Evaluation of technetium-99m-ciprofloxacin (Infecton) for detecting sites of inflammation in arthritis

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Objective. To study the frequency of technetium-99m-positive ciprofloxacin scans (Infecton scintigraphy) thought to be specific for bacterial DNA in patients with arthritis and to assess the clinical relevance of positive scans.

Methods. Four groups of adults with arthritis were studied. Group 1: 53 patients with inflammatory arthritis, 36 with spondylarthropathy (SpA) and 17 with rheumatoid arthritis (RA); group 2: five patients with crystal arthropathy; group 3: those patients with osteoarthritis (OA) of the knee, wrist or spine; and group 4: 28 patients who had no arthritis but were being investigated for renal infection. Patients were injected with 10 mCi 99Tcm-ciprofloxacin with isotope uptake analysis at 4 h. Clinically swollen joints were assessed by a rheumatologist and the positive scans assessed by a physician in nuclear medicine.

Results. Increased Infecton uptake was noted in inflamed joints independent of the pathology. It was seen in 10 of 17 patients with SpA, 12 of 17 with RA, all five with crystal arthropathy, eight with knee OA, two with wrist OA, none with spinal OA and none in uninflamed joints. A close correlation between clinically swollen joints and articular Infecton uptake was noted \( (P = 0.0003) \), with the uptake being in the distribution of the synovial perimeter. Additional uptake was noted in the abdomen \( (n = 9) \) and pulmonary region \( (n = 2) \) of SpA patients.

Conclusion. The Infecton scan is not specific for infection but may be a reliable procedure for identifying the presence and distribution of the inflammation within joints. It has the potential for monitoring the response of inflamed joints to treatment.

Key words: Infecton, Scintigraphy, Arthritis, Ciprofloxacin.

The spondylarthropathies (SpA) and perhaps even rheumatoid arthritis (RA) may represent forms of reactive arthritis (ReA), with microbial agents and biochemical factors together providing a possible explanation for enthesitis, diffuse osteitis, autoimmunity and large joint predilection in SpA. It is notable that microbial factors have been detected within the genitourinary and gastrointestinal tracts and within the joint [1, 2]. A recent study has demonstrated that bacterial DNA and/or bacterial cell wall constituents can be retained in the joints of some patients with RA [1] and also in inflammatory osteoarthritis (OA), crystal-induced arthropathy and even in patients following trauma [3]. Although there is some evidence linking some microbes with the development or flares of arthritis, it is not clear whether the process is primarily based in the joint or is due to a distant infection with a secondary sensitization against some microbial constituents with the subsequent transfer of the process to the joint cavity.

Ciprofloxacin is a synthetic 4-quinolone derivative with bactericidal activity against a wide range of Gram-negative and -positive micro-organisms with a wide distribution in the entire body including the bone and the joints, and has effective penetration into the inflamed tissue. When labelled with the radiochemical
technetium-99m, ciprofloxacin (Infecton) given intravenously identifies areas of bacterial infection with 84% sensitivity and 81% specificity. After binding, ciprofloxacin inactivates bacterial DNA gyrase, but the complex does not bind to dead bacteria (therefore sterile abscesses are negative) [4–7].

Thus, if (Gram-negative) bacteria have a pathogenic role in chronic diseases such as SpA and RA or even other rheumatic conditions, their presence should be visualized in the joint or other areas by $^{99m}$Tc-Infecton.

Patients and methods

**Infecton scintigraphy**

The technique has been reported elsewhere but is still experimental [4–7]. Briefly, 10 mCi of $^{99m}$Tc-Infecton (Draximage, Quebec, Canada) are injected intravenously over 40 s. Anterior and posterior whole-body static images are acquired at 4 h after injection, and read by a large-field gamma camera peaked to 140 KeV with a 15% window using a low energy, general purpose parallel-hole collimator. The image was read by an independent nuclear medicine physician.

**Patients**

Our population was divided into four groups of adult patients.

