Disease modifying treatment for feline rheumatoid arthritis

F. Y. Hanna

Summary
Feline erosive polyarthritis includes the more common periosteal proliferative polyarthritis (PPP) and the rarely seen rheumatoid arthritis (RA) (11). During the past three years, 12 patients with definite feline rheumatoid arthritis, which did not respond well to conventional therapy, were treated with 7.5 mg of Methotrexate and 70 mg Leflunomide, given weekly by the oral route. The average age of the cats was 5.9 years (range 2.5 to 10 years). Siamese cats were over represented. Seven of the 12 (58%) cats showed a marked improvement, usually within four weeks. Once maximum improvement was obtained the dosage was decreased. Serious toxicity was not noted and carcinogenetic effect was not seen during the course of this study.

Keywords
Disease modifying therapy, cats, rheumatoid arthritis

INTRODUCTION
Rheumatoid arthritis is rarely diagnosed in the cat (3). Blahser (8) described the pathological changes in a rheumatoid arthritis-like condition in a cat, Joshua (10) reported a similar syndrome in middle-aged cats, Pedersen et al. (13) described three cats with deforming chronic progressive polyarthritis that resembled human rheumatoid arthritis, and Bennett and Nash (7) described three cases of rheumatoid arthritis in the cat.

Clinically, all forms of non-infective polyarthritis in the cat are similar. Affected cats are stiff, unwilling to move and may resent any form of handling; joints are usually swollen and painful, and some cases are pyrexic and inappetent (7)

Rheumatoid arthritis can be difficult to recognise and is frequently misdiagnosed, especially in the early stages of the disease. Testing for rheumatoid factor is often used in the diagnosis of rheumatoid arthritis but not all cats with rheumatoid arthritis are positive.

Radiography demonstrates destructive changes within the joints; such changes may be absent in the early stages of the disease, but they can be used later to monitor the progression of the disease. Rheumatoid arthritis can be a very aggressive, destructive and irreversible disease, particularly if disease modifying therapy is not given.

For many years, the development of rational therapy for this debilitating condition was hampered by a lack of basic understanding of the pathophysiological processes underlying disease initiation and development. Although a variety of cell types (e.g. dendritic cells, fibroblast-like synoviocytes and B cells) are now recognised as contributors to the progressive joint destruction in rheumatoid arthritis, T-lymphocyte cells are still thought to be a central event in the initiation and progression of this disease.

This article briefly summarises current views on the role of T-lymphocyte cells in the pathogenesis of rheumatoid arthritis and provides an overview of a new therapy that has been used in this study.

MATERIALS AND METHODS

Patients
All of the patients admitted to the study were referred to the author and had been treated with steroidal/non-steroidal anti-inflammatory drugs on the basis they had some form of arthritis, but in none had a definite diagnosis been made. All had shown an unsatisfactory response to treatment. Steroidal/nonsteroidal anti-inflammatory drugs were withdrawn over a two week period. Details of the twelve cats are recorded in Table 1.

Clinical and radiological assessment
All of the cats were examined on several occasions, and under general anaesthesia, all of the limb joints were radiographed as well as the chests and abdomens.

Routine haematological and blood biochemical examinations were carried out.

An initial complete blood cell count was carried out at the first admission and repeated at four weeks, then monthly for three months and six months thereafter. Liver enzymes and bile acids were measured, before and during treatment, to screen for any damage. A modified ELISA, similar to that described by Bell et al. (1), was used to detect circulating rheumatoid factor found in dogs. Purified CAT IgG as antigen and a commercially available monoclonal mouse antibody to cat IgM (Serotec) were employed; a reading below five was con-
Considered normal and five or above positive (Professor S. D. Carter, Veterinary Pathology, University of Liverpool).

Comparisons of the initial RF titre with one obtained after treatment were carried out in three cats (case numbers 1, 3 and 9) during the course of this study.

An indirect immunofluorescence test was used to detect serum antinuclear antibody. This has been described by Bennett and Kirkham (6); a titre of 1:32 or greater was considered abnormal. They were used to detect feline leukaemia virus antigens and antibodies to feline immunodeficiency virus and feline corona virus. (Vet Laboratory).

Ultrasonography was carried out four weeks after the start of treatment and repeated monthly for three months and then every six months thereafter, in order to rule out any carcinogenic effects of the drugs used in this study.

While they were anaesthetised, synovial fluid was collected from several joints of each cat. The appearance and quantity of the fluid were recorded; the mucin clot test, fibrinogen clot test and total cell counts were performed on all of the samples. One synovial membrane biopsy was collected from each cat, and biopsy was taken from the most clinically affected joint with respect to swelling and pain. Swabs for bacterial culture were taken from all samples. In addition, urine samples were collected by manual expression of the bladder whilst the cat was anaesthetised and routinely analysed.

