

Anti-Tumor Necrosis Factor α Therapy in Fifteen Patients With AA Amyloidosis Secondary to Inflammatory Arthritides

A Followup Report of Tolerability and Efficacy

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Objective. Because anti-tumor necrosis factor α (anti-TNF) has emerged as a highly effective treatment for numerous inflammatory arthritides, which are a common cause of AA amyloidosis, we retrospectively evaluated the safety and efficacy of anti-TNF in a nationwide study.

Methods. The rheumatology departments of all French teaching hospitals were contacted by mail to obtain the files of patients with histologically proven secondary AA amyloidosis and renal involvement who were treated with anti-TNF. Efficacy was assessed as a sustained decrease in 24-hour proteinuria and a stable/improved glomerular filtration rate (GFR).

Results. Among the 15 patients studied, the 24-hour proteinuria was 4.5 ± 3.6 gm (mean \pm SD), creatinemia was 178.4 ± 74.9 μ moles/liter, and GFR was 46 ± 23 ml/minute before starting anti-TNF. Ten patients received infliximab, 4 received etanercept, and 1 received both types of treatment. The mean followup was 10.4 months. No severe adverse events were recorded; one episode of herpes zoster in the first branch

of the trigeminal nerve occurred after one infusion of infliximab. Amyloidosis progressed in 7 patients and was stabilized in 5 patients. Three patients (receiving infliximab alone, infliximab plus methotrexate [MTX], or etanercept plus MTX) experienced rapid, dramatic, and sustained decreases in proteinuria ($\geq 80\%$), with the GFR increasing 15–78%.

Conclusion. Anti-TNF was well-tolerated and safe in the 15 patients with AA amyloidosis and renal involvement. The pathogenic role of TNF in AA amyloidosis, the sustained proteinuria decrease in 3 patients, and the stabilization of renal parameters in 5 other patients make anti-TNF a promising candidate to treat AA amyloidosis secondary to inflammatory arthritides.

AA amyloidosis occurs most frequently in Western countries, in patients with chronic inflammatory diseases such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), or juvenile idiopathic arthritis (JIA). Renal involvement, which is observed in 70% of the patients, is revealed by proteinuria and/or impaired renal function. Secondary amyloidosis results from defective metabolism of the inflammatory acute-phase reactant precursor protein, serum amyloid A (SAA), whose concentration strongly correlates with inflammatory disease activity.

Accordingly, treating the underlying disease is the conventional approach in AA amyloidosis, since no specific treatment exists. Despite the poor prognosis of amyloid renal involvement, the outcome of AA amyloidosis might be improved by suppressing the acute inflammatory response. Some patients have benefited from treatment with azathioprine or methotrexate (MTX) (1,2). Chlorambucil has also shown some efficacy against

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JIA-associated renal amyloidosis, as compared with historical controls (3). However, the associated risk of myelotoxicity, leukemia, and sterility (4) prompts the continued search for alternative therapies.

Anti-tumor necrosis factor α (anti-TNF) therapy has emerged as a highly effective approach for inducing rapid and sustained clinical remission of several inflammatory arthritides, including RA and AS. Furthermore, TNF blockade dramatically reduces the systemic inflammatory response. Clinical experience with anti-TNF in AA amyloidosis has been extremely limited, since only 2 cases have been reported. In the present study, we examined the safety and tolerance of anti-TNF in 15 patients with histologically proven amyloidosis and renal involvement after a mean followup of 10.4 months. After treatment with anti-TNF, the rate of proteinuria sharply decreased in 3 patients, and their renal function subsequently improved.

PATIENTS AND METHODS

Patient selection. This retrospective study was initiated by the Club Rhumatismes et Inflammation (CRI), a subcommittee of the French Society of Rheumatology. The rheumatology departments of all French teaching hospitals were contacted by mail to obtain the files of patients with histologically proven secondary AA amyloidosis and renal involvement. We did our utmost to enroll all amyloidosis patients treated with anti-TNF by practitioner members of the CRI, but ascertainment bias always exists in such retrospective studies. These charts were reviewed by 2 of the authors (J-EG and XM).

Treatment. Patients were treated with etanercept ($n = 4$), infliximab ($n = 10$), or both ($n = 1$). Etanercept, a recombinant form of the human 75-kd TNF receptor fusion protein, was injected subcutaneously (25 mg twice per week). Infliximab, a humanized monoclonal anti-TNF antibody, was infused (3 or 5 mg/kg) at weeks 0, 2, and 6, and then every 8 weeks. Concomitant medications, including immunosuppressant agents and drugs affecting the glomerular filtration rate (GFR), such as angiotensin-converting enzyme (ACE) inhibitors, were noted.

