

Therapeutic approach to patients with familial Mediterranean fever-related amyloidosis resistant to colchicine

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Received on July 25, 2012; accepted in revised form on August 30, 2012.

Clin Exp Rheumatol 2012; 30 (Suppl. 72): S104-S107.

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Key words: familial Mediterranean fever, amyloidosis, colchicine

ABSTRACT

The frequency of FMF-related amyloidosis has been decreased by colchicine use over the past few decades. However, the beneficial effect of colchicine may differ in accordance with nephropathic stages. When used in proper doses and with compliance, colchicine is very effective in preclinical and proteinuric stages of FMF-related amyloidosis. Even so, a large number of patients with nephrotic range proteinuria, despite compliance and an ideal dose of colchicine, may still progress to end-stage renal failure (ESRF). We do not know exactly what we can do with such patients. This paper discusses the therapeutic approach to patients with FMF-related amyloidosis.

Introduction

FMF is an auto-inflammatory disease characterised by fever, abdominal and pleuritic attacks. Goldfinger and Ozkan reported positive effects of colchicine on FMF attacks 4 decades ago (1, 2). Though it has been reported to be very effective in most cases of FMF attacks, colchicine fails to show its positive effects between 5 to 15 percent of the sufferers of this disease (3), for whom IV colchicine (4), TNF-alpha inhibitors (5), IL-receptor antagonist (anakinra) (6), and thalidomide (7) have been successfully used in some patients. FMF-related amyloidosis, which is the worst complication of FMF, tends to result in end-stage renal failure (ESRF) and this is accepted as a direct reason for mortality (8). This review discusses a therapeutic approach to FMF-related amyloidosis resistant to colchicine.

The role of colchicine in the prevention of FMF-related amyloidosis

When colchicine is used in appropriate doses and compliance has been provid-

ed, it is capable of preventing AA-amyloidosis in FMF by 98% (9). The fact that there has been a significant fall in the number of cases with FMF-related amyloidosis over the past four decades is the result of colchicine treatment. The frequency of cases with amyloidosis has been reported to vary between 6.3 and 12.9 percent in recent years (8, 10), far away from the 60 % in the pre-colchicine era (11). However, such factors as delay in diagnosis, problems with compliance, or improper dosages of colchicine may cause some patients who are predisposed to develop amyloidosis to end up with FMF-related amyloidosis.

The role of colchicine in the treatment of FMF-related amyloidosis

Even today it is possible to hear of FMF-related amyloidosis, which is known to be the most significant predictor for mortality (8). Amyloidosis tends to emerge between 2 months and 14 years once FMF has started according to one report (12). Nephrotic amyloidosis is composed of four phases occurring one after the other. These phases are known as preclinical, proteinuric, nephrotic range proteinuria (NRP) and uremic phases. The period elapsing between the onset of proteinuria and ESRF varies from 2 to 13 years (12). The 3 most important factors indicative of a positive response to colchicine are as follows: a dose of colchicine higher than 1.5 mg/day, a creatinine level lower than 1.5 mg/day and compliance with colchicine (13). It is possible to provide stability and even regression in proteinuria in the proteinuric stage with the help of colchicine. Though some of the patients with NRP may respond favourably to colchicine (14), some others inevitably progress to ESRF

Competing interests: none declared.

despite colchicine use (9). For example, Cakar *et al.* have reported that in 80% of the patients in the proteinuric stage either stability or regression in proteinuria can be achieved on the condition that appropriate doses of colchicine are used and compliance has been secured (15). Unfortunately, no improvement can be observed in about 56% of patients with NRP on their first presentation to a clinic and 53% of these patients progress to ESRF (15). Similar results have been reported by Livneh *et al.* before (13), who stated that half of the patients suffering from proteinuria over 4 g/day had exhibited deterioration in their renal functions. Furthermore, Zemer *et al.* reported that all patients with a nephrotic stage deteriorated despite being on colchicine (9). All these results lead us to the conclusion that some action should be taken to avoid such an unfortunate outcome. What can we do about those patients with NRP? Which drug/s should be used in the management of FMF-related amyloidosis in addition to colchicine?

Do we need second-line drugs?

