the joint and are in a non-culturable state, so the lack of efficacy of antibiotics does not in itself refute the idea that bacteria are central to the pathogenesis of ReA or other spondyloarthropathies.

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Tumour necrosis factor blockade in rheumatoid arthritis

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Rheumatoid arthritis (RA) is one of a group of conditions frequently referred to as autoimmune diseases. Joint pain and joint immobility, which are characteristic of RA, arise from a chronic fluctuating inflammation in the synovial tissue of the joints. Although the mechanism by which this immune-mediated inflammation is triggered and the nature of the target antigen remain to be elucidated, mediators that perpetuate inflammation and destruction of cartilage and bone have been identified. On the basis of this increasing knowledge, new therapeutic principles have been developed with biological agents that act on more specific targets than the established antirheumatic drugs.

The possible targets for intervention that have recently received most attention are cytokines[1]. Cytokines can be categorised as those that enhance inflammation, such as tumour necrosis factor (TNF) or interleukin (IL)-1, and those that decrease inflammation, such as IL-10 or IL-4. Several natural endogenous inhibitors of TNF and IL-1 have been identified, including IL-1 receptor antagonist, soluble IL-1 receptors, and soluble TNF receptors. These natural inhibitors are present in healthy persons, with higher levels in RA patients in serum and at sites of inflammation. In RA, pro-inflammatory cytokines outnumber anti-inflammatory cytokines or natural inhibitors[2]. This has stimulated the search for agents that can restore this imbalance.

Tumour necrosis factor

TNF is a pleiotropic cytokine abundantly produced in the rheumatoid synovium. It binds to the surface receptors of cells, leading to a pattern of gene activation. This process causes:

- macrophages to produce pro-inflammatory mediators that amplify the inflammatory reaction
- endothelial cells to express adhesion molecules that allow access of more inflammatory cells to the site of inflammation
- fibroblasts to produce proteases that can destroy cartilage, bone and ligaments[2].

The spontaneous development of destructive arthritis in mice transgenic for TNF[3] can be prevented by the administration of TNF monoclonal antibodies (mAb) that bind and inactivate TNF. TNF given intra-articularly induces synovitis; if administered during the development of collagen-induced arthritis it leads to a more severe form of joint inflammation. However, mice receiving TNF mAb at the same time show significant amelioration of the disease process[4]. TNF may also contribute to systemic features of RA by stimulating acute-phase protein synthesis and inhibiting erythropoiesis[5].

Clinical trials

Tumour necrosis factor antibody

In the first half of the1990s, clinical trials using chimeric human/mouse or humanised TNF mAb in RA patients provided the first direct evidence that

Key Points

Tumour necrosis factor (TNF) plays a pivotal role in chronic inflammation

TNF blockade in rheumatoid arthritis decreases inflammation and joint destruction, and maintains function

TNF inhibitors might be useful therapeutic agents. An open label trial of the TNF mAb, infliximab (Remicade™)[6], showed that intravenous administration induced significant improvements in swollen joint counts and serum C-reactive protein levels. In a subsequent double-blind, multicentre European trial, patients were randomly assigned to receive single infusions of placebo, low-dose infliximab (1 mg/kg) or high-dose infliximab (10 mg/kg). Four weeks after treatment, 79% of patients with the high dose showed a response (20% Paulus), 44% of patients with the low dose and 8% on placebo[7]. Over 50% on the high dose achieved a strong response (50% Paulus). The antibody was well tolerated. Minor infections and rashes were the most common side effects.

In another study where patients with active RA despite methotrexate (MTX) treatment received five infusions of infliximab over 14 weeks, with or without continuation of a fixed low dose of MTX (7.5 mg). TNF mAb combined with MTX markedly suppressed inflammatory disease activity in RA, and the best results were obtained with 3 mg/kg and 10 mg/kg of infliximab[8]. The combination therapy enhanced the degree and duration of efficacy; it also appeared to promote immunological tolerance to infliximab therapy, with a reduction in antibodies to the monoclonal antibody (HACA). In patients with active RA who continued MTX therapy impressive clinical effects were still observed at 54 weeks in those who had received MTX plus infliximab compared with those who received MTX plus placebo[9,10]. Radiographs indicated that erosions did not progress in the patients receiving infliximab.

Side effects

Side effects observed in the clinical studies with infliximab have included infusion reactions (similar to those with intravenous immunoglobulin (Ig)), but these were uncommon. Serious infections were rarely observed, but they are a concern with all TNF inhibitors. These agents should not be used in patients with active infection or in those at increased risk for infection. Such patients include those with a history of untreated tuberculosis, chronic bone or joint infections, recurrent cellulitis or draining nodules. Antibodies against infliximab have been observed with treatment with infliximab alone, but their numbers are reduced with concomitant use of MTX. To date, there are no data on risk of lymphoproliferative disorders with this antibody or other TNF inhibitors.

