Immunosuppressive treatment of AA amyloidosis of familial Mediterranean fever

Sirs,

Although familial Mediterranean fever (FMF) patients with nephrotic syndrome (NS) receive colchicine regularly, one-third of them do not sufficiently benefit from colchicine and all FMF patients with chronic renal insufficiency and NS progress to end-stage renal failure (ESRF) (1). There is not sufficient knowledge in the literature about whether or not progression of NS to ESRF could be halted through a choice other than colchicine. I herewith report 3 FMF cases with nephrotic range proteinuria (NRP) who responded well to immunosuppressive drugs.

The cases fulfilled the criteria for the FMF described previously (2). The presence of amyloidosis was confirmed by rectal biopsy. AA amyloidosis was determined by the immunohistochemistry method. Throughout the follow-up, the patients were seen at regular intervals varying from 1-2 months in the outpatient clinic. Laboratory findings in Table I were determined based on the values obtained during their regular visits as the mean ± standard deviation. Urinary proteinuria was measured in 24-hour specimens. Written informed consent was obtained from all 3 patients.

Case 1 (29/F) was admitted with high fever, severe abdominal pain and pedal oedema. She had a history of recurrent abdominal attacks and fever, as well as periodic arthritis independent of the abdominal attacks since the age of 5. She was diagnosed as having nephrotic syndrome secondary to AA amyloidosis of FMF. She was commenced on colchicine 2 mg a day and enalapril maleat 10-20 mg a day. As I did not observe any noticeable benefits from this combination within the first 12 months, I resorted to adding prednisolone (PRD) 20 mg a day in three doses divided over the 24 h as well as azathioprine (AZA) 50 mg a day. After one month, while AZA was increased to 100 mg a day, the dosage of PRD was reduced by 2.5 mg decrements every 4-6 weeks down to a dosage of 10 mg a day. Afterwards, the decrement dosage of PRD was continued at a rate of 1.25 mg every 4-6 weeks down to a dosage of 5 mg a day. Ever since, the adjustment of the dosage of PRD has shown variations between 3.75-5 mg a day in our control.

Case 2 (25/M) was diagnosed with FMF at the age of 6, after which he was given colchicine. However, he failed to take this regularly. He had NRP and AA amyloidosis. He was commenced on colchicine 2 mg a day and enalapril maleat 10-20 mg a day. Twelve months later AZA and PRD were

Table I. Laboratory data during the follow-up period (mean ± SD).

