Controversies in the treatment of osteoarthritis

Osteoarthritis remains a poor relation in the shadow of rheumatoid arthritis, a disease that has seen massive drug development and investment with the advent of biological agents. This is in spite of osteoarthritis remaining a global problem, actually increasing in frequency worldwide as life expectancy increases dramatically in Third World countries. In the developed world healthcare budgets, now significantly stretched by the development of expensive drugs for the modification of rheumatoid arthritis, leave little in hand for this condition or the joint replacement that often remains the endpoint of treatment.

One problem in developing specific therapy is the diversity of conditions that lead to osteoarthritis as a common endpoint [1]. If osteoarthritis results from a metabolic cause, rational therapy comprises early identification of this and appropriate specific treatment. If the cause is biomechanical, management should be by avoidance of ergonomic stress. Among that group for which there is no obvious predisposing metabolic cause, subtle risk factors are emerging from epidemiological studies. For osteoarthritis of the knee [2] significant associations occur with obesity, certain sports, and particularly family history, as well as the presence of pyrophosphate deposition. Surprisingly, smoking seems to have a protective effect. The influence of these subtle factors also varies between joints [3]. Osteoarthritis of the hip is more frequently seen in Caucasians of either sex; osteoarthritis of the knee affects all races, with a female predominance. Osteoarthritis of the hip is less influenced by ageing; osteoarthritis of the knee is more influenced by obesity.

The slow progression of osteoarthritis also creates particular difficulties in the design of clinical trials, as it always has [4]. Imaging does not reach the same degree of detail and sophistication as is now available for rheumatoid arthritis, techniques that magnify conventional X-rays seeming to have more promise than alternative imaging modalities. Functional scales provide long-term surrogates and questionnaires, and visual analogue scales are traditionally used in the measurement of pain, although the presence or absence of this does not necessarily correlate with long-term damage, the prevention of which should always be the aim.

The benefits of physiotherapy should not be ignored [5,6]. Symptomatic relief may be obtained by heat and/or cold. Aerobic fitness training is important and simple quadriceps strengthening exercises, including straight leg raising in a sitting position and the more advanced straight leg raising in a lying position, have been demonstrated to relieve pain without the side effects of drugs, probably through their action in stabilising the joint by improving muscle bulk and tone. Local facilities may influence treatment. Spa therapy and balneo therapy, with access to relatively unlimited inpatient care, are time-honoured in eastern Europe, probably conferring psychological as well as physical benefits. Physiotherapy in western Europe has concentrated on outpatient remedies.

Analgesics are undoubtedly of value for symptomatic relief but their use may also be influenced by local practice. Paracetamol has emerged as the safest drug of choice [5] and is widely prescribed worldwide. At the periphery it is only a weak inhibitor of cyclooxygenase [7] and so has little anti-inflammatory effect. It has a short half-life and should be dosed ‘on demand’. When this fails to help, UK prescribing then traditionally moves to one of the three compound generic analgesics: co-proxamol (paracetamol plus dextropropoxyphene), co-codamol (paracetamol plus codeine) or co-dydramol (paracetamol plus dihydrocodeine), often in that order. The small admixture of the more potent opiate is thought to enhance the analgesic properties while sparing the side effects if such a drug were to be used alone. The difference in half-life sometimes present...
between the two constituents is felt to be of minimal theoretical risk if the drugs are prescribed on a regular basis. Other analgesics are available [8,9] which avoid the use of conventional injectable opiates, for which there is probably no place in the management of osteoarthritis.

The use of non-steroidal anti-inflammatory drugs (NSAIDs) is more controversial. For purely practical reasons their use may be greater in those countries that have a limited choice of analgesics. Worldwide the choice of available NSAIDs far exceeds the choice of available analgesics. When prescribed (which is only likely to be when analgesics alone have failed to control symptoms) the drugs are rationally reserved for episodes of inflammation, drugs of short half-life preferably being given a little before events that precipitate this. Usage should be restricted to the minimum dose, although in the elderly drugs that selectively block COX-2 [10] may be of particular value in spite of their greater expense.

