Efficacy of etanercept in patients with AA amyloidosis secondary to rheumatoid arthritis

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Abstract

Objective

The efficacy of biological therapies in rheumatoid arthritis (RA) is well known, but their hypothetical benefit in amyloid A (AA) amyloidosis secondary to RA still remains to be considered. We evaluated the efficacy and safety of etanercept in serum amyloid A (SAA) 1.3 allele Japanese patients with AA amyloidosis secondary to RA.

Methods

Seven RA patients with histologically confirmed AA amyloidosis and renal involvement who were treated with etanercept were enrolled. They all had the SAA1.3 allele, which has been shown to be a risk factor not only for the association of AA amyloidosis but also for a poor prognosis in Japanese RA patients. Efficacy was assessed as a sustained decrease in RA inflammation and an amelioration of renal function.

Results

RA inflammation and AA amyloidosis were improved and stabilized after 43.4 ± 16.5 weeks. At week 20 the number of tender (\( p = 0.017 \)) and swollen (\( p = 0.017 \)) joints, and levels of serum C-reactive protein (\( p = 0.018 \)) and albumin (\( p = 0.045 \)) had improved. The values for SAA, serum creatinine, calculated creatinine clearance, and proteinuria also ameliorated. No severe adverse events were observed. One patient eventually had to go on hemodialysis but her tolerance of etanercept remained stable.

Conclusion

Etanercept can be used safely and effectively in AA amyloidosis secondary to RA with renal involvement, and is of clinical benefit in the short-term, even in patients on hemodialysis. It appears that SAA1.3 allele may be used as a clinical parameter for the introduction of etanercept in Japanese RA with AA amyloidosis.

Key words

Etanercept, rheumatoid arthritis, amyloidosis, SAA1.3 allele.
Introduction

Secondary amyloid A (AA) amyloidosis is an uncommon yet important complication of rheumatoid arthritis (RA) and is a serious, potentially life-threatening disorder caused by deposition in organs of AA fibrils, which are derived from the circulatory acute phase reactant, serum amyloid A (SAA). Unless the disease activity of RA can be effectively controlled, the development of AA amyloidosis is associated with a poor prognosis and reduces the survival rate of patients (1). Up to now, therapeutic approaches have yielded poor results, with the sole exception of immunosuppressants (2). However, the associated risks of myelotoxicity, leukemias, nephrotoxicity and sterility necessitate the continued search for alternative therapies.

Tumor necrosis factor-alpha (TNF-α) antagonists have emerged as a highly effective approach for inducing rapid and sustained clinical remission of several inflammatory arthritides including RA (3, 4). However, clinical data with regard to AA amyloidosis secondary to RA is extremely scarce. We assessed the efficacy and safety of etanercept in patients with biopsy-confirmed AA amyloidosis and renal involvement who carry the SAA1.3 allele, which is not only a risk factor for the association of AA amyloidosis, but also a strong predictor of survival in Japanese RA patients (1).

Patients and methods

Patients and determination of SAA1 gene polymorphism

Each patient gave a written consent to take part in the study. Seven RA patients fulfilling the 1987 American College of Rheumatology criteria for RA were diagnosed as having AA amyloidosis, confirmed by histological examination. Despite continuous therapy with disease modifying anti-rheumatic drugs (DMARDs), their disease remained mostly active and they were refractory. To determine SAA1 gene polymorphism, polymerase chain reaction-based restriction fragment length polymorphism analysis was performed, as described previously (5).

Demographic and clinical variables

Demographic and clinical data were obtained from the patients’ medical charts. Sex, age, duration of RA, and duration of AA amyloidosis were recorded, and data on changes in laboratory test values for C-reactive protein (CRP), SAA, erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), serum creatinine (Crea), serum albumin (Alb), comorbidity, and use of DMARDs or prednisolone from the time of RA onset to the index time were obtained. Overall clinical symptoms and arthritis activity were also recorded.

Treatment

The patients were treated with etanercept by subcutaneous injection, 25 mg twice per week. Concomitant medications affecting renal function, such as non-steroidal anti-inflammatory drugs (NSAIDs) or angiotensin-converting enzyme inhibitors (ACEIs), were recorded. The effects on proteinuria of these drugs were monitored carefully to differentiate renal deterioration from AA amyloidosis.

Assessment

CRP, SAA, ESR, RF, Crea, Alb, complete blood cell counts, and transaminases were monitored. The numbers of swollen and tender joints were registered. Tolerance and adverse events were recorded and treatment failure was defined as either discontinuation of etanercept, increased proteinuria, or further impairment in renal functions (e.g., creatinine clearance (Ccr) according to the Cockcroft-Gault equation) and exacerbation of symptoms due to AA amyloidosis. Efficacy was defined as a sustained stability of both AA amyloidosis and RA inflammation.

Statistical analysis

Non-parametric analysis by Wilcoxon’s test was employed for the statistical analysis.

