Some Recent Advances in Rheumatology

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Introduction

Although rheumatic problems are not fatal, they are among the more frequent causes of morbidity and long term disability in the population. They range in severity from minor aches and pains affecting the joints and related structures, to serious and potentially fatal conditions. Most of the rheumatological patients have to be followed up and given treatment on a chronic basis. Accordingly, rheumatic diseases have a major impact on the function and productivity of a community. This impact is likely to increase dramatically over the next decade and beyond. In light of this, the World Health Organisation has declared the years 2000-2010 as the Bone and Joint Decade. This movement is supported by the United Nations and endorsed by almost 50 countries including Hong Kong as well as over 750 patient and health professional societies, academic and research institutions around the world. It is comforting to know that, in the midst of this World Health Organisation's designated decade for bone and joint disease, there have been a number of important advances in the field of rheumatology in the past few years with respect to both diagnostic modalities as well as therapeutic armamentarium.

The Bench

Much of the laboratory approach to management of rheumatic diseases has been consumed by the effort to establish the presence of autoantibodies in rheumatic patients and to identify their particular specificities. Increasingly, more sensitive methods of antibody detection are being used such as enzyme linked immunosorbent assay (ELISA) and immunoblotting. It is becoming clear that autoantibodies in the context of connective tissue diseases are directed against highly selected targets and not just the result of nonspecific polyclonal B cell activation. It is also getting apparent that certain autoantibody profiles are associated not only with a clinical diagnosis but also with particular clinical manifestations and as a consequence, the prognosis. Typical examples are photosensitivity and neonatal lupus syndrome associated with anti-Ro antibody, recurrent abortions and thromboembolic problems associated with anticardiolipin antibody and interstitial lung diseases in dermatomyositis associated with anti-Jo 1 antibody.

Enormous effort has also been made in the past years on defining the genetic predisposition of individuals to development of rheumatic diseases. The majority of known genetic associations with rheumatic diseases have been worked out to be with loci which map to the human major histocompatibility complex (MHC) or HLA region. Polymorphisms within this area have now been shown to play a role in many rheumatic diseases including rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis and pauciarticular juvenile chronic arthritis. Relatively recent advances in molecular biology offer new paradigms and even more importantly, new tools for understanding the genetic component of several rheumatic diseases. It is unlikely that the genetic component of the majority of rheumatic diseases will map to a single locus and be explained by a single or several dysfunctional alleles as is the case with sickle cell anemia and cystic fibrosis. Many rheumatic diseases appear to have a multifactorial basis and inheritance of susceptibility is likely to be oligogenic or polygenic. It is hoped that these genetic studies will eventually prove to be most useful by providing a rationale for the design of novel therapies prior to
direct exposition of the mechanisms involved. Clinical improvement will therefore be the ultimate test of susceptibility locus assignment.

Clinical Assessment Tools

Radiological imaging often provides, noninvasively, information on the gross pathological processes in the musculoskeletal system in rheumatic diseases. In some instance, a specific diagnosis may be possible. There have been quite a number of new imaging techniques for evaluation of rheumatic diseases developed in recent years.

Computed tomography with multiplanar reconstruction and magnetic resonance imaging have both been shown to offer the advantage of identifying early changes in the necrotic bone marrow before other changes in the bone have taken place. This would allow an enthusiastic orthopaedic surgeon to intervene early to hopefully abort the full development of avascular necrosis in the patients. On the other hand both positron emission tomography (PET) and magnetic resonance imaging (MRI) have been shown to be helpful in delineating the extent of neurological involvement in SLE patients. Recent studies also suggest that MRI may potentially be used quantitatively to determine several of the principal factors that contribute to the occurrence of osteoporotic fractures i.e. bone density, the spatial distribution of trabecular bone and the anisotropy as well as connectivity of trabecular bone structure. Such refined fracture risk discrimination might enable clinicians to target individuals in whom more aggressive intervention might then be initiated.

Within the past decade, musculoskeletal ultrasound (US) has become an established imaging technique for the diagnosis and follow up of patients with rheumatic diseases. This has been made possible through technological improvements, resulting in faster computers and higher frequency transducers. US is most commonly used in the assessment of soft tissue disease or detection of fluid collection and can also be used to visualize other structures, such as cartilage and bone surfaces. In the experienced hand, changes may be seen even before they are apparent on plain X-rays or even magnetic resonance imaging. Advantages of US include its non-invasiveness, portability, relative inexpensiveness, lack of ionizing radiation, and its ability to be repeated as often as necessary, making it particularly useful for the monitoring of treatment. US can also be used for guidance of aspiration, biopsy, and injection treatment. The place of US in patient management is becoming increasingly clear. However, it is important to realize that US is the most operator dependent imaging modality. The experience and expertise of the examiner will determine the value of the diagnostic information obtained. To standardize the quality of musculoskeletal US education, national and international societies have established training guidelines for US.

