Progress in the treatment of rheumatic disease

Angela Gause

Department of Rheumatology, University of Lübeck, D-23538 Lübeck, Germany

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Introduction

The progress in defining the immunological and inflammatory mechanisms that lead to the progressive joint destruction in rheumatoid arthritis (RA) [1,2] has led to the development of new inhibitory drugs. Large randomized controlled trials have shown the efficacy of the new treatments and led to the recent approval of several new drugs by American and European health authorities. These are the COX2 inhibitors rofecoxib and celecoxib, the anti-metabolite leflunomide, and the ‘biologicals’, the TNFα neutralizing substances etanercept and infliximab and the IL1-receptor antagonist anakinra. At the same time, epidemiological investigations have started to describe the socio-economic consequences of inflammatory joint diseases, which often start at a young age and lead to retirement in 50% of the patients in the initial 3 years of the disease [3]. Analysing the outcome of patients with RA, responsive or not to methotrexate (MTX) treatment, it could be shown that compared with age-matched healthy persons, patients with RA without efficient treatment have a >4-fold increased standardized mortality ratio. This is reduced to 1.5-fold by MTX and probably other efficient treatments [4]. For the evaluation of the patient before and during treatment, the DAS28 (disease activity score) has been developed as a standardized evaluation instrument using the swollen and tender joint count of 28 joints, the serologic inflammation and the patients self assessment of pain [5]. Since the nephrologist will see many patients with rheumatic disorders, it is useful to stay updated on recent progress in rheumatology.

Cox2 inhibitors in the treatment of rheumatic disease

Selective COX2 inhibitors have been developed with the aim to treat pain and swelling by inflammation efficiently and without the side effects, especially at the gastrointestinal tract, seen with standard non-steroidal anti-rheumatic (NSAR) drugs. For rofecoxib as well as for celecoxib, a 50% reduction of the risks for bleeding of the upper gastrointestinal tract has been shown for large cohorts. Peripheral oedema, decreased renal
function and cardiac insufficiency, however, are also reported during COX2 inhibitor therapy. For RA the COX2 inhibitors have a role in the initial phase for amelioration of arthritis before the definite diagnosis is established. Especially in patients aged over 60 years, patients with anti-coagulation and in cases of contraindications against steroids COX2 inhibitors are useful [6]. In principle, a disease-modifying therapy with the so-called DMARDs (disease-modifying anti-rheumatic drugs) or LAARDs (long-acting anti-rheumatic drugs) is to be instituted in every patient with RA, as soon as the diagnosis is established. This therapy should be so effective that glucocorticosteroids (GC) or NSAR are not necessary. Therefore, the German word ‘Basis-therapie’ for the treatment with DMARDs is not a bad descriptive, because it should be the basis of every treatment in RA.

**Standard therapy and combination therapy of RA**

The introduction of MTX into the therapy of RA has been the most important improvement in anti-rheumatic therapy in the last 30 years [7]. MTX is the drug of choice for every patient with the diagnosis of RA with bone erosions. In early non-erosive RA, sulfasalazine (SSZ) is efficient and safe; in very mild forms the anti-malarial hydroxychloroquine (HCQ) can also be used. A disadvantage of SSZ and HCQ is that both medications need to be applied for at least 12 weeks before they can be judged as ineffective. Furthermore, SSZ must often be given in a dose of 3 g/day. As long as there are no contraindications against GC all DMARDs are initially combined with prednisolone, which targets pain and stiffness of the patient and has been shown to reduce long-term joint damage [8]. The dose of prednisolone should be lowered to <10 mg/day as soon as possible and it should be accompanied by calcium and vitamin D for prophylaxis of osteoporosis.

If SSZ alone is inefficient, therapy is switched to MTX. Whenever MTX alone is inefficient it can be combined with SSZ and HCQ with a significant rate of improvement without increase in toxicity [9]. A further efficient combination with MTX is the additional application of cyclosporine A (CyA) in a dose of 2.5–3 mg/kg body weight. The response can already be expected within 6 weeks, the use of CyA is, however, limited by its renal toxicity [10].

