ABSTRACT
Objective. In the present study, the effects of plasmin antagonist tranexamic acid (TEA) on urinary pyridinoline excretion rates were investigated in rheumatoid arthritis (RA) patients.

Methods. The study was set up as a double-blind placebo-controlled pilot study. Ten patients received tranexamic acid and 9 received placebo for 12 weeks. Urinary excretion rates of hydroxylysylpyridinoline (HP) and lysylpyridinoline (LP) were used as molecular markers of articular cartilage and bone degradation. In addition, clinical parameters of disease activity were assessed and CRP levels were measured.

Results. Treatment with TEA did not reduce pyridinoline excretion, nor was any effect observed on clinical parameters of disease activity or on CRP levels.

Conclusion. The results of the present pilot study show no beneficial effect of TEA as adjuvant therapy in RA patients with respect to joint destruction or disease activity.

Introduction
Rheumatoid arthritis (RA) is a chronic inflammatory disease involving multiple joints, leading to irreversible destruction of the articular cartilage and bone. Proteolytic enzymes secreted at the site of destruction cause degradation of the articular cartilage and bone. Although all classes of proteolytic enzymes seem to be involved, cartilage destruction has mainly been attributed to matrix metalloproteinases (MMPs) and serine proteases (1). The serine protease plasmin is of interest because of its ability to degrade a wide variety of extracellular matrix proteins and to activate latent forms of MMPs (2, 3). Increased expression of urokinase-type plasminogen activator (uPA) and its receptor (uPAR) in synovial tissues of RA patients (4, 5), as well as the capacity of plasmin to degrade cartilage (6, 7) and a bone-like matrix (8) support the idea that the plasmin-system may play a role in the pathogenesis of joint destruction in RA.

Tranexamic acid (TEA) is a plasmin antagonist currently used as an anti-fibrinolytic agent to reduce bleeding in patients. TEA has only mild adverse effects. After oral administration, TEA is distributed over the extracellular and intracellular compartments and diffuses rapidly into the synovial fluid (9, 10). TEA appears to be an inhibitor of cartilage and bone degradation in arthropit conditions in vitro (8) and in vivo. Beneficial effects of TEA have been demonstrated in animal models of osteoarthritis (11, 12), in adjuvant arthritis (13), as well as in RA patients (open study) (13). In adjuvant arthritis and in RA patients, treatment with TEA reduced the excretion rates of hydroxylysylpyridinoline (HP) (13). HP is a collagen cross-link that is excreted in urine as a breakdown product of bone and cartilage, indicating a decreased degradation of these tissues in the affected joints (14). In RA patients treated with TEA, the suppressive effect disappeared after discontinuation of the treatment, suggesting that inhibition of the PA-system may slow down the progression of bone and cartilage degradation in rheumatoid arthritis.

To further investigate the effects of TEA, we performed a double-blind placebo-controlled study to determine the effects of 12 weeks of tranexamic acid treatment, as adjuvant medication in patients with RA, on cartilage and bone degradation as assessed by urinary HP and LP excretion.

Patients and methods
Patients
In 1999 nineteen patients from the outpatient clinic of Leyenburg Hospital in The Hague, The Netherlands, with RA diagnosed according to the 1987 criteria of the American Rheumatism Association (15) were included after informed consent was obtained. Inclusion criteria were: age of ≥16 years; stable second-line therapy (no changes in anti-rheumatic therapy since 4 weeks before start of the study); and a daily dose of corticosteroids of less than 7.5 mg prednisolone equivalent. Patients with a Steinbrocker stage of 1V, renal impairment, with a history of thromboembolic disease, and patients who were pregnant or planning to become pregnant were excluded from the trial.
Study design
The local institutional ethics committees approved the study protocol. The study was set up as a double-blind, placebo-controlled pilot study. Patients were treated with either TEA (Cyklokapron®, Pharmacia Upjohn BV, The Netherlands; 1.5 mg 3 times a day) or a placebo for 12 weeks. The patients visited the outpatient clinics at 2 weeks and 1 week before the start of the study, on the first day of the study period, at 4, 8, and 12 weeks during the study period, and at 4 weeks after the study period. No alterations in DMARD medication and no intra-articular injections were allowed during the trial. Concomitant therapies are listed in Table I. Patients were interviewed regarding the appearance of new symptoms and side effects that they attributed to the study medication.

Clinical assessments
At inclusion demographic and disease characteristics were recorded (Table I). At each visit, the following clinical assessments of disease activity were performed: a patient’s overall assessment of current disease activity on a visual analogue scale (VAS) of 0 – 100 mm; the duration of morning stiffness (minutes); swollen and tender joint count (28 joints) (16). The modified disease activity score (DAS) was calculated as defined by Prevoo et al. (16).

Laboratory assessments
At each visit serum and urine morning samples were collected and stored in -80°C until use. The CRP was measured and urinary HP and LP were measured using HPLC (17). Normal values for HP and LP in healthy subjects were assessed in a group of 36 adults.

Statistical analysis
To test for differences between the groups at baseline, Pearson Chi-square tests, Student’s t-tests, and Mann-Whitney tests were used as appropriate. The efficacy parameters were analyzed on the basis of an intention-to-treat analysis. For patients who prematurely discontinued the study, the data from the visit at which the trial medication was stopped were carried forward. Differences between courses for all outcome parameters during the treatment period were evaluated by Repeated Measures Analysis of Variance. All statistical calculations were performed using SPSS 10.0 for Windows. P values of less than 0.05 were considered to be statistically significant.

