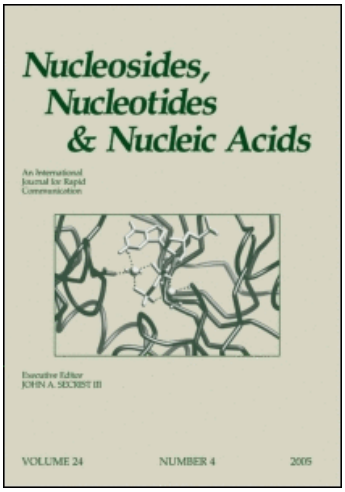

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Antimetabolites in the Treatment of Arthritis: Current Status of the Use of Antimetabolites

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ABSTRACT

Rheumatoid arthritis (RA) is an autoimmune disease characterized by a chronic inflammation of the synovial joints and infiltration of blood-derived cells. In daily practice rheumatologists use the antimetabolites methotrexate (MTX) and leflunomide for the treatment of patients with rheumatoid arthritis. The current clinical status (efficacy/toxicity) of these 2 antimetabolites in the treatment of RA will be discussed.

Key Words: Rheumatoid arthritis; Disease anti-rheumatic modifying drugs; Methotrexate; Leflunomide.

INTRODUCTION

RA is a disease with synovitis as a hallmark, involving cartilage and bone.[1] Moreover, RA is accompanied by general effects of inflammation, such as malaise, fatigue and an increased erythrocyte sedimentation rate. Medical therapy of patients with RA consists of NSAIDs, influencing pain and inflammation but not the course of the disease, and disease modifying anti-rheumatic drugs (DMARDs), influencing or

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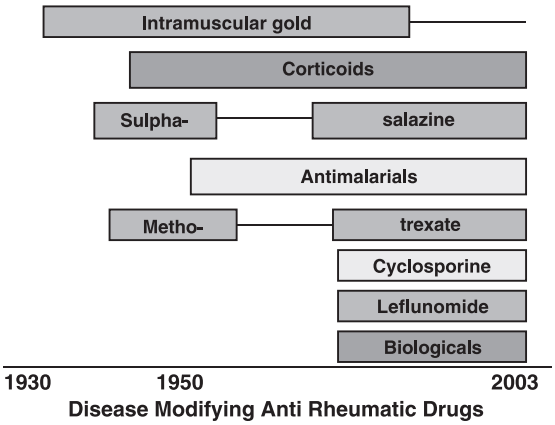

Figure 1. Time frame of DMARD utilization in the treatment of patients with rheumatoid arthritis.

modifying the course of RA.[2] The modifying effect of DMARDs is reflected in the Disease Activity Score (DAS), a composite index of the opinions of the patient and the physician and laboratory parameters of inflammation, and the parameters of radiographic damage, as read from X-rays of hands and forefeet. The most important DMARDs are listed on Fig. 1.

This figure illustrates that intramuscular gold is the eldest DMARD, followed by sulfasalazine. Corticoids are used since the 1940's with ups and downs. Two developments can be considered as real changes in the treatment for the patiënt with RA; first, the rediscovery of methotrexate (MTX) in the 1980's and, second, the introduction of ''biologicals'' in the 1990's. The biologicals are specifically aimed at interfering in the release of pro-inflammatory cytokines (e.g. TNF-α) that play a major role in the pathophysiology of RA.[3,4] Novel anti-TNF-α agents include Infliximab (antibody against TNF-α)[5] or Etanercept (TNF-α receptors).[6] The long term superiority of the expensive biologicals over DMARDs, with known efficacy and low costs, still needs to be established. This study will discuss the current status of MTX and a relatively novel DMARD, leflunomide, in the treatment of RA.

