Annals of the Rheumatic Diseases

The EULAR Journal

Leaders

The first annual EULAR Congress

The June 2000 congress in Nice is the first *annual* Congress of the European League against Rheumatism (EULAR). Until now congresses have been organised once every four years, with smaller sized symposia in between. Another change this year concerns the journal of EULAR. In January 2000 the *Annals of the Rheumatic Diseases* became the official journal of the organisation. For many of the congress delegates, the *Annals* is well known and a good old companion, being the oldest independent international rheumatology journal. For some of the readership it will be a new experience. As from now on all delegates of the annual congresses will receive the *Annals* the readership will automatically be considerably increased. The editorial team is well aware of this new situation and responsibility. We will continue our efforts to guarantee a journal of the highest educational and scientific standards. In addition, we will keep you informed about what is happening in

EULAR. To this end a special section, “EULAR news”, will be included and focused editorials will be written when appropriate.

In this June issue of the *Annals* we make a start with the “Series on education”, which is introduced by Anthony Woolf and Michael Doherty (see following editorial). In subsequent issues a number of specialists in the field will discuss various aspects of education and training in rheumatology. Hopefully, this will encourage a lively debate on these important themes. Last but not least the executive committee of EULAR and the editorial team of the *Annals of the Rheumatic Diseases* wish you a fruitful and, above all, enjoyable stay at the first annual EULAR Congress in Nice.

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Education to improve the health of the nation: Who should we educate?

The overall purpose of health care is to maintain health—to prevent and to treat disorders effectively to secure the greatest possible gain in health. Education is an important means of achieving this. In this issue of the *Annals* is the first of a series of articles on education, each focusing on different aspects that will result in the improvement of outcome of those with musculoskeletal conditions.

Any strategy that is aimed at influencing health must be based on evidence of clinical and cost effectiveness, but also it must be effectively implemented. Implementation requires compliance by the public and patients, in addition to priority and funding. Patients must have faith and confidence based on knowledge. This is especially important with chronic disorders that cannot be cured, are often progressive and, at most points of their natural history, have an effect on a person's quality of life. The enormous expenditure on alternative and complementary treatments testifies to our inability to meet the expectations of the public and to what lengths they will go to try to achieve their desired goals. This gap between what is desired to be achieved and what can be achieved needs to be closed by better treatments developed by research. However, the gap can more rapidly be narrowed by the better application of existing treatments and by more realistic expectations by patients and public. The more the public drives the provi-

sion of care, the more it chases the ideal and not the realistic. Public pressure is important to prevent complacency, but it must be balanced against the harmful effects of creating unfulfilled expectation. Education of patients about what can be achieved and how to gain self management skills, such as developed by Lorig *et al*¹ and promoted in the United Kingdom by Arthritis Care, can result in greater fulfilment.

There are now effective interventions for many musculoskeletal conditions. For example, pain can be effectively relieved, though not always eliminated, by a variety of pharmacological and non-pharmacological approaches; rheumatoid arthritis in many cases can be controlled by an increasing number of therapeutic agents; osteoporotic fractures can be reduced by bisphosphonates; and osteoarthritic joints can be replaced with restoration of mobility and independence. Clearly there is a need for further advances, but much more can be achieved by optimising the application of our existing management options. Much of the current suboptimal application is due to ignorance—not recognising the clinical need, not knowing sufficiently the role of modern interventions, and still retaining a mistaken negative attitude to conditions that are viewed as chronic, incurable, and often the inevitable consequences of age. As a result the patients' problems are not properly

recognised or considered important by professionals. Subsequently, many patients think that they should not complain and learn to cope with their condition and its inadequate treatment.

Recognition of the needs of the patient depends on recognising what is abnormal, what is important to the individual, and what priority is appropriate for action. For chronic diseases both short and long term goals have to be considered. This requires an understanding of the disease, its natural history and impact using the biopsychosocial model,² what can be achieved by interventions, and how to apply them. The use of appropriate interventions depends on knowledge of what is cost effective not only in randomised controlled trials but also in clinical practice to produce health gain. This may be by critical appraisal of the evidence or knowing how to access the assimilated evidence base in systematic reviews such as the Cochrane database.

Recognition of what is abnormal and what is important requires good clinical skills. For conditions as common and pervasive as musculoskeletal disorders, this needs to be acquired from early clinical experiences and reinforced and built on through subsequent stages of training. In many settings the emphasis and exposure to musculoskeletal conditions during training needs to increase to be commensurate with their burden—this is one of the aims of the Bone and Joint Decade 2000–2010. This is particularly true for those who will work in primary care where almost 10% of all consultations relate to musculoskeletal conditions.