Assessment. Tolerance and adverse events were recorded for every patient. Laboratory markers of disease activity included repeated determinations of creatinemia, 24-hour proteinuria, and C-reactive protein (CRP). Treatment failure was defined as either discontinuation of anti-TNF treatment, increased proteinuria, and/or further impairment in renal function. Efficacy was defined as a sustained decrease in 24-hour proteinuria, and a stable or improved GFR according to the Cockcroft and Gault equation (5).

RESULTS

Patient characteristics. The baseline clinical characteristics of the 15 patients (5 women, 10 men) are

reported in Table 1. RA (33%) and AS (40%) were the predominant underlying diseases. The mean age at the beginning of anti-TNF was 49.5 years (range 29–70 years), the mean duration of the underlying disease was 21.7 years (range 11–38 years), and AA amyloidosis had been diagnosed an average of 3.1 years before anti-TNF was started. The average number of previously taken disease-modifying antirheumatic drugs was 3.5 (range 0–6). Patients 1, 7, 8, and 10 had previously taken alkylating agents.

AA amyloidosis was histologically proven in all patients (by renal biopsy in 11 patients, by salivary gland or rectal biopsy or fat aspiration in patients 1, 3, 7, and 10). Renal biopsy samples from patients 4, 5, and 12 showed extensive amyloid deposits in the glomerular, interstitial, and vascular compartments, which were associated with features of tubulointerstitial nephritis in patients 4 and 5. Eight additional patients (patients 2, 6, 8, 9, 11, 13, 14, and 15) had amyloid deposits in the glomeruli. Patients 7, 14, and 15 had a nephrotic syndrome at the start of anti-TNF therapy. In addition to renal involvement, patients 8, 9, and 10 had profuse diarrhea associated with biopsy-proven digestive tract amyloidosis. Patient 8 (with chronic infantile neurologic cutaneous and articular syndrome) had renal, thyroid, digestive tract, and hematopoietic amyloid involvement. No clinical or echocardiographic signs of amyloid involvement in the heart were observed. At baseline, 11 patients had tender and/or swollen joints (Table 1).

Individual laboratory values from the initial and last visit are also reported in Table 1. For the whole population before the start of therapy, the mean \pm SD CRP level was 25.4 ± 22.4 mg/liter, 24-hour proteinuria was 4.5 ± 3.6 gm, creatinemia was 178.4 ± 74.9 μ moles/liter, and the GFR was 46 ± 23 ml/minute.

Effects of treatment. Eleven patients received infliximab (7 received 3 mg/kg, 3 received 5 mg/kg, while 1 received 3 mg/kg then 5 mg/kg), 5 patients were given etanercept, and patient 9 took both successively. Anti-TNF was taken alone or concomitantly with prednisone (mean dosage 8 mg/day) and/or in combination with other immunosuppressants (Table 1). ACE inhibitors were administered to patients 1, 3, 5, 6, 8, and 11 before anti-TNF and were introduced after therapy in patients 7, 9, and 12. The mean followup period was 10.4 months (range 3–18 months).

Anti-TNF effectively controlled the underlying inflammatory rheumatic disease in 11 patients. Patients 1, 2, and 3 discontinued use of infliximab because of inefficacy (at weeks 12, 12, and 24, respectively) and patient 10 stopped taking etanercept on her own (week

Table 1. Baseline characteristics of the 15 patients with AA amyloidosis (AAA) and their initial and last-visit laboratory values following treatment with anti-tumor necrosis factor α (anti-TNF)

