Predominant cell types involved in synovial inflammation include activated lymphocytes, macrophages, monocytes and neutrophils. Concurrent with the increased cellularity is an increased expression of proinflammatory mediators (i.e., cytokines and chemokynes) and of adhesion molecules.

Whether such autoantigens initiate the T-cell activation cascade and the consequent inflammatory changes, or step in at a later point in time to bolster and/or perpetuate the process, is unknown.

The T cells infiltrating the synovial membrane are primarily CD4+ memory cells, which produce IL-2 and IFN-α to a similar extent as antigen-triggered T cells and so clearly have a Th1 bias5.

These T cells, by cell-cell contact through CD11- and CD69-mediation - and activation by different cytokines, such as IFN-γ, TNF-α and IL-17, activate monocytes, macrophages and synovial fibroblast. These latter cells then over-produce pro-inflammatory cytokines-mainly TNF-α, IL-1 and IL-6 which seem to constitute the pivotal event leading to chronic inflammation6.

The role of B cells and autoantibodies, and/or immune complexes, could lie in the propagation and enhancement of the inflammatory process: it has long been known that complement is activated in RA synovial fluids and complement components are even locally produced7.

Within the past 3-4 years biological response modifiers (BRMs) that target specifically the proinflammatory cytokines interleukin-1 (IL-1) or tumor necrosis factor alpha (TNF-α) have been introduced into clinical practice. These cytokines play a crucial role...
in mediating the complex pathogenesis of RA. In several clinical trials, BRMs have been demonstrated to be effective in controlling the symptoms and signs of RA and in retarding joint destruction.

Safety of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Aspirin
The usual dose of aspirin for rheumatoid arthritis is about 3.6 grams per day. The salicylate level should range between 15 and 30 mg/dl. Because aspirin may be irritating to the stomach and duodenum, buffering agents have been added or modifications have been made to the aspirin molecule. Significant gastrointestinal bleeding with aspirin therapy is quite unusual, but endoscopic erosions are common. The drug produces a mild bleeding tendency by interfering with platelet thromboxane A2. Aspirin is an effective and valuable drug. However, the newer NSAIDs are used more commonly than aspirin today because of fewer gastrointestinal side effects and lack of ototoxicity, including tinnitus.

Other Nonsteroidal Anti-Inflammatory Drugs
All these drugs antagonize the enzyme cyclooxygenase and interfere with production of prostaglandins. These drugs are rarely sufficient by themselves to control rheumatoid arthritis. Usually they should be combined with a disease-modifying drug. NSAIDs need to be taken on a regular basis to maintain good blood levels. If this is difficult because of adverse events, such as gastrointestinal distress, the drugs may need to be changed or dosage reduced.

Corticosteroids
Prednisone and other corticosteroids are extremely effective anti-inflammatory drugs. However, they have not been shown to prevent bone erosion or joint damage, and they are associated with a considerable number of side effects when used over a long period of time. Corticosteroids cause iatrogenic Cushing’s disease (osteoporosis, cataracts, weight gain, moon-shaped facies) insomnia, myopathy, secondary diabetes, hypertension, glaucoma, muscle weakness, increased blood lipids and other alterations.

These molecules should be limited to those patients whose disease is uncontrolled despite thorough trials of other drugs and who must have relief of uncontrolled arthritis.

Intra-articular steroid injections are a valuable, often essential part of the treatment in patients with rheumatoid arthritis. Long-acting intra-articular preparations include triamcinolone, dexamethasone acetate, betamethasone, and prednisolone tebutate.

Safety of Conventional DMIRIDs

Organic Gold Compounds
These drugs have been used for the RA treatment with the benefits of therapy being well documented in their study compared with weekly administration of parenteral gold (50 mg) with weekly administration of i.m. methotrexate (15 mg): a higher number of patients obtained a clinical remission of the disease following gold therapy. Adverse events, such as cytopenias, mucocutaneous reactions and proteinuria, have limited the use of these compounds. It has been estimated that after 5 years of parenteral gold treatment only 15-20% of RA patients remain on therapy. About 60% of the patients discontinued drug administration on account of toxicity.