New Hopes in Management

The emergence of Cox II inhibitors has aroused intense interest among rheumatologists and gastroenterologists in the past decade. Since COX I is thought to be principally responsible for the gastrointestinal adverse effect of NSAIDs, COX II inhibitors, sparing the COX I isoform of the cyclo-oxygenase enzyme, are expected to cause less gastro-intestinal adverse events. This is of particular relevance in at risk groups such as the elderly and those with past history of gastrointestinal events. Indeed, there is evidence to suggest that, although the Cox II selective inhibitors increase the incidence of gastrointestinal adverse events compared to placebo in both RA and OA patients, the magnitude of this effect is less than that of standard NSAID therapy. Accordingly, in the absence of evidence of significant differences in anti-inflammatory efficacy between the COX IIIs and standard NSAIDs, the avoidance of serious adverse effects, particularly on the gastrointestinal tract, becomes the most relevant factor when considering their use. However, there remains
some concern regarding the potential cardiovascular risks associated with the COX II selective agents and therefore caution is needed, as it is for standard NSAID therapy, when prescribing in patients with preexisting cardiovascular disease. Moreover, although COX II inhibitors appear to have a better side effect profile, they are fairly expensive. Use of this group of drug therefore must be rational so that public resources can be utilized in the best way possible to benefit all patients.

Recently, the importance of early and aggressive treatment of rheumatoid arthritis has been emphasized. Disease progression is rapid in early stages and continuing inflammation leads to cumulative damage, hence the rationale for early treatment with disease modifying drugs. In difficult rheumatoid patients where a single agent has produced only partial or no benefit, many rheumatologists nowadays would recommend combination therapy. Although the exact mechanism of the disease modifying drugs is speculative, it is thought that by combining them they may produce an enhanced effect with less adverse reactions, although in practice the ideal has yet to be achieved. Another reason for combination therapy might be possible reduction of the so called drug resistance. Combination treatment can be used from the beginning or in a stepwise fashion. Various drug combination have been tried such as salazopyrine and hydroxychloroquine, or methotrexate and salazopyrine.

The development of biologic agents for treatment of patients with rheumatoid arthritis has progressed rapidly in the past few years, especially agents targeting the key proinflammatory cytokine tumor necrosis factor (TNF). The rationale for this treatment lies in the understanding that cytokines are critical molecules lying at the heart of the chronic autoimmune/inflammatory disease process. Investigations that focused on the major site of the disease, the rheumatoid synovium, have been essential in understanding that blockade of TNF-alpha might be an effective treatment. This has resulted in the introduction of the two inhibitors of TNF, the soluble TNF receptor construct, etanercept, and the anti-TNF monoclonal antibody(mAb), infliximab. Results of randomized placebo controlled trials have shown that both agents significantly decrease the progression of cartilage destruction, especially when combined with methotrexate. Their side effect profiles appear to be acceptable although rare cases of lupus like diseases and of severe infections have been reported. Their long term safety and continuing efficacy remain to be determined. From the cost effective viewpoint, anti-TNF therapy should be reserved for patients who have failed one or more disease modifying drugs including methotrexate. Patients who have failed a single disease modifying drug other than methotrexate should undergo a trial of methotrexate therapy first, unless contraindicated. Additional inhibitors of TNF, as well as biologic agents targeting other important inflammatory cytokines (e.g. Interleukin-1), have also been assessed in late phase studies in recent years.

Leflunomide, a de novo inhibitor of pyrimidine synthesis, represents an important and novel addition to the therapeutic armamentarium for rheumatoid arthritis. Recent clinical studies show that it retards disease progression and substantially improves patient function and health related quality of life. Its efficacy has been shown to be sustained for at least two years. Its advantages include convenient oral administration, simple once per day dosing and a satisfactory safety profile. The adverse events associated with its use have been gastrointestinal symptoms, skin rash, reversible alopecia and derangement in liver function tests.

Despite some success of modern antirheumatic treatment, there are certain patients whose disease is resistant to therapeutic measures. This is particularly true for patients with systemic sclerosis, for whom there is currently no remedy at all, except for some symptomatic measures. These patients, once vital organs or even the skin are severely affected, run a relentlessly bad and often rapidly fatal course. In the 1980s, remissions or
dramatic improvement of pre-existing autoimmune rheumatic diseases were occasionally seen in patients treated with high dose chemotherapy and subsequent bone marrow transplantation for their leukaemia or bone marrow aplasia. These observations fostered the idea that such therapeutic approach might be generally useful to treat or even cure autoimmune disorders. The fear of the relatively high procedure related risk of autologous bone marrow transplantation, initially hampering a more widespread acceptance of the above idea, was significantly reduced after peripheral blood derived autologous stem cell transplantation (ASCT) became established. Systemic sclerosis has been selected as model disease for evaluation of this mode of treatment because no treatment has been established for this disease to date. Thus, ASCT may become an interesting option for patients with inflammatory rheumatic disease refractory to conventional treatment. However, currently available data suggest that ASCT may be helpful only in a proportion of patients and may be curative in even fewer. There is a need for more well designed trials to prove its efficacy and its long term success.

Conclusion

There is no doubt that advances in rheumatology would continue to be made in the years to come. It is hopeful that, in the near future, the various musculoskeletal disorders can be better delineated and categorized and the management of patients with rheumatic problems can be further improved.