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RECOGNISING EARLY ARTHRITIS AMID THE ACHEs AND PAINS

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Arthritis is a clinical diagnosis characterised by joint pain, swelling and stiffness. Aspiration of synovial fluid, laboratory testing and imaging with X-ray, ultrasound examination and/or magnetic resonance imaging (MRI) are valuable adjuncts, but clinical pattern recognition based on training and experience and the interpretation of test results are essential in determining the underlying condition. Rheumatoid arthritis (RA) is the most prevalent inflammatory joint disease, and recent studies have provided convincing evidence that early diagnosis and prompt treatment with antirheumatic drugs are important determinants of outcome.

Autoantibody testing for the presence of antinuclear antibodies (ANA), rheumatoid factor and anti-cyclic citrullinated peptide (CCP) is useful in patients with confirmed early arthritis, as these patients in particular benefit from early treatment to prevent full-blown RA. Autoantibody testing is not considered a useful screening tool to diagnose RA in patients with non-specific musculoskeletal aches and pains because the positive predictive value is low (approximately 20%) due to the relative low prevalence of RA (pre-test probability). Imaging with X-ray, ultrasound or MRI can provide additional information, e.g. on the presence of erosions, bone marrow oedema or synovitis or to exclude non-articular causes of musculoskeletal aches, but interpretation requires the integration of clinical, laboratory and radiological findings.

The notion that many inflammatory joint diseases can be stopped in their tracks by early diagnosis and treatment with classical antirheumatic medication and biologicals has resulted in a paradigm shift from care to cure.

Declaration of interests None declared.

MANAGING EARLY RHEUMATOID ARTHRITIS

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Twenty years ago, rheumatologists were pottering around in the foothills of the challenges that faced them in treating RA. It was still hotly debated whether disease-modifying anti-rheumatic drug (DMARD) therapy was effective at all. Since then, we have had an explosion of well-designed and well-conducted randomised controlled trials that have expanded our knowledge about the optimal use of DMARDs, singly and in combination, and the arrival of targeted immunotherapy has added greatly to the rheumatologist's armamentarium.

Modern management of early RA is governed by some general principles:

1. Treat early.
2. Treat hard.
3. Aim high.

Current treatment strategies have resulted in substantial improvements in outcomes, but does it mean we have reached the summit? By no means: there is a need for large well-controlled trials comparing alternative treatment strategies, not every patient responds to current treatment strategies and the secondary loss of response to all DMARDs (conventional and biological) is a persisting problem. The potential for pre-clinical diagnosis and treatment, disease prevention, remission induction regimens and the sequential or concurrent use of multiple biologic drugs are areas that remain to be explored in any depth.

Further reading

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Declaration of interests Dr Porter has undertaken consultancy work for number of pharmaceutical companies, including Abbott, Roche and Schering-Plough, and has received research funding from Wyeth and Roche.

WHY THE IMMUNE SYSTEM MATTERS TO CLINICIANS

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The recent introduction of immune-targeted biological therapies makes it a necessity for clinicians to understand the immune system and how it can be altered to improve the lives of patients.

The immune system, in both its adaptive and innate guises, participates in every phase of rheumatoid arthritis. Although improved treatments have reduced disease burden, there remains much that we do not know about the role of the immune system in the pathogenesis of rheumatoid arthritis. Only by investigating these mechanisms can we hope to generate new therapies that will continue to combat the immunological aspects of disease pathogenesis and eventually lead to an arsenal of therapies that can result in disease remission in all patients with rheumatoid arthritis.

In addition to the role the immune system plays in the pathogenesis of rheumatoid arthritis, the associated immune/inflammatory reaction can have wider implications on health. These including the recently acknowledged increased risk for cardiovascular disease in patients with RA.

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IS THE IMMUNOLOGICAL DREAM BECOMING A REALITY?

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Immunopathology represents a breakdown of immune regulation and self-tolerance. Rheumatologists see immunopathology in diseases such as rheumatoid arthritis and connective tissue diseases, but similar processes take place in allergic disease and are also responsible for transplant rejection. Ever since the birth of monoclonal antibodies (mAbs) in the 1970s, immunologists have attempted to use these 'magic bullets' to target and 'reset' the diseased immune system, thereby restoring self-tolerance. Dramatic early successes in animal models were achieved using mAbs against T-cell surface targets such as CD4 and CD8, but translation to the clinic proved more difficult.