Sulphasalazine
This drug has a wide range of toxic effects. It has been documented that about 30% of RA patients discontinued the treatment because of adverse events. Some authors reported, in an analysis of six controlled trials, that adverse events withdrawals were about 3-fold greater with sulphasalazine compared with placebo. Adverse events include nausea, vomiting, aplastic anemia, neutropenia, reversible infertility in men, hemolysis, headache, rash, and malaise.

Methotrexate
Methotrexate (MTX) is better tolerated and more efficacious than other DMARDs such as gold salts, parenteral gold, penicillamine, azathioprine and hydroxychloroquine. Furthermore, a far longer percentage of patients remain on MTX for longer periods of time when compared to these older
DMARDs. Side effects of MTX include stomatitis, gastrointestinal intolerance and bone marrow suppression as well as idiosyncratic drug hypersensitivity reaction resulting in lung injury and liver damage.

Hydroxychloroquine
Hydroxychloroquine interferes with antigen processing, leading to reduced stimulation of CD4+T cells resulting in down regulation of autoimmune response. This drug has been used in early, mild disease primarily because it is relatively safe.

Leflunomide
Leflunomide is a new class of DMARDs and is converted on first-pass metabolism through the liver into its active metabolite (A77 1726), which has immunomodulatory and antiinflammatory effects.

In a five-year follow-up multinational study, Kalden et al. reported the efficacy and safety of leflunomide in a cohort of RA patients treated with 10 or 20 mg/day of the drug. Regarding clinical efficacy, of the 214 patients entering the open-label study, 163 (76.2%) received treatment until the study end point. The duration of morning stiffness was reduced at year 1 (mean 24.7 minutes) compared with baseline (mean 145.2 minutes) and this improvement was maintained until year 4 or the end point (mean 46.4 minutes). Improvements in the mean CRP level, ESR, and rheumatoid factor level compared with baseline (3.9 mg/dl, 50.3 mm/hour, and 295.1 units/ml, respectively) were documented at year 1 (1.3 mg/dl, 34.3 mm/hour, and 153.4 units/ml, respectively) and were maintained until year 4 or the end point (1.2 mg/dl, 33.4 mm/hour, and 176.1 units/ml, respectively).

Of the 214 patients, 85.5% of these (183) experienced 1 or more treatment-emergent primary adverse events; the most common were upper respiratory tract infection (23.4%), diarrhea (8.4%), back pain (6.5%), and pain in a extremity (6.5%). Safety data regarding changes in laboratory values were available for only 182 patients in this study because baseline laboratory values were not available for 32 patients. Abnormal findings on liver function tests did not resolve. Most patients had normal leukocyte counts at baseline and at the end point. High leukocyte counts at baseline were observed in 39 cases (21.4%), but these failed to normalize by the end point in only 11 patients. The majority of patients had normal platelet counts at both baseline and the end point. Seventy-three patients (40.1%) had a high platelet count at baseline, which normalized by the end point in 56 cases (30.8%).

The safety profile of leflunomide in this open-label, noncontrolled, multinational study is consistent with that reported in the previous studies: no new or different types of adverse events emerged during continued long-term leflunomide treatment.

Safety of Biological Response Modifiers (BRMs)

Because of the toxicity and limited efficacy of non-steroidal antiinflammatory drugs (NSAIDs), corticosteroids, and disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, sulfasalazine and hydroxychloroquine, there was a need for the development of new, effective and well tolerated agents for the long-term management of RA. These include molecules that block either TNF-α (e.g., infliximab, etanercept) or IL-1 (e.g., anakinra).

