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LESSONS FROM A SYMPOSIUM ON THERAPEUTIC CONTROVERSIES IN RHEUMATOLOGY HELD IN THE COLLEGE ON 5 JUNE 1997 *

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Many rheumatic diseases share the problem of chronicity. Rheumatologists try to address all aspects of the patients' condition and therefore a multi-disciplinary team approach is optimal. Our current therapeutic regimens at best achieve some degree of control rather than cure. In this setting it is increasingly important to be aware of any advances in therapy for specific conditions as well as critically appraising existing strategies. The Symposium held at the College on 5 June 1997 was an attempt to highlight a number of issues in rheumatology which are subject to controversy. A number of expert rheumatologists have carefully scrutinised our current practice, and their views are expressed in this article

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) affects up to one per cent of the population, with an incidence of between 90 and 290 new cases per 100,000 population per annum. RA causes progressive disability and mortality with an average loss of 10-15 years of life expectancy. Traditionally, management of early RA has been conservative with introduction of aggressive therapy only after the disease has deteriorated. However, the observation that remission of RA is rare in most hospital-based studies, coupled with the realisation that slow-acting antirheumatic drugs (SAARDs) are less toxic than originally believed, has led to use of SAARDs at a much earlier stage in the disease. It is also increasingly recognised that better management of co-morbidity such as obesity or hypertension, is as important as control of inflammation in the management of RA.

It is clear that the clinical manifestations of joint swelling, pain and stiffness relate to underlying synovitis and it has been assumed that synovitis results in damage, as measured by radiological deterioration. The progression of rheumatoid disease is non-linear with most of the damage and destruction occurring early on. For these reasons there has been interest in whether early intervention with slow-acting antirheumatic drugs (SAARDS) such as methotrexate, intramuscular gold or hydroxychloroquine might modify the course of the disease.

A large randomised controlled trial (RCT) of 238 patients with early RA has demonstrated that, over one year, early intervention with SAARDs achieves remission in 25 per cent of patients compared with only 13 per cent of patients given traditional delayed therapy, with no increased risk of toxicity.[1] Despite the very successful control of signs and symptoms there was no demonstrable benefit in outcome as measured by the number of radiological erosions. Perhaps this reflects failure to make the diagnosis at a sufficiently early stage to allow intervention with SAARDs to alter the rate of development of new erosions. The slow onset of action of these drugs (on average

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three months), coupled with the current practice of testing each SAARD for at least six months in an individual patient, means that many patients suffer uncontrolled disease for periods of 6-12 months before achieving adequate disease suppression.

Newer strategies include combinations of SAARDs to induce remission at an early enough stage to prevent radiological damage. Most studies of combination therapy have been small, with inconclusive findings. Gold and hydroxychloroquine have not been proven to be definitively more efficacious than either agent alone, although gold is clearly superior to hydroxychloroquine. Hydroxychloroquine or penicillamine combined with sulphasalazine have no advantage over sulphasalazine alone. Benefit has been demonstrated by the addition of anti-malarials and/or sulphasalazine to methotrexate therapy and, in a separate study, by the combination of cyclosporin with methotrexate.[2]

A meta-analysis of randomised trials has challenged the use of combination therapy and has suggested there is only marginal benefit from combination therapy compared to single agent therapy but with a significant increase in toxicity.[3] Since the mechanism of action of individual SAARDs is unclear, combination therapy lacks a credible theoretical basis. Furthermore, combination therapy also suffers the disadvantage that in the long term it substantially reduces the number of therapeutic options available to the clinician, and increases both the costs of monitoring and the risk of reduced patient adherence to therapy. To date, combination therapy has not proved its worth over monotherapy.

An alternative hypothesis to the conventional view that synovitis is inextricably linked to joint erosions has arisen from a trial of low-dose prednisolone, co-prescribed with SAARD, in early RA. This therapy resulted in significant slowing of the development of radiological erosions whereas there was no lasting effect on the symptoms or signs of synovitis. The study challenges the traditional model which holds that synovitis causes erosions, by demonstrating an apparent uncoupling of the two processes. While this raises the real possibility of altering the radiological progression of RA, there remain concerns over the potential long-term toxicity of corticosteroids.