Over the past five years, however, these efforts have started to bear fruit. For example, anti-CD3 therapy in recent-onset type 1 diabetes appears to provide, at

minimum, a significant retardation of the disease process; and intermittent administration of a T-cell targeted therapy has provided significant benefit to multiple sclerosis patients. While neither of these examples may represent true tolerance induction, in atopic disease peptide vaccination has been associated with both symptomatic improvement and evidence of quite sophisticated immune modulation. One of the major hurdles we face in autoimmune disease is our inability to readily measure tolerance to autoantigens. The situation is much simpler in transplantation, where biomarkers of tolerance induction are starting to be defined.

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Declaration of interests Professor Isaacs has acted as consultant for a variety of pharmaceutical companies from which he has also received educational and research grants, honoraria and speaker fees and sponsorship. He has a patent pending for the use of non-mitogenic anti-CD3 antibody, in relation to which he is in receipt of licensing fees from Tolerrx.

A STRATEGIC APPROACH TO IMPLEMENTING NEW THERAPIES

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Increasing resource pressures within all healthcare systems require a structured approach to the introduction of new, often expensive, medicines. This comprises horizon-scanning to identify new agents in development, rapid health technology assessment (HTA) of new agents to define their true benefits in relation to their cost, the development of evidence-based guidelines to maximise benefits and safety and then real-world monitoring of use to find true effectiveness and safety. No country has all these processes in place, although Scotland, with the Scottish Medicines Consortium (SMC) and Scottish Intercollegiate Guidelines Network (SIGN), is particularly well-placed.

The SMC has reviewed some 600 drugs since its formation in 2002, its decisions being reached in an 18-week time period to meet the needs of patients and clinicians. More than 65% of drug submissions are accepted for use in NHS Scotland, although sometimes with some restrictions on patients and/or prescribers. Rheumatology drugs have had a high success rate in the

SMC process, largely due to the substantial health gain seen with newer biologic agents which justifies their not inconsiderable cost. Rapid HTA of new drugs is possible and can identify real innovation and patient benefit even when the acquisition costs of the drug are high.

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ANTIPHOSPHOLIPID ANTIBODY SYNDROME

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Antiphospholipid antibody syndrome (APS) is an important form of acquired thrombophilia which is associated with thrombosis in arteries, veins and the microcirculation and with pregnancy failure. Despite extensive investigation, our understanding of the pathogenesis of the condition is incomplete and there are also difficulties in the diagnosis of the condition.

Antiphospholipid antibodies appear to have a direct role in the pathogenesis of APS. However, they represent a family of antibodies, only some of which are pathogenic. Antiphospholipid antibodies do not bind directly to phospholipids but to epitopes on some plasma proteins which have an affinity for negatively charged phospholipids. Key among these is a member of the complement control protein family, beta2 glycoprotein I. It is now known that the principal thrombophilic antiphospholipid antibodies bind to specific epitopes on this protein.

Numerous mechanisms whereby antibodies induce a prothrombotic state have been identified and it is likely that the pathogenesis of thrombosis in APS is multifactorial. For example, there is evidence for increased tissue factor expression by monocytes and some other cell types, increased platelet activation, inhibition of the protein C-dependent anticoagulant pathway and activation of vascular endothelium. Tantalising data from experimental models of APS suggest that some antiphospholipid antibodies may induce pregnancy failure and thrombosis through a mechanism involving the activation of complement via the alternative pathway.

The diagnostic tests for antiphospholipid antibodies, principally coagulation assays for lupus anticoagulant and solid-phase assays for anticardiolipin and anti-beta2 glycoprotein I, suffer from problems of inadequate standardisation and poor reproducibility. This is compounded by the frequent finding of low titre anticardiolipin antibodies which is of doubtful significance. These factors complicate the diagnostic process. In general, lupus anticoagulant positivity is more strongly linked to clinical events than are increased titres of anticardiolipin antibodies, IgG antibodies more than

those of the IgM class, and high titre antibodies more than low titre.

In thrombosis in APS the fundamental approach to treatment consists of anticoagulation with heparin and warfarin. In venous thromboembolism the risk of recurrent thrombosis appears to be especially high in APS and long-term anticoagulant therapy may be indicated. Although a target INR somewhat higher than that usually recommended has been promoted based on observational data, results from two randomised trials indicate that a target of 2.5 is at least as efficacious as one of 3.5. The recurrence rate for arterial events in APS has been less well established, as has the appropriate intensity of anticoagulation.

