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COLCHICINE IN THE PREVENTION AND TREATMENT OF THE AMYLOIDOSIS OF FAMILIAL MEDITERRANEAN FEVER

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Abstract To determine whether colchicine prevents or ameliorates amyloidosis in patients with familial Mediterranean fever, we followed 1070 patients with the latter disease for 4 to 11 years after they were advised to take colchicine to prevent febrile attacks.

Overall, at the end of the study, the prevalence of nephropathy was one third of that in a study conducted before colchicine was used to treat familial Mediterranean fever. Among 960 patients who initially had no evidence of amyloidosis, proteinuria appeared in 4 who adhered to the prophylactic schedule and in 16 of 54 who admitted noncompliance. Life-table analysis showed that the cumulative rate of proteinuria was 1.7 percent (90 percent confidence limits, 0.0 and 11.3 percent) after 11 years in the compliant patients and 48.9 percent (18.8 and 79.0 percent) after 9 years in the noncompliant patients ($P<0.0001$).

A total of 110 patients had overt nephropathy when they started to take colchicine. Among 86 patients who had proteinuria but not the nephrotic syndrome, proteinuria resolved in 5 and stabilized in 68 (for more than eight years in 40). Renal function deteriorated in 13 of the patients with proteinuria and in all of the 24 patients with the nephrotic syndrome or uremia.

We conclude that colchicine prevented amyloidosis in our high-risk population and that it can prevent additional deterioration of renal function in patients with amyloidosis who have proteinuria but not the nephrotic syndrome. (N Engl J Med 1986; 314:1001-5.)

FAMILIAL Mediterranean fever is an autosomal recessive disorder occurring most commonly in Sephardic Jews and Armenians.[1,2] Two phenotypic features characterize the disease: brief, episodic, febrile attacks of peritonitis, pleuritis, or synovitis beginning in childhood or adolescence; and the development of amyloidosis. The attacks are accompanied by striking elevations of acute-phase reactants, including serum amyloid A protein.[3] The amyloidosis, which is of the amyloid A type,[4] is manifested clinically by a nephropathy that passes through proteinuric, nephrotic, and uremic stages to death from renal failure.[1,5] Although there is an ethnic variation in the incidence of amyloidosis in familial Mediterranean fever,[2,6-8] early death from amyloidosis is common in our patient population, which is composed predominantly of Sephardic Jews of North African extraction.[1,8,9]

Since Goldfinger's suggestion in 1972 that daily administration of colchicine may prevent the painfully disabling febrile attacks of familial Mediterranean fever, the drug has become the mainstay of therapy for the disease.[10-15] Although a small percentage of patients do not respond to the agent, more than 90 percent have a complete remission or a marked amelioration of attacks as long as they take the colchicine. When the drug is discontinued, the attacks promptly resume.

In reporting our controlled trial of colchicine for the prevention of the febrile attacks of familial Mediterranean fever more than a decade ago,[11] we emphasized that

> Although their dramatic nature has justifiably made the febrile attacks the clinical hallmark of familial Mediterranean fever, it is the insidious development of amyloidosis that causes death, usually before the age of 40. Since . . . attacks and amyloidosis are independent phenotypic characters of a single pleiotropic gene, it does not follow that an agent effective in preventing attacks will a priori prevent amyloidosis. One can cite, cautiously but with hope, the fact that colchicine seems to protect mice from casein-induced amyloidosis.

In this article, we present evidence that colchicine does provide protection from amyloidosis in patients with familial Mediterranean fever.

METHODS

The 1070 patients in this study were advised to begin taking colchicine (1 to 2 mg daily) during 1973 to 1980. They were followed for 4 to 11 years after this recommendation. All patients fulfilled the diagnostic criteria for familial Mediterranean fever, as previously described.[1] Most of them were young, and most were Sephardic Jews of North African origin.

