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Short Communication

Recent Developments in Personalized Treatments for Familial Mediterranean Fever: Toward Precision Medicine in Autoinflammatory Disease

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Introduction

Familial Mediterranean Fever (FMF) is the most common monogenic autoinflammatory disorder worldwide, characterized by recurrent episodes of fever, serositis, arthritis, and elevated acute-phase reactants. The disease is caused primarily by pathogenic variants in the MEFV gene, which encodes pyrin, a key regulator of innate immune responses and inflammasome activation. For decades, colchicine has remained the cornerstone of therapy, dramatically reducing attack frequency and preventing secondary AA amyloidosis. However, increasing recognition of genetic heterogeneity, variable clinical phenotypes, and differential therapeutic responses has stimulated a shift from a "one-size-fits-all" approach toward personalized medicine. Recent advances in genomics, biomarker discovery, inflammasome biology, and targeted biologic therapies are transforming FMF management and providing the foundation for precision treatment strategies.

From Classical Management to Precision Medicine

Traditional FMF management relied largely on clinical diagnosis and empirical colchicine treatment. Although approximately 70–80% of patients achieve adequate disease control with colchicine, a substantial subgroup experiences colchicine resistance or intolerance. These patients remain at risk for persistent inflammation, organ damage, and amyloidosis. Recent international recommendations increasingly emphasize individualized therapeutic decisions based on genotype, disease severity, inflammatory burden, and treatment response rather than uniform protocols [1].

The updated EULAR/PReS recommendations published in 2025 reflect this paradigm shift, incorporating biologic therapies, refined definitions of colchicine resistance, and more personalized monitoring strategies [2].

Genotype-Guided Therapeutic Stratification

One of the most important developments in FMF precision medicine is the growing use of MEFV genotyping to guide prognosis and treatment intensity [1,3].

Specific mutations such as M694V homozygosity are associated with:

Earlier disease onset

More severe inflammatory attacks

Higher risk of chronic inflammation

Increased likelihood of AA amyloidosis

Greater probability of colchicine resistance

Conversely, variants such as E148Q often demonstrate lower penetrance and milder disease manifestations. Recognition of these genotype-phenotype correlations allows clinicians to stratify patients according to risk and tailor follow-up schedules and treatment intensity [1,2].

Emerging evidence also suggests that some heterozygous patients may develop clinically significant FMF due to modifier genes, epigenetic influences, and environmental factors. Such findings challenge traditional inheritance models and support individualized rather than mutation-count-based therapeutic decisions.

Biomarker-Based Personalization

A major limitation in FMF management has been the inability to accurately identify patients with persistent subclinical inflammation. Recent research has focused on biomarkers capable of guiding therapeutic decisions [3].

Serum Amyloid A (SAA)

SAA has emerged as one of the most clinically useful biomarkers. Elevated SAA levels between attacks may indicate ongoing inflammation despite apparent clinical remission and are strongly associated with amyloidosis risk. Personalized monitoring of SAA is increasingly recommended for high-risk patients, particularly those carrying severe MEFV variants [2,3].

Cytokine Profiling

Advances in cytokine analysis have revealed substantial inter-individual variation in inflammatory pathways. Elevated IL-1β activity is now recognized as a central pathogenic mechanism in FMF, providing a biological rationale for targeted anti-IL-1 therapies. Future approaches may involve cytokine-based patient stratification to identify individuals most likely to benefit from specific biologics.

Multi-Omics Approaches

Transcriptomics, proteomics, metabolomics, and epigenetic profiling are increasingly being explored in FMF. Although currently confined largely to research settings, these technologies may eventually identify molecular signatures predictive of disease severity, treatment response, and complication risk.

Personalized Colchicine Therapy

Colchicine remains the first-line therapy for all FMF patients. However, personalized dosing strategies have become increasingly important [1,3].

Recent studies have highlighted variability in colchicine metabolism and tolerance among patients. Factors influencing response include:

Genetic background

Drug transport mechanisms

Renal function

Hepatic function

Age

Coexisting inflammatory diseases

Rather than adhering to fixed dosing schedules, clinicians increasingly employ individualized titration protocols aimed at maximizing efficacy while minimizing gastrointestinal and neuromuscular toxicity [2,3]. New recommendations also advocate systematic assessment of adherence before labeling a patient as colchicine-resistant, recognizing that non-adherence remains a common cause of apparent treatment failure.

Anti-IL-1 Therapy: The Cornerstone of Personalized Biologic Treatment

Perhaps the most significant development in FMF treatment over the last decade has been the emergence of IL-1 blockade [2,4].

The pyrin inflammasome directly promotes IL-1β production, making IL-1 inhibition a highly targeted therapeutic strategy. Anti-IL-1 agents are increasingly viewed as precision therapies for colchicine-resistant FMF.

Anakinra

Anakinra is a recombinant IL-1 receptor antagonist with rapid onset of action.

