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- 2 *The COPE report 1999*. London: BMJ Publishing Group, 1999.
- 3 Nuffield Council on Bioethics. *Human tissue: ethical and legal issues*. London: Nuffield Council on Bioethics, 1995.
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- 5 Doherty M. The misconduct of redundant publication. *Ann Rheum Dis* 1996;55:783–5.

Anti-TNF α : a new dimension in the pharmacotherapy of the spondyloarthropathies !?

Introduction and overview

The therapeutic options for treatment of the spondyloarthropathies (SpA), especially for ankylosing spondylitis (AS), are limited. Physiotherapy is important and non-steroidal anti-inflammatory drugs (NSAIDs) provide significant symptomatic benefit, as has been shown in many studies, and recently in a six week/one year trial.¹ Apart from sulfasalazine, a disease modifying antirheumatic drug, which many rheumatologists use to treat patients with peripheral arthritis and gut disease in early and in active stages of SpA, few innovative treatments have arisen in the past decades since indometacin was developed.² The Cox-2 selective agent rofecoxib, recently introduced, causes fewer gastric ulcers but is no more effective than established NSAIDs.³ The efficacy of rofecoxib in ankylosing spondylitis (AS) has not been studied to date. Up to 20% of patients with AS do not respond well or at all to NSAIDs.⁴ Corticosteroids are effective when applied locally intra-articularly⁵ but not systemically in most patients—an interesting difference from rheumatoid arthritis (RA), the pathophysiological basis of which is unclear. Interestingly, quite a few rheumatologists use methotrexate to treat AS,⁶ though there are no randomised trials for this indication.

However, possibly positive effects of thalidomide⁷ and of pamidronate⁸ for the treatment of AS were recently reported from two open studies. Both drugs work, at least partly, by blocking the proinflammatory cytokine tumour necrosis factor α (TNF α),^{9,10} which is also the target of recently introduced new treatments for the treatment of RA¹¹ and Crohn's disease.¹² Shortly after the initial experience of our group with anti-TNF in AS¹³ and of others in psoriatic arthritis,¹⁴ both for the first time reported in Boston at the American College of Rheumatology meeting 1999, several studies with "biological" agents acting against TNF α in SpA were reported. One study from our Belgian colleagues is published in this issue of the *Annals*.¹⁵

Tumour necrosis factor α blockade

Tumour necrosis factor α is a cytokine that is mainly produced by monocytes and macrophages and, to a lesser degree, by T cells. Two specific receptors, a 55 kDa and a

75 kDa, are present on many cell types. TNF α mediates inflammatory and immunoregulatory activities. Effects on cells, such as lymphocyte activation and fibroblast proliferation, on mediators, such as other cytokines—for example, interleukin 1 (IL1), IL6, and IL8, chemokines, prostaglandins, and metalloproteinases, and on the vasculature by promoting angiogenesis, upregulation of adhesion molecules, and transendothelial migration of leucocytes, have been well described. In vitro and in animal models TNF α causes fever, pain, and cachexy, mobilises calcium from bone, and induces apoptosis (see review¹⁶). All these mechanisms are proinflammatory but, additionally, TNF α has important physiological functions in immune responses against pathogens and may contribute to suppression of autoimmunity and malignancy.¹⁷ Blocking these functions might lead to undesired side effects.

Biological agents blocking TNF α

The antibody used in both the Belgian and the Berlin study was infliximab, the first antibody which was available to treat patients with RA. Infliximab is a chimeric human murine monoclonal class IgG1 antibody (Infliximab, cA2, Remicade, Fa Essex/Centocor). The efficacy of anti-TNF α in Crohn's disease is remarkable because Crohn-like gut lesions have been detected in a significant percentage of patients with SpA.¹⁸ Other agents also act against TNF α , such as the TNF α 75 kDa receptor IgG1 fusion protein (etanercept (Enbrel), Fa Wyeth/Lederle), which has also been proved to be effective in patients with RA when treatment with methotrexate alone was insufficient.¹⁹ It is unclear whether etanercept works in Crohn's disease. The mode of action of these antibodies is probably not identical. However, this issue is beyond the scope of this article.