Soluble tumour necrosis factor receptors

Administration of soluble TNF receptors is another therapeutic strategy aimed at TNF blockade. The biological activities of TNF are mediated through membrane-bound receptors expressed by numerous cell types. To increase their half-life and affinity, soluble TNF receptors have been fused to the Fc portion of an IgG1, forming a fully human soluble TNF receptor fusion protein. The fusion protein investigated most extensively is etanercept (Enbrel™). In a dose escalation study in patients with refractory RA, subcutaneous administration of etanercept twice weekly was well tolerated and markedly decreased the number of painful and swollen joints and C-reactive protein levels[11]. TNF receptor fusion proteins (half-life 2–3 days) need to be given more frequently than mAb (half-life 10 days). These encouraging initial clinical results were confirmed in multicentre, randomised, double-blind, placebo-controlled studies[12–14]. A long-term study has demonstrated that the efficacy and safety of etanercept therapy were maintained for more than 18 months[15,16].

TNF blockade with etanercept was also found to be efficacious in patients with polyarticular juvenile chronic arthritis[17]. In a one-year trial comparing etanercept with MTX in 632 patients with early RA (disease duration <3 years), etanercept had a more rapid response and showed greater efficacy than MTX, and there was less radiographic progression (total Sharp score) at one year[18]. Etanercept was well tolerated in all studies. The only adverse events clearly associated with etanercept were mild injection-site reactions and a small increase in minor upper respiratory tract infections. The induction of antibodies against etanercept was reported in one patient.

Etanercept was approved by the US Food and Drug Administration in 1998 as therapy for active RA at a dose of 25 mg injected subcutaneously twice a week, and also for use in juvenile RA. The cost of one year's treatment is approximately $12,000.

Mechanisms of action

At present, infliximab and etanercept are the most extensively investigated TNF mAb, particularly in RA. Other mAb and soluble receptors are being developed and seem to be therapeutically effective against RA. The unanswered questions about this therapy are now becoming more important. The precise mechanism of action remains to be defined. The possibilities include:

- binding and inactivation of TNF in the fluid phase
- binding to transmembrane TNF
- downregulation of the expression of pro-inflammatory cytokines, suggested by the rapid reduction of C-reactive protein production and IL-6
- blockade of cell trafficking, suggested by the significant suppression of circulating levels of adhesion molecules and the reduced expression of adhesion molecules in synovial tissue following treatment
- blockade of metalloproteinase production[2,19,20].

It is not yet certain whether there are significant differences among the most important biological agents being developed. These agents may be cytotoxic to cells that express membrane-bound TNF. It remains to be seen whether this effect, the high affinity of the TNF-receptor-Fc fusion proteins, and the possibility that these proteins also bind TNF to lymphotoxin are relevant to their efficacy.

Toxicity and side effects

Considerably more information is needed on long-term toxicity.

Experimental data on the biology of TNF suggest that it mediates inflammation and modulates cellular immune responses. It is therefore theoretically possible for anti-TNF therapy to affect immune responses involved with host defence against infections and malignancies. The side effect spectrum was found to be benign in short-term studies. Sporadic cases of malignancy or severe infections have been documented in patients treated with TNF blockade, and there have been rare cases of lupus-like disease. Up to 10% of the patients so treated have developed anti-double standard DNA antibodies. Whether such cases are related to the natural history of RA or to the new treatment can be answered only by well designed, large long-term studies.

Conclusions

TNF inhibition is a viable approach to controlling disease activity in RA. TNF blockade induces a rapid improvement in clinical assessments of disease activity, and is associated with improvement in biological variables. Rheumatologists who participated in the early trials were particularly impressed by the significant decrease in fatigue reported by the patients.

The indications and contraindications for TNF blockade will expand in the coming years. At present, candidates for TNF blocking therapy are patients who have active disease despite a full and adequate trial of one or more disease-modifying antirheumatic drugs, unless precluded by toxicity. On an individual patient basis, the aggressiveness of the RA and its effects on quality of life should be taken into account when considering indications for TNF blockade. TNF blocking agents can be added to pre-existing MTX therapy. With the results of studies on the effect of TNF blockade on structural joint damage, application in early phases of the disease may be considered in selected patients. It is important to note that TNF blocking compounds should not be continued if severe infections, including joint infections, occur and should be resumed only if such infections have completely healed. In addition, decisions about starting treatment with these agents should be made in the context of their cost and long-term safety and efficacy.

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