Biological therapies have been available to treat inflammatory rheumatic diseases for at least ten years. These include recombinant reagents, soluble receptors, receptor antagonists and specific monoclonal antibodies. As our understanding of immune and autoimmune processes has improved, specific reagents have been developed that target sites of immune relevance. Monoclonal antibodies against Tumour Necrosis Factor-alpha (TNFα) have produced very effective, though short-lived, control of synovitis.[4] An alternative approach is to attempt to reprogramme the auto-immune response using short courses of specific immune-modulating therapy. Reprogramming, using T cell depletion, was used successfully to induce tolerance to multiple xenografts in animal models.

'Humanised' rat monoclonal antibodies have been used in patients to treat inflammatory conditions, although none of the early studies were placebo-controlled. Campath1H which is directed against the CDw52 antigen on monocytes and lymphocytes has reduced swollen joint counts in rheumatoid arthritis for up to six months following a single course of treatment.[5] Repeat courses of Campath1H have achieved similar clinical responses and, interestingly, these patients have profound reductions in CD4 counts for years following treatment without suffering adverse effects of immunosuppression. Another curious phenomenon is the return of arthritis in the setting of low CD4 counts, suggesting that synovitis cannot be entirely dependent on CD4 T cells. Non-depleting anti-T cell therapy has been shown to be effective in

small placebo-controlled trials, raising the possibility that this re-programmes aberrant autoimmune responses mediated by these cells. Despite the apparent specificity of this approach, the mechanism of action is uncertain and this therapy remains empirical.

Most published trials of biologic therapy in rheumatoid arthritis are limited by a number of factors. Patients recruited to these trials usually have advanced disease that has proved resistant to therapy. Furthermore, the dose of antibodies used and duration of therapy have been largely empirical, and repeated exposure to rat antigens leads to immunisation against the antibody which eventually renders it ineffective.

In other diseases such as vasculitis and severe autoimmune eye disease there are case reports of highly successful responses to monoclonal antibody therapy. The profound effects of targeted immunotherapy on the immune system in these patients suggest that these therapies could have a role in managing some forms of rheumatic disease.

VASCULITIS

The challenges in the vasculitides continue despite significant improvements in outcome as a result of the widespread use of cytotoxic therapy particularly cyclophosphamide. Classification of vasculitis is still not based on a firm understanding of the pathogenesis and remains dependent on consensus agreement and purely descriptive pathology or on clinical symptoms and signs. However, classification is crucially important since it is often used to determine the most appropriate therapy. The most recent Chapel Hill consensus classification[6] separates large vessel, medium vessel and small vessel vasculitis (as did one of the earliest classifications!). The new system differentiates between classical *polyarteritis nodosa*, which generally has a good prognosis following therapy with cytotoxic drugs, and its small vessel vasculitis partner, microscopic polyangiitis in which nephritis and pulmonary haemorrhage result in greater mortality. As a result of the new system of classification, classical polyarteritis has become a very rare disease, whereas microscopic polyangiitis is more frequently encountered. Epidemiological studies suggest that vasculitis occurs at frequency of 20-40 new cases/million/annum.[7] Most of these patients (up to 75 per cent) have an ANCA (anti-neutrophil cytoplasmic antibody) associated Wegener's granulomatosis or microscopic polyangiitis. Current therapeutic regimens of cyclophosphamide and prednisolone have been shown to be very successful in reducing short-term and long-term mortality.[8] Most series report mortality of 20-30 per cent for Wegener's granulomatosis compared to 80 per cent mortality in the first year without cytotoxic therapy. However, morbidity studies highlight the problem of chronic 'grumbling' disease and relapse, which affects the majority of surviving patients. As disease-free survival is unlikely, vasculitis can be seen as a chronic relapsing disease like many other rheumatic diseases.[9,10]

Drug toxicity, particularly from cyclophosphamide is significant and the 33-fold increased risk of bladder cancer is an important long-term outcome.[10] Current regimens of cyclophosphamide include an induction phase, whose duration varies from two or three months up to several years. Newer strategies which are being tested in randomised prospective trials include shorter courses of cyclophosphamide with an early switch to a less toxic remission therapy. Not all forms of vasculitis necessarily require cyclophosphamide. Methotrexate or cotrimoxazole combined with steroid can be effective in non-renal Wegener's granulomatosis. An alternative approach is to intensify the induction regimen using very high doses of cyclophosphamide in an attempt to achieve a cure, thereby avoiding the risk of relapse or chronic morbidity. With advances in management of marrow failure,

particularly autologous bone marrow transplantation, this currently theoretical approach could become a practical reality.

