

NEW MEDICINES REAL HOPE OR MERE HYPE?

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There has been an unprecedented series of apparent breakthroughs in the treatment of rheumatic diseases in the past three years without parallel since the introduction of cortisone into the treatment of rheumatoid arthritis more than half a century ago. Because psoriatic arthropathy is much less common than rheumatoid arthritis it has been difficult so far to organise trials of new medicines for this disease because the manufacturers for the most part have not felt it worthwhile to conduct trials for what it to them a small market. However happily this is beginning to change. Also the British Society for Rheumatology has put psoriatic arthritis very high up its list for new research resources.

Many of the medicines which are used to treat rheumatoid arthritis have been found to be of value in psoriatic arthritis too. Indeed one went in the opposite direction, methotrexate, starting off much earlier as a treatment for psoriasis and for the arthritis associated with it and later being adopted for use in rheumatoid arthritis.

NOVEL ANTI-INFLAMMATORY DRUGS

There are three main categories of new remedies. The well-established non-steroid anti-inflammatory drugs have all suffered from some problems,

the ill-effects on the stomach and sometimes the small intestine, a tendency to precipitate asthma in sufferers from that condition and a tendency to cause fluid retention which worsens heart failure and high blood pressure. We now have additional agents referred to as Cox-2 inhibitors. The older drugs inhibit the enzymes, cyclo-oxygenase 1 and 2, whereas progressively newer remedies have sought to inhibit Cox-2 only, hence their name. Of these the two drugs which make the separation most completely are rofecoxib (Vioxx) and celecoxib (Celebrex). How well do these shape up in the heat of the day in ordinary clinical rheumatology practice outside the rarefied atmosphere of the double-blind clinical trial? For trials patients are very carefully selected and must not have some of the risk factors which are encountered in everyday practice and for which, of course, these drugs are designed to be better than the older ones.

ORIGINAL AND BEST?

In this country Vioxx appeared first with a licence for osteoarthritis only, but as predicted rapidly became used for other kinds of arthritis too. In osteoarthritis of moderate severity, patients were fairly pleased with the results and very few complained of indigestion. However a number of patients complained that, although the drug did not upset them, it did not work in relieving their pain and this was the more obvious when it began to be used for inflammatory arthritis including that of psoriasis.

Gradually it became apparent that there were some patients in whom this drug tended to cause at least as much fluid retention as some of the older ones and withdrawal of the drug has been necessary in such cases. Trials compared it with quite high doses of ibuprofen (Nurofen) so that, not surprisingly, it came out better in terms of indigestion and gastric bleeding but this does not mean it is devoid of a tendency to cause such symptoms and certainly we do see them in everyday use. Celebrex was licensed later but for a much larger range of types of arthritis. It seems to be at least as good as Vioxx from the point of view of not causing indigestion and there is some evidence that it may be less likely to cause fluid retention. There is shortly to be a trial directly comparing these two drugs head to head, with particular respect to fluid retention and elevated blood pressure, so eventually we will know the answer to this.

BATTLE IN THE MARKET PLACE

There is obviously bound to be intense rivalry between the manufacturers of such similar products and a good deal of propaganda is put out on all sides. For instance, someone went through the figures very carefully with one of the Vioxx trials and put out the message that there was an increased number of heart attacks in those treated with it, compared with other drugs. What no-one seemed to point out at the time was that if you reduced the tendency for patients to have gastric bleeds, one of the ways you do this is by reducing the effect on platelet stickiness. The purpose of platelets is to block up little punctures in the walls of blood vessels. Aspirin-like drugs, which inhibit Cox-1 as well as Cox-2, protect against heart attacks by making the platelets less likely to stick and

therefore the blood less likely to clot. As they say, there is no free lunch, and you probably cannot have the advantage of reduced gastric bleeding and reduced incidence of heart attack at the same time with the same drug, or at least not with the ones available at the moment, although this may be eventually possible. At the same time, unfortunately, it is the case that neither of these new products are an improvement on the older ones from the point of view of induction of asthma, although no-one seems actually to have been mentioning this, and people have been given the feeling that the drugs are better all round. There is no evidence that either of them are more effective than previous ones from the point of subduing pain and swelling and they are only better from the point of view of not upsetting the stomach.

