Future prospects for anti-cytokine treatment

Marc Feldmann, Jadwiga Miotla, Ewa Paleolog, Richard Williams, Anne-Marie Malfait, Peter Taylor, Fionula M Brennan, Ravinder N Maini

Abstract
The era of anti-cytokine treatment in rheumatology has just begun. The first generation therapeutic agents, biological agents that block tumour necrosis factor alpha 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.

(Ann Rheum Dis 2000;59(suppl I):i119–i122)

The efficacy, safety and capacity of anti-tumour necrosis factor alpha (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.

In theory:
1 Increased degree of efficiency
2 Increased frequency of response
3 Prolonged response → remission
4 Reduced cost
5 Reduced toxicity

Figure 1 Rationale for combination therapies.

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 gamma, 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.\(^\text{17}\)

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.\(^\text{18}\)

Combination of anti-T and anti-TNF\(_\alpha\)
In collagen induced arthritis (CIA), there is a very clear synergy of anti-CD4 and anti-TNF\(_\alpha\). Non-effective doses of both reagents can synergise to yield an effective therapeutic regimen.\(^\text{19}\) While there has been controversy as to whether like RA it was T cell dependent,\(^\text{20}\) we are convinced by recent studies of Brennan et al\(^\text{15}\) that as fixed synovial T cells can activate monocytes to make TNF\(_\alpha\), 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.”\(^\text{21, 22}\) 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).\(^\text{23}\) It suggests that especially in combination with anti-TNF\(_\alpha\), 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.\(^\text{24, 25}\)

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.\(^\text{26}\)

There are multiple other approaches to blocking T cell function for example, drugs. Methotrexate does it, as evidenced by its capacity to reduce IFN\(_\gamma\) production, and reduce anti-idiotype responses to Inflixi-mab.\(^\text{27, 28}\) 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 TGF\(_\beta\) production.\(^\text{29}\) 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 DMARDS\(^\text{30}\) suggests that there is TCR activation. This concept will be tested more fully when antibodies to costimulatory molecules (CD86) and CTLA-4 Ig will be tested in RA patients.

In CIA, there is synergy of anti-TNF\(_\alpha\)\(^\text{31}\) and cyclosporin A and CTLA4 Ig is effective.\(^\text{32}\)

Angiogenesis is important in RA
As the synovium enlarges in RA, there is a massive increase in the number of cells, chiefly...
Future prospects for anti-cytokine treatment

derived from the blood, although there are also augmented numbers of fibroblast-like synoviocytes and endothelium. The endothelium is of importance, as the augmented synovial cell mass needs blood supply to ensure its survival. Hence there has been interest in the presence of angiogenic factors in synovium, of which there are a plethora. Whether one or more are rate limiting is not yet clear. We and others have studied VEGF as it is a relatively specific endothelial mitogenic, which is expressed in synovium, and excess spills into the blood. Serum VEGF levels correlate with disease activity, and serum VEGF is diminished after anti-TNFα (Infliximab) treatment. For a variety of reasons this suggests that VEGF may be a therapeutic target, and we have successfully tested this in the CIA model, in which inflamed synovium produces VEGF from an early stage, increasing as the inflammation augments. Pegylated soluble VEGF receptor (Flt-1), made by Astra-Zeneca was able to markedly diminish all aspects of CIA, if given early after disease onset, days 1–5. It reduced footpad swelling, not surprising as VEGF was also discovered as “vascular permeability factor”. More interesting was the diminution of “clinical score”, an index of disease progression, and protection of joint structure, as revealed by histological examination. These data have various interpretations. One is that in the absence of angiogenesis, the disease cannot spread and synovial cells do not survive and do not damage joints. Another is that perhaps VEGF receptors that are found in the macrophage lineage, including osteoclasts, have a special role in the disease process. Disentangling these hypotheses will not be easy, but testing other angiogenic agents will be a good start. Currently available data, for example, with drugs such as TNP 470 that block angiogenesis are not conclusive, as there may also be other effects that may influence arthritis (fig 4). A question of interest is whether anti-angiogenic treatment will synergise with anti-TNFα. In CIA there are some data that it does (Miotla, unpublished data), but the critical data needed are in RA. As anti-angiogenic treatment should not be pro-infective, it may be that this combination may be of particular relevance.

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 ben-efits 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 considerably 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.


917–20.

www.anmrheumdis.com

Downloaded from http://ard.bmj.com/ on August 29, 2017 - Published by group.bmj.com
Future prospects for anti-cytokine treatment

Marc Feldmann, Jadwiga Miotla, Ewa Paleolog, Richard Williams, Anne-Marie Malfait, Peter Taylor, Fionula M Brennan and Ravinder N Maini

*Ann Rheum Dis* 2000 59: i119-i122
doi: 10.1136/ard.59.suppl_1.i119

Updated information and services can be found at:
http://ard.bmj.com/content/59/suppl_1/i119

These include:

**References**

This article cites 34 articles, 7 of which you can access for free at:
http://ard.bmj.com/content/59/suppl_1/i119#BIBL

**Email alerting service**

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/