

Evidence-Based Practice in Rheumatology

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INTRODUCTION

It is fashionable these days to discuss evidence-based medicine (EBM). But what is EBM? 'EBM is the explicit, judicious and conscientious use of current best evidence in making decisions about the care of individual patients.¹ It requires the translation of population data into relevant patient-centered care decisions. The benefits offered by the EBM approach include selective reading of the literature (which saves time), direct patient relevance, and confidence in practice decision-making.² In effect, EBM provides 'bottom line' recommendations for clinical practice. This is the outcome of voluminous scientific information generated, pooled, analysed and reported in many reviews in journals. The Cochrane Collaboration, a worldwide effort to conduct systematic reviews, is continuously updating these reports and other systematic reviews on an electronic database called the Cochrane Library. This is accessible on CD ROMs and the internet.³

EBM trend is now percolating to rheumatology. Yes, it is a good idea to practice evidence based rheumatology in the hope of offering nothing but the best to our arthritic patients. Yet, there are gray areas in rheumatology practice where convincing evidence is not forthcoming and as yet, we have to practice rheumatology on empirical basis sometimes on the basis of half truths. This article examines some clearcut evidence and many areas where such convincing evidence in fact is lacking and there is a need to generate evidence through clinical research. This review goes beyond traditional EBM reports in rheumatology and examines some practical problems encountered in rheumatology practice.

EPIDEMIOLOGY: A LONG WAY TO GO

How often one comes across lay statements that 'Are rheumatic diseases less prevalent in India than they are in the West? Is severity of rheumatoid arthritis less in India than in Western patients?' Evidence to answer these questions is lacking.

For that matter what is the prevalence of rheumatoid arthritis? Worldwide figures vary from 0.5-1% of the normal population. What is the prevalence in India? One study carried out in India reported figure of 0.5%.⁴ Prevalence of rheumatoid arthritis in rural Indians is reported to be 0.7%.⁵ The author of this article has conducted free arthritis camps notably in Pune and other regions as well recording data of 6,400 patients. Osteoarthritis is prevalent at 36% rheumatoid arthritis at 22% and soft tissue rheumatism at 32% of all patients who

reported with musculoskeletal disorders at such camps. It is clear that organised epidemiological studies are necessary to answer vital questions on the prevalence of rheumatic diseases in India.

DIAGNOSTIC CHALLENGES: PROBLEMS AND PROSPECTS

Rheumatoid Arthritis (RA)

The diagnosis is based on ACR (American College of Rheumatology) criteria which are well known (Table 1).

Four out of seven criteria are necessary to diagnose RA. Confusion prevails in interpretation of the rheumatoid factor test popularly known as the 'RA' test. Although a misnomer, often the average practitioner makes the diagnosis of RA in a given patient if the 'RA' test is positive and rules it out if it is negative. A discerning practitioner demands the titre of rheumatoid factor, making a diagnosis of RA if the titre is more than 1:40. Optionally a cut-off value of 80 IU/ml with the latex agglutination test and a differential agglutination titre of 16 are more specific.^{6,7} Confusion is worse confounded while interpreting a negative rheumatoid factor result. There is little realisation amongst practitioners that the test is negative in about 25% of confirmed patients of RA since the latex detects only the IgM rheumatoid factor and not the others. There is a need for a convincing and a better detection test for the rheumatoid factor to facilitate diagnosis of RA.

Juvenile Chronic Arthritis (JCA)

The diagnosis is entirely clinical. The lab tests hardly help at all. Rheumatoid factor is positive in a mere 25% of patients.

The average general practitioner gets confused in the differential diagnosis of JCA and rheumatic fever. Confusion prevails in the interpretation of the ASO titre test. Just because the ASO titre is positive at 200 or 400 units is not diagnostic of rheumatic fever. It merely indicates infection with streptococci. Thus modified Jones criteria must be applied.

Even here, there is confusion. The major criteria such as erythema and chorea are hardly present in Indian patients. The minor criteria are present more commonly. There is a need for an organised study in children with rheumatic fever in India to modify the Jones criteria. Lack of evidence in this regard is noticeable.