The most basic approach to treating secondary, or using the more precise term, SAA amyloidosis is to bring down the level of SAA protein to less than 10 mg/L. There is a direct relationship between SAA levels and the amyloidosis load, which is also linked to mortality (16). Accumulation of amyloid causes organ damage not just through its invasive impact but also with its direct toxic effects. For instance, SAA is capable of stimulating cytokines as well as accelerating activation of neutrophils (17). Cytotoxic drugs and biological agents are known to decrease SAA levels, but biological agents have also been reported to reduce toxic effects of amyloid fibrils (18). The SAA amyloidosis that develops in FMF theoretically is no different from that develops in other chronic inflammatory diseases like rheumatoid arthritis or ankylosing spondylitis. Since these diseases are usually managed with anti-inflammatory, immunosuppressive or biological agents there is good reason

to think that such an approach could be useful in managing SAA amyloidosis as a complication of FMF. In fact, biological agents have been successfully used in FMF attacks, resistant to colchicine, while immunosuppressive drugs and steroids have been used in the treatment of FMF-related vasculitis, protracted arthritis, and febrile myalgia with remarkable success so far (19). Then it follows that the this same approach can be used to treat FMF-related amyloidosis, which is known for its high mortality.

When and to whom should we apply a second-line drug?

We know that a substantial number of NRP patients whose creatinine levels remain lower than 1, 5 mg/dl and are using appropriate doses of colchicine may also progress to ESRF. On the other hand colchicine is also known to help NRP regress in some patients with FMF-related amyloidosis (14). Finally we know of no reliable predictor that could tell us which group of patients will benefit from colchicine use (9). For this reason, physicians should also consider second-line drugs in addition to colchicine in NRP patients. The crucial question herewith is how long we should wait for colchicine to work. Even though it has been claimed that colchicine takes around two years to show its real effect, it is possible for proteinuria to exhibit its tubulotoxic effect, thus causing interstitial inflammation and irreversible fibrosis in the meantime. For this reason, there arises the need for an earlier intervention in order to avoid such a problem, since the interstitial inflammation that is induced by proteinuria seems to be the most crucial predictor for renal prognosis. A direct relationship has been reported between renal prognosis and interstitial involvement in FMF-related amyloidosis (20). Another factor that leads us to think of an additional drug to colchicine is amyloidosis-related gastrointestinal system (GIS) involvement, which then results in malabsorption and poor tolerability of the drug. It is for such patients that we should think of second-line drugs, biological agents in particular.

What role do immunosuppressive drugs or biological agents play in FMF-related amyloidosis?

These days, treatment of secondary or SAA amyloidosis is or should be based on pathogenetic mechanisms. Accordingly, an intensive anti-inflammatory or immunosuppressive treatment, or an anticytokine therapy if necessary, should be applied with a view to reduce SAA levels (21). Such cytokines as IL-1 and TNF-alpha are deemed culpable in the pathogenesis of FMF (22). While cytokine IL-1 is responsible for the rise in SAA levels, IL-6 is responsible for the rise in CRP levels (21). However, IL-6, IL-1 and TNF-alpha cytokines increase acute phase reactants cooperatively, thus accelerating the accumulation of amyloid fibrils by increasing SAA levels. It could be theorised that if the inflammation can be inhibited with cytostatic drugs non-specifically or if cytokines responsible for the rise in acute phase reactants can be blocked, then the amyloid load and possible toxic effects may be reduced once SAA levels have been brought down.

Second-line drugs used for FMF related amyloidosis

Immunosuppressive drugs

There exist no controlled studies into the role of immunosuppressive drugs in FMF-related amyloidosis apart from a couple of anecdotal reports. We gave appropriate doses of colchicine to two of our three patients with FMF-related amyloidosis. However, we observed no significant drop in their NRP levels. Therefore, we chose to add azathioprine (AZA) and prednisolone (PRD) to colchicine, thanks to which we began to observe a dramatic change in their NRP levels. The remaining patient, who was referred to us later than the others, was immediately given this combination unlike the other two. Interestingly, we observed a significant drop in his proteinuria in a much shorter time (23). This experience and a study by Sayarlioglu *et al.* (24) suggest that addition of immunosuppressive drugs to colchicine seems plausible in order to achieve a dramatic response in FMF-related amyloidosis. It could be argued that using PRD for such cases