Table 1  Details of twelve cats with rheumatoid arthritis.

<table>
<thead>
<tr>
<th>Case</th>
<th>Breed</th>
<th>Age</th>
<th>Sex</th>
<th>RF at the onset of therapy</th>
<th>FIV/FeLV/FIP coronaviru</th>
<th>ANA</th>
<th>RF after therapy</th>
<th>Follow-up period</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Siamese</td>
<td>10 yrs</td>
<td>Female</td>
<td>&gt;9</td>
<td>-ve</td>
<td>-ve</td>
<td>3</td>
<td>35 months</td>
</tr>
<tr>
<td>2</td>
<td>Domestic</td>
<td>6.9 yrs</td>
<td>Male</td>
<td>7</td>
<td>-ve</td>
<td>-ve</td>
<td>-</td>
<td>31 months</td>
</tr>
<tr>
<td>3</td>
<td>Siamese</td>
<td>2.6 yrs</td>
<td>Female</td>
<td>6</td>
<td>-ve</td>
<td>-ve</td>
<td>2</td>
<td>20 months</td>
</tr>
<tr>
<td>4</td>
<td>Siamese</td>
<td>10 yrs</td>
<td>Female</td>
<td>4</td>
<td>-ve</td>
<td>-ve</td>
<td>-</td>
<td>19 months</td>
</tr>
<tr>
<td>5</td>
<td>Domestic</td>
<td>9.6 yrs</td>
<td>Female</td>
<td>&gt;9</td>
<td>-ve</td>
<td>-ve</td>
<td>-</td>
<td>18.5 months</td>
</tr>
<tr>
<td>6</td>
<td>Foreign</td>
<td>3 yrs</td>
<td>Male</td>
<td>8</td>
<td>-ve</td>
<td>-ve</td>
<td>-</td>
<td>18 months</td>
</tr>
<tr>
<td>7</td>
<td>Domestic</td>
<td>4.2 yrs</td>
<td>Male</td>
<td>&gt;9</td>
<td>-ve</td>
<td>-ve</td>
<td>-</td>
<td>16 months</td>
</tr>
<tr>
<td>8</td>
<td>Burmese</td>
<td>3.8 yrs</td>
<td>Male</td>
<td>8</td>
<td>-ve</td>
<td>-ve</td>
<td>-</td>
<td>12 months</td>
</tr>
<tr>
<td>9</td>
<td>Siamese</td>
<td>9.5 yrs</td>
<td>Male</td>
<td>5</td>
<td>-ve</td>
<td>-ve</td>
<td>2.5</td>
<td>12 months</td>
</tr>
<tr>
<td>10</td>
<td>Siamese</td>
<td>4.5 yrs</td>
<td>Male</td>
<td>4</td>
<td>-ve</td>
<td>-ve</td>
<td>-</td>
<td>9 months</td>
</tr>
<tr>
<td>11</td>
<td>Domestic</td>
<td>2.5 yrs</td>
<td>Female</td>
<td>6</td>
<td>-ve</td>
<td>-ve</td>
<td>-</td>
<td>8.5 months</td>
</tr>
<tr>
<td>12</td>
<td>Siamese</td>
<td>5 yrs</td>
<td>Male</td>
<td>5</td>
<td>-ve</td>
<td>-ve</td>
<td>-</td>
<td>8 months</td>
</tr>
</tbody>
</table>

In addition, the following parameters were recorded:

- The time taken for the twelve cats to achieve maximum improvement.
- The numerical grade at the onset of therapy, compared with that measured when the patients had reached their peak improvement.
- An overall improvement score was obtained from all of the data collected from the owners, related to stiffness after rest and stiffness after exercise, together with the clinical assessment of disease severity and functional activity.

Results

Clinical and radiological assessment

Upon initial examination, all twelve cats had shown stiffness for over four weeks. There were varying degrees of muscle atrophy, but no neurological deficits, and the local reflexes were intact.

Clinically, the cats were lame on one leg only, the left front leg (case numbers 1, 5, 6, 7), right front leg (case numbers 2, 3, 4, 8, 9, 10), right hind leg (case number 11) and the left hind leg (case number 12). In all, 13 affected joints were identified showing swelling and pain on flexion and extension, the left carpus (case numbers 1, 5, 6, 7), right...
carpus (case numbers 2, 4, 8, 9, 10), right elbow (case number 3), right stifle and hock joints (case number 11) and left hock (case number 12). The degree of swelling was found to be comparable to the degree of pain in all cats.

Radiography demonstrated subchondral bone erosion in both carpi, (case numbers 1, 2, 4, 5, 6, 7, 8, 9, 10), both elbows and hocks (case number 3), both hocks and stifle (case number 11), both hocks (case number 12), and both carpi and hock (case numbers 4, 7, 8). A total of 34 joints were radiologically affected.