Anti-TNF α treatment in patients with active ankylosing spondylitis

In the study reported in this issue¹⁵ spinal pain of 7/11 patients with AS improved significantly at two and six weeks after anti-TNF α was given as an induction treatment at weeks 0, 2, and 6. Several years after the description of TNF α mRNA in sacroiliac biopsy specimens of patients

with SpA,²⁰ and the failure to detect bacterial DNA there,²¹ we have performed an open pilot study with infliximab in AS¹⁵ last year, with similar results. In our study 11 patients with active AS, mean age 36 years, mean disease duration five years, were treated with 5 mg/kg IV infliximab at weeks 0, 2, and 6. The mean disease activity index BASDAI (Bath Ankylosing Spondylitis Disease Activity Index)²² was 6.5 despite NSAID treatment. Ten patients had a raised C reactive protein (CRP) concentration and five patients had spinal x ray changes. Similar to the patients in the study reported here in the *Annals*,¹⁵ dramatic clinical improvement was seen on the day after the first infusion. Improvement of BASDAI values >50% persisted in almost all patients for six weeks. Function also improved significantly. As in the Belgian study, CRP values became normal after treatment. Also, similar to the Belgian study, in which 18 patients with SpA with peripheral arthritis were treated, the symptoms of knee and ankle arthritis vanished in the two patients affected in our trial. One of these patients is still in complete remission five months after a period of constant disease activity for almost two years. However, altogether three patients were withdrawn in the meantime because of significant infusion reactions (all easy to handle). To minimise such effects it has to be discussed whether methotrexate or azathioprine should be added to infliximab.

First positive therapeutic experiences with three patients with severe AS were also made in Canada (Russell A, personal communication) and Norway (Kvien T, personal communication). There is an ongoing study with etanercept for the treatment of AS in California.

Anti-TNF α treatment in severe psoriatic arthritis

In the study reported here¹⁵ eight patients with psoriasis were treated with infliximab. Peripheral joint and skin symptoms ameliorated significantly after seven and 14 days. In another open study¹⁴ six patients with severe psoriatic arthritis being treated with methotrexate (15–25 mg/week) received additional treatment with infliximab. The joint and skin symptoms of all patients quickly and persistently improved (Manger B, personal communication).

Etanercept in addition to methotrexate has been studied in a randomised controlled trial in patients with psoriatic arthritis.²³ Thus blockade of TNF α seems also to be effective in patients with severe psoriatic arthritis.

Treatment of undifferentiated spondyloarthropathy

Remarkably, no study dealing with the treatment of this condition has ever been performed to date. The two patients with undifferentiated spondyloarthropathy of the study reported here¹⁵ improved similarly to patients with the other SpA. This is in accordance with our experience in three cases (Braun J, unpublished). Of note, this included a patient with multilocal enthesitis who significantly improved after treatment with infliximab.

Effects of anti-TNF treatment on laboratory findings

Some rather unexpected laboratory findings after infliximab treatment have been reported. Feldmann measured increased TNF α serum concentrations while both soluble TNF receptor levels remained unchanged and raised. However, measuring serum TNF α is difficult (only 50% of the patients with RA treated had raised levels) as the half life is short and the TNF measured in that study was not in its bioactive state.²⁴ This might indicate that immune complexes of soluble TNF and infliximab were measured. In contrast, we found a somewhat increased TNF α secretion capacity after treatment in six patients (unpublished). In contrast, the TNF secretion capacity of peripheral blood T

cells was found to be reduced in patients with AS and in HLA-B27 positive healthy controls as compared with HLA-B27 negative normal subjects.²⁵ This might mean that the cytokine pattern of peripheral blood cells is the reverse of that in the gut, the synovium, or in the joints. This might indicate active regulatory suppression to prevent damage at other sites or it might be owing to effector cells having left the previously inflamed sites.

There is also a discrepancy in the reports of total lymphocyte counts after infliximab treatment. Whereas Paleolog *et al*²⁶ reported an increase, we found lower lymphocyte counts and fewer circulating CD3+ T cells (unpublished) in patients with AS one week after infliximab, as others have found in patients with RA.²⁷ This point is of interest for answering the question on possible cytotoxic effects of infliximab.

Side effects of anti-TNF α treatment with infliximab

Some undesired effects of infliximab treatment have been seen^{7 28 29}: side effects directly associated with the infusion (2–5%), autoimmune phenomena (DNA antibodies in 10–16%), and more upper respiratory tract infections, which were reported to have occurred in about 20–30% of the patients.¹¹ However, this was not statistically significant.

