Editorial

The decline of AA amyloidosis in familial Mediterranean fever is significant, but the story is not over

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The clinical features of familial Mediterranean fever (FMF) were first described in detail in the early 20th century (1, 2). Among the defining features was an increased risk of mortality due to renal involvement, which was later attributed to serum amyloid A (AA) amyloidosis (2). A post-mortem examination of one of the three patients who had died from renal complications revealed widespread AA amyloid deposits across nearly all organs (2). Based on these findings, the same group even proposed that amyloidosis represented a genetically determined and independent disease characteristic (3). Blum *et al*. subsequently reported that amyloidosis could develop after a few mild episodes, which an inexperienced physician might miss, while in other cases, it did not occur despite the patient experiencing numerous severe attacks over many years (4). These early observations also showed that amyloidosis could appear at any age, though it most commonly emerged during early youth.

What has changed after the use of colchicine in FMF?

AA amyloidosis is a serious complication associated with chronic inflammation, characterised by sustained overproduction of serum amyloid A protein, whose monomers are converted into amyloid fibrils. The effective treatment of underlying chronic inflammatory conditions, including infections and rheumatic disorders, has led to a substantial decline in the overall frequency of AA-type amyloidosis among the causes of all types of systemic amyloidosis. In the context of FMF, colchicine was introduced for treating the disease in 1972, and it has become the standard of care in FMF after 1974, as it proved effective in preventing the recurrent inflammatory attacks (5-7). Later, Zemer *et al*. demonstrated that regular colchicine use significantly reduced the risk of developing AA amyloidosis, emphasising for the first time the critical importance of adherence in FMF management (8). In their landmark study of 1070 FMF patients followed for 4 to 11 years, only 4 out of the 960 patients, who had no initial findings of renal involvement and who took colchicine regularly, developed amyloidosis. In contrast, 16 of 54 non-compliant patients developed amyloidosis, clearly showing the impact of non-adherence on the risk of amyloidosis. In addition, colchicine treatment was shown to help prevent the progression in patients with early stages of renal amyloidosis. Among 86 patients with non-nephrotic range proteinuria, colchicine treatment resulted in the resolution of proteinuria in 5 and stabilisation in 68 patients. However, the timing of the intervention was also critical, since the deterioration of renal function was noted in all 24 patients with nephrotic-range and 13 with non-nephrotic proteinuria despite treatment (8).

Following this important contribution, colchicine has remained the cornerstone of FMF management, with the primary goal of preventing attacks and the development of AA amyloidosis. In addition to the drug adherence, Livneh *et al*. emphasised the daily dose of colchicine required to prevent progression of the amyloidosis as >1.5 mg/day, which was effective in those patients without renal failure (serum creatinine <1.5 mg/dl) (9).

With the regular use of colchicine, the frequency of amyloidosis has significantly declined from 26.6% in the first large cohort of FMF patients to 12.9% (2005) and 11.4 (2007) in the subsequent two large series, and down to 10.2% in more recent data (10-13).

Disease duration and late diagnosis leading to long untreated periods have been critical factors affecting the risk. Amyloidosis has been reported at much lower frequencies in paediatric patients, even in those with accompanying inflammatory conditions (0.68%) (14), and Bourguiba *et al*. have noted a higher frequency of amyloidosis in patients with a delayed diagnosis (10% compared to 2.6%) (15).

Besides, the severity of the inflammatory response is a critical factor, influenced by both modifiable and non-modifiable determinants (Table I). Nearly all large series consistently report a strong association with a non-modifiable risk factor, homozygosity for the most penetrant p.M694V variant (12, 16). AA amyloidosis manifests itself earlier in patients with homozygous p.M694V (27 years) or compound heterozygous *MEFV* exon 10 variants (30 years) compared to the heterozygous patients (41 years). However, the country of origin of the patients, rather than the *MEFV* genotype, has been identified as the most significant risk factor, which suggests the possible interplay of the *MEFV* variants and environmental factors, correlated with the infant mortality rates (13).

Table I. Risk factors associated with increased risk for AA amyloidosis in FMF patients.