During the follow-up period, the patients were seen at intervals that varied from three months to one year, usually on an outpatient

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basis. At each visit, the patient was questioned carefully about compliance with the colchicine regimen; the importance of adhering to the daily prophylactic schedule was emphasized, and urinalysis was performed. When 1+ proteinuria (Albustix; detection threshold, ≥300 mg per liter) was found during consecutive visits of a patient who had previously had none, urinary protein was measured in a 24-hour specimen, and the serum creatinine level was determined. The results were used to stage the renal lesion. The same assessments were performed during the subsequent visits of the patients found to have proteinuria and during all the visits of the patients who had overt renal disease on entry into the study. In populations of young patients, persistent proteinuria has proved to be the best indication of renal amyloidosis; thus, biopsy confirmation is not routinely sought.[1,5,9]

Of the 1070 patients in the study, 960 had neither proteinuria nor other evidence of amyloidosis when colchicine was first prescribed. The remaining 110 patients were in the various stages of overt renal disease; 86 were in the proteinuric stage (persistent proteinuria of 1+ or more but <3.5 g per 24 hours and a serum creatinine level of <1.5 mg per deciliter [<130 μmol per liter]), 9 were in the nephrotic stage (proteinuria >3.5 g per 24 hours and a serum creatinine level of <1.5 mg per deciliter), and 15 were in the uremic stage (serum creatinine ≥1.5 mg per deciliter). Deterioration and improvement in the patients with overt renal disease were defined by a change of one stage.

During the study, 83 patients were lost to follow-up. At their last visits, however, all were doing well on colchicine therapy, and none had proteinuria. Since 59 of these patients dropped out before they had received four years of observation, they were not included among the 1070 analyzed. Twenty-four patients dropped out after four or more years. Although we do not know the reasons these patients left the study, long lapses in follow-up in the past have often been due to an unwillingness to miss school or work, family obligations, or military service among patients who were doing well and usually living at some distance from the study center. Patients who were doing poorly not only tended to preserve their connections to the study but also had often been referred by their family physicians.

The summary rate ratio, over age, of the cross-sectional prevalence of proteinuria in this series of patients and a series studied before colchicine was used to treat familial Mediterranean fever[9] was calculated by the Mantel–Haenszel method, with test-based confidence limits.

Life-table analysis was used to estimate cumulative prevalence rates of proteinuria according to the length of follow-up in patients who initially had no evidence of renal disease. The results are expressed as the rates and the 90 percent confidence limits.

Results

The cross-sectional prevalence of amyloid nephropathy, as indicated by proteinuria in the 1062 patients alive at the end of this study, is compared with that in our pre-colchicine study[9] in Table 1. Except in the patients under 20, the prevalence of proteinuria in all age groups was about three times higher in the pre-colchicine study (the summary rate ratio for ages over 20 was 3.1, with 90 percent confidence limits of 2.4 and 4.0). Of the 1070 patients in our current series, 8 died during the follow-up period — a mortality rate of less than 0.1 percent per year. Four deaths were due to renal failure. Four deaths were accidental (unrelated to the disease) and occurred in patients with no evidence of nephropathy.

To assess the extent to which the drastic reduction in the prevalence of proteinuria was attributable to colchicine, we analyzed the data according to the absence or presence of overt renal disease when colchicine was first prescribed and compliance or noncompliance with the treatment schedule.

Patients without Overt Renal Disease

Noncompliant Group

Fifty-four of the 960 patients whose urine samples were free of protein when colchicine was first prescribed did not take the drug for two or more years. These noncompliant patients, all of whom were under 40, provided an unplanned concurrent control group. The major source of noncompliance was the reluctance of primary care physicians, early in our experience with colchicine, to recommend continuous administration of the drug to a patient population consisting largely of children, adolescents, and young adults in their reproductive years. Only eight patients stopped taking the drug on their own, usually because they thought that their attacks were not sufficiently frequent or disabling to justify daily medication. In no case were side effects or deterioration in a patient's condition a reason for stopping the treatment.

Proteinuria appeared in 16 of the 54 noncompliant patients. It was first documented after two to nine years of noncompliance in five patients under 20, in four patients who were 20 to 29, and in seven patients who were over 30. It progressed to the nephrotic syndrome in two patients, one of whom had a rapid onset of end-stage kidney disease and required transplantation. None of the urine sediments that were observed contained formed elements suggestive of a primary renal disorder, and no patient had evidence of a disease other than familial Mediterranean fever. The ethnicity of the group with proteinuria was representative of our total patient population; 15 were Sephardic Jews (12 were of North African origin and 3 were from Baghdad), and 1 was an Israeli Arab.

Compliant Group

Among the 906 compliant patients, the urine samples of 902 remained free of protein during 4 to 11 years of follow-up. This group included 34 patients — who were representative of our total patient population in terms of age, ethnic group, and

Table 1. Cross-Sectional Prevalence of Nephropathy According to Age in Patients Alive at Completion of the Current Study, as Compared with the Pre-Colchicine Study.