DIFFICULT JUVENILE CHRONIC ARTHRITIS (JCA)

This condition is classified according to the pattern of onset into pauci-articular (fewer than four joints), polyarticular (four or more joints) or systemic onset (systemic features predominate) JCA. Challenging the traditional view that most children grow out of their arthritis, long-term follow-up data suggest that while only 12 per cent of children are significantly disabled (Steinbrocker Functional Class 3/4), four years from diagnosis; 16 years or more following diagnosis around 48 per cent of children are significantly disabled. The disease remains active ten years after onset in up to 35 per cent of children and 30 per cent of these children may have erosive arthritis. Remission rates for JCA in 5-10 year follow-up studies confirm the differential between pauciarticular (40-80 per cent in remission), polyarticular (20-54 per cent in remission) and systemic onset (0-35 per cent in remission) JCA. In other words, the majority of patients with polyarticular and systemic onset disease never go into remission.[11-13] Most rheumatologists do not start slow-acting anti-rheumatic drugs in children until 2.5 years after the onset of disease, by which time 50 per cent of the children with systemic onset or polyarticular onset JCA will already have developed erosions.

Poor prognostic features in JCA include patients with polyarticular disease, systemic onset disease that evolves into polyarthritis, extended pauciarticular disease and polyarticular disease attributable to psoriatic arthritis. The standard approach to therapy has been to use NSAIDs, adding intra-articular steroid injections to resistant joints, possibly with intravenous steroids if there are multiple active joints. If this regimen fails, methotrexate is added for at least two years (with additional hydroxychloroquine or cyclosporin A if methotrexate alone fails). Joint injections in children can have long-lasting benefits compared to adult joint injections which only give an average of three months improvement. Multiple joint injections can induce remission in 20 per cent of patients by one year.

Evidence to support earlier use of methotrexate has come from a randomised controlled study of methotrexate versus placebo in 88 patients with either systemic onset JCA or extended pauciarticular JCA with significant improvement in symptom control coupled with low toxicity rates. Studies of methotrexate use in the treatment of childhood malignancies report no increased risk of infertility or neoplasia in giving a child 20 mgs a week of methotrexate for 50 years.

In 12 children with systemic onset JCA, who had failed to respond to steroids or NSAIDs for at least two years, combination of methotrexate, cyclophosphamide and methylprednisolone with non steroidals and oral background prednisolone improved synovitis and produced remission in 11 children after one year, and a significant improvement in systemic symptoms.[14] A small series of four patients with very severe disease treated with cyclophosphamide, methotrexate, sulphasalazine and prednisolone reported significant improvement in three out of four patients with minimal toxicity, reduction in steroid dose and resumption of growth to normal. Other therapies for difficult JCA include the addition of cyclosporin A and prednisolone to background methotrexate. Studies of oral tolerance with Type II collagen are underway but the likelihood of benefit is small. The role of biologic therapies in JCA is uncertain.

The balance is swinging in favour of early aggressive treatment in children with defined risk factors for poor outcome with the hope that this will achieve better long-term results. It is essential that such regimens are subject to multicentre randomised controlled trials.

DISEASE-MODIFYING TREATMENTS OF OSTEOARTHRITIS

Contrary to common belief, the natural history of osteoarthritis is not inevitable deterioration. Up to five per cent of patients who have significantly damaged hips on X-ray will spontaneously remodel their joints and improve both symptomatically and radiologically. Osteoarthritis is now viewed as a form of decompensated remodelling which eventually results in joint failure. It is clearly a mechanically driven but reparative and active process which is biochemically mediated. There is active cell turnover in damaged cartilage as well as active cell division in the subchondral bone. The traditional remedies for osteoarthritis have been to reduce discomfort, optimise function and minimise risk of progression. The majority of patients benefit from simple measures such as reassurance, encouragement and a regimen of self-management without using any specific interventions. The exception to this is the one per cent of patients who have rapidly progressive disease. Osteoarthritis affects at least one in ten of the population, and should be regarded as a nuisance rather than a disaster. There is significant benefit from weight reduction in osteoarthritis of the knee and the majority of patients would benefit from appropriate cushioning footwear.[15,16]