Education needs to focus on specific objectives. From these will derive the most efficient methods of learning and appropriate means of assessment. Recommendations for undergraduate education in the locomotor system have been produced in various countries and a core curriculum has been proposed for undergraduate education in Europe.³ These recommendations focus on *rheumatology*, but it is often more appropriate to integrate fully teaching of the musculoskeletal *system* both vertically and horizontally. For example, learning about mechanisms of antigen presentation and acute phase response at the same time as assessment and management of rheumatoid arthritis, and learning about medical and surgical approaches to management together rather than separately. Priority within an overcrowded curriculum can be achieved by the value of basic skills, attitudes, and competencies that are essential to locomotor disease management but which also have general applicability in other areas of medical practice.

The evolution of undergraduate education is towards prioritisation of common conditions that reflect the community morbidity; an emphasis on skills and attitudes, as much as essential knowledge; learning that centres around the student; and encouragement of self directed learning that persists throughout their professional life. One of several ways of encouraging these is problem-based learning, which also requires acquisition of problem analysis skills. This approach is used in many medical schools where the curriculum is taught through a limited number of key illustrative cases.

Teaching is a skill that is frequently undervalued in academic establishments. Such establishments often rate research output and grant income above teaching endeavour. However, there is now increasing recognition of the skills that are necessary to be a good teacher and that good teaching is an essential feature of medical institutions. There are a growing number of “Teach the teachers” courses in many countries, and some have been organised specifically for rheumatologists by the EULAR Standing Committee for Education and Training.

Training in the European Community now reflects the mutual recognition of training and the legal ability, and reality in practice, of free movement of doctors. There is a need, therefore, to harmonise training between European countries, not to standardise practice, but to ensure the same benefits of health care are achieved wherever in Europe a person is treated. There are now recommended training standards,⁴ but audit is needed to see whether the goals are being achieved.

Many of the advances in the treatment of musculoskeletal conditions have been made in the past 10 years, but most current specialists trained before then. Maintaining competency and demonstrating maintained competency is increasingly recognised to be important for the provision of high quality and equitable care. There is a wide range of educational activities to fulfil this need and a move towards continuing professional development. The annual European Congress of Rheumatology will become a major focus of high quality continuing medical education, but it must be used to meet the individual's needs. Assessment of those in practice is becoming necessary in many countries by visitation and in some by re-accreditation. It is essential that the profession shows that it is maintaining its own high skills if it wishes to avoid external regulation.

The application of any strategy requires priority and funding. This priority is not just political at the highest level, but the recognition of importance must be with one's peers as well as the public. There must be much greater awareness of the burden of musculoskeletal conditions and of what can be achieved so that there is more priority both in education and also in the application of these interventions to achieve maximum gain in health. This is the aim of the Bone and Joint Decade 2000–2010.

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1 Lorig K, Lubeck D, Kraines RG, Seleznick M, Holman HR. Outcomes of self-help education for patients with arthritis. *Arthritis Rheum* 1985;28:680–5.

2 ICIDH-2: *International classification of impairments, activities and participation. A manual of dimensions of disablement and functioning. Beta-1 draft for field trials.* Geneva: World Health Organisation, 1997.

3 Doherty M, Woolf A. Guidelines for rheumatology undergraduate core curriculum. *Ann Rheum Dis* 1999;58:133–5.

4 Maini RN. The evolution of the core curriculum in the European Board of Rheumatology. *Rheumatology in Europe* 1998;27:71–5.

COPE guidelines on good publication practice

The Committee on Publication Ethics (COPE) was founded in 1997 by a group of UK medical editors who wished to discuss specific examples of possible research and publication misconduct that they were currently facing. A few, such as the editors of the *Lancet* and *BMJ*, were full time professional editors with a large publishing staff and ready access to expert advice. Most, however, were more isolated part time editors who had received no formal training in publication issues. Additional committee members provided expertise on medical ethics, law, and the practical consequences of actions such as “whistle-blowing”. The discussions of cases by COPE, published regularly in anonymised form,^{1,2} focus on the practicalities of what **should** and what **could** be done in each specific case. These case discussions have proved useful not only to guide appropriate action in individual situations but also as a learning resource for other editors. Importantly, such illustrative cases have highlighted the need for more generic guidelines for good practice on a wide spectrum of research and publication issues.

