May Colchicine Therapy Be of Value in the Prevention of Dialysis Amyloidosis?

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Dear Sir,

Dialysis-related amyloidosis (DA) is a major complication of long-term hemodialysis (HD) inducing carpal tunnel syndrome, diffuse osteoarthropathy, bone cysts, and pathologic fractures with soft tissue involvement [1-4]. β2-Microglobulin (β₂m) polymers are the principal constituents of this form amyloidosis [1, 5, 6]. β₂m is expressed on the cell surface of all nucleated cells and is also released from intragranular stores by degranulating granulocytes as occurs during HD with complement-activating membranes [5, 7, 8]. The exact pathogenetic mechanisms of DA have not been determined in HD patients dialysed by cupro-phane membrane, but some biocompatibility factors such as increased synthesis and release of β₂m by granulocytes, release of proteases and reactive oxygen species which favor polymerization of β₂m into amyloid and failure of clearance of β₂m from the circulation by low-flux cellulosic membranes have been suggested as the possible hypotetical factors in the genesis of DA [9]. Colchicine, a drug commonly considered as one of the most potent inhibitors of granulocyte de-granulation, has been reported to inhibit the decrease of circulating granulocytes during HD [10]. Besides this agent was reported to be able to prevent HD-induced polymorpho-nuclear neutrophil (PMN) degranulation [10].

In view of the latter data and the increased release of β₂m by PMNs during HD, which was suggested as one of the main causative mechanisms of DA, we wondered whether colchicine might be of value in the prevention of DA via inhibition of β₂m release from PMN during HD.

We studied 15 patients (5 men, 10 women) ranging in age from 17 to 57 (mean ± SD, 39.3 ± 14.0). All patients were on regular HD, performed for 4 h, 3 times a week with acetate-containing dialysate and cuprophane membrane. Informed consent was obtained from all patients prior to the study. A preliminary study was performed with parallel-plate dialyzers and hollow-fiber dialyzers, whereafter colchicine, at a total dose of 3 mg/24 h, was administered orally to all the patients. Just after the last dose of colchicine, we repeated the same protocol with only hollow-fiber dialyzers. Blood samples for plasma β₂m levels and white blood cell (WBC) counts were drawn from the arterielle site of the dialyzer at 0, 15, 60,
240 min after connecting the patients to the dialysis unit. As to the interpretation of β2m levels, in order to avoid the errors originating from volume changes during HD, plasma β2m levels were expressed as values corrected for hemoconcentration. Hematocrit (Hct) correction factor was calculated from the quotient (100 -Hct postdialysis)/(100 – Hct predialysis). Plasma β2m levels were determined by a commercially available immunoenzymatic assay (Abbott Laboratories).

Repeated-measures analysis of variance with two within-subject effects (time and membrane type; time and treatment) was performed. Difference contrast was performed for comparison of group means of β2m and WBCs. Difference contrasts were used for pairwise comparisons. Statistical significance was assigned to p values < 0.05 for repeated-measures analysis of variance. Student’s t test for paired samples was used for comparison of means at different times. Statistical significance was assigned to p values < 0.016 (0.05/3) (Bonferroni modification) in order to avoid an increase in type I error.

The changes in plasma β2m levels and WBC counts during HD before and after colchicine therapy are shown in tables 1 and 2. β2m levels and WBC counts changed with time on HD with parallel-plate and hollow-fiber dialyzers (time effect, p < 0.05). Neither type of membrane nor colchicine therapy affected the β2m alteration profile during HD (tables 3,4). (p: 0.74, p: 0.34). The parallelism of the time curves of β2m levels did not change with different types of membrane and short-term cholecic therapy (p: 0.54, p:0.31).

There were marked drops in mean WBC counts with two types of membrane at 15 min; subsequently, in dialyses with hollow-fiber dialyzers, mean WBC count returned to predialysis level at 60 min and remained so at 240 min. On the contrary, marked leukopenia persisted during all the measurements in dialyses performed with parallel-plate membranes (p < 0.05). We did not observe any effect of colchicine on mean WBC counts during the study (p: 0.09).

Mean baseline β2m level at 0min was 47.2 ± 13.8 mg/l before colchicine therapy.

<table>
<thead>
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<th>Membrane</th>
<th>β2m</th>
<th>WBC</th>
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<tr>
<td>Effect</td>
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<td>0.035</td>
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<tr>
<td>Time</td>
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<td>0.001</td>
</tr>
<tr>
<td>Parallelism</td>
<td>0.54</td>
<td>0.02</td>
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</table>

A = Mean plasma β2m levels with parallel-plate dialysers; B = mean plasma β2m levels with hollow-fiber dialyzers (pretreatment); C = mean plasma β2m levels with hollow-fiber dialyzers (posttreatment).

*p < 0.05.
D = Mean WBC counts with parallel-plate dialyzers; E = mean WBC counts with hollow-fiber dialyzers (pretreatment); F = mean WBC counts with hollow-fiber dialyzers (posttreatment).

*p < 0.05.

Table 4. Repeated-measures analysis of variance

<table>
<thead>
<tr>
<th></th>
<th>ß2m</th>
<th>WBC</th>
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<tr>
<td>Colchicine effect</td>
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<tr>
<td>Time effect</td>
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<td>Parallellism</td>
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</table>

with hollow-fiber dialyzers. Corrected mean ß2m level rose to $56.9 \pm 10.7$ at 240 min (p: 0.002). Mean plasma ß2m levels at 15 and 60 min did not differ statistically from the baseline value (p: 0.73, p: 0.11).

The precise mechanisms of the development of DA is not well understood; it has thus been difficult to prevent and no established effective treatment is available. Considering the complex physiopathologic picture of DA, we did not expect, colchicine to solve all the practical matters related to the prevention of DA in this preliminary study, but we wondered whether it might be of any value in the conservative management of DA. Unfortunately, colchicine administration did not affect the ß2m alteration profile during HD with cuprophane membranes in the present study. In other words, although colchicine was suggested to be a helpful drug in the prevention of some HD-associated events originating from the interaction of cellulosic membrane with blood constituents, our results do not encourage us to use it for the prophylaxis of ß2m amyloidosis [10].

In analogy to the favorable results obtained with colchicine in AA amyloidosis associated with FMF, a short-term study undertaken in a limited number of HD patients to determine the role of colchicine in the prevention of ß2m release was reported before [11]. The results of that latter study were not very encouraging either. The role of long-term colchicine treatment in the prophylaxis of DA has not been documented and could be worth studying.

References


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Aşık/Yüksel/Adam/Akpolat/Özdemir