Future prospects for anti-cytokine treatment

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Abstract
The era of anti-cytokine treatment in rheumatology has just begun. The first generation therapeutic agents, biological agents that block tumour necrosis factor α such as monoclonal antibodies or receptor Ig fusion proteins are safe and effective, and so this has generated much interest in how to increase the benefit or deliver it more cost effectively. This article provides a personal view of the coming trends in anti-cytokine treatment. Which of these will be realised in the future will be of interest.

The efficacy, safety and capacity of anti-tumour necrosis factor α (TNFα) therapeutic agents such as infliximab, etanercept and D2E7 are abundantly documented elsewhere and in this supplement. Most relevant are the recent data with all three agents in terms of joint protection, with the large phase III study of infliximab in conjunction with methotrexate (ATTRACT), presented at the November 1999 American College of Rheumatology meeting particularly striking.

These studies complete the evaluation of the effects of anti-TNFα in rheumatoid arthritis (RA), and indicate that effectively all aspects of the disease are influenced by TNFα. The interesting result that there is joint protection even in the patients who did not respond clinically by the preset criterion of ACR 20% suggests that there is no clear cut distinction between anti-TNF responders and non-responders, which is supported by prior findings that there are reductions in joint scores in all patients.

It has been argued at length previously, and in this issue, based on animal data that interleukin 1 (IL1) and not TNFα is the most important cytokine in terms of joint destruction. However, that view is not consistent with the degree of joint protection noted in the ACR 20 non-responders, who are the patients with the most residual joint inflammation. There is a continuing need to use clinical trials with biological agents that have clear cut modes of action to help us learn more about the pathophysiology of RA, as it actually is in humans, and not to hope that extrapolation results from animal models can be applied to humans.

Future prospects
The future builds on the present, and so new approaches will be run in conjunction with the existing. Thus combination therapy will be a major theme, using biological agents either with complementary or possibly synergistic therapeutic agents, which would include anti-T cell agents, anti-angiogenesis agents, or with cheaper approaches, drugs that block the TNF pathway (fig 1).

Blocking other cytokines is also a probable approach, and there are many candidates.

OTHER CYTOKINES OF POSSIBLE IMPORTANCE
A wide number of candidate therapeutic targets have been proposed. These include:

Interleukin 12
This is an inducer of Th1 subset that is of major importance in RA, and hence is a clear candidate. Against this is the possibility that treating patients with ongoing RA with IL12 inhibitors might be too late. This is the case in mice with CIA, in which anti-IL12 is very beneficial very early in the induction phase, but useless by itself after disease onset. However, at this late stage there is a good synergy of anti-IL12 with anti-TNFα, both at inhibiting inflammation and in protecting joints.

As anti-IL12 is in clinical development, it is probable that such combinations will be tested in the future. Anti-IL12 drugs might be particularly useful in this context, for example VitD3 or its analogues.

Interleukin 15
McInnes, Liew and others have espoused the importance of IL15 in RA. The properties of IL15 are certainly relevant, for example as an early activator of T cells made by antigen presenting cells, but whether it is still present in sufficient quantities later in the disease process is still controversial. As IL15 has the capacity to activate T cells in an antigen non-specific manner, yielding “cytokine activated” T cells that we think are a major subset of T cells in RA synovium, this is a molecule whose inhibition might be of benefit and might synergise with anti-TNFα.

Interleukin 18
First cloned as an inducer of interferon γ, IL18 is now known to be IL1 related and have much broader effects. It is a potential target, together with IL12 with which it synergises.
Interleukin 17
This T cell derived inducer of fibroblast activation has been espoused as a possible target.17

Oncostatin M
This is a cytokine member of the IL6 family, and has profound effects on cartilage and bone. So it is a possible target, especially to augment joint protection.18

Combination of anti-T and anti-TNFα
In collagen induced arthritis (CIA), there is a very clear synergy of anti-CD4 and anti-TNFα. Non-effective doses of both reagents can synergise to yield an effective therapeutic regimen.19 While there has been controversy as to whether like RA it was T cell dependent,20 we are convinced by recent studies of Brennan et al15 that as fixed synovial T cells can activate monocytes to make TNFα, late stage RA is still T cell dependent. Other possible reasons for combination therapy are illustrated in figures 2 and 3.

Anti-CD4 agents have not done well in RA trials in the late 1980s or early 90s, however these first generation antibodies were lytic anti-CD4 antibodies that did not induce “tolerance.”21 22 Hence there have been trials of non-lytic anti-CD4 antibodies, and these have seemed to yield better results. For example, one OKTCDr4a was tested in a small group of RA patients, and the response, while brief (one month or so) was clear cut, with both clinical and serological markers of improvement (P Lipsky, presentation at Newport Beach Meeting on Autoimmunity, February 2000).23 It suggests that especially in combination with anti-TNFα, there is a role for anti-CD4. There have been attempts to test out this combination in RA patients in vivo and the results were reported to be excellent, but as the numbers were small, comparison was with historical controls, this combination is promising but not yet established in vivo. However, there was no problem with infections, which is an important result of these small trials.24 25

