Review

Current management

Management of rheumatic diseases in the era of biological anti-rheumatic drugs

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New treatment strategies (i.e. early treatment with various combinations of drugs administered according to the continuously reorientating "sawtooth" principle), the availability of new conventional and biological anti-rheumatic drugs and access to ultrasound-guided liberal use of intra-articular glucocorticosteroid injections have revolutionized the treatment of rheumatic diseases. The greatest gains can be achieved when early cases with difficult and active disease are treated, before permanent destruction and joint deformities have developed. This means that the rheumatologist has an important role in planning the treatment of newly diagnosed patients. In the long run, this treatment policy may lead to a reduced need for joint replacements and other types of surgery. The use of biological anti-rheumatic drugs is associated with iatrogenic complications including skin reactions, infections, infusion reactions and autoimmune manifestations.

The management of rheumatoid arthritis has changed

Drug treatment of rheumatic diseases has changed, and is nowadays based on early treatment, combination treatment, the continuously reorientating sawtooth principle and the use of new biological anti-rheumatic drugs. The sawtooth strategy refers to evidence and experience-based changes of drug combinations in a "zig-zag" manner at intervals of a few months if a satisfactory treatment response has not been obtained. In addition, intraarticular glucocorticosteroid injections are being used more extensively than before.

Initiation of treatment early during the course of the disease is at best done in so-called Early Arthritis Clinics. In the Nordic countries, it is recommended that doctors from the basic healthcare system should send arthritis (synovitis and synovial effusion, spondyloarthropathies) patients without delay to a specialist in rheumatic diseases. The pyramid of the treatment of rheumatoid arthritis was lying very stable on its wide foot, but has now been inverted upside-down, steadily standing in its new bottom up position. Earlier, the treatment was initiated with symptomatic non-steroidal anti-inflammatory drugs (NSAID). If this was not helpful, one disease-modifying anti-rheumatic drug (DMARD) was added (monotherapy), usually aurothiomalate (gold) intramuscularly. If even this was not helpful, a cytostatic drug, usually azathioprine, was added. A step-up model was applied and the rheumatoid patient was kept in basic healthcare for as long as possible.

Nowadays, in the optimal situation, patients who contract seropositive, polyarticular rheumatoid arthritis receive effective combination treatments early during the course of the disease. For exam-

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ple, a combination consisting of methotrexate, sulphasalazine, hydroxychloroquine and prednisone is effective. With the use of properly selected DMARD combinations, adverse events are not any more frequent than with high-dose single-drug therapies. This is perhaps because the individual drugs in these combinations affect disease cascades at different checkpoints in a synergistic manner, making it possible to use them in relatively low doses. If the medication does not lead to an adequate clinical treatment response within three months (due to the slow starting effect of the anti-rheumatic drugs), a new drug is added or a new combination is tried. Several new conventional (leflunomide) and biological (tumor necrosis factor blockers, interleukin-1 receptor antagonists, anti-CD20 B cell therapies) anti-rheumatic drugs have already become available and interesting new drugs modulating mast cells and adhesion molecules are already in the pipeline. This makes the number of different potential permutations and combinations of drugs very high. Ultrasound is being used increasingly for diagnosis of joints that remain active in spite of systemic medication, and for guided corticosteroid injections. These new strategies emphasize the role of the rheumatologist in the process of planning evidence-based, individualized treatment strategies for patients.

The main function of a general practitioner is 1) to send new arthritis patients to a rheumatologist as early as possible, and 2) to take care of the follow-up of these patients when they are returned back from the specialist for follow-up of the medication and disease. As long as the drug combinations are being changed and the patient needs close and preferably structured follow-up, she is seen by the rheumatologist. If the patient attains remission, the rheumatologist refers the patient to a general practitioner for drug safety controls, although such patients are usually also seen by a rheumatologist every 1–2 years. This allows radiological examinations to detect eventual structural damage, indicating changes in disease management—e.g. consultation of the orthopaedic or rheumatoid surgeon. It is suspected that local joint tissue destruction may proceed in spite of a good control of the systemic inflammation.

Biological anti-rheumatic drugs, mabs and septs

Almost without exception, conventional anti-rheumatic drugs were invented by chance, when some other disease such as syphilis and malaria was being treated. In contrast, the new biological anti-rheumatic drugs have been produced as a result of rational drug development and have well-defined and specific molecular sites of action.

Infliximab (Remicade) is a chimeric tumor necrosis factor-α-specific antibody (Maini et al. 1999, Lipsky et al. 2000). TNF-α is an effective proinflammatory cytokine with multiple effects ranging from upregulation of endothelial cell adhesion molecules and proteinases to stimulation of osteoclastogenesis. Infliximab treatment should be started by a rheumatologist or an expert in the field. Initially, 3 mg/kg is given in a 2-hour intravenous infusion at 0, 2 and 6 weeks, and every 8 weeks thereafter. The dose can be increased to 10 mg/kg, or the infusion interval can be shortened if an adequate response is not attained. Infusion must be given under the supervision of a medical doctor. A nurse follows the well-being and any symptoms and signs, as well as the blood pressure of the patient. This is continued for at least one hour after the infusion. Infusion reactions can manifest in form of pruritus, influenza-like symptoms, headache and hypotension. These can be treated with antihistamines, glucocorticosteroids or adrenalin. Occasionally, serum sickness-like symptoms in the form of urticaria, arthralgia and myalgia, abdominal discomfort, breathing difficulties and headache can appear after 1–2 weeks.