The size of the erosions varied. Soft tissue swelling was commonly seen. Periosteal new bone formation was seen in one or more joints of the twelve cats, although it was never extensive.

Laboratory features

The haemogram revealed leucocytosis with an absolute neutrophilia in all of the cases. An increase in serum globulin was seen in four of the cats. The mucin clot was generally poor with occasional clots. Ten cats were significantly seropositive for rheumatoid factor, all were negative for FELV, FIV and FIP virus infection. The synovial fluid aspirated from the clinically affected joints was increased in volume and appeared to be cloudy and watery.

Synovial fluid analysis revealed an increase in leucocyte cell counts (average 27,000/mm³), and neutrophils were the predominant cell type (average 86%); the polymorphonuclear neutrophils did not contain intra-cytoplasmic bacteria.

Pathological features

All of the synovial membrane biopsies showed an active chronic synovitis (Fig. 1). The synovium showed villous hypertrophy, with the supporting layer containing a marked inflammatory infiltrate consisting mainly of lymphocytes and plasma cells.

All 12 cats fulfilled the criteria for definite rheumatoid arthritis, as described by Bennett (4).

Treatment

The numerical grade at the onset of therapy (Table 2) indicates the severity of disease at start of treatment. This grade, at onset of therapy, was compared with that measured when the patient had reached its peak improvement where additional improvement could not be gained, despite continuation of treatment. See Fig. 2 for time taken in 12 cats to achieve maximum improvement.
A change of three grades was considered to be a ‘marked’ or ‘outstanding’ improvement, two grades a ‘moderate’ or “good” improvement, and one grade a ‘mild’ improvement. The improvement according to this scheme is shown in Table 3.

An overall improvement score was made by adding the number of animals who showed various degrees of improvement, which included: no change, mild change, moderate change and marked change in all of the parameters, i.e. stiffness after rest, stiffness after exercise, severity of disease activity, and ability to move the affected limbs. Then the total was divided by four, which was the total number of parameters measured. For example, the number of patients who showed marked improvement in grades with therapy were five in stiffness after rest, nine in stiffness after exercise, eight in the degree of swollen and painful joints and six in the ability to move the affected leg, giving a total of twenty-eight, which was then divided by four to equal seven.

The overall improvement according to this scheme is shown in Table 4.

Little or no improvement was noted in two cats, as opposed to marked improvement in seven. Of the latter group, two were judged to be in complete remission.

The criteria for complete remission were transient or no stiffness after rest, absence of joint swelling and pain on palpation of the affected joints; insignificant or complete absence of subchondral erosions on radiography of the affected joints (Fig. 3A, B and Fig. 4A, B) and return of RF titre to the normal range. Since RF titres were not re-measured on a regular basis, data are available in only three cats – case 1 (initial RF titre was more than 9, which decreased to 3 after 20 months of therapy), case 3 (initial RF titre was 6, which decreased to 2.5 after 19 months of therapy) and case 9 (initial RF titre was 5, which decreased to 2.5 after 12 months of therapy).

At the onset of therapy, ALT, ALP and bile acids were found to be within normal limits. A mild elevation of ALT (average 95 IU/L) and ALP (average 126 IU/L) occurred in only three cats (cases 2, 7, 12), four weeks after starting the treatment, but had returned to normal 4 weeks later.

Lethargy following the weekly dose of Methotrexate occurred in two cats (cases 2, 7); one cat (case 10) showed increased frequency of defaecation.

In the course of this study, signs of infection or neoplasia were not detected in the 12 cats.

**Table 3**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>No change</th>
<th>Mild change</th>
<th>Moderate change</th>
<th>Marked change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stiffness after rest (owner assessment)</td>
<td>0</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Stiffness after exercise (owner assessment)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Severity of disease activity</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Degree of swelling and pain (clinical examination)</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>

**Table 4**

<table>
<thead>
<tr>
<th>Overall improvement.</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Marked</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 (0%)</td>
<td>2 (17%)</td>
<td>3 (25%)</td>
<td>7 (58%)</td>
</tr>
</tbody>
</table>

**Discussion**

Immune-based polyarthritis is classified radiologically into two broad categories: erosive and non-erosive, depending upon whether or not there are destructive changes within one or more joints.

The erosive type includes two syndromes: one showing marked periosteal new bone formation (periosteal proliferative form), and another showing minimal changes.
periosteal new bone formation (rheumatoid arthritis) (7). It is of interest that twelve patients with definitive rheumatoid arthritis were seen in this study over a three-year period which may indicate that rheumatoid arthritis is not as rare in cats as has previously been stated by Mitchell (11), Bennett and Nash (7), and Pederson et al. (13). Contrary to the previous study by Bennett and Nash (7) that suggested a poor prognosis for both types of erosive polyarthritis, the present study indicated that seven of the twelve patients with rheumatoid arthritis (58%) showed marked improvement without any serious side effects. All twelve cats fulfilled the criteria described by Bennett (4) for the diagnosis of rheumatoid arthritis. Siamese cats were over represented. The radiographic features of the affected joints were similar in all twelve cats. Soft tissue changes were most evident (e.g. distension of joint capsules) although it was never extensive and periosteal new bone formation was present in one or more joints of all of the cats. Destructive change was the significant feature of all affected joints, which concurs with other studies (7, 13).

