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LIPID-LOWERING STRATEGIES BEYOND STATINS TO REDUCE CARDIOVASCULAR BURDEN IN IDIOPATHIC INFLAMMATORY MYOPATHIES

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ABSTRACT – Patients with idiopathic inflammatory myopathies (IIM) have an elevated risk of atherosclerotic cardiovascular disease, yet statin therapy may be complicated by muscle-related symptoms and challenges in clinical monitoring. Non-statin therapies offer safe alternatives. Bempedoic acid lowers LDL-cholesterol *via* liver-specific activation, minimizing myotoxicity while demonstrating cardiovascular benefit in statin-intolerant patients. Ezetimibe provides modest additional LDL-C reduction, and PCSK9 inhibitors achieve potent lipid lowering with favorable safety in small IIM cohorts. These agents enable individualized lipid management when statins are contraindicated or poorly tolerated. Further studies are needed to define optimal lipid-lowering strategies in this high-risk, understudied population.

KEYWORDS: Myositis, Statin, Idiopathic inflammatory myopathies, Lipidology, Lipid lowering, Rheumatology, Bempedoic acid, PCSK9 inhibitor, Ezetimibe, Inflammatory myositis.

INTRODUCTION

Idiopathic inflammatory myopathies (IIM) confer a markedly elevated risk of coronary heart disease, with a recent meta-analysis reporting a relative risk of 2.19[1]. Statins remain first-line for lipid-lowering and cardiovascular risk reduction. However, while some statin-associated muscle symptoms (SAMS) are in part driven by the nocebo effect[2], true statin intolerance poses challenges in the context of IIM. Beyond rare statin-induced anti-HMGCR positive immune-mediated necrotizing myopathy (IMNM) (where statins are contraindicated), patients may experience laboratory abnormalities, including elevated creatine kinase (CK) and transaminases, that can confound disease monitoring[3]. Small cohort trials suggest that statins can be used safely in carefully selected IIM patients[4,5], yet non-statin agents warrant consideration as alternative therapies in this population. Current guidelines offer no disease-specific ther-

apy recommendations for IIM, emphasizing individualized care, weighing ASCVD risk reduction against potential adverse medication effects[3]. In this review, we summarize recent evidence on the safety and efficacy of non-statin lipid-lowering therapies in IIM, with particular emphasis on bempedoic acid, and additional discussion on ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors.

METHODS

For this review, we conducted a focused search of the gray literature as well as Embase and MEDLINE from database inception through October 1, 2025, using key terms for idiopathic inflammatory myopathies (including myositis, dermatomyositis, polymyositis, anti-synthetase syndrome, IMNM/anti-HMGCR) and non-statin lipid-lowering therapies (including bempedoic acid, ezetimibe, PCSK9 inhibitors, inclisiran). We prioritized human studies reporting lipid effects and/or safety in IIM and excluded non-human studies.

REVIEW

Bempedoic acid lowers LDL-C *via* inhibition of ATP-citrate lyase, an enzyme upstream of HMG-CoA reductase. Uniquely, it is a prodrug activated by an enzyme predominantly expressed in hepatocytes but not in skeletal muscle, which minimizes muscle-related side effects[2]. This liver-specific activation makes bempedoic acid favorable in IIM, where the adverse effects of myalgia, myotoxicity, and CK elevation seen with statins can confound disease monitoring. The recently published CLEAR Outcomes trial[6] examined the use of bempedoic acid in statin-intolerant patients and showed a significant reduction in the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or coronary revascularization compared with placebo. Importantly, bempedoic acid did not increase the risk of myalgia or CK elevations compared to placebo[6]. While IIM patients were not a predefined subgroup, the cardiovascular benefit and favorable muscle-safety profile of bempedoic acid support its use in statin-intolerant patients, in patients at increased risk of statin-associated adverse effects, or when poor disease control complicates interpretation of laboratory values and symptoms. A recent case series[7] of 10 patients with anti-HMGCR antibody-positive statin-induced IMNM reported that treatment with immunosuppressive agents combined with bempedoic acid led to significant reductions in antibody titers, CK, and aldolase, with LDL-C maintained in the target range. The improvement in muscle disease activity was attributable to immunosuppression, whereas bempedoic acid provided safe lipid lowering without additional muscle-related adverse effects[7]. Bempedoic acid has been associated with increases in serum uric acid and gout incidence, as well as elevations in liver enzymes. Uric acid levels and hepatic enzymes should be assessed and monitored when clinically indicated, particularly in patients with a history of gout or underlying liver disease[8].