TNF-α plays a crucial role in inflammation. It initiates production and secretion of a cascade of mediators such as cytokines and adhesion molecules. Inhibition of TNF-α results in a decrease in adhesion molecules and pro-inflammatory cytokines, as well as regulation of chemokines.

Actually, two compounds are available to neutralise the biological action of TNF-α: a monoclonal antibody (infliximab) and a soluble TNF receptor (etanercept).

Although the role of TNF-α in the human immune response to mycobacteria is incompletely understood, in animal models TNF-α plays a crucial role in the formation of granulomata and containment of disease. There are now a large number of reports of tuberculosis in close temporal association with the initiation of TNF-α inhibitors, as compared with available data on background rates. Although passive surveillance data do not
prove a causal relationship between infliximab and tuberculosis, the association is not thought to be coincidental. In most instances, tuberculosis appears to be secondary to reactivation of latent infection25.

Concerning IL-1, this cytokine is produced by monocytes, macrophages, endothelial cells, B cells and activated T cells. To determine the effects of interleukin-1 receptor antagonist (IL-1ra) on inflamed synovial tissue in a group of RA patients has been demonstrated by synovial biopsy a notable reduction in intimal layer macrophages and subintimal layer macrophages and lymphocytes after treatment with this molecule27. Down-regulation of the cell adhesion molecules E selectin, vascular cell adhesion molecule-1, and intercellular adhesion molecule-1 also are associated with IL-1ra. Expression of these molecules is regulated by IL-128. In addition, the apparent arrest of progressive joint damage is significantly associated with the cessation or reversal of intimal layer macrophage accumulation. These observations represent the inhibition by IL-1ra of biologically relevant IL-1 mediated pathogenetic effects and may help explain some of the critical mechanism involved.

**Infliximab**

Infliximab is a chimeric immunoglobulin Ig1 monoclonal antibody that neutralizes the biological activity of TNF-α by binding with high affinity to soluble and transmembrane forms of TNF-α and inhibiting binding of TNF-α to its receptors29,30. More recent studies have demonstrated that TNF blockade using infliximab not only ameliorates acute findings of inflammation but also inhibits joint destruction over a period of at least three years31.

A placebo-controlled trial confirmed efficacy of infliximab in RA with a 60 to 70% decrease in measures of disease activity32. A similar study repeated treatment cycles of the drug either as monotherapy or combined with methotrexate confirmed safety and the fact that MTX protects against the development of human anti-chimeric antibodies (HACA)s33.

A 102 week placebo controlled trial investigated the clinical response, x-ray progression and change in patient function of infliximab in a population of RA patients with an incomplete response to methotrexate24. Repeated infusions occasionally were associated with flushing, headache or rash. No increased risk of serious infections or sepsis was observed. The development of tuberculosis, as well as other fungal infections, has been reported postmarketing with the use of infliximab: anti double stranded DNA, has been reported in 7% of patients treated with infliximab, but clinical lupus was rare34.

Despite the convincing clinical benefit of the TNF-blocking agents in RA, several questions remain unanswered. Reports of severe mycobacterial infections point to compromise intracellular killing of bacteria35.

**Etanercept**

Etanercept is a recombinant protein consisting of human p75 tumor necrosis factor receptor (TNFR) fused to the Fc fragment of human immunoglobulin G1. The molecule has increased TNF binding affinity, a longer half-life and more potent TNF inhibitory activity both in vitro and in vivo.

Etanercept has been studied in randomised, double-blind, comparator studies in adult patients with RA who did not respond to treatment with DMARDs, as sole treatment and in combination with methotrexate. A 3 month trial included patients with active RA who did not respond to treatment with DMARDs, as sole treatment and in combination with methotrexate. Patients were evaluated at baseline and then every 2 weeks for the next 3 months and were randomly assigned to one of four treatment groups: placebo or etanercept 0.25, 2 or 16 mg/m². Study drug was administered twice weekly by subcutaneous injection. The results of study showed a significant dose response relationship. Most of the patients treated with the highest dose of etanercept completed the study. The only adverse effects reported were wild, transient injection site reactions and mild upper respiratory infections that resolved on continued therapy with etanercept. This trial showed that the molecule particularly in the 16 mg group was very efficacious in patients with refractory RA and had a relatively benign safety profile.