Patient/ age/sex	Underlying disease*	Disease duration, underlying/ AAA, years	Prior DMARDs/ AlkA, no.†	Tender/swollen joints, no.‡	Type of anti-TNF/dose, mg/kg§	Associated therapy¶	C-reactive protein, mg/liter				Proteinuria, gm/day				Creatinemia, μ moles/liter		Followup, months	Still taking anti-TNF, yes/no
							Initial	Last	Initial	Last	Initial	Last	Initial	Last				
1/60/M	AS	38/11	3/2	8/6	I/5	CS	6	44	0.54	0.46	260	295	3	No				
2/70/F	RA	18/1	4/0	12/12	I/3	-	30	4	2	6	93	130	3	No				
3/55/F	RA	21/4	3/0	11/6	I/3	CS	15	21.3	3	3.6	80	85	6	No				
4/37/M	AS	24/1	2/0	NA	I/3	NSAID	29	4	9.2	13	133	217	18	Yes				
5/68/M	PA	17/1	0/0	13/11	I/3	AZA	6	22	4.3	3.75	316	517	5	Yes				
6/59/F	RA	13/4	5/0	12/6	E	-	11	5	1.2	0.2	398	425	12	Yes				
7/32/M	aSD	14/2	5/2	5/2	I/3 (3 times) + I/5 (once)	MTX, CS	127	52	17	35	88	230	5	Yes				
8/47/M	CINCA	30/7	4/1	6/0	E	MTX, CS	7	5	3.4	3.2	251	256	15	Yes				
9/35/M	AS	22/3	2/0	NA	I/5 and E	NSAID	24	4	0.2	0.8	138	165	14	Yes				
10/59/F	RA	13/4	5/2	12/6	E	-	5	6	1.2	0.72	229	246	7	No				
11/37/M	RA	22/2	4/0	NR	I/3	-	64	20	3	0.9	134	145	17	Yes				
12/66/M	AS	23/<1	6/0	13/11	I/3	AZA	<5	<5	3	1.22	130	134	8	Yes#				
13/35/F	JIA	33/3	3/0	7/4	E	MTX	2	5	1.4	0.15	150	137	14	Yes				
14/53/M	AS	27/2	2/0	NA	I/5	NSAID	45	5	3	0.6	126	86	18	Yes				
15/29/M	AS	11/1	4/0	1/1	I/3	MTX, CS	<5	<5	14.5	2.3	150	118	11	Yes				
All**	-	21.7/3.1	3.5/0.47	9.1 \pm 3.4/5.9 \pm 3.2	-	-	25.4 \pm 22.4	4.5 \pm 3.6	178.4 \pm 74.9	10.4	-	-	-	-				

* AS = ankylosing spondylitis; RA = rheumatoid arthritis; PA = psoriatic arthritis; aSD = adult-onset Still's disease; CINCA = chronic infantile neurologic cutaneous and articular syndrome; JIA = juvenile idiopathic arthritis.
 † DMARDs = disease-modifying antirheumatic drugs; AlkA = alkylating agents (chlorambucil and/or cyclophosphamide).
 ‡ NA = not applicable; NR = not reported.
 § I = infliximab; E = etanercept (25 mg \times 2/week); I and E = infliximab (3 mg/kg for 4 months) then etanercept (for 10 months).
 ¶ CS = corticosteroid (prednisone); NSAID = nonsteroidal antiinflammatory drug; AZA = azathioprine; MTX = methotrexate.
 # The glomerular filtration rate decreased from 61.5 to 54.3 ml/minute and an angiotensin-converting enzyme inhibitor was introduced.
 ** The mean age of all patients was 49.5 years. Values for all patients are the mean \pm SD.

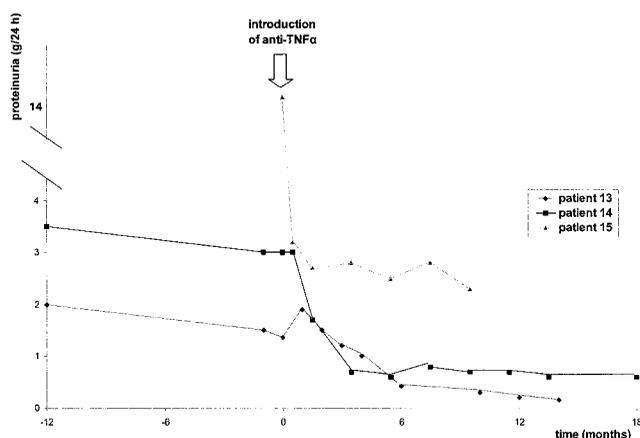


Figure 1. Decreases in the rate of proteinuria (in gm/24 hours) in patients with AA amyloidosis secondary to inflammatory arthritides (patient 13 with juvenile idiopathic arthritis, and patients 14 and 15 both with ankylosing spondylitis; see Table 1) after introduction of anti-tumor necrosis factor α (anti-TNF α) therapy, over a followup period of 3–18 months.

