Early rheumatoid arthritis: focus on RA in the developing world

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A review was undertaken of pathogenic mechanisms in early rheumatoid arthritis (RA) and strategies for cost-effective management of RA in the developing world. Pitfalls in early disease are explored and the importance of aggressive measurable disease control is emphasised.

Keywords: cost-effective management, developing world, early rheumatoid arthritis, measures of disease activity, pathogenesis

Introduction

There are numerous challenges peculiar to the developing world, including burden of communicable diseases, poor socio-economic factors and limited resources, all of which make the management of non-communicable diseases more difficult with the high prevalence of infections such as tuberculosis (TB), HIV and viral hepatitis posing significant threats. In the case of rheumatoid arthritis (RA), a paucity of data exists on the epidemiology of this debilitating disorder in developing countries. There is a perception, however, that the current presumptive prevalence of 0.5–1% of RA is increasing in developing countries, in contrast to developed regions such as Europe and North America where the prevalence is decreasing with a shift to a more elderly onset of disease. Most studies in developing areas reflect an increased prevalence in urban areas in comparison with rural areas. Although an earlier West African study seemed to suggest that RA may be milder in Africa in comparison with a British cohort, more recent data from Africa report a disease phenotypically similar to that seen in the developing world. Genetic susceptibility to RA may also vary geographically with a lower frequency of the RA-associated risk allele, HLA-DR4, reported in Nigerians compared with South Africans.

This brief overview of RA in the developing world is focused primarily on the importance of early diagnosis and management, as well as therapeutic options, preceded by a brief update on disease pathogenesis.

Pathogenesis

Immune dysregulation as a consequence of genetic and environmental factors is the key driver of chronic inflammation in RA. Smoking has recently received much interest in the possible initiation of a chemical change in lung tissue—a process called citrullination. Citrullination involves a chemical change in certain proteins containing the amino acid arginine, which is converted to citrulline. This immunogenic citrullinated protein is now exposed to the immune system and in genetically predisposed individuals results in the generation of anti-citrullinated peptide antibodies (ACPA). Citrullination also occurs in the rheumatoid synovium where these antibodies may not only initiate disease, but also account for disease persistence. Inflammation and tissue destruction may contribute to increasing the antigenic load, resulting in auto-inflammation and ongoing disease. The pathogenic mechanisms of inflammation in RA appear to be different in early as opposed to established disease. This contention is supported by the findings of Raza et al., who demonstrated a different and transient cytokine profile in patients with early RA compared with those who have established disease. Importantly, the early immunopathology of RA appears more amenable to therapy such that patients with early disease have a greater probability of achieving disease remission. This has been demonstrated in several studies, which reported that therapy is most effective in the setting of disease duration of less than four months, underscoring the need to seize this window of opportunity.

Early diagnosis and management

As mentioned above, early diagnosis and initiation of therapy are key factors that will ultimately result in achieving cost-effective outcomes for all patients with RA, which is of particular importance in developing countries. The benefits of early intervention have been clearly shown in several studies which have documented improved disease control and less radiographic progression in patients who have a shorter disease duration at the time of initiation of therapy with disease-modifying anti-rheumatic drugs (DMARDs). In developing countries, conventional synthetic DMARDs (csDMARDs) are the anchor drugs used to manage RA with relatively few patients having access to expensive biological therapies. The use of csDMARDs can have remarkable efficacy if started in early disease. Recommended guidelines suggest that patients should be assessed within 6 weeks of presentation with symptoms and treatment initiated within 12 weeks of disease onset. However, studies have highlighted the all too frequent delay in the diagnosis and institution of appropriate management of RA in the developing world, with a consequent negative impact on quality of life, functional status, prognosis and burden on society.

Developing countries also have fewer resources for managing the medical, surgical and social consequences of uncontrolled
RA, more often seen in patients presenting with established disease. For example, in a cohort of csDMARD-naive South African RA patients with disease duration less than two years, many patients had significant functional impairment, with 52.4% presenting with radiographic findings. In addition people in the developing world are often involved in manual labour with a study from Chile having noted that most manual workers with RA ceased active work within two years from the time of disease diagnosis.18