Gout

A delightful disease to treat, there are common fallacies in diagnosis due to clearcut evidence. Gout can be precipitated even with normal serum uric acid and hyperuricaemia can exist without gout. It is commonly fallacy that gout occurs only in the great toe when in fact other joints can be affected as well. Gout is not uncommon in vegetarian and teetotalers and even in females after menopause.

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Table 1: ACR Criteria for Classification of RA*

1. Morning stiffness	Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement.
2. Arthritis of three or more joint areas	At least three joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle and MTP joints.
3. Arthritis of hand joints	At least one area swollen (as defined above) in a wrist, MCP or PIP joint.
4. Symmetric arthritis	Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs or MTPs is acceptable without absolute symmetry)
5. Rheumatoid nodules	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxtaarticular regions, observed by a physician.
6. Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5% of normal control subjects.
7. Radiographic changes	Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritic changes alone do not qualify).

* For classification purposes a patient shall be said to have rheumatoid arthritis if he/she has satisfied atleast 4 of the 7 criteria. Criteria 1-4 must have been present for atleast 6 weeks.

Fibromyalgia

A fashionable disease, to talk about which is not at all uncommon in rheumatology practice. There is lack of clearcut evidence about diagnostic markers. First of all, the diagnosis is entirely clinical with no help from the laboratory. Secondly, the symptoms reported by the patients are vague in description. The so called trigger points are not easy to elicit with clarity.

Therefore, thanks to lack of clearcut evidence, the diagnosis of fibromyalgia can often be wrong.

The prognosis and management are equally confusing in the absence of clearcut diagnosis. The NSAIDs do not work, antidepressants are recommended with equivocal results and the patient floats from one doctor to another, may be from one system to another.

Ankylosing Spondylitis (AS)

Thanks to brilliant research in the 70's, the association between HLA B27 and AS is firmly established. In the Western population this is at 95%, in the Indians around 80%.⁸ Even so, there is clearcut evidence of predisposition to AS.

Whereas NSAIDs have been tried and it is said indomethacin is the best NSAID but there is lack of clearcut evidence. The role of DMARDs is controversial. Sulfasalazine is supposed to be useful in primary peripheral manifestations of AS. Methotrexate is recommended by some rheumatologists with doubtful results. There is a need for organized studies to define the role of DMARDs in AS.

Recent data suggests that TNF alpha notably infliximab has been shown to be very useful in controlling inflammatory manifestations of AS.

Antiphospholipid Syndrome

Thanks to brilliant research by Graham Hughes and colleagues, this new disease entity has been firmly established. Generally seen in lupus patients, Thrombotic disorders, rash, recurrent foetal loss, thrombocytopenia, are the cardinal clinical manifestations. Together with this, there is positive lupus anticoagulant test and/or anticardiolipin or antiphospholipid antibodies.^{9,10} There is clearcut evidence to support the use of these lab tests in diagnosing antiphospholipid syndrome. Even so, sometimes there can be patients of antiphospholipid syndrome where the anticardiolipin antibodies may be negative.

Seronegative Spondyloarthropathies (SSA)

It is generally believed that infection triggers arthritis in an HLA B27 positive individual. But how often do we come across evidence in given individual patients? It is almost impossible to identify the causative organism in patients of reactive arthritis although we believe that *Salmonella*, *Shigella*, *Campylobacter* and *Chlymadia* are the common organisms. It is hard to find evidence in individual patients and hence the treatment with antibiotics is largely empirical rather than evidence based.

THERAPEUTIC DILEMMAS

Non-Steroidal Antiinflammatory Drugs (NSAIDs) in Today's Context

Which NSAID to choose? So many clinical trials by the hundreds have been conducted which speak of superiority of one NSAID over another but convincing evidence is lacking. Many rheumatologists believe therefore that all NSAIDs are nearly equal in efficacy due to lack of convincing evidence.