Months / Laboratory findings	0	0 – 6		6 – 12		12 – 18		18 – 24		24 – 30		30 – 36	
Case 1													
Proteinuria (g/day)	4.8	4.6 ± 0.5	(4 – 5)	4.2 ± 0.2	(4 – 4.5)*	2 ± 0.5	(1.5 – 2.5)	0.8 ± 0.3	(0.3 – 1.2)	0.65	(0.6 – 0.7)	0.6 ± 0.4	(0.3 – 1)
Albumin (g/dl)	2.6	2.2 ± 0.8	(1.4 – 3)	2.9 ± 0.1	(2.8 – 3)	3.4 ± 0.1	(3.3 – 3.6).	3.7	(3.7 – 3.9)	4.3	(4.3 – 4.3)	3.8 ± 0.2	(3.7 – 4)
Creatinine (mg/dl)	0.8	0.5	(0.4 – 0.6)	0.3	(0.2 – 0.4)	0.35	(0.2 – 0.4)	0.45	(0.4 – 0.5)	0.6	(0.5 – 0.7)	0.56	(0.5 – 0.62
ESR (mm/h)	95	107 ± 1	3 (93 – 119)	92 ± 16	(81 – 104)	67 ± 7.5	(60 – 75)	50 ± 8	(38 – 61)	41 ± 1.4	(40 – 42)	36 ± 8	(30 – 42)
CRP (mg/dl)	2.5	2.4 ± 0.3	(2.1 – 2.8)	nt		0.76 ± 0.5	(0.2 – 1.2)	0.3 ± 0.2	(0.1 – 0.6)	0.15	(0.1 – 0.2)	0.2 ± 0.1	(0.1 – 0.3)
Case 2													
Proteinuria (g/day)	7	5.9 ± 0.2	(5.8 – 6.1)	4.1 ± 0.8	(3.2 – 5)*	1.1 ± 0.1	1 – 1.2)	0.8	(0.75 – 0.85)	0.7 ± 0.1	(0.6 – 0.8)	0.6	(0.6 – 0.7)
Albumin (g/dl)	2.5	2.6 ± 0.1	(2.5 – 2.7)	3.3 ± 0.2	(3.2 – 3.5)	3.7	(3.7 – 3.8)	3.8 ± 0.2	(3.7 – 4)	4.03	(4 – 4.1)	5.4 ± 0.5	(5 – 5.8)
Creatinine (mg/dl)	0.9	0.5	(0.52 – 0.5)	0.58	(0.54 – 0.6)	0.45	(0.4 – 0.49)	0.6	(0.5 – 0.7)	0.65	(0.6 – 0.7)	0.7	(0.62 – 0.8)
ESR (mm/h)	98	86 ± 4.9	(83 – 90)	69 ± 12	(60 – 78)	30 ± 7.7	(25 – 36)	33 ± 15	(22 – 44)	21 ± 6.5	(15 – 28)	9.5 ± 2.1	(8 – 11)
CRP (mg/dl)	1.2	1.5 ± 0.1	(1.4 – 1.6)	1.3 ± 0.1	(1.2 – 1.4)	0.7 ± 0.1	(0.6 – 0.8)	0.9 ± 0.8	(0.3 – 1.5)	0.8 ± 0.1	(0.7 – 0.9)	0.65	(0.6 – 0.7)
Case 3													
Proteinuria (g/day)	7.2*	4.7 ± 1.5	(3 – 6.2)	2.7 ± 1.2	(1.2 – 4)	0.7 ± 0.2	(0.4 – 1.1)	0.55	(0.5 – 0.6)				
Albumin (g/dl)	2.7	3.1 ± 0.2	(2.9 – 3.4)	3.8 ± 0.3	(3.5 – 4.3)	4.2 ± 0.1	(4.1 – 4.3)	4.8 ± 0.1	(4.7 – 4.9)				
Creatinine (mg/dl)	1.3	1.2	(1.1 – 1.3)	1.3	(1.29 – 1.39)	1.5	(1.4 – 1.6)	1.4	(0.8 – 1.6)				
ESR (mm/h)	79	54 ± 15	(34 – 70)	39 ± 18	(20 – 65)	33 ± 3.5	(31 – 36)	23 ± 4	(20 – 26)				
CRP (mg/dl)	1.4	1.2 ± 0.3	(0.8 – 1.4)	0.8 ± 0.7	(0.2 – 1.9)	0.3 ± 0.1	(0.2 – 0.4)	0.5 ± 0.2	(0.4 – 0.7)				

Case 3 was monitored for 24 months; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; nt: not tested. Normal levels: albumin: 3.5 – 5.5 g/dl; Creatinine: 0.5 – 1.6 mg/dl; ESR < 20 mm/h; CRP < 0.8 mg/dl. Values in parentheses give the range; *refers to the point at which immunosuppressive treatment was commenced. Creatinine levels were shown as the mean (range).