To address these critical public health issues, it is clearly imperative that national health authorities establish early arthritis clinics and educate primary care physicians about the importance of timely diagnosis and introduction of appropriate therapy (Table 1). This has to be coupled with a public awareness programme to avoid the significant delays resulting from delayed presentation of patients to available health services. In this context, arthritis public awareness initiatives have been shown to be successful in some regions, resulting in earlier presentation to health care centres. Symptoms such as persistent joint swelling, morning stiffness greater than 30 minutes, especially with involvement of the metacarpophalangeal (MCP) and metatarsophalangeal (MTP) joints, symmetrical disease and a family history of RA should prompt immediate referral to an early arthritis clinic (summarised in Table 2).19 Awareness of an over-reliance on laboratory investigations and imaging is also an important factor, as in early RA the utility of serology and imaging may be limited, with the C-reactive protein (CRP) and rheumatoid factor (RF) serologic findings and/or X rays being normal in a significant proportion of patients. Rheumatology Associations and patient-based foundations need to be developed and supported, to educate the public on the importance of early diagnosis and the availability of potentially life-changing cost-effective therapies.

Although the establishment of early arthritis clinics necessitates significant investment by national health authorities, the potential cost-benefit to both the individual and national health budgets makes it a particularly important aspect in the management of RA in the developing world.

**Pharmacological therapy**

The shortage of rheumatologists in many developing countries is clearly an impediment to both the early institution and the monitoring of DMARD therapy. An important pitfall to consider is the initial very good symptomatic benefit of non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids in early RA, often delaying initiation of appropriate csDMARD therapy. NSAIDs have no effect on modifying disease progression and should be used for symptomatic relief only. In the case of corticosteroids, these agents have only a minor effect on disease progression and should only be used as a short-term adjunct to csDMARDs, preferably at doses of less than 10 mg daily. Methotrexate (MTX), a csDMARD, is the anchor drug in the management of RA and educating primary care physicians and specialist physicians (internists) with an interest in the management of RA in the appropriate use and complications of this agent should be considered, as the positive risk–benefit ratio of MTX in RA is well established. Prior to initiation of therapy pre-existing infections such as HIV and viral hepatitis must be excluded.

Measurement of disease activity is essential in relation to optimising therapy. All practitioners involved in RA management should include some form of validated RA disease activity measure in the care of their patients, with the aim of achieving adequate response within three to six months. Clinical disease activity measures such as the clinical disease activity index (CDAI) and the simplified disease activity index (SDAI) are validated and easy to apply in routine clinical practice. In developing countries, recently diagnosed patients are often re-evaluated clinically only after three- to four-monthly intervals, which may contribute to an inadequate clinical response. Rapid escalation of csDMARD therapy in early RA using sequential monotherapy or initial combination therapy is likely to be most effective, resulting in therapeutic efficacy comparable to that of biologic DMARDs such as tumour necrosis factor (TNF) antagonists. However, apart from the financial burden, the high risk of endemic infectious diseases associated with the use of biologic DMARDs also poses an additional threat to their indiscriminate use.

The combination of different csDMARDs may have a lot to offer. For example, combining salazopyrin (SZP)/chloroquine (CQ)/MTX and steroids has been shown to be very effective. Combining MTX with leflunomide is potentially more hepatotoxic, but a recent review seems to challenge this contention, such that this combination may be an option when used with appropriate monitoring.17 Cyclosporine, either as monotherapy or in

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**Table 1: Recommendations for the management of RA in developing countries**

- Public education
- Training primary health care workers in the diagnosis of RA
- Educating medical practitioners on the safe use of csDMARDs
- Establishment of early arthritis clinics
- Rapid escalation of therapy to achieve low disease activity within 3–6 months
- Consider combinations of non-biologic DMARDs
- Biologic DMARDs for well-selected refractory cases

**Table 2: Features supporting the early diagnosis of RA**

- Morning stiffness > 30 minutes
- Symmetrical disease
- Involvement of small joints of the MCP and MTP joints
- Family history of RA
- Elevated acute phase response (ESR/CRP)
combination with MTX, also seems to be an effective alternative to explore. However, there is clearly a need for additional studies to evaluate the safety and efficacy of some of these combinations as alternatives to biologic therapies.

**Conclusion**

There is no question that biologic therapies have revolutionised the landscape of RA management, particularly in patients refractory to csDMARDs. However, in a developing world setting, prudent and judicious use of these agents is vital and, consequently, their application is somewhat limited. In this context, an awareness of the clinical efficacy and cost-effectiveness of csDMARD-based therapeutic strategies when RA is diagnosed and appropriately managed within the first 12 weeks of symptoms is imperative.

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