measurement of monocyte procoagulant activity (MPA) after challenge with cartilage-derived antigens in OA patients might provide such a marker [4].

Therapies currently available for the treatment of OA, for the most part, only modify the symptoms of the disease rather than the underlying cause. From laboratory studies [5] and our previous clinical investigations [6], we considered that pentosan polysulphate (PPS) offered potential as an agent with disease modifying activities in OA. The objective of the present investigation was to evaluate this hypothesis.

Methods and Results

In this study the effects of 4 weekly intramuscular injections of PPS (3 mg/kg) were determined on OA patients ($n = 11$) symptoms, peripheral blood monocyte procoagulant activity (MPA) [7] and blood white cell populations over an initial 24 h period and then 8 weeks thereafter. Clinical assessment continued for weeks 12, 16, 20 and 24 from initiation of the study. In all patients MPA was reduced relative to baseline pre-drug values for up to 24 h post-PPS treatment. In those patients with a moderate, but not mild, grade of OA this reduction in MPA was sustained for up to 4 weeks following the last (4th) i.m. injection of PPS. The reduction in patient's MPA correlated for the moderate OA group, with a decline in many of their clinical symptoms including: global pain ($r = 0.958$), effectiveness of treatment ($r = 0.915$), pain on walking ($r = 0.800$) and time to climb 15 steps ($r = 0.768$). The precentage of leucocytes increased in blood of all OA patients receiving PPS, maximum levels being achieved after 8 h. The major contribution to this rise in leucocytes was from lymphocytes since monocytes and neutrophils actually decreased after PPS treatment. Significantly, 4 weeks after the last PPS injection the lymphocyte populations were still elevated ($p < 0.04$) and neutrophils depressed ($p < 0.04$) in the blood 8 of the 11 patients studied. Platelet levels were also elevated in PPS-treated patients relative to their baseline values ($p < 0.005$).

Conclusion

The present findings leads us to conclude that monocyte procoagulant activity could provide a useful means of monitoring disease progression and patients response to disease modifying drug treatments in OA. This study also demonstrated that PPS altered the distribution of leucocytes present in blood of OA patients. Most notable was the elevation of the percentage of lymphocytes present and the depression of neutrophil levels for up to 4 weeks after the last injection of the drug. Although numbers were small, in those OA patients whose lymphocytes and neutrophils levels returned to their baseline values, symptoms re-appeared. From these investigations, we conclude that PPS is a drug with an unusual mechanism of action. Apart from its known pleotropic actions on connective tissues and epithelium, it now appears that it is also immunoregulatory both in terms of leucocyte recruitment and in the expression by these cells of activities which are implicated in the pathogenesis of OA.

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PROBLEMS ASSOCIATED WITH CLINICAL ASSESSMENTS OF INTRA-ARTICULAR THERAPIES FOR GONARTHRITIS

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The aim of this paper is to present some of the questions that need to be addressed before interpreting current data and conducting future trials and evaluation of intra-articular therapies for asteoarthritis (OA). Patient selection, disease subsets, outcome measures, trial setting, symptoms control, drop-outs and placebo response will be discussed.

Patient Selection

We need to be aware that patients assessed by a specialist will be different to those referred by a general practitioner and even more so to the highly motivated volunteer OA sufferer who was recruited for the trial after reading a newspaper advertisement.

Disease Subsets

It is now well recognised that OA of different joints has varying disease onset and progression. combining patients in global OA trials may dilute important subset effects. However, the move in recent intra-articular therapy trials to find the homogenous unilateral medial tibio-femoral OA in select age, sex and racial groups leads to many potential recipients being excluded and makes trial recruitment at a single site impractical. Can we use patients with bilateral disease as their own controls? Can we expect patients with bilateral disease to accurately assess outcomes? Can we mount large multi-centre trails that include suficient numbers in multiple disease subsets?

Outcome Measures

Are the current measures that have been well validated for the advanced OA patient undergoing joint replacement surgery suitable for the young active patient with early OA whose main aim is to get back to running or competition tennis?

Trial Setting and Conduct

How much influence does the special research clinic and the attentive metrologist have on the patient responses? Could or should we mimic "usual patient care"?

Symptom control

To evaluate disease modification patients will need to be observed over periods of at least two years. Are we expecting too much of the new therapies that they should control symptoms in the immediate and long-term? Will combination therapy be required?

Drop-outs

Analysis should be by intention-to-treat as placebo-controlled long-term studies for OA to date have had a significant differential in drop-out rates between active and placebo arms. Should we encourage patients to maintain trail protocol and avoid all other therapies or are we just increasing the chance of finding no difference? Drop-out rates should be an important outcome measure.

Placebo Response

How can we see a treatment effect when the placebo group report up to 60% treatment satifaction and improvement in pain and function?

Osteoarthritis is a common and disabling condition and the implications of a disease modifying therapy are substantial. Once the challenges of radiological biochemical and histopathological assessment of disease progression have been met then large multi-centre trials with randomisation within subsets of OA must be undertaken.

A DOUBLE-BLIND PLACEBO-CONTROLLED STUDY OF INTRA-ARTICULAR PENTOSAN POLYSULPHATE (CARTROPHEN) IN PATIENTS WITH GONARTHRITIS-LABORATORY AND CLINICAL FINDINGS

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Objective

Pentosan polysulphate (PPS) (Cartrophen) is a new anti-osteoarthritis drug which from laboratory and animal studies [1] offers potential for disease modification in osteoarthritis (OA). The present study was