Modifiable	Non-modifiable
- Delay in diagnosis	- M694V/M694V genotype
- Drug adherence	- Patients with arthritis
- Drug dosage	- *SAA1* polymorphisms (α/α genotype)
- Environmental factors including infections	- *MICA* alleles
	- Family history for amyloidosis
	- Male sex
	- Country of origin

Response to colchicine and beyond

In the last 50 years, it has become evident that the complete response to colchicine is less frequent than previously thought, and the issue of adherence cannot be solved (17, 18). Amyloidosis has continued to be diagnosed even in compliant patients, usually at a later age (8, 16). Subsequent studies documented the ongoing risk of amyloidosis associated with higher inflammatory load not controlled with colchicine alone, usually related to the most penetrant p.M694V variant, experiencing particular forms of attacks such as arthritis and exertional leg pain, diagnostic delays, country of origin, and additional inflammatory disorders.

Advances in the understanding of the molecular pathogenesis enabled us to use more effective treatments in colchicine-refractory or intolerant patients, mainly targeting the inflammasome-associated IL-1β signalling. Treatment of the patients by targeting IL-1β or IL-1 receptor 1 (IL-1R1) has been shown to be effective in better controlling inflammation, but their role in the prevention of amyloidosis has yet to be documented (19). When necessary, other options targeting TNF or IL-6 signalling have also been considered in selected cases.

Unexplained issues of AA amyloidosis

Despite significant progress, several unanswered questions remain. One example is Phenotype 2, characterised by amyloidosis as the initial and in some cases the only manifestation, reported in a small subset (0.6%) of patients (4, 10). If such cases exist, they may suggest that the risk of amyloidosis can be influenced by additional factors coexisting with the highly penetrant pathogenic *MEFV* variants, particularly in families with other members affected by AA amyloidosis. Notably, the risk may not correlate with the number and severity of attacks, and the potential contribution of *SAA1*, *MICA (20)*, epigenetic changes, and environmental factors remains to be fully elucidated.

Although amyloidosis tends to occur more than 10 years later in heterozygous patients compared to homozygous or compound heterozygous individuals, the extent of organ involvement has been reported as more severe (16). This may reflect less rigorous monitoring and treatment in heterozygous patients or the contribution of additional genetic or environmental risk factors to the disease progression.

Additionally, most of the investigators focused only on renal involvement, yet AA amyloidosis is a systemic disease. Uncontrolled inflammatory activity can result in progressive involvement of other organs, including the liver, spleen, intestines, and, finally, the heart. Furthermore, in some patients with limited amyloid deposition, infections or other inflammatory events can trigger the rapid deterioration of clinical findings. The so-called amyloid storm, a condition associated with a very high mortality rate in 1 year, is defined as the increase of creatinine and proteinuria values at least 2 times compared with the baseline, and the elevation of CRP values more than 10 times compared with the highest normal level in less than 2 weeks (21). The presence of an amyloid nidus is necessary for further deposition, but the underlying factors associated with the tendency to this quick deterioration of amyloidosis have yet to be defined.

In conclusion, the risk of amyloidosis in FMF patients has not disappeared completely with the advances in the treatment, and current evidence suggests a shifting pattern, with amyloidosis now emerging at older ages than in earlier descriptions. Optimum control of inflammatory findings with the available drugs should be a lifelong goal, and getting older or being heterozygous for penetrant mutations should not be an 'automatic' indication for dose reduction or discontinuation of colchicine. Particularly, heterozygous individuals should not be regarded as mere carriers when they develop significant disease manifestations. Heterozygosity for the penetrant variants may increase the risk of developing other inflammatory conditions such as periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome, spondyloarthritis, and Behçet's disease (22-24). However, these associations should not be mistaken for the FMF phenotype developing in patients carrying only heterozygous pathogenic variants. While the clinical presentation of FMF in heterozygous patients is often milder and may respond well to colchicine, the

risk of developing amyloidosis remains, potentially driven by environmental influences or additional genetic modifiers that shape disease expression despite heterozygosity.

While the original Zemer *et al*. 1986 study confirmed the efficacy of colchicine in preventing amyloidosis, it also underscored the residual risk, especially as patients age. Whether this is due to suboptimal adherence or insufficient dosing remains unclear. As amyloidosis now tends to develop later in life, any decision to discontinue colchicine must be made with caution. We need long-term data by close monitoring using clinical and laboratory parameters of inflammation for making recommendations, particularly for the 'heterozygous patients', who develop disease manifestations with the complex interaction of *MEFV* and other genes, epigenetic changes, and environmental factors, including the living standards in association with the country of origin.

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