In April 1999 COPE organised an open one day meeting in London to discuss draft guidelines on good publication practice. Attendance was good with input not only from European and North American editors but also the UK General Medical Council, the Royal College of Physicians, and the pharmaceutical industry. The various research and publication misdemeanours that may be unearthed by the editorial and peer review process were fully debated. The emphasis, however, was on **what action** should be taken by the editor once possible misconduct was suspected or confirmed. The guidelines were modified in the light of those discussions and are now published² and available on the web site:

www.publicationethics.org.uk

Although of potential interest to a wide and diverse audience, these guidelines mainly address **practical issues** and therefore are of particular value to authors, editors, editorial board members, and peer reviewers. The first part of the guidelines considers 10 specific areas—namely:

- Study design and ethical approval
- Data analysis
- Authorship
- Conflicts of interest
- Peer review
- Redundant publication
- Plagiarism
- Duties of editors
- Media relations
- Advertising.

Each is firstly defined and then appropriate standards and conduct for each are specified under “action”. For example, the sections on “Study design” read as follows:

Definition

Good research should be well justified, well planned, appropriately designed, and ethically approved. To conduct research to a lower standard may constitute misconduct.

Action

- (1) *Laboratory and clinical research should be driven by protocol; pilot studies should have a written rationale.*
- (2) *Research protocols should seek to answer specific questions, rather than just collect data.*
- (3) *Protocols must be carefully agreed by all contributors and collaborators, including, if appropriate, the participants.*

- (4) *The final protocol should form part of the research record.*
- (5) *Early agreement on the precise roles of the contributors and collaborators, and on matters of authorship and publication, is advised.*
- (6) *Statistical issues should be considered early in study design, including power calculations, to ensure there are neither too few nor too many participants.*
- (7) *Formal and documented ethical approval from an appropriately constituted research ethics committee is required for all studies involving people, medical records, and anonymised human tissues.*
- (8) *Use of human tissues in research should conform to the highest ethical standards, such as those recommended by the Nuffield Council on Bioethics.³*
- (9) *Fully informed consent should always be sought. It may not always be possible, however, and in such circumstances, an appropriately constituted research ethics committee should decide if this is ethically acceptable.*
- (10) *When participants are unable to give fully informed consent, research should follow international guidelines, such as those of the Council for International Organisations of Medical Sciences (CIOMS).⁴*
- (11) *Animal experiments require full compliance with local, national, ethical, and regulatory principles, and local licensing arrangements. International standards vary.*
- (12) *Formal supervision, usually the responsibility of the principal investigator, should be provided for all research projects: this must include quality control, and the frequent review and long term retention (maybe up to 15 years) of all records and primary outputs.*

Similarly, this is the section on “Duties of editors”:

Definition

Editors are the stewards of the journals. They usually take over their journal from previous editor(s) and always want to hand over the journal in good shape. Most editors provide direction for the journal and build a strong management team. They must consider and balance the interests of many constituents, including readers, authors, staff, owners, editorial board members, advertisers, and the media.

Action

- (1) *Editors’ decisions to accept or reject a paper for publication should be based only on the paper’s importance, originality, and clarity, and the study’s relevance to the remit of the journal.*
- (2) *Studies that challenge previous work published in the journal should be given an especially sympathetic hearing.*
- (3) *Studies reporting negative results should not be excluded.*
- (4) *All original studies should be peer reviewed before publication, taking into full account possible bias due to related or conflicting interests.*
- (5) *Editors must treat all submitted papers as confidential.*
- (6) *When a published paper is subsequently found to contain major flaws, editors must accept responsibility for correcting the record prominently and promptly.*

The second part of the guidelines summarises the principles involved when dealing with suspected misconduct, advises on how to investigate both serious and less serious misconduct, and then suggests eight possible sanctions that may be applied (separately or in combination and ranked in approximate order of severity). Finally, details of other guidelines on research ethics and published codes of conduct are listed in an Appendix.

COPE has no statutory powers and the guidelines are intended to be advisory rather than prescriptive. Although COPE consulted widely in the development of the guidelines, it is expected that they will evolve with time. They will be reviewed and refined as necessary each year.

In common with many editors of other biomedical journals these guidelines were endorsed by the editor of the *Annals*, who feels that they usefully summarise acceptable, expected standards of conduct by authors, reviewers, and editors. The *Annals* has a tradition of interest in all aspects of professional conduct relating to research and publication, and has recognised the importance of appropriate process and editorial responsibility when misconduct arises.⁵ We hope that submitting authors and reviewers for the *Annals* will read the COPE guidelines with interest and join the editor and his board in advancing awareness of the issues involved, and in promoting the highest standards of ethical conduct for research and publication.