The use of NSAIDs in the management of osteoarthritis is declining in favour of simple analgesia. There are concerns about the potential effects of NSAID on the health of joints and some evidence that indomethacin may cause progressive cartilage damage. The 'LINK' study has shown 47 per cent progression of osteoarthritic changes in indomethacin-treated patients versus 22 per cent progression in placebo-treated patients. Effective strategies for the management of OA include attempts to realign the joints or improve joint stability.[17] Simple mechanical measures such as a lateral heel wedge for knee osteoarthritis may have a 55 per cent improvement rate which may be as good as a joint replacement. Drug therapy has little to offer and transplant or implant therapy is at an early stage.[18]

The concept of enhancing repair in OA is an area of considerable interest. Growth factor therapy, and the implantation of cells into cartilage defects by autologous chondrocyte grafting may have a role in the future. Despite the wide range of less orthodox agents such as oral collagen and cartilage extracts, there is no evidence to support their use and some of these agents have been withdrawn from the market because of failure to produce any benefit. The concept of second-line or disease-modifying drugs in osteoarthritis is essentially non-existent. This would require a drug that demonstrated efficacy in terms of X-ray appearance within a few years of treatment and safety for treating elderly patients for many years to come. So far, no such drug is available.

USE OF INJECTABLE STEROIDS IN RHEUMATOLOGY

Although Philip Hench used steroids in rheumatoid arthritis in 1949, James Cyriax was the first to apply this therapy directly into joints in 1952. Since that time intra-articular injections with a variety of steroid preparations have become standard treatment for rheumatoid arthritis. There are relatively few controlled trials of this therapy. A recent study of 91 patients given knee injections for inflammation of the knee (the majority had rheumatoid arthritis), with or without bed rest

showed significant improvement in pain, stiffness and knee circumference at 12 weeks following injection, and the benefit was higher in the group given additional bed rest. Differences in efficacy seems to exist between triamcinolone hexacetonide which is more effective than methylprednisolone or triamcinolone acetonide, both of which are more effective than hydrocortisone.[19]

Local steroid injections are commonly used for soft tissue disorders. Subacromial impingement clearly benefits from local anaesthetic and steroid injection, whereas other soft tissue injections are less successful. Up to 50 per cent of patients have persistent symptoms of 'tennis elbow' despite an initial 90 per cent success rate. Similarly, following injections for carpal tunnel syndrome, 82 per cent of patients improved at eight-months' follow-up, but by one year only 20 per cent had sustained benefit. Undoubtedly local steroids can have transient systemic effects through absorption. This therapy has a potential for damage to local structures; skin atrophy and depigmentation are particularly common. Rarer complications include tendon rupture, nerve damage and a transient increase in pain. It is uncertain how steroids might be working in conditions such as adhesive capsulitis where there is no clear histological evidence of inflammation.

Correct placement of steroid injections has been traditionally regarded as essential. In a study by Hollingsworth *et al*, shoulder injections performed at the point of maximum tenderness were far inferior to more carefully anatomically-placed injections in the shoulder. More recent data from Nottingham suggests that a significant number of so-called intra-articular injections are actually peri-articular, and that the outcome of such injections does not differ from truly intra-articular injections.[20]

Epidural injections of steroids for back pain are widely used, but meta-analysis of their effects in over 900 patients from 11 studies suggest modest benefit at best but without long-term adverse effects.[21] Recent guidelines from the British Society of Rheumatology have advised against the use of depomedrone (a form of methylprednisolone), since the polyethylene glycol it contains can, if inadvertently injected intra-thecally, induce arachnoiditis. Most rheumatologists performing this procedure have switched to using triamcinolone hexacetonide in place of depomedrone for this reason.

PSYCHO-SOCIAL ASPECTS OF RHEUMATIC DISEASE

Psycho-social factors may profoundly influence the residual disability and handicap which results from rheumatic disease.[22,23] The best predictors of worse future disability are poor functional capacity at onset of disease, female sex and being single, i.e. unmarried, divorced, separated or widowed. Studies of inter-personal relationships suggest that individuals who have strong community ties are much less likely to die or suffer ill-health. The effect of rheumatoid arthritis on employment depends on pre-existing factors such as the ability to control pace of work; whether or not patients are self-employed and the flexibility allowed in their workplace. Patients with rheumatoid arthritis have lower income levels (up to 48 per cent less) than individuals without rheumatoid arthritis, and reduced income is also further associated with increased levels of pain and depression as measured by self-report health status instruments.