Although women with APS and recurrent pregnancy failure tend to be treated with aspirin and low-dose heparin in subsequent pregnancies, the randomised trial data supporting this approach are rather meagre. Of note, experimental data suggest that heparin may be effective as an inhibitor of complement activation, rather than through its antithrombotic properties, in this situation.

Other treatments have been explored. Although well-conducted clinical trials are required, there are limited data suggesting that hydroxychloroquine may reduce the incidence of thrombosis in subjects with antiphospholipid antibodies and there are mechanistic data to support this. In the life-threatening multiorgan failure associated with so-called catastrophic APS, intensive immunomodulatory therapies have been advocated.

With improved understanding of the pathogenesis of APS, novel approaches to treatment may be worthy of exploration. For example, the pleiotropic effects of statins may include anti-inflammatory actions and inhibition of complement activation pathways which could be of benefit in APS. However, this remains speculative at present.

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INTERSTITIAL LUNG DISEASE IN RHEUMATIC DISEASE

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Traditionally, chest physicians have made great efforts to distinguish the interstitial lung diseases (ILD) associated with connective tissue disease (CTD) from their idiopathic counterparts. Part of the motivation has been to generate homogenous disease populations in which to study the natural history of disease and in whom to perform clinical trials. This approach has proven very successful to the extent that we now understand the

natural history of, for example, idiopathic pulmonary fibrosis (IPF), and several multicentre clinical trials have been reported. However, despite the 'hype' there is as yet no effective therapy for IPF.

Despite sharing common lung histological patterns, there appear to be major differences in disease progression and response to drugs between idiopathic and non-idiopathic disease. For example, acute exacerbation is well recognised in idiopathic usual interstitial pneumonia (UIP), but rare in rheumatoid-UIP, in which rapid acceleration is usually a consequence of drug toxicity.

There have been recent developments in the management of systemic sclerosis-associated ILD, but despite high-quality studies, physicians still struggle to determine which patients might derive most benefit from treatment.

Hence much of what we practise when managing CTD-ILD is based on loose evidence-based foundations. The following may be useful in making clinical decisions:

- Idiopathic and CTD-associated ILD may share common histological patterns but differ significantly in their natural history. Extrapolating promising therapies from one to another is not likely to be fruitful.
- Screening for ILD in rheumatoid arthritis is worthy and will probably confer benefit to patients in the long term.
- At present, drug-induced ILD is probably a greater threat to patients with rheumatoid arthritis than intrinsic lung fibrosis. Predicting toxicity is possible and probably saves lives.
- Treatment of systemic-sclerosis ILD with cyclophosphamide should be targeted; those with evidence of progressing disease gain the most from treatment.

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CARDIOVASCULAR RISK IN RHEUMATIC DISEASE

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[Aims:] To summarise recent evidence for elevated cardiovascular (CHD) risk in rheumatoid arthritis (RA) and detail mechanisms and modalities which may lessen such risk.

Evidence for elevated CHD risk in RA is convincing – a recent meta-analysis suggests RA has on average a 1.5 fold higher risk for CVD compared to persons without RA. Such excess risk appears to be driven by systemic inflammation, both directly via its deleterious effects on blood vessels and indirectly by its accentuation of multiple risk pathways including lipids. Established therapies which lessen RA disease activity and systemic inflammation are predicted to lessen CHD risk and current evidence, albeit from observational studies, supports this notion, especially for methotrexate and TNF-based biologics. In view of elevated CVD risk, routine CVD risk factor screening is recommended for all patients with RA (EULAR paper), with a multiplication factor, to take account of RA-associated risk, employed in specific circumstances. Ongoing trials with statins and other anti-inflammatory agents should add useful information relevant to the management of CVD risk in RA patients.

Conclusion: Systemic inflammation appears to be the major driver for the excess vascular co-morbidity in RA, beyond that attributable to conventional risk factors. Controlling systemic inflammation should help attenuate vascular risk, but complete, long term suppression of articular inflammation is rarely achieved. Regardless, the use of conventional CHD risk-reduction strategies, in particular statins, should be considered in RA subjects with prevalent CHD or at elevated risk, determined on the basis of recent EULAR recommendations.

Further reading

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Declaration of interests Ongoing consultancy work for Hoffman-La Roche.