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- 1 The COPE report 1998. London: BMJ Publishing Group, 1998.
- 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.
- 4 Council for International Organizations of Medical Sciences (CIOMS). *International guidelines for ethical review of epidemiological studies*. Geneva: WHO, 1991.
- 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 AS¹³ 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 α 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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- Dougados M, Gueguen A, Nakache JP, Velicitat P, Veys EM, Zeidler H, *et al.* Ankylosing spondylitis: what is the optimum duration of a clinical study? A one year versus a 6 weeks non-steroidal anti-inflammatory drug trial. *Rheumatology* 1999;38:235–44.
- Leirisalo-Repo M. Prognosis, course of disease, and treatment of the spondyloarthropathies. *Rheum Dis Clin North Am* 1998;24:737–51.
- Langman MJ, Jensen DM, Watson DJ, Harper SE, Zhao PL, Quan H, *et al.* Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. *JAMA* 1999;282:1929–33.
- Amor B, Dougados M, Khan MA. Management of refractory ankylosing spondylitis and related spondyloarthropathies. *Rheum Dis Clin North Am* 1995;21:117–28.
- Braun J, Bollow M, Seyrekbasan SF, Haberle HJ, Eggens U, Mertz A, *et al.* Computed tomography guided corticosteroid injection of the sacroiliac joint in patients with spondyloarthropathy with sacroiliitis: clinical outcome and follow up by dynamic magnetic resonance imaging. *J Rheumatol* 1996;23:659–64.
- Ward M, Kuzis S. Treatment used by patients with ankylosing spondylitis. Comparison with the treatment preferences of rheumatologists. *Journal of Clinical Rheumatology* 1999;5:1–8.
- Breban M, Gombert B, Amor B, Dougados M. Efficacy of thalidomide in the treatment of refractory ankylosing spondylitis. *Arthritis Rheum* 1999;42:580–1.
- Maksymowych WP, Jhangri GS, Leclercq S, Skeith K, Yan A, Russell AS. An open study of pamidronate in the treatment of refractory ankylosing spondylitis. *J Rheumatol* 1998;25:714–17.
- Corral LG, Kaplan G. Immunomodulation by thalidomide and thalidomide analogues. *Ann Rheum Dis* 1999;58(suppl 1):1107–13.
- Pennanen N, Lapinjoki S, Urtti A, Monkkonen J. Effect of liposomal and free bisphosphonates on the IL-1 beta, IL-6 and TNF alpha secretion from RAW 264 cells in vitro. *Pharmacol Res* 1995;12:916–22.
- Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, *et al.* Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. *Lancet* 1999;354:1932–9.
- Present DH, Rutgeerts P, Targan S, Hanauer SB, Mayer L, van Hozegand RA, *et al.* Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med* 1999;340:1398–405.
- Brandt J, Haibel H, Cornely D, Golder W, Gonzalez J, Reddig J, *et al.* Successful treatment of active ankylosing spondylitis with the anti-tumor necrosis factor α monoclonal antibody infliximab. *Arthritis Rheum* (in press).
- Antoni C, Dechant C, Lorenz H, Olgivie A, Kalden-Nemeth D, Kalden J. Successful treatment of severe psoriasis arthritis with infliximab [abstract]. *Arthritis Rheum* 1999;42(suppl):S371.
- Van den Bosch F, Kruijthof E, Baeten D, De Keyser F, Mielants H, Veys E. Effects of a loading dose regimen of three infusions of chimeric monoclonal antibody to tumour necrosis factor- α (infliximab) in spondyloarthropathy: an open pilot study. *Ann Rheum Dis* 2000;59:428–33.
- Beutler BA. The role of TNF in health and disease. *J Rheumatol* 1999;26(suppl 57):16–21.
- Cope AP. Regulation of autoimmunity by proinflammatory cytokines. *Curr Opin Immunol* 1998;10:669–76.
- De Vos M, Cuvelier C, Mielants H, Vexs E, Barbier F, Elewaut A. Ileocolonoscopy in seronegative spondyloarthropathy. *Gastroenterology* 1989;96:339–44.
- Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Fox RI, *et al.* A trial of etanercept, a recombinant tumor necrosis factor receptor: Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med* 1999;28:253–9.
