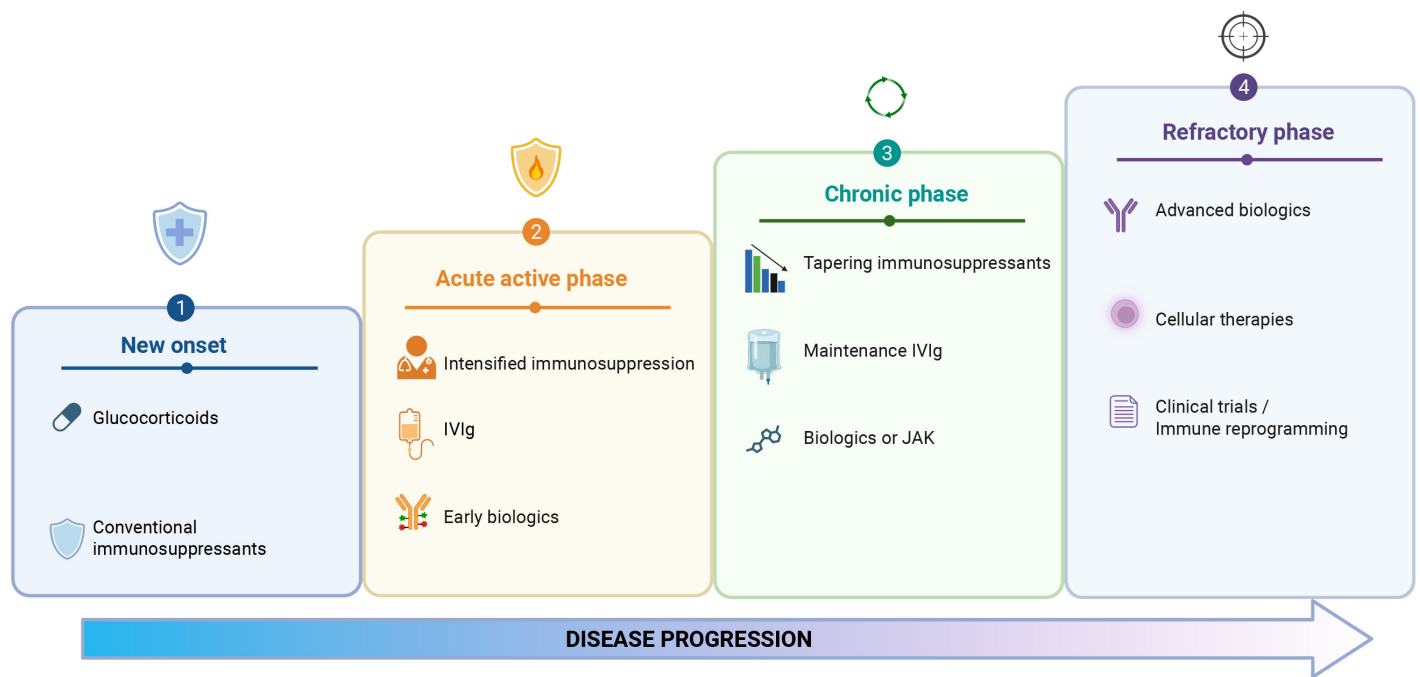


Figure 4. Therapeutic landscape across disease stages in IIMs Initial management of new-onset disease relies on glucocorticoids and conventional steroid-sparing immunosuppressants. During the acute active phase, treatment is escalated with intensified immunosuppression (e.g. cyclophosphamide, tacrolimus), IVIg, or early biologics in selected phenotypes such as MDA5-DM. In the chronic phase, therapy focuses on tapering, maintenance IVIg, and the use of biologics or JAK inhibitors, particularly when lung or cutaneous involvement persists. Patients with refractory disease may require advanced biologics, novel cellular approaches (e.g. CAR-T), or enrollment in clinical trials targeting immune reprogramming. The figure is designed to assist clinical prioritization rather than to imply a fixed sequence applicable to all adult IIMs phenotypes. Notes: IIMs: idiopathic inflammatory myopathies. IVIg: intravenous immunoglobulin. DM: dermatomyositis. JAK: Janus kinase. CAR: Chimeric antigen receptor.

ing periods. A Swedish registry similarly highlights variable mortality rates over extended follow-up, complicating consistent prognostication.⁹³ While real-world experiences with antifibrotics in ILD suggest slowed functional decline, evidence on their transplant-free survival benefits remains inconclusive and limited by short-term endpoints. Moreover, outcome measures across studies lack standardization—definitions for progression, relapse, and survival differ, and assessments seldom include patient-reported outcomes or functional status beyond FVC and survival. Future MA-ILD trials should extend follow-up duration, employ uniform, multidimensional outcome sets, and integrate quality-of-life metrics to fully capture long-term therapeutic impact.