Results

Patients’ characteristics

The clinical characteristics of the patients are shown in Table I. The age at commencement of etanercept was 60.7 ± 7.5 years old (mean ± SD), the dura-
Table I. Patients’ characteristics.

<table>
<thead>
<tr>
<th>Patient/ Age/ Sex</th>
<th>Disease duration (years)</th>
<th>SAA1 gene polymorphism</th>
<th>Prior DMARDs</th>
<th>Associated Prednisolone (mg/day)</th>
<th>Organ involvement</th>
<th>Proteinuria (g/day)</th>
<th>Serum creatinine (mg/dl)</th>
<th>Follow-up (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/53/F</td>
<td>12/11</td>
<td>1.3/1.3</td>
<td>CYC, MTX, BU, SASP</td>
<td>0</td>
<td>Kidney</td>
<td>2.6</td>
<td>4.3</td>
<td>68</td>
</tr>
<tr>
<td>2/57/F</td>
<td>25/2</td>
<td>1.1/1.3</td>
<td>CYC, MTX, GST, CyA, TCR, SASP</td>
<td>5</td>
<td>Kidney Digestive tract, Thyroid</td>
<td>3.2</td>
<td>5.3</td>
<td>56</td>
</tr>
<tr>
<td>3/70/M</td>
<td>43/5</td>
<td>1.3/1.3</td>
<td>GST, BU, MTX, AU</td>
<td>10</td>
<td>Kidney</td>
<td>1.9</td>
<td>2.3</td>
<td>20</td>
</tr>
<tr>
<td>4/60/F</td>
<td>37/9</td>
<td>1.2/1.3</td>
<td>MTX, IM, CYC, BU, LEF, SASP</td>
<td>2</td>
<td>Kidney Heart, thyroid, Bladder, Digestive tract</td>
<td>1.8</td>
<td>0.9</td>
<td>37</td>
</tr>
<tr>
<td>5/59/F</td>
<td>6/2</td>
<td>1.2/1.3</td>
<td>BU, D-p, AU, TCR, CYC, MTX</td>
<td>5</td>
<td>Kidney Thyroid Digestive tract</td>
<td>2.5</td>
<td>4.0</td>
<td>38</td>
</tr>
<tr>
<td>6/72/F</td>
<td>4/2</td>
<td>1.3/1.3</td>
<td>CYC, MTX, BU, CyA</td>
<td>10</td>
<td>Kidney</td>
<td>1.2</td>
<td>0.5</td>
<td>37</td>
</tr>
<tr>
<td>7/54/F</td>
<td>15/4</td>
<td>1.3/1.3</td>
<td>BU, MTX, SASP, TCR, CYC</td>
<td>3</td>
<td>Kidney Thyroid Digestive tract</td>
<td>2.9</td>
<td>2.6</td>
<td>54</td>
</tr>
</tbody>
</table>

**Table I.** Patients’ characteristics.

| CYC: cyclophosphamide; MTX: methotrexate; BU: bucillamine; SASP: sulfasalazine; GST: sodium aurothiomalate; CyA: ciclosporin; TCR: tacrolimus; AU: auranofin; IM: azathioprine; LEF: leflunomide; D-p: D-penicillamine.

*, ** The value of initial (before etanercept) - and last (the index time) - visit following treatment with etanercept between follow-up periods.

Disease duration of RA was 20.3 ± 15.2 years, and the duration of AA amyloidosis was 5.0 ± 3.7 years. All patients had the SAA1.3 allele, 4 were heterozygous, and 3 were homozygous. The average number of previously taken DMARDs was 5. Only patient 4 had methotrexate (MTX) (2 mg/week) in combination with etanercept. All except patient 1 had from low to middle dosage prednisolone. NSAIDs were administered to patients 1, 3, 4, and 6 through the entire course of etanercept treatment, and ACEIs to patients 2 and 4 before etanercept. ACEIs were introduced after etanercept therapy in patients 5 and 7. In addition to renal involvement, patients 2, 4, 5, and 7 had diffuse diarrhea associated with digestive tract amyloidosis with histologically proven-amyloid deposits. They had also thyroid dysfunction due to amyloid involvement. Patient 4 had clinical or echocardiographic signs of cardiac amyloid involvement. She also had massive hematuria due to bladder amyloidosis (6). The follow-up period of etanercept treatment was 43.4 ± 16.5 weeks.

**Effects of treatment**

Etanercept showed efficacy not only with regard to RA inflammation but also AA amyloidosis with renal involvement. All of the surrogate markers improved and remained stable. Although the observation period differed for each patient, the values for SAA, Crea, and calculated Ccr between the initial and last visits following treatment with etanercept were changed from 433.9 ± 308.3 (µg/ml) to 31.3 ± 24.7, from 2.8 ± 1.8 (mg/dl) to 2.4 ± 1.4, and from 36.1 ± 23.8 (ml/min) to 50.4 ± 32.4, respectively. Proteinuria, in particular, showed improvement in all patients (Table I) from 2.30 ± 0.70 (g/day) to 0.90 ± 0.51.