- Braun J, Bollow M, Neure L, Seipelt B, Seyrekbasan F, Herbst H, *et al.* Use of immunohistologic and in situ hybridization techniques in the examination of sacroiliac joint biopsy specimens from patients with ankylosing spondylitis. *Arthritis Rheum* 1995;38:499–505.
- Braun J, Tuszewski M, Ehlers S, Haberle J, Bollow M, Eggens U, *et al.* Nested PCR strategy simultaneously targeting DNA sequences of multiple bacterial species in inflammatory joint diseases. II. Examination of sacroiliac and knee joint biopsies of patients with spondyloarthropathies and other arthritides. *J Rheumatol* 1997;24:1101–5.
- Calin A, Nakache J-P, Gueguen A, Zeidler H, Mielants H, Dougados M. Defining disease activity in ankylosing spondylitis: is a combination of variables (Bath Ankylosing Spondylitis Disease Activity Index) an appropriate instrument? *Rheumatology* 1999;38:878–82.
- Mease P, Goffe B, Metz J, Vanderstoep A. Enbrel (etanercept) in patients with psoriatic arthritis [abstract]. *Arthritis Rheum* 1999;42:S377.
- Charles P, Elliott MJ, Davis D, Potter A, Kalden JR, Antoni C, *et al.* Regulation of cytokines, cytokine inhibitors, and acute-phase proteins following anti-TNF- α therapy in rheumatoid arthritis. *J Immunol* 1999;163:1521–8.
- Rudwaleit M, Siebert S, Thiel A, Yin Z, Radbruch A, Sieper J, *et al.* Low T cell production of TNF α and IFN γ in ankylosing spondylitis: 1st relation to HLA-B27 and influence of the TNF-308 gene polymorphism. *Ann Rheum Dis* (in press).
- Paleolog EM, Hunt M, Elliott MJ, Feldmann M, Maini RN, Woody JN. Deactivation of vascular endothelium by monoclonal anti-tumor necrosis factor alpha antibody in rheumatoid arthritis. *Arthritis Rheum* 1996;39:1082–91.
- Ohsima S, Saeki Y, Mima T, Sasai M, Nishioka K, Ishida H, *et al.* Long-term follow up of the changes in circulating cytokines, soluble cytokine receptors, and white blood cell counts in patients with rheumatoid arthritis after monoclonal anti-TNF α antibody therapy. *J Clin Immunol* 1999;19:305–13.
- Kavanaugh AF. Anti-tumor necrosis factor- α monoclonal antibody therapy for rheumatoid arthritis. *Rheum Dis Clin North Am* 1998;24:593–614.
- Moreland LW. Inhibitors of tumor necrosis factor for rheumatoid arthritis. *J Rheumatol* 1999;26(suppl 57):7–15.
- Sandborn WJ, Hanauer SB. Antitumor necrosis factor therapy for inflammatory bowel disease: a review of agents, pharmacology, clinical results, and safety. *Inflammatory Bowel Disease* 1999;5:119–33.
- Ward M. Health-related quality of life in ankylosing spondylitis: a survey of 175 patients. *Arthritis Care Research* 1999;12:247–55.
- Carette S, Graham D, Little H, Rubenstein J, Rosen P. The natural disease course of ankylosing spondylitis. *Arthritis Rheum* 1983;26:186–90.
- Gran JT, Skomsvoll JF. The outcome of ankylosing spondylitis: a study of 100 patients. *Br J Rheumatol* 1997;36:766–71.
- Amor B, Santos RS, Nahal R, Listrat V, Dougados M. Predictive factors for the longterm outcome of spondyloarthropathies. *J Rheumatol* 1994;21:1883–7.
- McGonagle D, Gibbon W, Emery P. Classification of inflammatory arthritis by enthesitis. *Lancet* 1998;352:1137–40.
- Zink A, Braun J, Listing A, Wollenhaupt J, and the German Collaborative Research Centers. Disability and handicap in rheumatoid arthritis and ankylosing spondylitis - results from the German rheumatological database. German Collaborative Arthritis Centers. *J Rheumatol* 2000;27:613–22.
- Spoorenberg A, de Vlam K, van der Heijde D, de Klerk E, Dougados M, Mielants H, *et al.* Radiologic scoring methods in ankylosing spondylitis: reliability and sensitivity to change over one year. *J Rheumatol* 1999;26:997–1002.
- Braun J, Bollow M, Sieper J. Radiologic diagnosis and pathology of the spondyloarthropathies. *Rheum Dis Clin North Am* 1998;24:697–735.

