Rheumatoid arthritis—changing theories and treatment modalities

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Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder with symmetrical polyarthritis as the most characteristic clinical sign. Etiology and pathogenesis of the disease are basically unknown and therefore causal treatment modalities are currently not available. However, recent studies in the field of pathogenesis and therapeutic intervention have provided fascinating and promising data. The present paper focuses on some of these observations.

Clinical observations and their relevance to pathogenesis

Although clinical data are often difficult to interpret, they sometimes can give valuable hints to which pathogenetic mechanisms may be involved. The polyarticular involvement and often striking symmetry of the joints affected, point to the systemic nature of RA. The fact that the distal interphalangeal joints are rarely affected, is an important indication that local factors, indeed, play a crucial role in disease expression and moreover that there are considerable differences in structure and/or function of individual diarthrodial joints.

With respect to the synovium, it has been noticed that (early) synovectomy is often not successful in that inflammation may recur. As mentioned above it is striking that similar, be it not identical, structures like pleura and pericardium are often affected. For various, mainly practical reasons, data on the earliest alterations in the synovium are virtually lacking, this being a major obstacle for further insight into what initiates the disease.

Some clinical observations point to a major role for cartilage, at least in the perpetuation of the disease: joints, in which all cartilage has been eroded, often show disappearance of inflammation ('burned out joints') and after joint arthroplasty, synovial inflammation usually wanes away spontaneously (Boerbooms et al. 1982). On the other hand there is the observation that synovium-like structures of tendon sheaths and bursae are also frequently involved, indicating that the presence of cartilage is not a sine qua non for sustaining inflammation.

An intriguing phenomenon is that sometimes, although rarely, radiographic cartilage and bone destruction is seen without apparent clinical inflammation. However, recent clinical trials with disease modifying drugs in early rheumatoid arthritis indicate that there is a definite decrease in radiographic progression, when inflammation is effectively suppressed, suggesting that the inflammatory process is at least the major factor in joint destruction. Although the presence of rheumatoid factor has definitely been associated with a more severe disease course, the role of rheumatoid factor in the pathogenesis of RA is as yet uncertain. One interesting study in experimental animals has suggested that rheumatoid factor may amplify existing inflammation (De Horatius and Williams 1972).

Current hypotheses

Until recently it was thought for a variety of reasons that T cell immunity was at the heart of the etiopathogenesis of rheumatoid arthritis (Panayi et al, 1992). However, some problems with this hypothesis have come up; the T cells present in the synovial tissue are apparently not very active and in addition, anti T cell therapy of different kinds have so far not shown to be very effective.

Recently Firestein and Zvaifler (1990) have provided arguments that it is the (synovial) macrophage, rather than the T cell that orchestrates the whole inflammatory process. At least compatible with that view, may be the recent observation that interfering with TNF α has a dramatic, be it transient, effect on the disease activity.

This of course does not exclude the possibility that later on specific immunity, for instance to cartilage antigens, plays an additional role.

Treatment of rheumatoid arthritis—towards disease control?

Pharmacotherapy of rheumatoid arthritis (RA) has changed considerably in recent years. An increasing number of patients are now treated with second line agents in an earlier phase of their disease. In addition, the number of second-line agents has increased, including now the rediscovered drugs sulphasalazine and methotrexate, which have become increasingly popular, because of their relatively fast mode of action and favourable drug survival curve. Short term data suggest that these therapies really result in retardation of disease progression and long term studies are currently on the way. Below we will deal with some aspects of pharmacotherapy of RA, with a focus on new promising developments.

Pharmacotherapy of rheumatoid arthritis

Drugs used in the treatment of RA can be divided in first-line and second-line drugs. The former category consists of non-steroidal anti-inflammatory drugs (NSAIDs). These drugs have an analgesic and anti-inflammatory effect with a rapid onset of action, but in general do not influence the disease process itself. The drugs in this group have a roughly comparable pattern of efficacy and toxicity.