Etanercept (Enbrel) is a soluble dimerized human p75 receptor/Fc fusion protein for TNF (Moreland et al. 1997, 1999). This decoy receptor binds TNF-α, but also lymphotoxin or TNF-β. For this and for other reasons, different TNF blockers are not similar and individual patients may benefit from a change of TNF modulator, as stipulated in the sawtooth strategy. In contrast to antibodies, which cross-link cell-surface TNF, blockers of soluble receptors are not effective in granulomatous diseases such as Crohn's disease. Patients take etanercept 25 mg subcutaneously twice a week or lately increasingly often 50 mg (in two 25 mg doses) subcutaneously once a week. Injection site reactions in the form of redness and swelling can

occur. They do not usually require interruption of the treatment, but can be treated with topical corticosteroid ointments.

Chimeric products contain components derived from mice, which are foreign to the human immune system. They can induce formation of human anti-chimeric antibodies (HACA), which may lead to neutralization and dose escalation. This is one of the reasons why TNF modulators are usually not used as monotherapies, but preferentially together with methotrexate or other anti-rheumatic drugs. Furthermore, to increase the efficacy and to cut costs, other biological anti-rheumatic drugs are often also used in combination with methotrexate or other conventional DMARDs. In randomized controlled clinical trials, etanercept has been found to be very effective when used together with metotrexate (Weinblatt et al. 1999). Adalimumab (Humira) is a totally humanized TNF blocker, which has been produced by phage display technology. Although effective as a monotherapy (van de Putte et al. 2004), it is recommended that adalimumab be used in combination with methotrexate (Keystone et al. 2004). Patients take this drug 40 mg subcutaneously every two weeks.

Interleukin-1 receptor blockers are also available for the treatment of rheumatic diseases. Interleukin-1 blockers bind to interleukin-1 receptor and prevent binding of a co-activator necessary for the functional activity of this receptor. Interleukin-1 is also an effective pro-inflammatory cytokine. Anakinra (Kineret), in combination with methotrexate, has been reported to be an effective and safe treatment for patients with rheumatoid arthritis who have inadequate responses to methotrexate alone (Cohen et al. 2004). The dose of interleukin-1 receptor antagonist anakinra (Kineret) is 100 mg once a day. There are also ongoing trials on the treatment of rheumatic diseases with rituximab, which recognize cell-surface CD20 on B lymphocytes. This leads to programmed cell death (apoptosis) of the B lymphocytes. Thus, the titer of rheumatoid factor decreases. Stem cells, plasma cells and memory cells are not affected. This explains, at least in part, why the use of this drug seems to lead to iatrogenic infections less frequently than has been reported for TNF modulatory treatment. Rituximab has been used in rheumatoid arthritis in two 1 000-mg infusions on days 1 and 15, together with oral methotrexate (10 mg per week), with good clinical results (Edwards et al. 2004). Other drugs being evaluated include interleukin-6 blockers, stem cell factor receptor or c-kit blockers (imatinib, Glivec), and β-interferon. In addition to CD20 modulation, other cell-surface molecules, such as CD4 and CD154 (CD40L) are also in clinical trials.

Treatment indications

General indications for treatment of arthritis with biological drugs are treatment-resistant and active disease which responds adequately to biological treatment. In rheumatoid arthritis this means active disease despite combination treatment; in Finland, this has included at least 15 mg/week peroral methotrexate for at least three months. Many patients receive higher doses, e.g. 25 mg/week intramuscularly. According to the Finnish guidelines, the patient should have 6 tender and swollen joints together with high ESR (30 mm/t), CRP (28 mg/L) and/or morning stiffness (45 min). After three months of treatment, the patient must have at least 50% treatment response as defined by the American College of Rheumatology (ACR50): the number of tender and swollen joints must have diminished by at least one-half and a similar change must be observed in at least three of the following: patient's overall assessment, doctor's overall assessment, pain, ESR and function as estimated using the VAS scale, laboratory tests and the Health Assessment Questionnaire (HAQ).

In ankylosing spondylitis, treatment with biological anti-rheumatic drugs is indicated when, despite treatment with conventional NSAIDs (a minimum of two different preparations for at least 3 months) and sulphasalazine (minimum 4 months), the patient continues to have an active disease. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is used to assess fatigue, back pain, joint pain, joint swelling and the severity and duration of morning stiffness. For continued treatment, the patient should have at least 50% improvement or two unit changes for the better in BASDAI after 6–12 weeks.

On purely medical indications, it can be estimated that conventional DMARDs give adequate results in approximately 70% of rheumatoid arthritis patients. In Finland, we estimate that approxi-

mately 20% of rheumatoid arthritis patients need and tolerate continuous long-term treatment with biologicals, although many more would gain from them. The correponding percentage in ankylosing spondylitis is approximately 10–15%. These are only estimates, but it is clear that on purely medical grounds these drugs should be used more frequently than is the case at present.