The risk of developing malignancy has been discussed thoroughly, but there is no evidence of a significantly increased risk to date. Lymphomas were seen in a few patients with Crohn's disease treated with anti-TNF.³⁰ However, all such reported increases were not significantly different from the normal prevalence in the population.

The murine and the human part of anti-TNF antibodies have significant immunogenic potential. Human anti-chimeric antibodies, possibly associated with hypersensitivity infusion reactions, and human antihuman antibodies have been described.³⁰ However, it is not clear whether the production of human antichimeric antibodies influences the efficacy and frequency of particular side effects. Concomitant treatment with methotrexate or azathioprine might reduce the risk of antibody development, but further study is clearly needed.

Course and severity of SpA—which patients should be treated?

Can there possibly be an indication for the use of expensive anti-TNF or other biological treatments in SpA at all? Is the course of disease in SpA sufficiently severe to justify such costly interventions? In a recent discussion with experienced rheumatologists the suggestion was made that one could just wait for ankylosis to occur in patients with AS who had inflammatory back pain and sacroiliitis—then the symptoms might just improve during the natural course of disease. This statement is partly true, but also seems typical of doctors who have had no major treatment to offer to these patients for decades.

However, rheumatologists are well aware of the rapidly progressing severe course in AS³¹ and it is well known that most of the burden of the disease develops in the first 10 years.^{32 33} This would argue for early treatment. However, there is limited knowledge about prognostic factors in SpA.³⁴ The recently raised hypothesis suggesting that enthesitis is a favourable prognostic sign in arthritic conditions³⁵ clearly needs confirmation.

The total burden of disease in AS is incompletely defined, but a significant percentage of young patients with AS have a chronic recurrent course of disease resulting in significant disability.³⁶ Because there is still a significant diagnostic delay of five years and more, there are almost no studies on patients with AS with a disease duration of <10

years. This is an important difference between the Belgian study (in which the mean disease duration was 15–19 years) and ours (mean disease duration five years).

Although the study of radiographic progression seems to be difficult,³⁷ we should aim at preventing widespread spinal ankylosis—an essential factor for disability in AS. Modern imaging techniques, such as magnetic resonance imaging, are promising new tools for measuring activity and outcome variables.³⁸

In summary, treatment directed against TNF α seems to work in AS and other SpA. However, controlled trials need to be performed to compare the effects with those of a standard treatment regimen. We do not yet have significant long term experience and so we do not know about the long term side effects. Because of the high costs of treatment we need to determine the minimum dose required and should also consider the possibility of high dose induction treatment, which might be even more effective (20 mg/kg is probably the highest dose ever tried, but no more than 10 mg/kg has been used in studies). Do we have to treat regularly and what are the best intervals? (We will treat every sixth week in the randomised controlled trial on AS now planned in Berlin.) Which patients should be treated? Initially, probably only those with severe disease as early as possible. Later we might also think about early treatment to interrupt inflammation as soon as possible and prevent cartilage damage from occurring.

If the present promising results can be confirmed we have, for the first time, an effective therapeutic option in severe SpA. This might become a major breakthrough in the treatment of this group of diseases. In AS there might even be the hope of preventing progressive ankylosis by effective suppression of inflammation.

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Do patients with osteoarthritis get the clinical research they need?

The most obvious and laudable reason for doing clinical research is, of course, to benefit the patients. Other motives that are sometimes important are to earn money, to increase chances of getting the next post, to become famous, or to satisfy curiosity. Such incentives are not necessarily bad. Indeed, the high level of competition in healthcare research may very well be more innovative and productive—and therefore more beneficial to the patients—than more centralised research approaches.

A particular piece of research may occasionally fulfil all five motives, but it would be the exception rather than the rule if research agendas overall matched even remotely what the patients need most. For example, according to the WHO, the combined investment in research and development into acute respiratory infections, diarrhoeal diseases, and tuberculosis—which kill over seven million people a year—amounts to 0.2% of global spending on health research and development, though these three diseases account for almost one fifth of the global disease burden.¹

Most new interventions, by far, are developed by industry and it is no wonder that industry chooses to go where the market is. For common diseases in the developed world this leads to the development of an array of drugs belonging to the same therapeutic class. Clinical testing of all those drugs consumes a considerable amount of financial and human resources, and clinicians sometimes complain that their colleagues have “occupied” the patients by trivial trials of “me too drugs” for years to come, making it impossible to start trials of greater relevance to the patients.