**Anakinra**

An association between interleukin-1, joint inflammation, and joint damage has been observed in studies of rheumatoid arthritis. IL-1 is produced by macrophages that accumulate
at the cartilage-pannus junction and in the lining and sublining layers of the synovial membrane.

Recombinant human IL-1 receptor antagonist (IL-1ra) treatment has been evaluated in experimental models of arthritis, and dramatic therapeutic effects have been observed. IL-1ra is generally well tolerated. Injection site reaction was the most frequent adverse event, reported in 25% of patients receiving placebo and 81% of patients receiving the maximum dose of IL-1ra (150 mg/d) in the randomized clinical trial. Premature withdrawal among patients receiving IL-1ra occurred in 24% of patients receiving the 30 mg dose, 22% of patients receiving 75 mg, and 28% of patients receiving 150 mg. Injection site reactions accounted for the greatest number of withdrawals, particularly among patients receiving higher doses of IL-1ra. Other adverse events, including infections, were uncommon. The adverse events observed during the combination study with MTX were similar in frequency and severity to those seen in the randomized clinical trial.

A nticytokine therapy offers new hope to those suffering from RA. The prospect of specifically targeting and modulating the effects of key proinflammatory cytokines or destructive mediators in a complex pathogenic network may represent a new therapeutic era. These observations strongly suggest a potential role for IL-1ra as a novel therapeutic modality in the future management of RA. Further phase III studies are in progress.

In conclusion, the goal of RA therapy is to induce the complete remission of the illness using immunosuppressive drugs or the sinergism of drugs that could interfere with the inflammation process.

Safety data from clinical studies are the only means to evaluate adverse events due to long-term treatment. The available results, evaluating numerous RA patients, suggest that BMRs treatment is fairly tolerated. The improved tolerability profile of BMRs is in contrast to those of older DMARDs. In fact, these last agents are associated with significant adverse events, including bone marrow suppression and hepatic and renal dysfunction.

Adverse events emerged during molecules treatment in RA are reported in Table II.

Unfortunately, we cannot compare the clinical trials conducted with infliximab, etanercept and anakinra, and with DMARDs. The

<table>
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<th>Table I. Treatment of rheumatoid arthritis.</th>
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<tr>
<td>1. Use a full dose of one NSAID (avoid using two NSAIDs, simultaneously)</td>
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<td>2. In most cases add a disease-modifying drug. Generally, patients need two medications (e.g., NSAID plus methotrexate)</td>
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<tr>
<td>3. Intra-articular steroid injections, when needed</td>
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<td>4. Oral corticosteroids (with vitamin D plus calcium or other anti-osteoprotic drugs)</td>
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<td>5. Physical therapy and rest</td>
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<td>6. Biologic agents</td>
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<td>7. Surgery</td>
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<th>Table II. Side effects of DMARDs and biologic agents in RA.</th>
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<td><strong>Molecules</strong></td>
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<tr>
<td>Organic gold compounds</td>
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<tr>
<td>Sulphasalazine</td>
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reasons for this is that the trials were all conducted in different patient populations who had different disease characteristics. In addition, there were significant differences in study design. Direct comparison of the safety and efficacy of the new biologics and older DMARDs are difficult to make. Further investigations are required to accurately assess the efficacy and safety of the new biologic agents in relation to one another.

However, the relative lack of systemic adverse events associated with these agents is promising. The safety profile, combined with the demonstrated efficacy, suggests that these drugs have the potential to play a crucial role in the treatment of patients with rheumatoid arthritis.

References

20) Villiger PM. Zytokine und rheumatische Erkrankungen. 1998 Verlag Hans Huber, Bern.