Age Group*	Current Study		Pre-Colchicine Study†		Rate Ratio	90% Confidence Limits
	No. of Patients	Patients with Nephropathy	No. of Patients	Patients with Nephropathy		
yr		%		%		
<20	342	7.9	147	10.2	1.3	0.8, 2.2
20–29	367	10.6	74	29.7	2.8	
30–39	211	12.8	63	44.4	3.5	3.1 2.4, 4.0
40–49	100	18.0	16	56.3	3.1	
≥50	42	23.8	16	68.8	2.9	

*At completion of the study. †Adapted from Table 2 of Gafni et al.[9]

length of follow-up — who continued to take colchicine even though it did not modify their febrile attacks.

Proteinuria appeared in only four patients, all of whom were experiencing a complete remission from febrile attacks. It occurred at age 13 in a Sephardic Jew who had been taking colchicine for seven years and who had had Schönlein–Henoch purpura at age 10. Proteinuria appeared after two, six, and six years of colchicine therapy, respectively, in two Ashkenazic Jews at ages 63 and 55 and in a Sephardic Jew at 51. The latter two patients had diabetes mellitus, and rectal biopsy studies were negative for amyloid.

Life-Table Analysis

The cumulative rate of proteinuria was 48.9 percent (90 percent confidence limits, 18.8 and 79.0 percent) after 9 years of follow-up in the noncompliant patients but only 1.7 percent (0.0 and 11.3 percent) after 11 years of follow-up in the compliant patients (Fig. 1). The difference between the groups was especially prominent ($P<0.0001$) when comparisons were made between patients who were in the same age groups when colchicine was first prescribed (Table 2). It is of interest to note that in our pre-colchicine study, the cross-sectional prevalence of proteinuria in those 20 to 29 and those 40 to 49 was 29.7 percent and 56.3 percent, respectively.[9] When we estimated the cross-sectional rates (from the cumulative rate) at comparable ages (<20 and 20 to 40 when colchicine was prescribed) in the noncompliant group in this study, we found them to be almost identical — 27.5 percent and 59.6 percent, respectively.

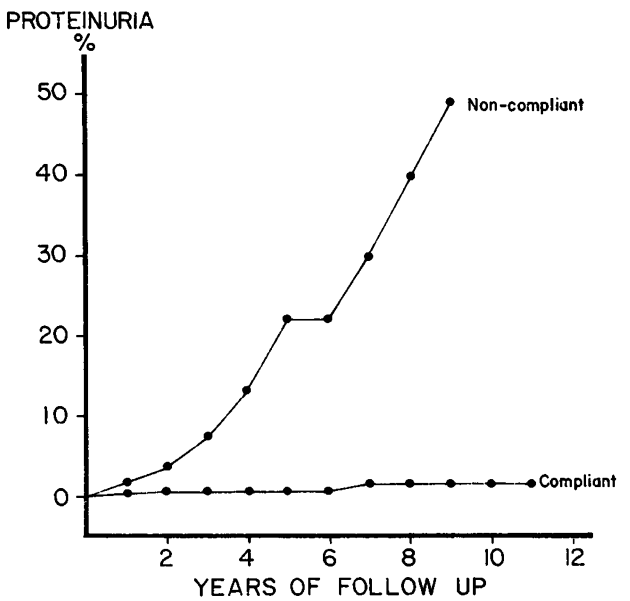

Figure 1. Cumulative Percentage of Proteinuria, According to Years of Follow-up, among Compliant and Noncompliant Patients Who Had No Proteinuria When Colchicine Was Prescribed (as Estimated by Life-Table Analysis).

Table 2. Prevalence of Proteinuria after Nine Years of Follow-up, as Calculated by Life-Table Analysis, According to Age in Compliant and Noncompliant Patients Who Had No Proteinuria When Colchicine Was First Prescribed.

	Patient Group					
	Compliant			Noncompliant		
Age group (yr) →*	*<20*	*20–39*	*≥40*	*<20*	*20–39*	*≥40*
No. of patients	483	351	72	27	27	—
Patients with proteinuria (%)	0.5	0.0	5.7	27.5	59.6	—

*Age when colchicine was first prescribed.