**Group 1: chronic inflammatory arthritis group.** This comprised 53 patients; 36 had SpA according to the European diagnostic criteria (psoriatic arthritis (PsA) = 19, and ankylosing spondylitis (AS) = 17), and 17 had RA according to the American College of Rheumatology criteria for the diagnosis of RA, with 12 being seropositive. Nine were treated with methotrexate, 7 with low-dose methylprednisolone (less than 7.5 mg daily) and all received regular NSAID therapy.

**Group 2: crystal arthritis group.** This consisted of five patients suffering either from a crisis of gout ($n = 2$) or pseudogout ($n = 3$).

**Group 3: OA group.** This included 20 patients suffering from osteoarthritis (OA), 10 with low back pain of more than 3 months duration associated with spinal degenerative changes, eight with severe and painful knee OA and two with thumb OA.

**Group 4: control group.** This consisted of 28 patients being investigated for kidney infection without joint symptoms.

Prior to the Infecton scan, the rheumatologist undertook a careful evaluation of the tender and swollen joint count and documented their distribution (maximum inflamed joint number = 28).

The protocol was accepted by the Ethical Committee of Erasmus University Hospital and patient informed consent was obtained prior to the study.

**Statistics**

They include the $\chi^2$ test for differences between proportions for comparing the positive scans among the different clinical conditions, and the Phi coefficient plus the Fisher exact test for the correlation between the uptake and the inflamed joints.

**Results**

**Infecton scan in group 1 (chronic arthritis)**

All the patients with symptomatic SpA or RA (respectively 10/36 and 12/17) exhibited a clear-cut uptake at the sites of inflamed joints but not at a non-inflamed site. A strong correlation ($P = 0.0003$) was seen between the radionuclide articular uptake and the clinical joint involvement assessed by two blinded investigators (one rheumatologist and one nuclear medicine physician) (Figs 1 and 2).

The uptake image delineated the synovial perimeter and the labelling intensity depended on the severity of the inflammation (more severe, more intense), with the maximum uptake seen at 4 h. Interestingly, a few patients were measured on more than one occasion and, when the arthritic process entered into remission (four patients), a dramatic uptake reduction was observed and sometimes disappeared. Conversely, when a new joint became affected, an uptake was observed (two patients).

In the SpA group, the abdomen was visualized in 20 patients, none of whom had abdominal symptoms although subclinical inflammatory bowel disease had not been excluded. The abdominal uptake was not related to the presence of peripheral involvement. The positive scans were in isolated parts of the intestine (7/20) and/or the gall bladder (3/20) (Fig. 3). These positive abdominal scans were not observed in any of the RA patients. Whilst in a further two SpA patients there was positive uptake at the attachment of the Achilles tendon, which was clinically swollen. Of interest, images suggestive of tenosynovitis of the
finger tendon sheaths were observed in three RA patients. However, no uptake was demonstrated in the spine and/or sacroiliac joints of any patients, including those with clinical evidence of sacroiliitis and spondylitis.

**Infecton scan in group 2 (crystalline arthropathy)**
This was positive in all cases with the uptake varying from slight to intense, depending on the severity of the symptoms. The images were not different from those observed in chronic arthritis.

**Infecton scan in group 3 (OA)**
Slight articular uptake was limited to the previously noted, swollen osteoarthritic joint (6/8 with knee OA and 2/2 with thumb OA). No uptake could be visualized along the spine or the sacroiliac joints of 20 patients suffering from low back pain. On the other hand, two patients in this group exhibited a persistent uptake in the ileum (one patient had suffered intestinal tuberculosis 20 yr previously and the other had a diagnosis of spastic colitis of unknown origin).

**Infecton scan in the group 4 (control)**
No significant isotope uptake could be detected at 4 and 8 h in the articular or the spinal region of these patients (although the kidney was labelled in 18/28 with suspected pyelonephritis).