All of the cats in this study were negative for FELV, FIV and FIP virus infection (Table 1) suggesting that the association between feline leukaemia virus and immune based polyarthritis described by Pederson and others (13) may be coincidental.

Watery synovial fluid with a high white cell count of polymorphonuclear / and mononuclear cells characterised all of the cases

The histological lesions observed in this study are consistent with those observed in previous reports (7), all biopsies showing an active chronic synovitis.

All but two cats were strongly seropositive for rheumatoid factor, which suggests that the detection of serum rheumatoid factor is an important diagnostic test for feline rheumatoid arthritis, although not specific for the disease. It has also been the experience of the author that rheumatoid factor in cats, with the other form of feline erosive polyarthritis (periosteal proliferate polyarthritis), was negative (below 4) using the test reported herein.

Traditional pharmacological approaches to treating rheumatoid arthritis have included symptom-modifying drugs to control pain and inflammation. Such drugs, including the non-steroidal anti inflammatory drugs (NSAIDS) and low dose corticosteroids, do not alter the progression of the disease. In the treatment of humans, there has been a shift towards the early use of aggressive treatment with disease modifying anti-rheumatic drugs (DMARD’S) such as Leflunomide, Methotrexate, Hydroxychloroquine, Sulphasalazine, gold salts, Penicillamine, Azathioprine, Tetracycline, Etanercept and Infliximap (14). A delay of as little as eight or nine months in starting DMARDS has a significant impact on disease parameters in later years (15).

Toxic side effects, especially hepatic, have discouraged the widespread use of Methotrexate and Leflunomide. All of the cats in this study had their blood screened for liver damage prior to and after starting treatment. ALT, ALP and bile acids were screened for determination of hepatic toxicity. If ALT and ALP are persistently increased, which was not the case in this study, then the case would have been managed by either monitoring liver enzymes while reducing the dose of Methotrexate and Leflunomide, and also obtaining liver biopsies to assess the extent of liver damage or to discontinue the drugs. DMARDS therapies directed against T-lymphocyte cells have the potential for reducing both the inflammation of early rheumatoid arthritis and the joint destruction of more established disease. Therefore, by suppressing, arresting or even reversing the erosive changes, both clinical and radiological improvement can occur.

Leflunomide is an isoxazol derivative structurally unrelated to other known immuno-regulatory drugs. At a certain dosage it serves as an immuno-modulatory agent inhibiting inflammation and joint destruction by preferentially causing cell arrest of T-lymphocytes through its action on dehydro-orotate dehydrogenase (DHODH), an enzyme for uridine monophosphate (rUMP) synthesis. At a higher dose, leflunomide causes an immuno-suppressive effect by inhibiting tyrosine kinases.

Leflunomide is rapidly converted to its active form A77 1726 in the gut wall and liver. A77 1726 has been shown to prevent the proliferation of T cells and T cell dependent
B cell antibody formation including IgA and IgG. Unlike Leflunomide, Methotrexate has little effect on T cell proliferation, but promotes adenosine release which inhibits inflammation and joint destruction. In terms of combination drug therapy for rheumatoid arthritis, it may be useful to combine drugs that have different modes of action, such as Leflunomide and Methotrexate.

**Conclusion**

The results of this small study suggest that the combination of Methotrexate and Leflunomide provides a beneficial clinical response with acceptable tolerability, however, careful dose titration and patient monitoring is necessary to prevent liver damage.

It is important to use the correct dose to achieve an immuno-modulatory effect but not immuno-suppression. The dose of Leflunomide and Methotrexate used in this study was a fraction of the dose used in humans. It was sufficient to achieve an immuno-modulatory effect required to inhibit inflammation and joint destruction without causing any side effects which may be associated with immuno-suppression, such as infection.

Trials with different dosage regimes may be investigated in the future and therapy may involve a different combination of drugs that have a different mode of action.

**References**

2. Bennett D. The naturally occurring inflammatory arthropathies of the dog. (1980) Ph D thesis. Faculty of Veterinary Medicine, University of Glasgow.

**Correspondence to:**

F. J. Hanna BVSc, MRCVS. CSMD
3 Rosebery Ave
Hampden Park
Eastbourne
BN2 2QU U.K.
Phone: +44 1323 50361, Fax: +44 1323 50364
E-mail: Rosebery3@itsColi.co.uk