Once rest, physiotherapy, weight reduction and analgesics by oral and topical routes (or even topical counterirritants) have been tried, consideration should be given to intra-articular therapy, particularly if the osteoarthritis is relatively localised. Rationally this is reserved for joints where there is clinical evidence of inflammation, but it is surprising how often pain is relieved by steroid injection even if the synovial swelling and fluid are not clinically apparent. The substantial chemical and therefore pharmacological differences between steroids are often forgotten [11]. Hydrocortisone is the least potent (though the safest), and the efficacy of the more potent prednisolone is enhanced if this is methylated (to give methylprednisolone) or fluorinated (to give triamcinolone). Solubility can be reduced (and hence the duration of action prolonged) by the addition of appropriate insoluble side chains. However, this molecular modelling has proved so successful that some licensing authorities consider the side effects of these potent steroids to outweigh their advantages, leading to their withdrawal. Worldwide, methylprednisolone or triamcinolone remain the gold standards against which other therapies are judged. There is also proven value in synovial lavage at arthroscopy, normally under local anaesthetic, when steroid injection has failed [12], this being most useful when the osteoarthritis is complicated by crystal deposition [13].

Against this conventional background, a variety of recently introduced compounds (some long-standing but recently popularised) for which disease-modifying activity is claimed in osteoarthritis have to be considered. This concept is not new but has been more popular in some countries, notably eastern Europe and German-speaking European countries, than in others. Candidates once in vogue include Dona-200S, which had undesirable heparin-like properties, Tribesanoside, which was not effective in trials, and the more widely prescribed Arteparon (glycosaminoglycan polysulphate) [14,15] and Rumalron (glycosaminoglycan-peptide complex) [16,17]. Following the success of short-term studies, groups of patients were treated with both Arteparon and Rumalron in a longer-term controlled trial with radiological evaluation [18]. Although significant change with active treatment was claimed for both drugs, the lack of injection therapy (with its psychological benefit) in the control group compared to the injected compounds in both treatment groups, together with the relatively small change seen radiologically, which appeared not always to have been standardised by restriction to a single centre, caused some anxiety in interpretation.

The promise (or otherwise) of these earlier attempts at cartilage regeneration led to the development of a range of hyaluronic acid preparations, which are given by the intra-articular route. A wide variety of these have been developed (particularly in Japan for use in the Far East), and in most European countries at least three are available. Interestingly, those classified as ‘appliances’ have been subjected to less stringent pharmacological and pharmacokinetic assessment than those classified as ‘drugs’. The prototype hyaluronic acid has long been used in eye surgery, but reformulation of this compound is needed to concentrate it into a volume suitable for injection into the knee joint. The preparations vary according to their molecular weight and viscosity, those with the higher molecular weight being preferred. Disease-modifying action has been claimed [19,20]. Compared to steroids the injections are expensive and ungainly, requiring repeated joint puncture with its risk of infection. A single trial against the rational comparator, intra-articular triamcinolone, although small, suggested that short-term benefits were better with the steroid [21].

Less expensive, and with the advantage of being taken by mouth, is glucosamine sulphate. This is the most widely purchased of a group of comparable compounds, including hyaluronan, chondroitin sulphate, glucosamine sulphate and glucosamine hydrochloride. There are theoretical and clinical reasons for suspecting that glucosamine hydrochloride might be more potent than the sulphate, but the sulphate has achieved wider popularity [22]. An 8-week placebo-controlled trial of glucosamine in osteoarthritis of the knee in 118 patients [23], which evaluated the WOMAC score, pain during the trial and radiological score, demonstrated significant improvement over matched placebo, and a further study in 202 patients with primary osteoarthritis of the knee [24] compared glucosamine 500 mg t.d.s. with placebo over 3 years using the WOMAC index, Lequesne index and radiological evaluation as outcome measures showed significant improvement in most parameters. Not all studies have been so convincing [25], but a recent prospective randomised double-blind 3-year study from Reginster [26] showed significant improvement radiologically (in terms of protection of joint space) and symptomatically, so the pendulum probably just swings in favour of efficacy. More data are clearly required to ensure that the results are not an artefact of the relatively small number of patients so far treated in a controlled fashion, but if efficacy continues to be