Ezetimibe lowers LDL-C by inhibiting intestinal cholesterol absorption[2] and has traditionally been used in patients who do not reach LDL-C targets with statins or who experience SAMS. In a recent Hungarian myositis cohort[4], ezetimibe was used instead of statins in patients with anti-HMGCR antibody positivity, prior statin-induced myalgia or CK elevation, or CK levels more than three times the upper limit of normal. While ezetimibe has a clear LDL-C-lowering benefit, its effect is relatively modest compared with high-intensity statins. Although no randomized controlled trials have evaluated long-term cardiovascular outcomes with ezetimibe monotherapy, it has demonstrated cardiovascular event reduction when added to statin therapy[2]. In the same Hungarian myositis cohort, SCORE2-based cardiovascular risk did not significantly improve after six months of ezetimibe monotherapy[4], indicating that while ezetimibe provides LDL-C–lowering benefit in IIM, it may necessitate combination therapy with agents such as bempedoic acid in higher-risk patients[9]. Of note, ezetimibe is not recommended in moderate to severe liver disease[8], which often coexists with systemic autoimmune rheumatic diseases.

PCSK9 inhibitors are injectable monoclonal antibodies that block PCSK9, increasing hepatic LDL receptors, enhancing LDL-C clearance[2]. A case series of 8 patients with statin-associated, anti-HMGCR-positive IMNM showed that PCSK9i were safe over a mean of 18 months, with no muscle weakness and reductions in CK and antibody titers[10]. In two patients, treatment was followed by unexpected clinical improvement, including tapering of immunosuppression, leading the authors to hypothesize that PCSK9i may confer immunologic benefit by lowering anti-HMGCR levels[10]; however, given the small sample size and observational design, causality cannot be inferred, and mechanistic studies are lacking. In another observational cohort of 11 patients[11] with statin intolerance and neuromuscular disorders

(IMNM, dermatomyositis, inclusion body myositis, myasthenia gravis, mitochondrial myopathy) found that PCSK9i and inclisiran (small interfering RNA that blocks hepatic PCSK9 synthesis) significantly lowered LDL-C over 14 months without worsening underlying disease, CK elevation, or hepatotoxicity.

Bempedoic acid, ezetimibe, and PCSK9-targeted therapies reduce LDL-C through complementary mechanisms—namely inhibition of hepatic cholesterol synthesis, reduced intestinal absorption, and enhanced LDL receptor–mediated clearance—thereby supporting a more individualized approach to lipid management in IIM. The key features of these non-statin therapies are summarized in Table 1.

Table 1. Comparative summary of non-statin lipid-lowering therapies in idiopathic inflammatory myopathies (IIM). Expected LDL-C reductions are approximate (based on prescribing information/ major trial data in non-IIM populations), while the "Evidence" column reflects the limited IIM case series and small observational cohorts currently available. Prescriber considerations highlight practical issues (route, access, and cost), which may vary by jurisdiction.

Therapy	Expected LDL-C Reduction	Evidence in IIM/ Statin Intolerance	Prescriber Considerations
Bempedoic acid	~24.5% (monotherapy)[8]	CLEAR Outcome Trial in statin-intolerant patients (non-IIM); small IMNM case series in anti-HMGCR; no IIM RCTs	Oral; higher cost; may require prior authorization
Ezetimibe	~18% (monotherapy)[8]	Myositis cohort data; no IIM RCTs	Oral; well tolerated; widely available
PCSK9 mAbs	~45%-64%[8]	Small anti-HMGCR IMNM case series; limited broader neuromuscular cohorts; no IIM RCTs	Injectable; higher cost; may require prior authorization
Inclisiran	~48%-52%[8]	Limited neuromuscular/statin-intolerance observational data; no IIM RCTs	Injectable; higher cost; may require prior authorization

When selecting a lipid-lowering agent, clinicians should weigh both the expected LDL-C reduction and the patient's risk of statin side effects. The likelihood of SAMS is higher in older adults, women, and those with diabetes, chronic kidney disease, or untreated hypothyroidism. Additional risk factors include high statin doses, drug interactions *via* cytochrome P450 metabolism, intense physical activity, and genetic predisposition[5]. As illustrated in Figure 1, decision-making is relatively straightforward when patients have minimal risk of statin adverse effects, when a statin trial is appropriate, or when clear contraindications exist, in which case non-statin therapy is required. The intermediate group with poorly controlled disease and lab abnormalities is more complex, as unstable disease activity can confound interpretation; in these cases, non-statin therapy may be more appropriate.

Additional lipid-modifying agents, including icosapent ethyl (a purified eicosapentaenoic acid derivative), have shown mixed effects on cardiovascular risk reduction[2], though it has not been specifically studied in IIM populations. Elevated lipoprotein(a) represents another unique challenge, as current therapies have minimal effect on its levels. However, several siRNA and antisense therapies targeting Lp(a) are in late-stage development and will expand future treatment options.