24). Under treatment with etanercept, frequency of diarrhea was markedly reduced in 2 of the 3 patients with digestive tract amyloidosis (in patients 8 and 9, the number of stools per day declined from 6 and 5, respectively, to 2 in each). Proteinuria and/or renal function worsened in 7 patients (patients 1, 2, 3, 4, 5, and 7 in the infliximab group, and patient 6 in the etanercept group), whereas these manifestations stabilized in 5 patients (infliximab-treated patients 11 and 12, etanercept-treated patients 8 and 10, and patient 9, who received both treatments).

Of note, a rapid, dramatic, and sustained decrease in proteinuria and attenuation of the clinical parameters of inflammatory disease activity (e.g., duration of morning stiffness, number of tender and swollen joints, and the patient's general assessment of well-being) were obtained following treatment with anti-TNF in patients 13, 14, and 15 (Figure 1). For patient 13, a 35-year-old woman with JIA who took etanercept and MTX, the proteinuria declined 90%, while her GFR rose from 41 ml/minute to 47 ml/minute after 14 months of followup. The daily proteinuria declined 80% following infliximab therapy in patient 14, a 53-year-old man with AS, and his GFR improved from 52 ml/minute to 93 ml/minute after 18 months of followup. In addition, his serum albumin level returned to normal and his nephrotic syndrome resolved within 2 months of starting treatment. Patient 15, a 29-year-old man with AS, experienced an 85% lower 24-hour proteinuria under treat-

ment with infliximab, MTX, and prednisone, while his GFR rose from 64 ml/minute to 81 ml/minute after 11 months of treatment.

No severe infectious event occurred in any of the patients. Patient 9 developed herpes zoster in the first branch of the trigeminal nerve after one infusion of infliximab, and patient 14 had two episodes of venous thrombosis without pulmonary embolism, but treatment was not discontinued.

DISCUSSION

This retrospective study of 15 patients suggests that anti-TNF is well tolerated, safe, and a potential treatment for some patients with AA amyloidosis. Patients with amyloidosis can have either renal, hepatic, and/or cardiac insufficiencies that might alter the pharmacokinetics of anti-TNF and/or the tolerance to treatment, and these patients can be at risk for infections and thrombosis. Although all of our patients had impaired renal function, tolerance to the treatments was excellent and the anti-TNF dose did not have to be lowered; none of the patients had clinical signs of hepatic or cardiac amyloidosis, which could have impaired tolerance. The only severe side effect occurring during followup was recurrent venous thrombosis in 1 patient, but this did not require treatment discontinuation.

Every patient had histologically proven AA amyloidosis, proteinuria, and impaired renal function at baseline, and efficacy of anti-TNF was assessed on the basis of the evolution of the latter 2 parameters during followup. The retrospective design of this survey prevented evaluation of the course of SAA levels. Radio-nuclide scintigraphy with serum amyloid P (SAP) is not authorized in France. During treatment, the 24-hour proteinuria and/or GFR worsened in 7 patients, stabilized in 5 patients, and dramatically improved in 3 patients. Of note, articular symptoms were well controlled in 7 (87.5%) of 8 patients whose amyloidosis was stable or attenuated, as compared with 4 (57.1%) of 7 patients whose amyloidosis progressed.

Initially, the proteinuria and GFR, CRP level, interval between diagnosis of amyloidosis and treatment with anti-TNF, levels of hypertension, and concomitant drugs (e.g., nonsteroidal antiinflammatory drugs [NSAIDs]) were similar regardless of subsequent evolution (data not shown). However, the renal histologic characteristics seemed to differ in patients whose amyloidosis progressed. First, the 3 patients whose amyloidosis was proven by digestive tract biopsy belonged to this group. The extent of proteinuria associated with salivary

gland or digestive AA amyloidosis deposits does not prove renal amyloid involvement. Janssen et al (6) reported that 16% of renal biopsy samples from patients with proteinuria and amyloidosis could reveal non-amyloid etiologies of proteinuria. A possible cause of proteinuria in patients with inflammatory arthritides might be NSAID-related tubulointerstitial nephritis. Notably, 2 of the 4 renal biopsy samples obtained from these 7 patients whose amyloidosis progressed had histologic features of amyloidosis and tubulointerstitial fibrosis. The stabilization of proteinuria and renal function in 5 patients might be interpreted as the deterrence of amyloid deposition under anti-TNF therapy, since we would have expected these patients to undergo progression to renal failure without it.