In sharp contrast with the considerable number of NSAIDs is the small number of drugs, belonging to the category of second-line drugs. These drugs differ from each other with respect to efficacy and toxicity and have a characteristic slow onset of action (4–12 weeks) and in some way or another influence the disease process. Recently a new classification of anti-rheumatic therapy has been proposed catagorizing drugs according to their effects into symptom-modifying antirheumatic drugs (SM-ARDs) and disease-controlling antirheumatic therapy (DC-ART) (Edmonds et al. 1993). The NSAIDs and corticosteroids belong to the SM-ARDs; second-line drugs, depending on their effects on radiographic progression and functional outcome could be assigned to either SM-ARDs or DC-ARTs.

Efficacy of second-line drugs

Drugs that have been shown to be at least clinically effective in placebo controlled and comparative trials are listed in Table 1. The efficacy of second line drugs can be demonstrated at several different levels, as discussed below.

At a clinical level a minimum requirement for efficacy is a beneficial effect on the symptoms and signs of arthritis. After a few weeks or months of therapy with second-line agents, a decrease of the number of painful and swollen joints can be observed. Through this the total amount of pain and stiffness as well as fatigue diminishes. No clear-cut effects of second-line agents have been shown on extra articular manifestations. In terms of laboratory variables, treatment with second-line drugs nearly always leads, among other effects, to suppression of the acute phase response, improvement of the hemoglobin level and a (slow) decrease of the rheumatoid factor titre. An exception seems to be azathioprine, which can influence clinical activity without affecting, for example the ESR.

Recently, certain second-line drugs, such as sulphasalazine and methotrexate have been shown to retard radiographic progression of destructive joint lesions (van der Heijde et al. 1989; Jeurissen et al, 1991). It has been demonstrated for sulphasalazine that this effect can be sustained for at least a period of 12 to 36 months (van der Heijde et al. 1990).

As a result of the above mentioned effect, an improvement in functional outcome, predominantly demonstrated with self-administered questionnaires, has been observed for nearly all second-line drugs.

Why is the efficacy of second-line drugs disputed?

Despite these effects of second-line agents on process and outcome variables, their long term efficacy is being disputed by a number of rheumatologists. Although shortcomings in study design (such as patient selection, retrospective nature of the study or the lack of a control group) may have contributed to the negative opinion about the long term efficacy of second-line drugs, this probably is not the only, or even main, cause for the controversy.

The most important reason for this therapeutic nihilism may relate to the small number of second-line agents available (at least until recently), their fre-

Table 1. Second-line agents for rheumatoid arthritis

Azathioprine
Cyclophosphamide
Cyclosporine
Hydroxychloroquine
Methotrexate
Oral gold (auranofin)
Parenteral gold (aurothioglucose or sodium aurothiomalate)
Penicillamine
Sulphasalazine

quent toxicity and (as a result) their conservative use. This means that these drugs were instituted at a time that the disease process had already caused considerable joint damage (see below).

The most important disadvantage of all second-line drugs is the high percentage of, sometimes serious, adverse reactions. This is the main reason why after a few years only a small percentage of patients are still being treated with their original second-line drug (Wolfe et al. 1990). In the years before 1980 only a few second-line agents were available, which influenced the timing of the treatment. At that time it was customary in many institutions to treat patient with early active rheumatoid arthritis with NSAIDs only, at least for 6 to 12 months, before adding a second-line drug. In addition in case of marginal efficacy, treatment with a second-line agent was continued as long as possible for want of anything better. In general the principle "go low, go slow" was supported. Moreover, in the absence of a sufficient number of second-line drugs, it was practically impossible to suppress disease activity effectively over longer time periods.

Since all studies evaluating the long term efficacy of second-line agents were started in this period, it is not surprising that negative conclusions about the efficacy of second-line drugs were reached. However, in the last decade the armamentarium of second-line agents has increased considerably, making it possible to treat patients for longer periods. Besides, some of these agents, such as sulphasalazine and methotrexate, have a faster mode of action and in addition a better drug continuation rate. These facts, as well as newly appreciated data on the disease course of rheumatoid arthritis (van der Heijde et al. 1992), led to the growing insight that the disease probably should be treated as early as possible.