Is osteoarthritis an exception to this general state of affairs? In this issue of the *Annals*, Chard and colleagues review 50 years of research on interventions for osteoarthritis of the knee.² They report that most of the research was on drugs (59%) or on surgery (26%). The remainder of the research concerned physiotherapy, alternative treatments, education, and behavioural change. The authors note that these less commonly researched areas have gained momentum in more recent times and they state that these shifts in the research agenda are in the same direction as calls for change by consumers. They conclude that the current research agenda appears to mirror consumers’ wishes.

Before accepting this interesting conclusion we need to ask two questions. Firstly, what are the consumers’ wishes? Secondly, and equally important, what type of research has actually been done? It might also be relevant to ask what was its quality? Did it in general lead to reliable conclusions?

Chard and colleagues do not say what the consumers’ wishes are but refer to an unpublished manuscript and to a report from the National Health Service. Whatever consumers’ wishes might be they are indisputably important, but they are not necessarily the best basis for research prioritisation, and they should certainly not be the only basis. For example, many consumers call for more research on alternative treatments, though the likelihood that such research will lead to important improvements is quite small. It might also be argued, for example, that it is important for patients to consider the use of resources in the National Health Service as patients fundamentally “compete” for a share of the limited resources made available to health care. When large resources are used on interventions which are suspected of being ineffective,

there is an urgent need to summarise the treatment results in a systematic review, or, if no high quality randomised trial has ever been done, to ensure that one is performed.

As for the second question, it is useful that Chard and colleagues divide the research into six major areas, but this does not provide a sufficient level of detail for the type of conclusion they draw from their review. For example, the authors do not report the number of drug trials which involved non-steroidal, anti-inflammatory drugs (NSAIDs), though it must have been high. One of the authors previously identified 149 trials of NSAIDs in osteoarthritis and noted that no fewer than 147 of them had compared one NSAID with another.³ Only two trials compared an NSAID with an analgesic, and these trials were only published quite recently, in 1991 and 1993. It is noteworthy that in Australia in 1994, 36% of the people taking NSAIDs received them for osteoarthritis, 42% for sprain and strain or low back pain, and only 4% for rheumatoid arthritis.⁴ This corresponds poorly with the fact that NSAIDs do not seem to be better than simple analgesics for osteoarthritis,⁵ and that official guidelines recommend acetaminophen as the initial drug of choice.⁶ For sprain and strain, the situation is even worse: not a single high quality trial has compared an NSAID with acetaminophen,⁷ although—or because, depending on whose perspective one takes, that of the patient or that of industry—there is no reason to believe that NSAIDs would be any better. As these examples indicate, research agendas can have profound effects on subsequent practice.

There are no important differences, in effect, between different NSAIDs or different doses of the same drug.^{6,7} It is therefore reasonable to say that consumers deserve less “me too research”. They also deserve better research,⁸ particularly on surgical methods. Half of the papers included in the review were reports of randomised trials, but only 13 of the 239 (5%) papers on surgery described randomised trials. Although observational studies on long term outcome after surgery may be useful as a quality control, the effect and adverse effects of surgery need to be documented in randomised trials just as for any other type of intervention. There are special problems in designing and performing surgical trials, but they can be overcome,⁹ and if such trials are not done, the patients may fare badly. For example, a new cement for hip and knee replacements, Boneloc, turned out to lead to instability and many patients had to have a further operation.¹⁰ If the cement had been studied initially in a randomised trial, as described in the original development plan for the cement, this detrimental effect would have been detected much earlier, and the ensuing scandal might have been avoided.

I agree with Chard and colleagues that systematic reviews, including Cochrane reviews, should allow high quality observational data to be included. But it should be done with great caution and only in exceptional cases—for example, when adverse effects have been insufficiently described in randomised trials. When no randomised trials have been performed, it is usually better to report this deficiency rather than to include cohort studies, as they are too unreliable for estimation of any possible therapeutic effect. The Cochrane Non-randomised Studies Methods Group is currently working on guidelines on when and how, and with what precautions, such data might be included in Cochrane reviews.¹¹ The possible bias that may be