However, the most striking finding was the dramatic decline in proteinuria in 3 patients with renal AA amyloidosis, without any sign of tubulointerstitial nephritis, after the introduction of anti-TNF. These proteinuria decreases were verified by several 24-hour urine analyses and have been sustained throughout followup (18, 14, and 11 months). Furthermore, the GFR improved in all 3 of these patients. No cyclosporine, ACE inhibitors, or angiotensin II blockers, known to reduce proteinuria flow, were prescribed. Patients 13 and 15 were also taking MTX, which has been reported to reduce proteinuria in patients with AA amyloidosis but with far slower kinetics than was observed in the present study. The proteinuria decreases occurred during the first 2 months of treatment with anti-TNF and seemed to parallel the rapid and spectacular efficacy in terms of attenuation of articular symptoms in these 3 patients. These urinary protein reductions were very rapid, compared with those observed under treatment with chlorambucil (which averaged 12–24 months). This suggests that anti-TNF could lead to a dramatic change in the renal hemodynamics, which might be followed by mobilization of the amyloid deposits. However, the reduction in proteinuria might not correlate with anatomic resolution of amyloidosis. Of course, the objective assessment of amyloid resorption would require a second renal biopsy.

Anti-TNF efficacy in other involved organs was not evaluated, since renal amyloidosis was the predominant feature. However, the almost total disappearance of diarrhea in 2 of the 3 patients with digestive tract amyloidosis merits further investigation. Neither the type of the underlying inflammatory disease (1 with JIA, 2 with AS) nor the TNF blocker administered (2 receiving infliximab, 1 receiving etanercept) appeared to be important.

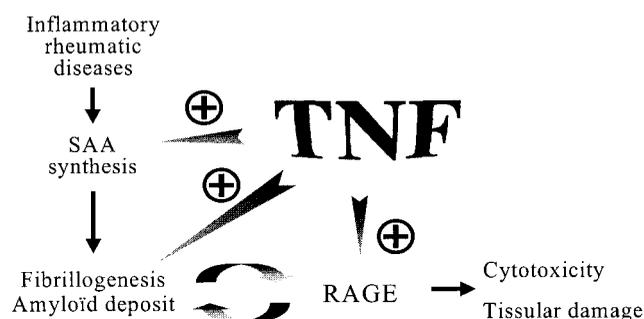


Figure 2. The pathogenic role of tumor necrosis factor α (TNF) in AA amyloidosis. SAA = serum amyloid A protein; RAGE = receptor for advanced glycation end products.

Only 2 case reports describing the effect of anti-TNF on AA amyloidosis have been published (7,8). Drewe et al reported clinical efficacy of etanercept in a patient with TNF receptor-associated periodic syndrome and AA amyloidosis (not histologically proven). This patient experienced a rapid attenuation of the nephrotic syndrome and substantial regression of the amyloid load according to radionuclide scintigraphy with SAP (7). Elkayam et al (8) administered infliximab and MTX to an RA patient whose renal function was almost normal; following treatment, this patient's mild proteinuria (0.8 gm/24 hours) regressed rapidly. These 2 patients differ markedly from ours, since our patients had a mean proteinuria of 4.5 gm/24 hours and impaired renal function.

The rationale for using a TNF-blocking agent stems from our understanding of the role of this cytokine in the pathogenesis of AA amyloidosis. TNF is known to induce SAA production in hepatocytes during the acute phase of the inflammatory response, as well as the production of interleukin-1 and interleukin-6 (9). In addition, recombinant TNF enhances amyloid deposition in the Syrian hamster (10). Furthermore, TNF favors the expression of receptors for advanced glycation end products (11), whose interaction with amyloid fibrils is responsible for cytotoxicity and tissue damage (12). Thus, TNF-blocking agents might not only reduce the synthesis of amyloid precursors but also slow amyloid deposition and thus attenuate the consequences of the interaction between amyloid fibrils and their receptors in the cells and tissues (Figure 2).

A prospective study that would involve patients who are comparable in terms of the type of inflammatory disease, amyloid involvement, and anti-TNF treatment would require repeated objective assessments of amyloid load (fat aspiration biopsies and radionuclide

scintigraphy with SAP) to confirm the tolerance, safety, and efficacy of anti-TNF and to identify predictive factors of efficacy. The pathogenic role of TNF in AA amyloidosis and the observations of a sustained lowered proteinuria in 3 patients make anti-TNF a promising treatment for AA amyloidosis secondary to inflammatory arthritides.

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