

Rheumatology

RECENT MAJOR ADVANCES in rheumatology have been given further impetus by the declaration of 2000–2010 as the Bone and Joint Decade. This initiative, endorsed by the United Nations, aims to improve health-related quality of life for people with musculoskeletal disorders worldwide.

Prevention. The imperative to prevent chronic disability from musculoskeletal conditions is increasingly being recognised. For instance, beliefs and behaviour associated with acute back pain, which may have potentially costly and prolonged sequelae in the workplace, can be altered with early appropriate intervention.¹ The incidence and severity of knee osteoarthritis, the most important cause of musculoskeletal disability, can be reduced by better weight control and avoiding excessive deep-knee bending, while corticosteroid-induced osteoporosis can be prevented by concomitant use of bisphosphonates.²

Diagnosis. Assessment of osteoporosis and monitoring of response to interventions will be improved by combining bone densitometry with ultrasound (to define other important bone characteristics, including fragility) and better methods of determining biochemical markers of bone turnover.

The difficulty of identifying osteoarthritis at an early stage (when interventions are most effective) will be overcome by refining the use of MRI and other imaging techniques and developing specific markers of cartilage breakdown and repair, such as proteoglycans. Likewise, early intervention in rheumatoid arthritis significantly affects symptom control, joint damage and functional ability. Both MRI and ultrasound will soon be used to accurately detect early inflammation and joint damage in rheumatoid arthritis and allow for stratification of different intervention strategies.

Intervention. Osteoporosis management has been significantly improved by the newer-generation bisphosphonates (alendronate, risedronate). The selective oestrogen-receptor modulators (SERMs), such as raloxifene, also offer fracture protection, lower lipid levels and a reduced risk of breast cancer. Newer SERMs will provide more selective and potent effects in bone and breast tissue. Pulsed daily parathyroid hormone therapy, which increases bone mineral density and possibly reduces fracture rates, and osteoprotegerin, a potent inhibitor of osteoclast action, will both improve management of osteoporosis.

Glucosamine may reduce knee cartilage loss, but the full significance of its effect on osteoarthritis has yet to be established.³ More definitive osteoarthritis treatment may be possible within the next five years, with progress in elucidating the mechanisms of cartilage breakdown and repair. Several potential agents are currently undergoing clinical trials.

Selective COX-2 inhibitors suppress joint inflammation and, compared with non-selective agents, significantly decrease rates of major gastrointestinal adverse events. They do not affect platelet function, but provide no advantage in regard to salt and water retention.⁴ Selective inhibitors of inflammation-induced isoforms of the upstream precursors of



phospholipase A2 may have equivalent anti-inflammatory effects, with less disturbance of homeostasis.

Methotrexate remains the baseline medication of choice for early intervention in rheumatoid arthritis, with current trends being to use higher doses and drug combinations. Leflunomide, a pyrimidine pathway inhibitor, provides significant benefits, especially when

introduced early and in combination with methotrexate. The effectiveness of cyclosporin is also improved by combining with methotrexate, but it must be used with care because of its adverse effects on blood pressure and renal function.

Suppression of specific components of the rheumatoid arthritis inflammatory cascade has proved effective. Tumour necrosis factor (TNF) suppression by TNF fusion protein (etanercept), chimeric anti-TNF antibody (infliximab) or human monoclonal anti-TNF (adalimumab) all result in significantly less inflammation and reduced joint damage in the short term. Early data on safety and cost-effectiveness are encouraging.⁵ Suppression of interleukin-1 by the IL-1-receptor antagonist anakinra may decrease bone damage proportionally more than inflammation. Combinations of such agents will target the different components of the rheumatoid arthritis process. Future development of less expensive, oral agents with similar specificity will permit broader application of targeted therapies. Longer-term toxicity issues may yet emerge.

Applying pharmacogenomics (the study of genes relevant to drug therapy) and modulation of pro-inflammatory intracellular enzymes will further refine possibilities for modifying inflammatory processes. Recognition that corticosteroids act via these pathways has opened this field to the development of novel broad-spectrum immunomodulatory agents, some of which are in early-phase clinical trials.

Drugs that modulate the sensitised pain mechanisms of fibromyalgia and regional pain syndromes include, among others, derivatives of gabapentin and inhibitors of the 5-hydroxytryptamine receptor. Clinical trials suggest that these approaches will provide useful ancillary treatments.

Conclusion. With the impetus that the Bone and Joint Decade will bring to research in rheumatic diseases, we can expect further elucidation of disease mechanisms, and an increase in management options.

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