is controversial; however, steroids are known to contribute positively to immunosuppressive drugs in regression of amyloidosis secondary to other rheumatic diseases (25). Could this be true for FMF-related amyloidosis, too? Previous studies have reported that FMF patients with amyloidosis may suffer from subclinical adrenal insufficiency (26). Moreover steroids might also be useful in the early blunted cortisone response reported in insulin-induced hypoglycemia in FMF patients in general (27). Glucocorticoid administration may complement what is missing. Glucocorticoids are also known to inhibit cytokines that increase the SAA levels. However, a long period of glucocorticoid use may lead to unwanted effects on carbohydrate and lipid metabolisms, as well as accelerating atherosclerosis. Thus, caution should be exercised when prescribing cortisone for long-period usage. One point that needs to be elucidated is that we are not sure how long AZA should be used in FMF-related amyloidosis and what role this drug has in SAA levels and the amyloid load, and what kind of long-term adverse effects it may have. Similarly, we also need to know more about the long-term effects of other immunosuppressives such as chlorambucil, cyclophosphamide, mycophenolatemofetil or methotrexate in FMF-related amyloidosis

Biologic agents used for FMF-related amyloidosis

Infliximab was used for the first time by Metyas *et al.* in a patient with FMF-related amyloidosis who had failed to respond to colchicine. Following the sixth infusion, the NRP decreased to 1.47g / 24 h (28). Yüksel *et al.* also determined a significant decrease in acute phase reactants and proteinuria levels within a period of twenty months (29). Still others have referred to the benefit of infliximab in their studies (30, 31). Ozcağkar *et al.* reported a case with GIS involvement in addition to NRP. During the six and a half years of treatment including infliximab, GIS involvement completely disappeared while NRP partially decreased (32). IL-1 is a cytokine responsible for inflammation in

FMF, antagonisation of which has been suggested as a means of suppressing inflammation (6). There is some concrete evidence as to the benefit of the IL-1 receptor antagonist drugs used in patients who are resistant to colchicine (6). There is only a limited amount of information on the benefit of this drug in FMF-related amyloidosis. Bilginer *et al.* used a-IL-1 therapy for secondary amyloidosis in a patient with both Behçet's disease and FMF diseases (33). They were able to stabilise proteinuria levels. Another study by Stankovic-Stojanovic *et al.* used a-IL-1 treatment for FMF-related amyloidosis in a patient with both renal failure and GIS involvement (34). After 17 months, they observed that the FMF attacks were effectively suppressed, and that there was stability in renal functions, and that there was a partial remission in GIS manifestations. There are reports of intermittent or continuous use of alpha-interferon decreasing the frequency and severity of FMF attacks. As to FMF-related amyloidosis, Vandecasteele *et al.* reported a FMF case who developed NRP while under colchicine treatment in traditional dose of 1.5 mg a day. Peginterferon-alpha-2a was started at 180 micro g per week. After 22-months of its use, a complete resolution in renal amyloidosis was noted (35). Some patients with rheumatoid arthritis-related amyloidosis are reported to have greatly benefitted from IL-6 receptor antagonist (tocilizumab) (36). However, there are no studies of tocilizumab use in FMF-related amyloidosis. Further studies of biologics in greater number of patients with FMF are clearly needed. As a word of caution we should not also disregard a publication bias in the favourable case reports we have just discussed.

Promising new drugs

It may not always be possible to completely inhibit SAA production in secondary amyloidosis. In this case, we need alternatives that could affect different steps of the amyloidogenic pathway. Eprodisate is a sulphonated molecule similar to heparan sulphate, and is a small molecular glycosaminoglycan (GAG) analogue. The most im-

portant effect of this drug is its ability to prevent SAA from binding to GAG. In a multicentre, randomised placebo controlled study, it slowed down the decline of renal function in secondary amyloidosis. Admittedly however, the effect was rather moderate. (37). Another approach targets amyloid deposits directly, by destabilising the amyloid fibrils. Serum amyloid P (SAP) was considered to protect amyloid deposits from proteolytic enzymes and mononuclear phagocytes. Destabilisation can be managed by small molecular SAP binding ligands. A small SAP ligand was observed to mobilise the tissue SAP effectively, though the clinical efficacy remains unclear (38).

Conclusion

Colchicine is still the best drug for the treatment of FMF-related amyloidosis. It is an agent that successfully regresses amyloidosis deposition of patients during both the pre-clinic and proteinuric stages. However, there is an overall resistance to colchicine in patients with NRP. Therefore, a need has arisen for extra drugs that could be used in combination with colchicine in order to avoid ESRF. Our suggestion for possible additional drugs would be AZA and biological agents. Still, it is clear that we need further controlled studies in order to collect more convincing evidence.

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