A UNIQUE MOLECULE

The second category of important medications is occupied by only one drug, Leflunomide, which has been little tried in psoriatic arthritis but the subject of a number of successful trials in rheumatoid arthritis. This is a very novel drug chemically, and this carries inherently the disadvantage that, although the trials have shown up very few major problems so far, we have no knowledge at all of what the long-term rare side-effects may turn out to be because it is insufficiently similar to other drugs for us to know what to look out for. Experience with this drug in this country is still not extensive and we do not know whether using it for psoriatic arthritis will be more or less successful than with rheumatoid arthritis. My own personal experience is very limited with it so far but the first patient with psoriatic arthritis to whom I have given it and who was not responding to a mixture

of other powerful drugs, does seem to be responding better to this new one, so there is clearly a very strong case for a properly conducted trial of it in this disorder.

ANTI-TNF ALPHA

The third and major group of drugs which are the focus of most interest at the moment are those which act on tumour necrosis factor alpha, which could be described as the conductor of the cytokine orchestra. Cytokines are chemical messengers between certain types of cells which keep the inflammatory process going and as a result of a great deal of research, much of it done in the UK, under the direction of Professor Maini at the Kennedy Institute of Rheumatology, an antibody to this agent has been developed for clinical practice. There has recently been published a study of its effectiveness in psoriasis and it is very impressive in clearing even stubborn plaques of psoriasis within a surprisingly reasonable period of time. There are a number of trials of rheumatoid arthritis which show it to be effective even at a level of 70% improvement, according to the American College of Rheumatology criteria, if a sufficient dose is given. The problem is the cost and the fact that it has to be given by intravenous infusion. The NHS estimates the cost at £10,000 per year, so that we have the same problems in obtaining it as we have in trying to treat patients with gamma-interferon for their multiple sclerosis and postcode prescribing is the order of the day at the present time.

FORTHCOMING TRIAL IN PA

There is to be a proper double-blind controlled study of this biological agent, known as infliximab (Remicade) set up by the manufacturers very soon and we hope to be able to

recruit patients for this, but they will initially be only those with very severe psoriatic arthropathy who are not responding to methotrexate. When this drug is used it is used in combination with low-dose methotrexate, so that those who cannot take that drug will obviously be unable to participate in the trial.

There are obviously side-effects with this treatment and the elimination of patients who have had tuberculosis or who may have any deep-seated chronic infection, does seem to be an important move in selecting those who should be treated with it. A wide range of minor side-effects have been reported, the most common being a flu-like feeling which follows the infusion and sometimes allergic reactions and this is the reason why it is given by infusion only under hospital supervision, usually as a day-case.

TRIALS AND TRIBULATIONS

The alternative to Remicade is etanercept (Embril), already shown effective in trials for psoriatic arthritis, this works in a similar manner to Remicade although its structure and precise mechanisms of action are somewhat different. This is given by subcutaneous injection in the same way that diabetics give insulin to themselves, which obviates the need for hospital attendance and needs to be given much more frequently and patients have to adapt to self-injection. The range of side-effects is slightly different and since I talked about these medicines in the conference last year, there have been rather more problems with blood count abnormalities and particularly there has been reported a clinical picture resembling multiple sclerosis, which is rather worrying. The American authorities believe that what one is seeing with such patients developing

neurological abnormalities, is the unmasking of unsuspected mild multiple sclerosis which the treatment worsens. This would argue for careful scrutiny of patients for such an underlying problem before commencing the treatment. We are not sure whether this is really the whole explanation and demyelination, the process involved in multiple sclerosis, has just been listed as an additional complication of the treatment itself in the etanercept literature, which would make one feel rather more cautious than before about prescribing this agent, the cost of which is very little different from that of Remicade. In addition there have been recurrent supply problems so that there is uncertainty about

how many patients can be supported long term with its use.

There remains the problem of how we are to persuade the Department of Health of the importance of giving such treatments to severely affected patients and surely the strongest argument must be the huge saving in cost if severe disability can be avoided, bearing in mind the huge expense incurring on carers, housing adaptations and other less effective medications used to try to fight the disease. The British Society of Rheumatology is collecting information about the policy of every health district as to which are providing treatments of this type and will be lobbying for changes

in the priorities given to different types of treatment in favour of these medicines. Our support in this matter, as individuals and as an association, is vitally important.

If we can succeed there is real hope.



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