In clinical practice, patients with IIMs-associated ILD should be stratified by disease tempo and serological profile, distinguishing RP-ILD—most often observed in MDA5-DM—from chronic or non-rapidly progressive forms. For non-RP disease, high-dose glucocorticoids combined with a steroid-sparing immunosuppressant such as MMF or AZA remain the preferred first-line regimen, providing effective disease stabilization and corticosteroid-sparing benefits. IVIg can be considered in cases of overlap or refractory myositis. In contrast, MDA5-positive RP-ILD requires early, intensive combination therapy—typically glucocorticoids plus a calcineurin inhibitor and/or CYC (“triple therapy”)—which has been associated with improved short-term survival. Regular follow-up with pulmonary function tests and HRCT during the first 3–6 months is essential to detect nonresponders early. Patients with disease progression despite optimal immunosuppression, or those with elevated IL-6 or type I interferon activity, may be candidates for biologic or targeted therapies such as tocilizumab or JAK inhibitors in a clinical-trial setting.^{3,94} This framework does not define a rigid algorithm, but it provides a practical hierarchy for clinical decision-making when evidence is incomplete or heterogeneous.

CONCLUSIONS AND FUTURE PERSPECTIVES

Looking ahead, the absence of adult IIMs remission criteria—and the evolving view that at least part of so-called “muscle damage” may be reversible—argue for endpoint strategies that prioritize sustained functional gain, patient-reported outcomes, and biomarkers of regeneration. The therapeutic land-

scape of IIMs is undergoing a paradigm shift driven by advances in immunology, omics technologies, and cell-based therapies. As shown in Figure 4, the therapeutic landscape of IIMs can be translated into a practical decision-support framework in which treatment selection is guided by disease stage, refractory status, organ involvement, and the evidentiary maturity of available interventions. Single-cell and spatial transcriptomics are increasingly illuminating the cellular and molecular heterogeneity of IIMs, enabling refined disease classification and the development of precision-targeted interventions. Although molecular profiling is reshaping the conceptual landscape of IIMs, its near-term clinical value lies mainly in refining existing stratification frameworks rather than replacing phenotype-based decision-making. In parallel, the adaptation of CAR-T cell therapies from oncology to autoimmunity represents a groundbreaking translational leap, offering the potential for immune reprogramming in treatment-refractory cases. Integrative therapeutic strategies that simultaneously target multiple pathogenic cell types—such as B cells and long-lived plasma cells (e.g., via dual CD19- and BCMA-directed approaches)—may enhance treatment durability and overcome resistance. Importantly, despite rapid therapeutic expansion, much of the evidence for emerging targeted and cellular therapies in adult IIMs still derives from small, non-randomized, or early-phase studies, highlighting the need for cautious interpretation and rigorous validation before routine clinical implementation. Moreover, the development of robust clinical phenotyping frameworks and predictive biomarkers for treatment response will be essential for personalizing therapy, minimizing overtreatment, and guiding the rational application of high-cost interventions such as CAR-T. Conceptually, this review proposes that therapeutic decision-making in adult IIMs should be increasingly organized along three intersecting axes: clinical phenotype, dominant immune pathway, and evidence maturity, thereby moving beyond a one-size-fits-all escalation model. In this context, the present review is intended not only as an update on emerging therapies, but also as a practical framework for translating heterogeneous evidence into phenotype-aware therapeutic decision-making in adult IIMs. These converging innovations mark a new chapter in the management of IIMs, in which precision immunology and mechanistic targeting are expected to reshape clinical outcomes.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AND CODE AVAILABILITY

Not applicable.