added to his treatment, as with Case 1.
Case 3 (37/M) referred to us for cutaneous vasculitis, confirmed by the skin biopsy. He had a history of recurrent fever, abdominal and chest pain, and erysipelas-like erythema since he was 3. He was diagnosed with FMF at the age of 27 and colchicine was administered at the dosage of 0.5-1 mg/day. Since case 3 had a cutaneous vasculitis, I administered PRD and AZA in the aforementioned dosages in addition to colchicine (2 mg a day), enalapril maleat (10-20 mg/day) immediately after the diagnosis of AA amyloidosis and vasculitis. The dosage of PRD and AZA was adjusted as in cases 1 and 2.
Laboratory findings for the patients obtained during the follow-up period are presented in Table I.
Three cases with NRP secondary to FMF amyloidosis responded markedly to AZA and PRD while still receiving colchicine. It is possible for FMF patients to suffer from non-amyloid renal involvements, such as glomerulonephritis (3), and to respond favourably to immunosuppressants (3). To be frank, I could not exclude the possibility of glomerulonephritis or other glomerulopathies in my cases due to the failure to perform a renal biopsy. It is well documented that FMF patients with glomerulonephritis do suffer from hematuria and leukocyturia (3). However, my cases were determined to have neither of these urinary abnormalities during the follow-up period. Based on this result, I think the chances for the presence of such possibilities, as glomerulonephritis are low with my cases.
Although the first two cases showed a mild stabilization of NRP before the start of AZA and PRD, a noticeable improvement was determined after the start of AZA and PRD. This can best be seen in case 3, who showed the earliest noticeable improvement in NRP because of receiving the combination of AZA and PRD and colchicine upon presentation. At this point, it could be argued that addition of the AZA and PRD was made fairly early when taking into account that one year may not be a sufficient period for the effect of colchicine to begin for cases 1 and 2. However, it should be noted that the optimum length of time needed for the effect of the colchicine to begin has not be determined precisely thus far. The natural duration between the emergence of proteinuria and ESRF has been determined to range from 2 to 13 years (4). It is well known that long-term proteinuria due to other diseases might lead to tubulointerstitial nephritis (5). Also, histological evidence of tubulointerstitial injury has been found to be a better predictor of impaired renal function than glomerular injury (5). Moreover, it has been reported that tubulointerstitial injury is also a predictor for the poor outcome of FMF amyloidosis (6). Based on the data above, early interventions for reducing NRP could help renal prognosis in a positive way. The dramatic decrease in the levels of proteinuria following the commencement of the combination of AZA and PRD seems to be suggestive of its workability.
There exist only a few studies into endogenous cortisol levels in FMF patients. Early blunted cortisol response was reported in FMF patients without amyloidosis in the face of stressful situation during attack-free periods (7). Sub clinical adrenal insufficiency was reported in most FMF patients with AA amyloidosis (8). Based on these data, it could be argued that small dosages of steroids may compensate for the possible cortisol deficiency in FMF patients complicated by amyloidosis. Steroids are also used to suppress inflammation and prevent interstitial inflammation in the kidney likely to arise during long-term proteinuria (9).
In conclusion, I suggest that a combination of AZA and PRD in addition to colchicine could be useful in regression of NRP in selected cases with FMF complicated by AA amyloidosis. I also suggest that further controlled studies be conducted for a better emphasis of this aspect.

C. KORKMAZ, *MD*

Associate Professor Division of Rheumatology, Department of Internal Medicine, Osmangazi University Medical Faculty, Eskisehir, Turkey.

Address correspondence to: Cengiz Korkmaz, MD, Visnelik M. Alifuat Güven C. Akasya S. 11/11, Eskisehir, Turkey.
E mail: ckorkmaz@ogu.edu.tr

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Behçet's disease associated with Trisomy 8 in a male Caucasian patient from Great Britain – A case report

Sirs,
We would like to report a 54-year-old Caucasian male from Great Britain who was referred to our Rheumatology unit with a history of increasing tiredness associated with polyarthralgia, night sweats and recurrent punched out orogenital ulcerations. Further questioning revealed that he had suffered from erythema nodosum associated with uveitis in the past, which was diagnosed as sarcoidosis about 2 years ago. He had no clinical features to suggest systemic vasculitis.
Physical examination revealed orogenital ulcers with scar marks of previous ulcers in scrotum. Examination of the joints revealed no evidence of any inflammatory arthritis.
Lab investigations showed decreased haemoglobin 12g/dL (NR-13-18), Neutropaenia (0.6×10^9/L), macrocytosis (MCV-103) and raised ESR of 70 mm in 1st hour. Rheumatoid factor was positive (282 iu/ml)(NR $\leq$ 40). Renal and liver function tests were normal. Anti-nuclear, anti-ds-DNA and Extractable Nuclear antigens were negative as were anti cardiolipin and ANCA.Serum and urine protein electrophoresis were normal HLA studies were negative for B51.
In view of his persistent neutropaenia, a bone marrow biopsy was performed which showed hypercellular marrow with adequate number of megakaryocytes some of them showing dysplastic changes. Myelopoeisis was reported to be dysplastic.
He was initially treated with oral corticosteroid followed by azathioprine and folic acid. However there was no improvement in either the neutrophil count or his clinical symptoms of orogenital ulcerations. He was then treated with G-CSF without much clinical improvement. Further cytogenetic studies confirmed the presence of Trisomy 8 in a significant number of metaphases.
As he did not improve with conventional immunosuppressive therapy, he was referr-