**Leflunomide**

As an inhibitor of the de novo pyrimidine synthesis, leflunomide (LFN) has been shown to block the proliferation of activated lymphocytes, an additional inhibitory effect on TNFα production in vitro has been demonstrated. For the treatment of RA, LFN is characterized by its fast onset of action after ~4 weeks with further improvement up to 1 year. Its effect on swollen and tender joint counts and on radiologic progression has been demonstrated [11,12]. Main side effects are diarrhea, nausea, rash and alopecia. LFN is a first line drug in patients with intolerance of MTX and those with renal insufficiency, because of its main gastrointestinal mode of excretion. The combination with MTX is possible when liver function and peripheral blood counts are carefully monitored.
TNFα neutralizing substances

TNFα has a key function in the inflammatory process by its action on macrophages for the production of further proinflammatory cytokines and chemokines, on endothelial cells for expression of adhesion molecules, on hepatocytes for production of acute phase reactants, and on fibroblasts and chondrocytes for the synthesis of growth factors (e.g. VEGF). It leads to increased activity of matrix metalloproteinases and decreased collagen production [1,2].

Neutralization of TNFα by the TNF-receptor-construct etanercept [13,14] as well as the chimeric monoclonal antibody infliximab [15,16] has profound effects on all activity parameters of RA with often extremely fast remission of inflammation and joint counts. Also, in the long term, the effect on inflammatory activity is sustained and the radiologic progression as a parameter of joint destruction is significantly reduced. The rate of infections in patients with etanercept is not increased compared with the control group treated with conventional DMARDS in the clinical trials [17]. An alarming high absolute number of cases with tuberculosis has been registered under the treatment with infliximab mainly in Europe [18]. The tuberculosis occurs mainly in the first 3 months after the start of infliximab treatment and is thought to be due to reactivation. It is recommended that an X-ray of the thorax and a purified protein derivative of tuberculosis (PPD) test are performed before treatment, and that only negative patients are treated or when treatment is inevitable INH prophylaxis is administered.

As anti-TNF therapy is expensive and long-term toxicities unknown, it is recommended by the German Society for Rheumatology that besides the firmly established diagnosis, patients should have been treated with at least two DMARDS, one of the two being MTX, with an adequate dose and duration (in general 6 months).

Extremely positive results have been obtained with anti-TNF treatment of ankylosing spondylitis and psoriatic arthritis. A third TNFα neutralizing fully humanized antibody will be available in the near future. Etanercept as well as infliximab have been used successfully in ANCA-associated vasculitis and should be further investigated for these indications.

Immuno-adsorption

For refractory cases of RA, immuno-adsorption with a protein A column has been applied with reasonable success and without major side effects [19]. The use of this treatment can be offered in desperate cases.

IL-1-receptor antagonist and further perspectives

Since this year, the recombinant IL-1-receptor antagonist anakinra [20] is available as another biological treatment option for patients still active under classical DMARDs. This drug has to be injected every day and is applied in addition to any other DMARD, mainly MTX. The most important adverse events are strong skin reactions at the injection site. Long-term effects have not yet been reported.

For desperate disease courses the application of autologous bone marrow transplantation is already applied, here further controlled studies are justified [21]. Further therapeutic approaches for the future imply the application of recombinant IL10, IL4 and antibodies against CD20 and CD40. Combinations of the classical DMARDs with new immunosuppressive drugs as mycophenolate mofetil and rapamycine are discussed and oral inhibitors of the TNF processing enzyme [TACE (TNFα-converting-enzyme) inhibitor] are in development [22,23]. Immunologic approaches also aim at vaccine development with T-cell receptor or MHC specific peptides and somatic gene therapy for local interference with inflammation is being developed in animal models [2,24].

Conclusions

The modern therapy of inflammatory arthritis (Figure 1) has improved the prognosis for many patients. For those (~5%) also unresponsive to modern treatment, special care and research is necessary [25].

References