Infectious complications

The prevalence of opportunistic infections is increased in rheumatoid arthritis patients as compared to the general population (Doran et al. 2002). Biological drugs have also been associated with the activation of latent tuberculosis, which has been described after initiation of anti-rheumatic biological drugs—in particular infliximab—and usually after 3 months of treatment (Keane et al. 2001). As TNF-blockade impairs macrophage function and their ability to organize themselves to granulomas, approximately half of these cases have extrapulmonary manifestations and one-quarter presents with military tuberculosis.

Anti-tuberculosis prophylaxis is regarded differently in different countries. In Finland, it is a convention to give 300 mg q.d. (10 mg/kg) isoniazid and pyridoxine B6 vitamin 20 mg q.d. during the first 6 months of treatment, if three warning signs are positive: 1) a patient history of contact with open tuberculosis, 2) primary tbc complex in radiographs of the lungs, and 3) at least 15 mm induration to 2 TU (tuberculin units) PPD (purified protein derivative) in Mantoux test reaction. This is done in spite of the Bacillus Calmette-Guérin vaccination program. It is considered that in adults, this 15 mm value can be used for pragmatic purposes. If the patient is on immunosuppressive treatment (> 15 mg prednisone), 10 mm induration can be considered to be significant, and in patients with lymphopenia ($< 0.6 \times 10^9$/L) or low CD4 counts ($< 0.3 \times 10^9$/L) even 5 mm can be considered to be positive.

Other opportunistic infections include listeriosis, oral and deep candida infections, herpes labialis (which can also spread to eczema herpeticum), varicella-zoster, cytomegalovirus, Pneumocystis carinii pneumonias, Aspergillus infections, histoplasmosis, Cryptococcus infections and other fungal infections. Orthopantomography and consultation of a dentist should also be arranged so that latent tooth infections can be treated before biological treatment is started. The patient should receive live, attenuated vaccines that are considered necessary before initiation of the treatment (for example MPR, BCG, yellow fewer). With live vaccines, care must be taken when immunosuppressive drugs are already in use. The practice followed in rheumatology patients is similar to that followed in the management of organ transplant patients, who receive immunosuppressive drugs to prevent transplant rejection.

Rheumatoid patients are at increased risk of infections as a result of joint and bone inflammation and injury, which predispose to septic arthritis and osteomyelitis. Disease-caused deformations may lead to skin injuries, for example in hallux valgus and olecranon bursitis, and this can become a route for entrance of skin infections. Retropharyngeal abscesses have also been described. Respiratory tract infections such as bronchiolitis and bronchopneumonias are more common than usual.

Before biological treatment is started, risk factors should be evaluated and—if possible— treated. These risk factors include difficult, active and destructive arthritis, medication (corticosteroids, cytostatic drugs, NSAID) and other treatments (e.g. joint replacements and other rheumatoid surgery, arthrocentesis and intraarticular injections, splenectomy), comorbidity (e.g. diabetes, chronic obstructive pulmonary disease, alcoholism, smoking) and undetected latent infections (e.g. banal infections, latent tuberculosis or odontogenic infections). Underlying disease and medication, and also dementia, may delay diagnosis and treatment. New biological anti-rheumatic drugs should not be used during pregnancy or lactation.

To avoid infections and delayed healing linked to joint replacement and rheumatoid surgery, biological anti-rheumatic drugs should be stopped before operation and should not be started again until initial repair has already occurred after the operation. Nobody knows the exact times, but based on the half-lives of the new biological anti-rheumatic drugs, there are certain recommendations—one of which is shown in the Table. These represent the recommendations used in Finland, but the details of such recommendations vary between countries, even between close neighbors such as the different

The Finnish recommendation on the use of the new biological anti-rheumatic drugs in joint replacement surgery patients

Biological drug	Interruption before operation	Reinitiation after operation
Infliximab (Remicade)	6 weeks	6 weeks
Etanercept (Enbrel)	2 weeks	6 weeks
Adalimumab (Humira)	6 weeks	6 weeks
Anakinra (Kineret)	1 week	3 weeks

Half-lives are 8–10 days for infliximab, 70 h for etanercept, 10–20 days for adalimumab, and 4–6 h for anakinra.

Nordic countries. The new information becoming available may show that it will not be necessary to put forward very strict regulations regarding interruption and reinitiation of treatment with biologicals before and after surgery.

According to the Registry of Biological Treatments in Finland (ROB-FIN, Nordström et al., in press) adverse events have been reported in approximately 16% of patients taking biological drugs. Skin changes such as pruritus, eczema and injection site reactions form 41% of all adverse events reported. They have rarely led to interruption of the treatment. Different infections account for about 18% of all adverse events. Infusion reactions form approximately 7% of all reported adverse events. Headache, nausea and vomiting have also been relatively common, and laboratory abnormalities such as increased levels of transaminases, creatine kinase, antinuclear antibodies and anti-DNA antibodies have been reported.

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