LIMITATIONS AND EVIDENCE GAPS

Evidence for non-statin lipid-lowering therapies in IIM remains limited, as available data are largely derived from small observational cohorts and case series, rather than randomized trials. Generalizability is constrained by heterogeneity across IIM subtypes (e.g., dermatomyositis, polymyositis, IMNM, overlap syndromes), which differ in baseline ASCVD risk and susceptibility to SAMS. Interpretation is further confounded by concurrent glucocorticoid use, immunosuppression, and fluctuating disease activity, all

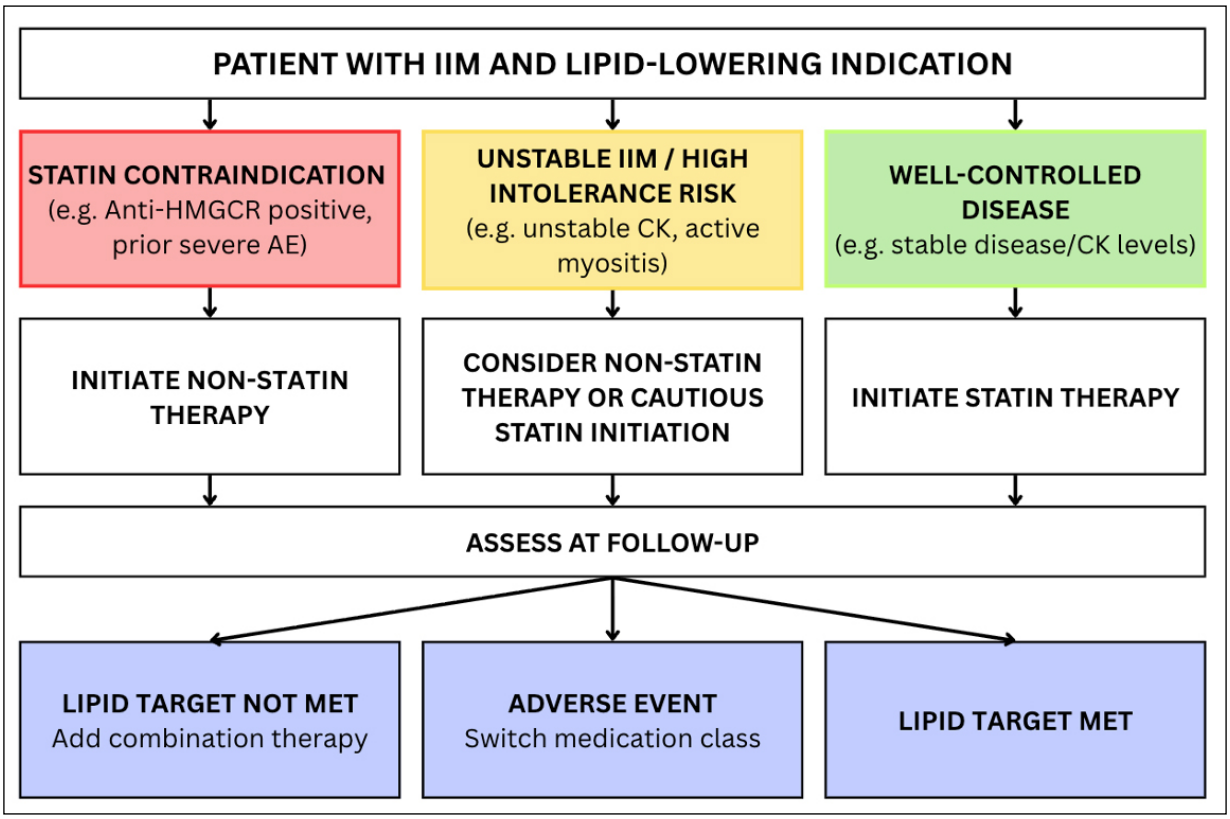

Figure 1. Proposed algorithm for lipid-lowering therapy in idiopathic inflammatory myopathies (IIM). The decision pathway stratifies patients by contraindications and disease stability, prioritizing non-statin therapies (e.g., bempedoic acid, ezetimibe, PCSK9 inhibitors) for individuals with anti-HMGCR positivity, prior severe adverse events, or unstable disease where fluctuating muscle enzymes may confound statin safety monitoring. Statin therapy is recommended for well-controlled, low-risk patients with IIM, with follow-up for escalating to combination therapy or switching drug classes if adverse drug events occur. Abbreviations: Anti-HMGCR, anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase; CK, creatine kinase; IIM, idiopathic inflammatory myopathies; AE, adverse event.

of which can independently influence lipid profiles, symptoms, and CK levels. Additional limitations include likely publication bias within the statin-intolerance literature, variability in CK thresholds across studies, and potential misclassification of myositis subtypes, particularly in cohorts lacking contemporary autoantibody testing. Accordingly, management should be individualized, and prospective IIM-specific studies are needed to better define safety and clinical benefit.

CONCLUSIONS

While statins can be safely prescribed in select patients with IIM, non-statin therapies such as bempedoic acid and PCSK9 inhibitors represent effective and safe alternatives, with ezetimibe serving as a useful adjunct in combination with other agents, particularly as these therapies become increasingly accessible. Ultimately, management should be individualized, balancing cardiovascular risk reduction against potential drug-related adverse effects. Further prospective studies evaluating non-statin agents in IIM are essential to establish evidence-based strategies in this high-risk population.

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