Depression affects up to 22 per cent of patients with RA, although this is not usually the more severe biological form of depression. A similar prevalence of depressed mood is found in other chronic illnesses and other rheumatic diseases. It is influenced by a combination of disability, pain, social isolation and economic resources.

Adherence to medication amongst patients with RA is between 50 and 80 per cent

whereas it is only 30-60 per cent for physical therapy. This contrasts with adherence rates of about 50 per cent in other disorders. Adherence can be increased to between 60 and 80 per cent by explaining to patients why therapy is necessary and by making sure that patients understand their prescriptions.

Disability as a result of disease is influenced by coping strategies and these are defined by what patients do, think and feel about the illness. Patients often go through phases of information seeking, re-interpretation of their lives and look for help. These are positive features which can reduce their disability. Wishful thinking (hoping that their disease will go away) is usually not helpful. To cope effectively with their disease patients need to be encouraged to acquire greater understanding, motivation to manage their disease and assistance with their emotional distress. Close social supports are not always beneficial; for example, patients with highly critical spouses often acquire unhelpful coping strategies and may in fact cope better alone. A sex bias also exists; male patients tend to rely on social support from their partners, whereas female patients have to rely on wider networks.

An interesting difference in illness beliefs can be shown between North American and British populations. Common lay perceptions include the beliefs that diseases are influenced internally (i.e. by one's self), or by 'powerful others' such as doctors, or by chance. In the USA the majority of individuals believe that the influences of self and those of 'powerful others' are the most significant influences on disease or illness, whereas in the UK the more common belief is that chance is the main factor.

EVIDENCE-BASED RHEUMATOLOGY

Current approaches to the study of RA and its long-term outcome need to be challenged, with more emphasis given to the chronicity of the disease, its psychosocial aspects and non-medical interventions.[24] Randomised controlled trials (RCT), the usual gold standard for establishing therapeutic efficacy, may be misleading – one example being the demonstration of the efficacy of auranofin, a drug which in clinical practice is now regarded as largely ineffective.[25] Long-term observational studies of effectiveness (i.e. does a drug work?) as opposed to efficacy (can it work?) may be of greater value because of their focus on the patient rather than the drug. RCT are subject to selection and spectrum bias in a way which can be avoided in observational studies.[26,27] 'Left censoring', that is exclusion of patients with early disease, is a common problem in many RCT's. Because of strict selection criteria, patients with mild disease at onset may be excluded from trials until their disease is well established, whereas those with severe disease at onset tend to be recruited earlier. Exclusion of patients who spontaneously remit is a further source of bias. Conversely, patients who die or are lost to follow-up tend to have lower socioeconomic status and worse health; such patients are often excluded from analysis (i.e. are subjected to 'right censoring') which may improve the apparent outcome of an RCT.

The effect of publication bias is important to consider. Chance observations are more likely to be published if they show significant differences between treatment regimens as compared to studies which fail to demonstrate such differences. If observations are continued over long periods, chance variations may disappear.[28] Many studies are unreliable because of inappropriate sample size, inappropriate use of statistics such as multiple hypothesis testing, and extrapolation beyond the data.

Professor Fred Wolfe has been collecting long-term observational information on all patients attending the Witchita rheumatology centre since 1974.[29] These observations have shown that measures such as the disability index of the Stanford Health Assessment

Questionnaire (HAQ), pain scores, arthritis scores and depression scores are very different at any early stage in the disease compared to late stage disease. Whereas these scores deteriorate progressively during the first five years, beyond that time they plateau. Thus studies involving patients with longer duration of RA are less likely to demonstrate a good response to therapy compared with those with early disease.[24,28] Work disability in rheumatoid arthritis over ten years is significantly influenced by pain, rheumatoid factor levels, signs of disease activity, the presence of depression, educational ability and obesity. A strong case, therefore, can be made for long-term observational studies in routine clinical care.[30]

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