As summarized in Figure 1, at week 20 the number of tender or swollen joints was decreased (both \( p = 0.017 \)) in accordance with the amelioration in rheumatoid activity. Levels of serum CRP normalized rapidly (\( p = 0.018 \)) by week 20 except in patient 2. Levels of serum Alb increased gradually (\( p = 0.045 \)), along with the amelioration in RA inflammation. Due to an accelerated exacerbation in renal function, patient 2 was forced to stop etanercept at week 32 and to go on hemodialysis (HD). After etanercept had been interrupted for 8 weeks, it was reintroduced and the patient is continuing on HD with etanercept and is clinically stable. The frequency of diarrhea was markedly reduced in patients 2, 4, 5, and 7, and had almost completely disappeared by week 4.

**Adverse events**

There were no serious adverse clinical or laboratory events during the study, and no severe infectious events occurred.

**Discussion**

This retrospective study on the short-term administration of etanercept for AA amyloidosis secondary to RA suggests that etanercept is well-tolerated, safe, and potentially effective for patients with AA amyloidosis and renal involvement. It is worth noting that a
rapid, dramatic, and sustained decrease in RA inflammation and a gradual attenuation of renal dysfunction due to AA amyloidosis were also obtained following treatment with etanercept (Fig. 1). Though we realize that the study involved a small patient series and short-term observation, we believe that the availability and rapid efficacy of etanercept have been shown. A case report has demonstrated that the effect of etanercept in the treatment of renal amyloidosis complicating RA is present after 36 months of treatment (7). We are continuing the present study by accumulating RA patients with AA amyloidosis and renal involvement who are on treatment with etanercept and analyzing their long term effects. It is known that one of the most important prognostic factors for preventing renal failure in AA amyloidosis secondary to RA is baseline renal function (8). Renal involvement is the most common manifestation of AA amyloidosis, and if not treated there is an inexorable decline in renal function, culminating in end-stage renal failure with a 5-year survival of 50% (1). Although it is crucial to initiate therapy early, before renal function is impaired, such therapy is likely to be postponed due to high rheumatoid activity. Etanercept appears to have an excellent ability to suppress SAA levels and could therefore be an important therapeutic strategy in AA amyloidosis secondary to RA. As etanercept can be self-injected, clinical compliance seems to be superior to other biologics. While MTX is the most common and effective drug to treat RA as an anchor drug, the management of patients with AA amyloidosis secondary to RA and renal involvement is too complex to limit the discussion simply to the therapeutic acceptability of MTX. Even in end-stage renal disease, etanercept may be advantageous, and...
the present study seems to suggest the efficacy of etanercept even if not administered in combination with MTX.

It has been reported that hemodialysis has no effect on the plasma concentration of etanercept, and that the pharmacokinetics of etanercept in patients on HD for chronic renal failure were similar to those with normal renal function (9). It would therefore appear feasible to administer etanercept to HD patients. Patient 2, who is on HD, is also being treated with etanercept, which is showing good tolerance, efficacy, and safety in spite of the end-stage renal disease (Fig. 1).

Although limited information is available about biologics in patients with AA amyloidosis, a few cases with favorable outcomes have been reported (10-14). Recently, a case report demonstrated that tocilizumab, a humanized anti-interleukin (IL)-6 receptor antibody, has an excellent ability to suppress SAA levels (15). The rationale for using biologics in AA amyloidosis stems from the fact that they lower the serum proinflammatory cytokines that regulate the synthesis of SAA. TNF-α stimulates the induction of SAA in hepatocytes during the acute phase, and may play a direct role in renal damage, resulting in monocyte proliferation and differentiation within the mesangium, as well as an increase in glomerular permeability to protein (12). TNF-α also favors the expression of receptors for the advanced glycation end product, whose interaction with amyloid fibrils is responsible for cytotoxicity and tissue damage (16). Thus, etanercept may not only reduce the synthesis of SAA but may also slow amyloid deposition, and attenuate the consequences of the interaction between amyloid fibrils and their receptors on the cells and tissues. Because AA amyloid is thought to exist in a state of dynamic turnover (13), the efficacy of etanercept in other involved organs should be evaluated in addition to the kidney. In fact, the almost total disappearance of diarrhea in patients 2, 4, 5, and 7 with digestive tract amyloidosis (Table I) merits further investigation.

The notion that the SAA1.3 allele is not only a risk factor for the association of AA amyloidosis with RA, but is also a strong predictor of survival in Japanese RA patients with AA amyloidosis suggests an important role of SAA1.3 allele as a clinical indicator for the early diagnosis of AA amyloidosis and for early therapeutic intervention in RA (1, 2, 5, 6). Although we have no clinical data on the treatment of AA amyloidosis in SAA1.3 allele-negative patients with etanercept, taking the above notion into consideration, it would appear desirable to follow RA patients carrying the SAA1.3 allele carefully, to diagnose AA amyloidosis as early as possible, and to start etanercept in order to slow the progression of AA amyloidosis by controlling the inflammatory aspects of rheumatoid activity.

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