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

introduced by relying on non-randomised comparisons of interventions can be large. For example, a meta-analysis of cohort studies of hormone replacement therapy¹² showed protection against coronary heart disease, with a relative risk (RR) of 0.50 (95% confidence interval 0.43 to 0.56), which was not confirmed in a large randomised trial, RR=0.99 (0.80 to 1.22).¹³ Thus a 50% reduction in heart disease, with a narrow confidence interval, proved to be spurious and it is remarkable that there was not even an overlap between the two confidence intervals. The importance of randomisation as a principle and, indeed, of correct randomisation where it is impossible to foresee which treatment the next patient will receive, cannot be overstated. It has been shown that randomised trials with inadequate or undescribed allocation methods exaggerate the estimated effect by 33 to 41%, on average.^{14 15}

Chard and colleagues call for more research comparing different types of interventions, in various stages of the disease. This is important not only for osteoarthritis but for most other diseases. One way of promoting this might be to form transdisciplinary research teams, whose aims should be to identify gaps in knowledge and propose specific research projects. Cochrane reviews and the type of review reported by Chard and colleagues can be helpful in this respect.

Skewnesses in research priorities can be changed for the better—for example, by governmental initiatives providing funding for research that is unattractive to industry. By setting aside 1.5% of its annual budget for systematic reviews and clinical trials, the National Health Service in the UK has given its researchers a unique possibility, envied by most other countries, for increasing the share of research which is directly relevant for the patients. It is tempting to propose that the medical industry—which is generally much more wealthy than governments—should be taxed a certain percentage of its gross income for subsequent allocation to such research. After all, the industry could not exist without the willingness of the patients to contribute to clinical research and of society to provide the facilities for such research. In Denmark, for example, a modest 2% taxation of this income would, for drugs alone, amount to

more than 200 million Kr annually. Such taxation would have a trivial impact on the industry, and if agreed at a supranational level, there would be even less incentive for the industry to move elsewhere. But it would mean that the necessary research could be done.

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- 1 Anonymous. Removing obstacles to healthy development. In: *World Health Organization report on infectious diseases*. Geneva: World Health Organisation, 1999:1–68. (WHO/CDS/99.1.)
- 2 Chard JA, Tallon D, Dieppe PA. Epidemiology of research into interventions for the treatment of osteoarthritis of the knee joint. *Ann Rheum Dis* 2000; 59:414–18.
- 3 Dieppe PA, Frankel SJ, Toth B. Is research into the treatment of osteoarthritis with non-steroidal anti-inflammatory drugs misdirected? *Lancet* 1993;341:353–4.
- 4 McManus P, Primrose JG, Henry DA, Birkett DJ, Lindner J, Day RO. Pattern of non-steroidal anti-inflammatory drug use in Australia 1990–1994. A report from the drug utilization sub-committee of the pharmaceutical benefits advisory committee. *Med J Aust* 1996;164:589–92.
- 5 Dieppe P, Chard J, Faulkner A, Lohmander S. Osteoarthritis. *Clinical Evidence* 1999;2:437–48.
- 6 Hochberg MC, Altman RD, Brandt KD, Clark BM, Dieppe PA, Griffin MR, *et al.* Guidelines for the medical management of osteoarthritis. Part II. Osteoarthritis of the knee. *Arthritis Rheum* 1995;38:1541–6.
- 7 Götzsche PC. Non-steroidal anti-inflammatory drugs. *Clinical Evidence* 1999;2:430–6.
- 8 Altman DG. The scandal of poor medical research: we need less research, better research, and research done for the right reasons. *BMJ* 1994;308: 283–4.
- 9 Russell I. Evaluating new surgical procedures. *BMJ* 1995;311:1243–4.
- 10 Furnes O, Lie SA, Havelin LI, Vollset SE, Engesaeter LB. Exeter and Charnley arthroplasties with Boneloc or high viscosity cement. Comparison of 1,127 arthroplasties followed for 5 years in the Norwegian Arthroplasty Register. *Acta Orthop Scand* 1997;68:515–20.
- 11 The Cochrane Library. Oxford: Update Software, 2000: issue 1.
- 12 Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. *Prev Med* 1991;20:47–63.
- 13 Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, *et al.* Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/Progestin Replacement Study (HERS) Research Group. *JAMA* 1998;280: 605–13.
- 14 Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;273:408–12.
- 15 Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, *et al.* Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet* 1998;352:609–13.