Anti-CD3 antibodies were the first ever monoclonal antibodies in clinical practice, for graft rejection (OKT3). These are effective, but can cause considerable side effects, because of cytokine release. So there is a lot of interest now in mutated anti-CD3, which does not activate as it does not bind to Fc receptors, and such antibodies are being tested in transplantation and in newly diagnosed type I diabetes and transplantation.26

There are multiple other approaches to blocking T cell function for example, drugs. Methotrexate does it, as evidenced by its capacity to reduce IFNγ production, and reduce anti-idiotypic responses to Inflixi-mab.27 28 Cyclosporin may also do it, as it acts by blocking the phosphatase calcineurin, involved in the activation of NF-AT via the T cell receptor, and upregulates TGFβ1 production.29 It is unclear how much of T cell function is mediated via the T cell receptor, as there is increasing evidence that cytokine activated T cells are also involved. However, the capacity of cyclosporin A to ameliorate RA, by itself to some degree, and even more in conjunction with other DMARDS30 suggests that there is TCR activation. This concept will be tested more fully when antibodies to costimulatory molecules (CD86) and CTLA4Ig will be tested in RA patients.

In CIA, there is synergy of anti-TNFα31 and cyclosporin A and CTLA4Ig is effective.32

Angiogenesis is important in RA
As the synovium enlarges in RA, there is a massive increase in the number of cells, chiefly

Figure 2 Rationale for anti-T cell/anti-TNFα combination.

Active RA is T cell dependent
synovial TNF is T cell dependent (Brennan et al, 2000)

Animal models are T cell dependent
respond to anti-T/anti-TNFα
(Williams et al, 1994)

Figure 3 Combination treatment—suboptimal anti-TNFα plus anti-CD4. A suboptimal concentration of anti-TNFα (50 µg/injection) was administered at days 1, 4, and 7 together with an optimal concentration of anti-CD4 (200 mg/injection) 18–19 mice per group. Reproduced with permission from Williams et al Proc Natl Acad Sci USA 1994;91:2762–6.
Future prospects for anti-cytokine treatment

Targeted treatments, such as anti-TNF, are being used to ameliorate RA and many other diseases, they currently have a major liability: their cost to the organisations that pay. Regardless of the potential long-term benefit to the individual patient, family and society, this will continue in the foreseeable future to restrict the potential benefits to patients. Competition from new entrants with biological agents, such as D2E7 from BASF/Knoll, Amgen/Celltech, to the field will probably reduce prices, but not that dramatically.

The major reductions in cost will come from using small organic chemicals, when sufficiently specific and safe ones appear. One approach that might heighten safety is to use biological agents for inducing rapid disease control, and with the patient consequently improved the response to the drug would be anticipated to take place at lower and hence safer concentrations.

**What drugs might be used in synergy with anti-TNF?**

Virtually any TNF synthesis or signalling inhibitor could be anticipated to be effective. For example, there are a number of p38 MAP kinase inhibitors in development in large pharmaceutical companies. This type of drug has been reported in the past to be toxic, but if used for maintenance rather than induction of benefit, the concentrations of drug needed may remain well clear of the hazardous regions. The same could be true of phosphodiesterase type 4 inhibitors that tend to cause gastrointestinal side effects. Of course there are advantages to biological agents with their greater specificity, but compromises have to be made in every market place (fig 5).

Thus it is evident that anti-TNF biological agents have taught us a lot about the pathogenesis of RA, and about the cytokine network as it really is in vivo. Widespread fears about “cytokine redundancy”, a difficult concept in evolutionary terms, have proved to be unfounded and the role of TNF as the body’s fire alarm, initiating recruitment of cells to local lesions also explains the benefits seen in an increasing spectrum of diseases: RA and Crohn’s disease most conclusively, but also ankylosing spondylitis, psoriasis in small trials. Most important has been the evidence that biological agents can be used repeatedly over years, and the concomitant evidence that molecular mechanisms of chronic inflammatory disease such as RA do not alter over the years in chronic inflammation, in contrast with cancer.

The extent of use of the current generation of biological agents in RA (antibodies and TNF-R Fc fusion proteins) will depend on their effectiveness, safety and their relative cost/efficiency/safety compared with new entrants in the field. The competition will be fierce, to the benefit of the patient population.

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**Figure 4** Interesting combinations.

- Anti-T + anti-TNFα
- Anti-VEGF + anti-TNFα
- Anti-IL12 + anti-TNFα

**Figure 5** Drug-biological combination treatment.

- Induction
  - anti-TNF biological – rapid onset of benefit
  - reduce disease activity
- Maintenance
  - drugs
    - less toxic doses if used on patients with less activity
    - cheaper

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**Conclusions**

THE REALITY: PHARMACO-ECONOMICS TO THE FORE?

Despite the enormous potential of accurately targeted treatments, such as anti-TNFα antibodies or TNF-R fusion proteins to ameliorate RA and many other diseases, they currently have a major liability: their cost to the organisations that pay. Regardless of the potential long-term benefit to the individual patient, family and society, this will continue in the foreseeable future to restrict the potential benefits to patients.
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