**Discussion**
Infecton is only available for research studies and so far does not have a product licence.

From the literature, the uptake of labelled ciprofloxacin is specific for the DNA gyrase of Gram-negative bacteria and therefore allows infected sites to be visualized. But in this study, the radiopharmaceutical is seen localized within the inflamed joints of patients (with SpA, RA, microcristalline arthropathy, OA) and additionally within some periarticular structures (tendon sheath or attachment). Thus the scan is linked to inflammation independent of clinical infection. The uptake superimposes the joint space and, when the degree of inflammation is severe, it moulds the synovial membrane; conversely, it appears to disappear as inflammation resolves.

Therefore, from our experience, Infecton may become a valuable tool for identifying synovial inflammation from any origin, but does not appear to have a role as an indicator of septic arthritis (as originally proposed) [4–6, 8]. On the other hand, no uptake was observed in the spine or in the sacroiliac joint, possibly owing to our experimental conditions and the small amount of synovial tissue in these structures. However, this was not the purpose of this investigation.

This synovial uptake differentiates Infecton from other well-established radiopharmaceuticals used in

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**Fig. 2.** The uptake corresponds here to the clinical examination with a more severe involvement of the left than of the right metacarpophalangeal joints, and with a tenosynovitis of the tendons (in addition to the articular synovitis) of the right wrist.

**Fig. 3.** The Infecton scan in SpA patients frequently reveals at 4 h an uptake along the ascending portion of the intestine and/or in the gall bladder.
arthritis, in particular gallium-67 citrate, which extravasates from the sites of inflammation and produces a diffuse image of the joint region including the adjacent bone. 99Tc(M)-Methylene bisphosphonate, like gallium, also reflects adjacent bone turnover due to inflammation, but remains at the site even though the signs of inflammation have resolved [9]. With Infecton, the labelling is essentially of synovial tissue or synovial fluid origin; accordingly, Infecton is comparable with scintigraphy with polyclonal immunoglobulins (99Tcm-HIG) and indium (III) leucocyte imaging, which also provide objective, non-invasive tests to detect and measure synovitis [9, 10].

The mechanism of localizing to the inflamed joint is not clear. Labelled ciprofloxacin specifically binds to DNA gyrase, but other factors (such as local congestion and alteration of synovial membrane anatomy) and specific receptors may be relevant.

Interestingly, the uptake in the inflamed joints of RA and SpA patients (and also in the abdominal region of the latter group) was much more intense and longer lasting (over 8 h) than in the other conditions. Since the antibiotic specifically binds the DNA gyrase of living bacteria, the persistence of bacteria (essentially Gram negative) at the site of joint inflammation could account for some of the uptake. This hypothesis is supported by positive scans in patients with decayed teeth and/or after tooth extractions, but alternative explanations are not excluded.

Ciprofloxacin is normally excreted in the kidneys but not detected in the intestine before 24 h. The very early uptake in the intestine in the majority of SpA patients may therefore be due to an inflammatory state of the intestine or to local specific binding of the marker to Gram-negative bacteria. Similarly, the presence of ciprofloxacin in the gall bladder of some patients suggests that these organs could act as a reservoir for Gram-negative bacteria in SpA.

In conclusion, these preliminary data suggest that Infecton scans could be an additional method of (nonspecifically) imaging the inflammatory synovial process in arthritis. When compared with the other radiopharmaceuticals, the image produced by Infecton seems to delineate with more accuracy the inflamed synovium in the joint and in the tendon sheaths, and could potentially be useful for monitoring the response to therapy. This study also provides an explanation for the false-positive effects of Infecton for the diagnosis of infectious arthritis [4–6]. These results are consistent with the concept that a part of the inflammatory process is mediated by micro-organisms either directly or indirectly, not only in SpA but also in RA. Also in RA, crystalline arthropathy and in some patients with OA it is possible that the role of micro-organisms is superimposed on a pre-existing inflammatory process and that the micro-organisms may exacerbate the flare of arthritis.

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References