THE PREVENTION OF AMYLOIDOSIS IN FAMILIAL MEDITERRANEAN FEVER WITH COLCHICINE


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Summary

Colchicine has been used since 1972 to prevent the acute attacks of familial Mediterranean fever. The present study shows that colchicine is also effective in the prevention of amyloidosis. If initiated in patients without evidence of renal disease there is no appearance of proteinuria and no progression to renal insufficiency over long follow-up periods. Moreover, it ameliorates the course of the disease in patients with amyloid nephropathy and normal renal function. It does not alter the course of the disease if initiated after renal function is even mildly impaired. These findings suggest that colchicine prevents the new deposition of amyloid.

Introduction

Familial Mediterranean fever (FMF) is a hereditary disorder affecting peoples of Mediterranean origins, mainly Sepharadic Jews, Armenians, Arabs of the Near East and Turks. The disease becomes manifest in childhood or adolescence when febrile attacks of peritonitis, synovitis and pleuritis appear. Systemic amyloidosis of the AA type develops in most untreated patients causing end-stage renal disease (ESRD) [1].

In 1972 continuous prophylactic treatment with colchicine was introduced [2], and subsequently proved effective in preventing or ameliorating the acute attacks in 85 per cent of patients [3].

This paper evaluates the effect of colchicine on the development and course of renal amyloidosis.

Patients and methods

Since 1972 colchicine has been prescribed in a minimal dose of 1mg/day (up to 2.5mg/day) for all FMF patients, children and adults. One thousand and forty-one patients had no evidence of renal disease (no proteinuria and normal renal
function) when the drug was prescribed. Assuming that assessment of its effect on the prevention of amyloidosis requires an adequate period of follow-up, only 840 who had been followed-up for four or more years were studied. Fifty-four of them proved to be non-compliant regarding colchicine therapy for a variety of reasons, providing an unplanned control group of untreated patients.

One hundred and fourteen patients were in various stages of overt renal disease when colchicine was initiated. Fifty-two had proteinuria of less than 3.5g/day and normal renal function; fourteen had proteinuria exceeding 3.5g/day with normal serum creatinine; twelve had renal insufficiency (serum creatinine ≥1.6mg/dl) and progressed to ESRD — in those patients the logarithms and reciprocals of serum creatinine values were plotted against time and their period of progression from creatinine of 1.6mg/dl to ESRD was determined using linear regression analysis [4]. This group was compared to 10 patients who progressed to ESRD before the colchicine era.

Results

Among the 840 non-proteinuric patients, proteinuria has appeared in only three of 786 patients (0.4%) who complied with treatment. In the group of the 54 patients who did not comply, proteinuria appeared in 10 (18.5%). In our earlier series [1] of 470 patients not treated with colchicine the prevalence of amyloidosis was 27 per cent (the rate of appearance of new cases nearly equalling the mortality rate from the disease).

Among the patients with evidence of renal amyloidosis when treatment was initiated, the 52 patients with proteinuria below the nephrotic range and normal renal function have now been followed up for an average period of 5.7 years without progression to the nephrotic syndrome and renal insufficiency. In contrast the mean interval between the appearance of proteinuria and the onset of nephrotic syndrome was 2.2 years before the colchicine era.

Of the 14 nephrotic patients with normal renal function, six have progressed to renal failure, four remained stable and four showed some decrease of the proteinuria.

Twelve of the patients in mild renal insufficiency when colchicine treatment was begun who progressed to ESRD did so over a mean period of 31.6 ± 6 months, as compared to 33.9 ± 6 months in the group of 10 untreated patients before the introduction of colchicine.

Discussion

Our results establish the effectiveness of daily colchicine therapy in the prevention of amyloidosis in FMF. The extremely low cumulative incidence (0.4%) of proteinuria among treated patients as compared to 18.5% in untreated patients, is the most striking finding. Colchicine also definitely ameliorates the course of amyloid nephropathy if treatment is started when kidney function is normal. This beneficial effect is pronounced in the patients who had proteinuria below the nephrotic range, as judged by long follow-up period without progression into renal insufficiency or nephrotic syndrome in none of the patients.
These findings suggest that colchicine might prevent de novo formation of amyloid. If the structural damage to the kidney is not severe the condition of the treated patients remains stable — patients with no proteinuria or proteinuria below the nephrotic range. If there is severe deposition of amyloid in the kidney, as in some nephrotic patients and in all patients with renal insufficiency, the functional damage is not reversible.

However, as these patients face long-term dialysis and/or transplantation it is advisable to prescribe colchicine even in the presence of irreversible renal damage in order to prevent further deposition of amyloid in other organs, as well as the febrile attacks of FMF.

References

Open Discussion

PAPADIMITRIOU (Greece) I should like to congratulate Dr Aviram for this report. We have the same experience as you in some of our cases. We notice that if we transplant these patients and they do not take colchicine after transplantation they develop the same attacks of pain etc. Of course they have to take colchicine for ever.

AVIRAM We have exactly the same experience.

DAVISON (Chairman) How do you check compliance in your patients? Is it from the symptoms and their fever?

AVIRAM Usually just by asking patients. In the group we presented here of non-compliant patients they definitely did not take the drug by their own admission.

DAVISON And have you seen any side effects from the use of the drug?

AVIRAM We give in a very minimum dose of up to 2.5mg a day so if there are any side effects like diarrhoea it lasts only a few days and then disappears.

DAVISON Would you be prepared to comment on the value of colchicine in other forms of amyloidosis?

AVIRAM There is only a very limited experience and it seems that it is not useful because those patients usually appear when renal function has already deteriorated so we cannot really compare the groups.