Results
Ten patients received TEA and 9 patients placebo. Sixteen patients completed the study, 8 patients in each group. The compliance was good. One patient in the TEA group discontinued the study medication after 4 weeks because of a history of thrombosis risk that had not been previously reported. One patient in the placebo group discontinued the study medication because of a panaritium of her finger. She was excluded from the analysis. Thus 10 patients in the TEA group and 8 patients in the placebo group remained for analysis.

Table I. Demographic and disease characteristics of the patients taking tranexamic acid or placebo.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Tranexamic acid (n = D)</th>
<th>Placebo (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males/females (no.)</td>
<td>1/9</td>
<td>1/7</td>
</tr>
<tr>
<td>Age: mean (SD)</td>
<td>60.8 (13.9)</td>
<td>49.1 (11.0)</td>
</tr>
<tr>
<td>Disease duration (yrs.): median (range)</td>
<td>5.7 (1 - 30)</td>
<td>9.9 (1 - 20)</td>
</tr>
<tr>
<td>RF positive (no.)</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Erosions present (no.)</td>
<td>4*</td>
<td>7</td>
</tr>
<tr>
<td>NSAIDs (no.)</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>DMARDs** (no.)</td>
<td>10</td>
<td>8</td>
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<tr>
<td>Methotrexate</td>
<td>5</td>
<td>6</td>
</tr>
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</tr>
<tr>
<td>Cyclosporin</td>
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<td>0</td>
</tr>
<tr>
<td>Corticosteroids (no.)</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

RF: rheumatoid factor; NSAIDs: non-steroidal anti-inflammatory drugs; DMARDs: disease-modifying anti-rheumatic drugs.
* There were significantly fewer patients with erosions in the tranexamic acid group than in the placebo group (Pearson Chi-square, p = 0.04).
** Patients used one DMARD only, in two cases combined with a corticosteroid.

No effect of TEA on pyridinoline excretion or disease activity
For all outcome parameters at baseline, there were no significant differences between the treatment groups. Normal values in healthy volunteers were < 40 nmol/mmol creatinin for HP and < 10 nmol/mmol creatinin for LP (data not shown). Urinary pyridinoline excretion of the patients participating in the present study was significantly higher than in the healthy control subjects (p < 0.001). In all cases pyridinoline excretion was above normal values (data not shown). The CRP levels were low for both groups. Repeated Measures Analysis of Variance did not reveal any effect of TEA on HP or LP excretion (Fig. 1, Table II) nor on clinical parameters of
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Subgroup analysis of the patients with erosions at baseline or subgroup analysis of the patients with the HP excretion of more than 100 nmol/mmol creatinin at baseline revealed no effect of TEA either (data not shown).

Discussion

The aim of the present study was to investigate whether TEA may be beneficial for RA patients as adjuvant therapy to inhibit the degradation of articular cartilage and bone as measured by pyridinoline excretion rates. In contrast to the open study performed by our group previously (13), no such effect of TEA on urinary pyridinoline excretion was found here. In line with previous findings (18), neither was any effect of TEA on disease activity observed.

One can postulate that the present study was too small to be able to detect an effect of TEA. However, not even a trend towards a beneficial effect of TEA was observed.

An explanation for the lack of effect in the present study may be that the patients used in the present study were different from the ones used in the open study. Mean disease activity was lower in the patients of the present study compared with those of the open study. This is a result of overall better treatment possibilities in current medical practice as compared with a couple of years ago. Nevertheless, pyridinoline excretion was still elevated in the patients of this study as compared with healthy control subjects. An effect of TEA could therefore still be expected. Perhaps treatment with plasmin antagonists is only effective in RA patients with very active disease. Therefore, it would be interesting to study the value of TEA treatment in a subgroup of RA patients with high disease activity scores despite adequate anti-rheumatic therapies.

Another possible explanation for the inconsistency between the present results and those of the open study may be that the observed effect in the latter, not being controlled by a placebo, may have been due to other factors than the treatment with TEA. TEA inhibits the conversion of plasminogen into plasmin by both tPA and uPA. Plasmin-mediated fibrinolysis is predominantly regulated by tPA, whereas plasmin-mediated extracellular matrix degradation is regulated by uPA and its membrane receptor uPAR. If plasmin is a key player in the proteolytic cascade towards cartilage destruction in RA, a more specific approach, such as inhibiting plasmin at the cell surface of destructive synovial cells, specifically inhibiting uPA or uPAR, or the interaction between the two may be more effective. In vitro and in vivo experimental models for RA cell surface-targeted plasmin inhibition, using a plasmin inhibitor that binds to uPAR, appears to be successful (6). Another possibility is that plasmin is not the key enzyme in the proteolytic cascade so that inhibition of plasmin only may not be sufficient to produce a relevant inhibition of joint destruction in RA patients. If this is the case, other or a combination of proteinases should be targeted.
In the present study TEA did not prove to be an effective inhibitor of cartilage destruction in RA patients with mild to moderate disease activity. Further studies should be carried out, in order to develop therapeutic strategies that effectively target the key players in the proteolytic cascade mediating joint destruction in RA.

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References