Recent real-world studies have demonstrated:

Significant reduction in attack frequency

Improvement in quality of life

Decreased inflammatory markers

Acceptable safety profiles

Anakinra is particularly valuable when rapid control of inflammation is required and offers flexible dosing that can be individualized according to disease activity.

Canakinumab

Canakinumab, a monoclonal antibody targeting IL-1β, has become a major therapeutic option for patients with severe FMF.

Advantages include:

Long dosing intervals

Sustained suppression of inflammation

Improved adherence

Excellent efficacy in colchicine-resistant disease

Recent multicenter studies have demonstrated durable remission in many patients, including those with amyloidosis or severe inflammatory phenotypes. The drug has become central to personalized management algorithms for refractory disease [1,3,4].

Rilonacept

Although less widely used, rilonacept provides another IL-1-targeted option. Meta-analytic evidence supports its efficacy in reducing attack frequency and inflammatory activity. Future comparative studies may help determine which patients benefit most from each anti-IL-1 strategy.

Defining Colchicine Resistance: A Precision Medicine Milestone

Historically, the concept of colchicine resistance lacked standardization. Recent international consensus efforts have established more objective criteria incorporating:

Attack frequency

Persistent inflammatory markers

Physician assessment

Patient-reported outcomes

This standardization has major implications for personalized medicine because it enables earlier identification of patients who require biologic escalation rather than prolonged ineffective colchicine therapy [1,4].

Personalized Management of AA Amyloidosis

AA amyloidosis remains the most serious complication of FMF and a major cause of morbidity and mortality [1,2].

Precision approaches increasingly focus on:

Early identification of high-risk genotypes

Routine SAA monitoring

Aggressive suppression of inflammation

Earlier use of biologic therapies

Emerging evidence suggests that IL-1 blockade may stabilize or improve renal outcomes in selected patients with FMF-associated amyloidosis, highlighting the importance of individualized intervention before irreversible organ damage develops.

Pediatric Precision Medicine

FMF often begins during childhood, making early personalized treatment particularly important.

Recent developments include:

Genotype-guided risk assessment

Age-adjusted colchicine optimization

Earlier introduction of biologics in severe disease

Longitudinal monitoring of growth and development

Studies indicate particularly favorable responses to anti-IL-1 therapy in pediatric populations, with high remission rates and acceptable safety profiles. These findings support earlier individualized intervention rather than prolonged exposure to uncontrolled inflammation [2,4].

Artificial Intelligence and Predictive Modeling

Although still in early stages, Artificial İntelligence (AI) may represent the next frontier in FMF personalization.

Machine-learning approaches are being explored to:

Predict disease severity

Identify patients at risk for amyloidosis

Forecast treatment response

Integrate genomic and clinical datasets

Future AI-assisted decision systems may enable truly individualized treatment algorithms based on multidimensional patient profiles. While such applications remain largely investigational, they align closely with broader precision medicine initiatives in inflammatory diseases (3,4).

Epigenetics and Future Therapeutic Targets

Recent investigations have highlighted the role of epigenetic regulation in FMF pathogenesis. DNA methylation patterns, microRNAs, and chromatin remodeling mechanisms appear capable of influencing inflammatory activity independently of MEFV genotype [1,3,4].

These discoveries suggest that future precision therapies may extend beyond IL-1 inhibition to include interventions targeting:

Pyrin regulation

Inflammasome signaling

Epigenetic modifiers

Downstream cytokine networks

Such approaches could be particularly beneficial for patients who fail conventional biologic therapies.

Challenges and Future Directions

Despite remarkable progress, several obstacles remain [2,4,5].

Key challenges include

1. Limited availability of predictive biomarkers.

2. High cost of biologic therapies.

3. Lack of head-to-head comparisons among IL-1 inhibitors.

4. Incomplete understanding of modifier genes and epigenetic influences.

5. Need for validated precision medicine algorithms.

Future research will likely focus on integrating genomics, biomarkers, digital health technologies, and real-world data into comprehensive treatment frameworks. International collaborative registries will be essential for identifying rare phenotypes and optimizing individualized care [3,5].

Conclusion

The management of Familial Mediterranean Fever is undergoing a profound transformation from empirical therapy toward precision medicine. Advances in MEFV genotyping, biomarker-guided monitoring, standardized definitions of colchicine resistance, and targeted IL-1 inhibition have substantially expanded opportunities for individualized care. Personalized treatment strategies now enable clinicians to tailor therapy according to genetic risk, inflammatory activity, complication burden, and therapeutic response. As multi-omics technologies, artificial intelligence, and novel biologic agents continue to evolve, FMF may become a model disease for precision medicine in autoinflammatory disorders. The ultimate goal is not merely suppression of attacks but comprehensive, patient-specific control of inflammation, prevention of long-term complications, and optimization of quality of life [6,7].

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