METHOTREXATE IN RHEUMATOID ARTHRITIS

After an initial phase in the 1950's, MTX was rediscovered in the late 1980's.[7] The mode of action of MTX was partly unraffled after is success in RA. The following mechanisms are supposed to be important for the efficacy of MTX: 1) induction of apoptosis in T cells or monocytic/macrophage cells, 2) decrease in production of proinflammatory cytokines: IL-1 and IL6, 3) increase in production of anti-inflammatory cytokines: IL4 and IL10, and 4) inhibition of metalloproteinase production, thereby reducing cartilage/bone destruction.[8–10] MTX influences the DAS and the effect is fast (4–6 weeks) compared to the older DMARDs. Moreover, it has been proven that MTX

inhibits radiographic progression.[11] Slowing-down of radiographic progression has become more and more important as outcome variable. At present there is a lot of discussion whether bone erosion is the result of inflammation or a process in itself.[12]

The initial dose of MTX is 7.5 or 15 mg/week in most instances as (one) oral gift. Other routes of administration are subcutaneous or intramuscular. The weekly dose can be increased to a maximum of 25 or 30 mg/week. Adminstration is accompanied by a lot of adverse events such as hematologic abnormalities, disturbances in liver enzyme tests and subjective complaints, especially gastro-intestinal problems. Administration of MTX requires regular control of parameters of hematologic cells and liver enzymes. The renal function must be controlled; in case of impairment of the renal function accumulation of MTX will occur resulting in increased toxicity. Both folic acid and folinic acid/leucovorin supplementation resulted in less toxicity-related discontinuation of MTX than placebo.[13] Therefore, co-medication with folic acid (0.5 mg twice daily) is advocated to diminish the number of adverse events.

As mono-therapy MTX has proven to be very successful. The drug is effective in 70%–80% of the active RA patients and more than 50% of the RA patients use MTX even after 5 years. MTX has become the anchor drug for the treatment of patients with RA, as mono-therapy and in almost all kind of combinations with other drugs.[14] Combinations of MTX with other drugs include: 1) sulphasalazine; this combination proved to be disappointing since no synergy could be proven,[15,16] 2) sulphasalazine plus prednisone as part of the COBRA schedule,[17,18] 3) sulphasalazine plus hydroxychloroquine as part of the O'Dell schedule,[19] and 4) in combination with the anti-TNFα agents infliximab[5] and etanercept.[6] Apart from its use in RA, MTX is administered in several other immune diseases, and/or as corticosteroidsparing agent.

LEFLUNOMIDE IN RHEUMATOID ARTHRITIS

Following oral administration, leflunomide is rapidly converted in the gut wall and liver to an active metabolite, A77 1726. Binding of A77 1726 to the enzyme dihydroorotate dehydrogenase results in the inhibition of pyrimidine biosynthesis.[20–22] A consequence of this inhibition is reversible cell cycle arrest in rapidly dividing cell populations such as activated lymphocytes, the immune cels that mediate joint inflammation.[21,23] Elimination of leflunomide takes place through both renal and fecal routes. The mean half-life of leflunomide is from 14–16 days. Administration of cholestyramine in a dosage of 4 g, 3 times daily, reduces the half-life of leflunomide to approximately 1 day, indicating that significant enterohepatic circulation is taking place. Due to the long mean half-life of the active metabolite, a loading dose of 100 mg, taken daily for 3 days, has been suggested to allow patients to reach steady-state blood levels within 4–6 weeks.[24]

Leflunomide was statistically superior to placebo and leflunomide was statistically equivalent to MTX and sulphasalazine in relieving the signs and symptoms in active RA.[25–27] The onset of the treatment's effect occured earlier with leflunomide administration than with other active treatments. Leflunomide, MTX and sulphasalazine were not statistically different from each other in retarding radiographic progression.

Events considered related to leflunomide administration included diarrhea, skin rash, reversible alopecia and asymptomatic liver transaminase elevations. The diarrhea was

generally mild to moderate and caused less than 5% of patients to discontinue treatment. Although the incidence of hypertension was higher in the leflunomide treatment groups the percentage of patients with new-onset hypertension were similar in all active treatment groups, suggesting that leflunomide may aggravate existing hypertension in some persons. Clinically significant elevations of liver transaminases were generally asymptomatic and reversible.

In summary, leflunomide treatment is an alternative to MTX and sulphasalazine and is a wellcome addition to the therapeutic armamentarium for treatment of patients with active RA.

SUMMARY

The two antimetabolites are now established DMARDs. MTX is the anchor drug for the treatment of RA patients and leflunomide is an established DMARD.

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