Patients with Overt Renal Disease

Of the 86 patients who were in the proteinuric stage when they were advised to begin taking colchicine, only 1 admitted noncompliance; this patient is now on hemodialysis. Nephrosis or uremia developed in 12 of the 85 compliant patients, 9 of whom eventually required dialysis or renal transplantation. Sixty-eight patients remained stable (proteinuria without nephrosis), 40 of them for eight or more years after initiation of therapy. In five patients, three of whom had rectal biopsy specimens that were positive for amyloid, the proteinuria subsided gradually during the one to six years after they began taking colchicine; their urine has remained free of protein for four to eight years at this writing (Table 3).

All 24 patients who were in the nephrotic and uremic stages when colchicine was started have had renal deterioration. Five of the 9 with nephrosis and 14 of the 15 with uremia required dialysis or renal transplantation (or both). Four patients with renal failure have died — one of a myocardial infarction, one of a cardiac arrest during hemodialysis, and two (one patient on peritoneal dialysis and one with a renal allograft) of causes relating to surgical procedures.

Discussion

Our results are a confirmation in humans of the efficacy of colchicine in preventing amyloidosis — an effect that was demonstrated earlier in laboratory mice.[16,17] The effectiveness of the agent is illustrated by the two-thirds reduction in the cross-sectional prevalence of proteinuria in all patients above 20 years of age with familial Mediterranean fever in this series, as compared with its prevalence among patients with the disease in our pre-colchicine experience. This difference does not reflect selective mortality, since the mortality rate in this study was less than 0.1 percent per year, as compared with about 2 percent per year in our earlier investigation.[9] The only additional change in our management of familial Mediterranean fever has been an increase in the use of dialysis and transplantation, which could only have added to the number of survivors with amyloidosis in the current series. In this study, 85 percent of the patients had no clinical evidence of amyloidosis initially and adhered to the prophylactic colchicine regi-

Table 3. Present Status of the 85 Compliant Patients Who Were in the Proteinuric Stage When Colchicine Was Started.

Years of Treatment	Patient Status		
	Recovered	Stable	Deteriorated
	no. of patients		
4	0	8	0
5	0	10	1
6	0	5	1
7	0	5	1
8	1	6	1
9	0	16	5
10	2	17	3
11	2	1	0
Total	5	68	12

men. As estimated by life-table analysis, proteinuria has appeared among only 1.7 percent of these patients after 11 years of follow-up, a striking contrast to the nearly 50 percent occurrence in a nine-year concurrent follow-up of the unanticipated control group (the noncompliant patients). Therefore, the reduced prevalence of proteinuria in our surviving patient population must be attributed to the protective effect of colchicine in the compliant patients who did not have amyloidosis.

Although the greatly reduced cross-sectional prevalence of proteinuria in the surviving population seems to preclude the possibility of bias, questions may arise about the control group, which was not established by randomization. However, the similarity between the prevalence of proteinuria (as estimated by life-table analysis) in the control group and that among patients of comparable ages in the pre-colchicine study indicates that the noncompliance of the patients in the present study was not related to their underlying propensity toward the development of amyloidosis, and that the number of unidentified noncompliant patients was not important.

In both studies, persistent proteinuria was considered to indicate amyloidosis, and the possibility that this led to overdiagnosis of amyloidosis must be addressed. An overestimation of amyloidosis in the control group seems highly unlikely for the following reasons: all the noncompliant patients were young when proteinuria appeared as an isolated urinary abnormality, all were members of ethnic groups in which the development of amyloidosis is the rule rather than the exception, and none had signs of any disease other than familial Mediterranean fever. If equating proteinuria with amyloidosis introduced a bias through overdiagnosis, it is much more likely to have occurred in the group of compliant patients, in which all four in whom proteinuria developed either had concurrent disease that could have caused the condition or came from an ethnic group in which the development of the amyloidosis of familial Mediterranean fever is the exception rather than the rule.[2,6-8]

Although colchicine provides prophylaxis against amyloidosis in patients with familial Mediterranean fever in whom amyloidosis has not yet developed but whose ethnicity places them at high risk of the condition, its effectiveness is limited in patients who already have clinical amyloidosis. Colchicine does not apparently alter the deleterious effects on cellular and organ function of the amyloid fibrils that have already been deposited in the basement membranes and the ground substances of connective tissues. Our experience indicates that a point from which colchicine can provide no return has been reached when proteinuria has progressed to nephrosis. Although another study has reported different results,[18] we observed a deterioration in the condition of all our patients who reached the nephrotic stage. We also found no indication that either the nephrotic or uremic stage was prolonged by colchicine therapy. In the proteinuric stage, however, when amyloid involvement is presumably more discrete, colchicine can prevent deterioration, probably by suppressing new amyloid formation. This suppression of new deposition could provide time for the tedious processes by which the old fibrils are mobilized and dispersed to become effective.