Fast mode of action is important

The "traditional" second-line agents, including hydroxychloroquine, parenteral gold and penicillamine, usually become effective 3 to 6 months after starting these drugs. In contrast, the "new" drugs sulphasalazine and methotrexate, may already show clinical efficacy after 3 to 6 weeks.

Apart from patient and doctor's satisfaction, this has the great advantage of easier handling and titration of therapy. The fact that already at 6 weeks a yes/no answer in terms of clinical efficacy is obtained, implies that dose adjustment can be done earlier and therefore optimal efficacy be earlier obtained. That fast mode of action may be of crucial importance as suggested by data of a comparative study of hydroxychloroquine and sulphasalazine showing that at 48 weeks both drugs were comparable in clinical efficacy, but that the latter drug had a significant earlier effect, leading to less progression of radiographic joint damage (van der Heijde et al. 1989). The other side of the coin is that stopping fast acting second-line drugs may result in a rapid flare, which in our experience may also have an unexpected positive effect, i.e. that the patient is really motivated to restart and continue medication.

Early treatment

In the past, treatment with second-line drugs has frequently been postponed to a later phase of the disease because of the fear of serious adverse effects. However understandable this may be, it should be noted that the adverse effects of second-line drugs are almost always reversible, whereas joint damage is virtually never reversible. This fact is now increasingly appreciated and has led to earlier treatment.

There are, however, other observations in favour of early treatment. First, it has been shown that a considerable amount of radiographically detectable damage in RA occurs in the first years of the disease (van der Heijde et al, 1992), Secondly, recent studies have indicated that especially in the early phase of the disease, radiographically detectable damage (which usually underestimates actual damage in the joint) can be favorably influenced by early treatment with second-line agents (van der Heijde et al. 1989). Another important argument for early treatment comes from recent studies by Pincus et al. (1992), who demonstrated that RA is not a benign disease and that apart from morbidity, there is considerable mortality associated with the disease. The number of swollen joints was one of the important risk factors for mortality in this study. It might therefore be possible that adequate treatment of joint inflammation may ultimately improve patient survival. Studies to detect such an effect are currently on the way.

Probably the most important aspect of early treatment of RA and the availability of a range of second-line drugs is that such "early and aggressive" therapy increases the number of years for which patients are adequately treated and therefore experience a better quality of life.

Combination therapy

Despite improvements in pharmacotherapy, there are still a considerable number of patients which are difficult to treat with a single second-line agent. Therefore different combinations of second-line agents have been studied. As in oncology, where individual drugs often perform poorly, the combination of various drugs was thought to be potentially addi-

tive or even synergistic. Studies, many of them uncontrolled, so far have been unimpressive. Recently, data have been obtained, suggesting that the combination of sulphasalazine and methotrexate may be better than either of the individual drugs (Haagsma et al. 1994). In the near future data from ongoing controlled studies will become available.

Biologic agents

Fascinating data have been obtained in studies using biological agents directed against molecules or cells, thought to play an important role in the immuno-inflammatory process. Interestingly, until now, T cell directed therapies have not shown definite clinical efficacy, although it was generally believed that the T cell was at the heart of the rheumatoid joint inflammation. Promising results have recently been published on the use of anti-TNF monoclonal antibodies. In a controlled trial these antibodies were able to significantly influence a number of disease activity variables in RA (Elliot et al. 1994). An important observation was that the clinical effect lasted from weeks to, in some cases, months. Although the potential of these agents for clinical use is still uncertain, these observations suggest that interfering with certain targets of the immuno-inflammatory process is possible, effective and so far without major side effects.

Disease monitoring should be improved

Summarizing the above data it appears that in the last decade definite improvement has been made in the pharmacotherapy of RA. Second-line agents with improved treatment characteristics, namely sulphasalazine and methotrexate, are now widely used in a relatively early phase of the disease, and have been shown to retard progression of radiographic joint damage in the short and middle term. In addition, promising results have been obtained with biologic agents, the most important currently being anti-TNF monoclonal antibodies. To take optimal advantage from these improved treatment modalities, it now becomes mandatory to further develop relevant measures for monitoring the disease process. This means better variables for both inflammatory and destructive processes, not only at the clinical, but also at the molecular level.

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