Minocycline in Rheumatoid Arthritis
Rationale and Trial Results

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Summary
Interest in the use of tetracyclines, especially minocycline, in arthritis is described in relation to the historical background. The scientific basis for the use of tetracyclines in rheumatoid arthritis is discussed in the light of new insights into the pathophysiology of the disease. During the past 2 years several studies have been published on the use of minocycline in rheumatoid arthritis. The results of these studies were to a large extent similar, in that minocycline was beneficial in terms of clinical outcome measures, but had more pronounced effects on laboratory assessments. Finally, we speculate about the future role of minocycline in rheumatoid arthritis.

Interest in the use of tetracyclines, especially minocycline, in connective tissue diseases has had a long history. In vitro work showed a decreased collagenase activity in both inflamed gingival and synovial tissue after administration of tetracyclines.[1-4] In line with this effect, tetracyclines reduced tissue resorption in models of bone resorption or in rabbits with corneal ulcers.[5,6] The effect of tetracyclines on collagenase activity seems to be ascribed to the chelation of calcium, since inhibition of purified collagenases by tetracyclines was partly reversible after addition of calcium.[1] However, lymecycline can prevent the oxidative activation of latent collagenase.[7]

The anti-arthritic properties of the tetracycline minocycline were recognised in 2 generally used animal models of chronic arthritis, collagen- and adjuvant-induced arthritis in rats. Administration of this drug decreased the incidence and the severity of collagen- and adjuvant-induced arthritis in rats.[8] and CMT (chemically modified tetracycline without antibacterial activity) in combination with flurbiprofen prevented bone loss in rats with adjuvant arthritis.[9] Furthermore, another tetracycline, doxycycline, reduced the severity of experimentally induced canine osteoarthritis.[10]

Previous studies have provided additional support in favour of investigating the antirheumatic properties of tetracyclines. These drugs have beneficial anti-inflammatory effects in a number of noninfectious dermatoses.[11] In vitro studies demonstrating neutrophil chemotaxis, cell killing, phagocytosis and the production of reactive oxygen species provide direct evidence that tetracycline might act as an anti-inflammatory agent.[12-15] Furthermore, tetracyclines have immunosuppressive properties based on a decreased proliferative activity of peripheral blood mononuclear cells[16,17] and the suppression of delayed type hypersensitivity responses.[18,19]

1. Scientific Basis for the Use of Tetracyclines in Rheumatoid Arthritis

On the basis that persistent mycoplasma infection might cause rheumatoid arthritis, lengthy courses of tetracyclines have been prescribed.[20] However, no significant benefit could be demonstrated in a small placebo-controlled double-blind
study of tetracycline 250 mg/day for 1 year. New interest in tetracyclines for rheumatoid arthritis developed after the recognition that minocycline in particular inhibits matrix metalloproteinases. Minocycline given orally twice daily for 10 days significantly decreased collagenase activity in rheumatoid synovial tissue. Further studies revealed that minocycline 125 mg/kg/day significantly decreased the incidence and severity of arthritis in the collagen and adjuvant models of arthritis.

The possible antirheumatic effect of tetracyclines can be explained by several biochemical anti-inflammatory and immunosuppressive properties. Tetracyclines exert their antimicrobial activity by inhibiting protein synthesis. Tetracyclines can also interfere with protein synthesis in mammalian cells, but the required concentrations are higher than those needed to show the same effect in bacteria. Cytoplasmic ribosomal protein synthesis is affected by tetracyclines at higher concentrations than mitochondrial protein synthesis.

1.1 Immunomodulating Effect

In vitro, tetracyclines influence the following neutrophil functions: phagocytosis, migration, chemotaxis, intracellular killing and degranulation. The inhibitory effect on neutrophil functions occurs at concentrations measured in serum after oral tetracycline administration. The suppression of phagocytosis, migration and chemotaxis was confirmed ex vivo in neutrophils from individuals treated with tetracycline. Moreover, tetracyclines have been reported to inhibit the generation of free reactive oxygen species by neutrophils. The neutrophil inhibiting effects are partly mediated by chelation of the bivalent cations Mg++ and Ca++, since the addition of these ions reverses the effects.

Studies on the effect of tetracyclines on human monocytes have reported less consistent results. Doxycycline did not influence phagocytosis by human monocytes from volunteers. Tetracyclines inhibit proliferation of peripheral blood lymphocytes at concentrations that are achieved in vivo. The mechanism by which lymphocyte functions are inhibited may be explained by impairment of mitochondrial protein synthesis or by an effect on intracellular calcium levels in lymphocytes.

1.2 Inhibition of Matrix Metalloproteinase Activity

In the early 1980s, Golub et al. reported that minocycline reduced elevated levels of gingival collagenolytic activity in rats with experimentally induced diabetes and in gingival fluid from humans with inflammatory periodontal disease. These findings led to further research in the field of matrix metalloproteinases.

Tetracyclines inhibit matrix metalloproteinases from various cells, including neutrophils, macrophages, osteoblasts, chondrocytes, rheumatoid synovium and cartilage. The tetracycline derivatives minocycline and doxycycline were more potent in inhibiting matrix metalloproteinase activity than tetracycline itself. In vitro studies showed that the inhibition of matrix metalloproteinase activity by tetracyclines may mediate a reduction in bone resorption. Tetracyclines were also shown to inhibit bone resorption in vivo, as could be demonstrated in animal models. Moreover, tetracycline combined with nonsteroidal anti-inflammatory drugs suppressed radiographically assessed joint destruction in animals with adjuvant arthritis.

The effect of tetracyclines on collagenase activity in tissue was suggested to be mediated by chelation of cations. Mammalian collagenases are calcium-dependent metalloproteinases. The addition of Ca++ to leucocyte collagenase in vitro completely overcame the inhibitory effect of minocycline. It has also been demonstrated that tetracyclines can prevent the oxidative activation of latent collagenase.

2. Clinical Studies with Minocycline

The effect of tetracyclines has been studied in reactive arthritis and in rheumatoid arthritis. Clinical studies on the therapeutic effect of tetracycline in reactive arthritis have given conflicting results. However, it has become clear that long term treatment is beneficial in reactive arthritis. Apart