Before the introduction of colchicine, the duration of the proteinuric stage in a group of our patients with familial Mediterranean fever who were followed closely from the onset of proteinuria to the development of the nephrotic syndrome was two to nine years (it was usually three to five).[1] Today, most of the patients who were in the proteinuric stage when colchicine therapy was started are in stable condition. Well over half these patients are still in the proteinuric stage eight or more years after the initiation of therapy and certainly longer than that after the onset of proteinuria. In five of these patients, the proteinuria has resolved. It seems, therefore, that the benefit accruing from colchicine therapy begun in the proteinuric stage is already evident in most of our patients. Because the amyloidosis of familial Mediterranean fever is systemic and death from renal failure can be prevented, the protection of kidney transplants and other organ systems from continuing amyloid deposition will become essential in determining how long life can be extended.[19,20] Therefore, with suppression of amyloidogenesis as an additional objective, we recommend daily lifelong administration of colchicine for all our patients with familial Mediterranean fever, including those whose attacks do not respond to the drug and those with irreversible renal lesions.

Colchicine has been shown in vitro to inhibit the secretion of serum amyloid A protein, an acute-phase reactant that is synthesized by hepatocytes.[21] Serum amyloid A is the precursor of amyloid A protein, the major constituent of the amyloid deposits in laboratory mice[22] and in patients with a variety of predisposing diseases[4] or familial Mediterranean fever.[4] If the pathogenesis of amyloidosis involved a simple progression of overproduction of serum amyloid A protein that overwhelmed the proteolytic processes by which it is normally degraded, and thus led to the polymerization of excess amyloid A protein to form

fibrils, the effectiveness of colchicine could be understood readily. Since the attacks of familial Mediterranean fever are accompanied by a dramatic rise in serum amyloid A levels,[3] it might be tempting to assume — as we naively did 30 years ago[23] — that the amyloidosis of familial Mediterranean fever is "secondary" to the attacks.

However, the amyloidosis of familial Mediterranean fever, albeit of the amyloid A type, is genetically determined. Attesting to its hereditary nature are the lack of any correlation with the number, duration, severity, and type of attacks that precede the amyloidosis and the observation in some patients (phenotype II) that the amyloidosis precedes the attacks.[5,24] The idea that the attacks and the amyloidosis are indeed independent characters of a pleiotropic gene is supported by our finding that colchicine provided the same protection against amyloidosis in the 34 patients whose attacks were not alleviated by the drug as it did in those whose attacks were relieved. Contrary to the in vitro evidence that colchicine suppresses secretion of serum amyloid A, the serum levels of amyloid A during attacks in patients receiving colchicine were only slightly less elevated than those in untreated patients with familial Mediterranean fever.[3] It would seem, therefore, that prevention of amyloidosis by colchicine cannot be directly attributed to either suppression of the attacks or suppression of secretion of the amyloid precursor.

These observations imply that the pathogenesis of amyloidosis, at least in patients with familial Mediterranean fever, is more intricate than the simple mechanism suggested above. They also suggest that the prophylactic effect of colchicine on febrile attacks and on amyloidosis may be mediated by different mechanisms. In addition, our findings expose the semantic trap in the widespread use of the terms "secondary" and "reactive" to describe amyloid-A amyloidosis. Nonetheless, the efficacy of colchicine in alleviating both the hereditary amyloid-A amyloidosis in patients with familial Mediterranean fever and the casein-induced amyloid-A amyloidosis in mice may warrant a trial of the drug in the treatment of the acquired amyloid-A amyloidosis that complicates rheumatoid arthritis and other diseases. Patients with these predisposing diseases should be assessed for proteinuria periodically, so that the presence of amyloidosis can be detected at a stage when colchicine can be effective. An evaluation of the prophylactic efficacy of colchicine would be better directed if markers were available (perhaps specifically amyloidogenic variant serum amyloid A proteins) to help identify the 10 to 20 percent of patients with predisposing diseases in whom amyloidosis will develop.

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