D isruption of the cortical plate and erosive destruction of the subchondral bone are characteristic features of active rheumatoid arthritis (RA), potentially leading to progressive damage. Until recently, damage progression as documented on radiographs has been regarded as an irreversible process. However, several case reports now indicate that this process may be stopped or even reversed, leading to healing or repair of bone lesions. Under physiological conditions there is a balance between bone resorption by osteoclasts and bone formation by osteoblasts. In a state of active inflammation, bone resorption usually exceeds new bone formation, resulting in bone destruction. However, as soon as the inflammatory process has been stopped in an individual joint, osteoblastic activity may exceed bone resorption, leading to new bone formation and repair. This process is regulated by osteoprotegerin. Because bone formation takes time, reparative changes can be expected to be clearly visible on radiographs only 6–12 months after distinct clinical improvement occurred. These may present as reappearance of the cortical plate or filling in of erosions. As clinical remission rarely occurs within the timeframe of clinical trials, and as patients experiencing remission outside clinical trials often do not visit their rheumatologist, x ray pictures showing healing phenomena have only occasionally been reported. Recent clinical trials with tumour necrosis factor α inhibitors indicate that clinical improvement and halting of radiographic progression occur earlier than with conventional disease modifying antirheumatic drugs (DMARDs). They have also shown a reduction in the radiographic scores in a considerable number of patients, probably indicating repair if measurement error can be excluded. As interleukin 1 (IL1) plays an important part in bone destruction, its inhibition might also result in a preponderance of repair over further destruction in eroded joints.

We wish to demonstrate here an example of healing during treatment with the IL1 receptor antagonist (IL1Ra) anakinra in a patient with active RA who did not respond sufficiently to conventional DMARD treatment.

CASE REPORT

In 1991, the patient, who was then 55 years old, first experienced pain and some swelling in several joints (feet, wrists, elbows, shoulders, knee joints, etc). She also had early morning stiffness lasting 2–3 hours. At her first presentation in November 1991, there was tenderness of the metacarpophalangeal joints, and some swelling of the metatarsophalangeal (MTP) joints and the left ankle joint. The erythrocyte sedimentation rate (ESR) was 41/77 mm/1st h, rheumatoid factor was positive (latex test 149 U/ml, Rose-Waaler test 1/160).

Radiographically, there was soft tissue swelling of the MTP joints I–V on both feet, and erosions at the left first MTP joint and the interphalangeal (IP) joint of the left great toe. There were no changes indicative of RA in the hands or wrists.

Non-steroidal anti-inflammatory drugs and parenteral gold treatment were started. Gold had to be stopped three months later because of an exanthema. DMARD treatment was continued with 10 mg methotrexate intramuscularly a week. This dose was increased to 15 mg intramuscularly a week owing to increasing disease activity, with an ESR of 58/96 mm/1st h. Methotrexate had to be withdrawn in June 1993 because the patient reported retrosternal pain after each application. In January 1994 treatment with sulphasalazine (3 g/day) was started. One year later, in April 1995, the disease was still active with a C reactive protein (CRP) of 43 mg/l, an ESR of 29 mm/1st h, although rheumatoid factor had become negative. Most importantly, an x ray examination demonstrated severe radiographic progression in the forefoot. For this reason, the patient was included in a randomised, double blind, placebo controlled trial with IL1Ra (anakinra) over six months, where she was treated with subcutaneous injections of 75 mg anakinra a day. Clinical improvement was seen within four weeks. The patient also participated in a six month continuation study. After one year, her RA was almost in remission (ESR 10 mm/1st h, CRP <5 mg/l).

When the study ended the patient continued to be treated with the same dose of anakinra until January 2001.

Radiographs of the forefoot

The following radiographs of the forefoot were obtained:

1991: Small erosions were seen at the IP I joint and the MTP I joint of the left great toe and a small erosion at the right MTP IV.

1992: New erosions had developed at the IP joint of the left great toe, the MTP III and IV joints of the left foot, and at the right MTP II joint.

1995: Severe destruction of the IP joint of the left great toe. Erosions of the left MTP I and II joints had increased. At the right foot, erosions at the IP joint of the right great toe, the MTP III and IV joints (here with luxation) were visible.

1996: All erosions appeared to be stabilised/inactivated.

The radiographs from 1997 to 1999 showed no progression, which indicates that the process continued to be inactive.

Radiographs of the hands and wrists

The following results were shown in the radiographs of the hands and wrist:


1993: Several erosions at the right wrist and the metacarpal basis had developed.

1995: Severe erosive damage of the right wrist could be seen.

1997 and in the following years: Signs of inactivation and repair. No changes in the left hand and wrist were seen at any time.

Abbreviations: CRP, C reactive protein; DMARDs, disease modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; IL1Ra, interleukin 1 receptor antagonist; IP, interphalangeal; MTP, metatarsophalangeal; RA, rheumatoid arthritis
Figure 1 shows the development of radiographic changes at the IP joint of the left great toe between 1991 and 1999.

1991: There is a small superficial erosion at the tibial aspect of the proximal phalanx. The joint surface is normal with a normal cortical plate at the proximal and distal articulating bone. The width of the joint space is normal.

1995: The proximal joint surface is completely destroyed, there is no cortical plate, the outline of the joint surface is irregular and indistinct. There is an indication that part of the bone at the distal joint surface has also been resorbed. The margin is indistinct.

1996: One year after starting anakinra treatment the cortical plate at the proximal joint surface has reappeared, at least at the fibular and middle part of the surface. At the tibial edge new bone formation appearing as a “bud” can be observed. There is an indication, on the one hand, that other smaller defects seen in 1995 have been filled in and, on the other hand, that parts of the original bone have been resorbed. At the distal joint surface the cortical plate is restored in part. Whereas the (normal) joint surface seen in 1991 appeared nearly linear, joint surface and joint space now have a curved outline.

1999: The cortical plate at the proximal and distal joint surface is completely restored, the edge of the surface is distinct. There is once again a well defined normal wide joint space with a symmetrically curved shape (S-shape).

DISCUSSION

The case reported here clearly shows destruction of the IP joint of the left great toe from 1991 to 1995. In 1991 the joint appeared completely normal, with the exception of a small superficial erosion at the tibial aspect of the proximal phalanx. In 1995 both joint surfaces were damaged with complete disappearance of the cortex and major bone resorption. Only one year after starting IL1Ra treatment at a dose of 75 mg a day, the repair of both joint surfaces with reconstruction of the cortical plates combined with new bone formation was in progress and was completed during the following years. Obviously, the shape of the joint surface is different from that seen in 1991: a new joint surface has been constructed by resorbing (necrotic) bone and simultaneously filling in small defects with new bone. This remodelling followed the requirements of function thus guaranteeing a nearly normal mobility of the
Erosion healing in RA after anakinra treatment

Rau R, Sander O, Wassenberg S, Authors’ affiliations

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