Gastrointestinal ulcers occur in 15-20% of patients taking NSAIDs, 70% of them in the stomach. Around 2-4% of patients develop ulcer reported complications mainly bleeding and perforations especially in those over 70 years of age.¹¹ Measures to prevent complications include H₂ receptor antagonists, proton pump inhibitors, and misoprostol (not available in India). More recently, selective cyclooxygenase-2 inhibitors are introduced. These are as effective as conventional NSAIDs. The incidence of endoscopic ulcers with these drugs is similar to that in the placebo group.¹¹

Langman et al reported pooled analysis of eight studies comparing conventional NSAIDs with placebo and rofecoxib in patients with osteoarthritis (sample size, 5435). Fewer side effects were noticed with rofecoxib.¹²

Role of Disease Modifying Anti-Rheumatic Drugs (DMARDs) for Rheumatoid Arthritis

A conservative, old styled rheumatologist uses a single drug such as sulfasalazine or methotrexate or hydroxychloroquine. But aggressive rheumatologists prescribe combinations in the belief that these work better. But what is the evidence? There are reports that support both the views. For want of convincing

evidence the conservatives use single drugs although the author of this article believes that combining DMARDs is better than singles towards inducing remission in RA.¹³

Early use of DMARDs is recommended by at least four recent studies. Two retrospective analyses showed patients treated early were more likely to maintain vital functional benefit at five years.^{14,15} Another study in 199 patients reported better pain and physical outcomes at three years of patients given early treatment compared with patients in whom treatment was delayed for nine months.¹⁶

Where traditional drugs such as chloroquine and sulfasalazine or methotrexate or their combinations fail, now we have leflunomide to offer. This is an immunomodulatory drug that inhibits synthesis of pyrimidine and has shown promising results.¹⁷

And now we have targeted immunotherapy namely, tumour necrosis factor-alpha (TNF-alpha) blocking biological agents. Both etanercept and infliximab are now available. These agents are particularly useful in treating methotrexate-resistant RA cases with favourable results. Of the two, infliximab is more convenient to use as it is given by i.v. infusions on day-0, day-14 and day-16 and then repeated every 60 days if necessary. Etanercept is given subcutaneously twice a week. Unfortunately, both the agents are very expensive the world over and especially so in India restricting its application.¹⁸

Intra-Articular Steroid Injections in RA/OA

Practiced the world over by the rheumatologists, particularly in Britain, a lot of orthopaedic surgeons in India doubt its efficacy. This is really disappointing and surprising because there is substantial evidence that intra-articular steroid injection is a cost-effective treatment modality to control pain and inflammation in cardinal joints. A recent review of all the literature pertaining to clinical studies by Buckwalter comes to a conclusion that patients with acute exacerbation of pain and effusion may gain temporary pain relief and improve quadriceps function with minimum risk.¹⁹ It is pertinent to note the American College of Rheumatology (ACR) guidelines for OA (2000 Update): 'Intra-articular glucocorticoid injections are of value in the treatment of acute knee pain in patients with OA, and may be particularly beneficial in patients who have signs of local inflammation with a joint effusion. When joints are painful and swollen, aspiration of fluid followed by intra-articular injection of a glucocorticoid preparation is an effective short term method of decreasing pain and increasing quadriceps strength.'¹⁹

Nutraceuticals for Osteoarthritis (OA)

Glucosamine and chondroitin sulphate have been introduced as nutraceuticals for the treatment of OA with a claim that they lead to cartilage regeneration in OA joints. Quite popular in the West these preparations are introduced by a number of companies in India recently. The absence of side effects makes them attractive therapies. A meta-analysis showed short term evidence of benefit.²⁰ A three year randomised placebo-controlled trial concluded less radiographic progression of OA of the knee in those taking glucosamine.²¹ A number of reports are available to support efficacy of the drugs although some trials are not rigidly controlled. In the absence of specific promising remedy for OA, the author of this article recommends a fair trial of nutraceuticals in patients.

Viscosupplementation for OA

Derivatives of hyaluronic acid are introduced for intra-articular injection. These are Hylan G-F 20 and hyaluronic acid sodium salt. They have somewhat varying dosage schedules. A number of studies have been carried out to support the utility in relieving pain and inducing positive biomechanical features. There is some criticism that some of the studies are not adequately controlled. Nonetheless, in the absence of any specific remedy for OA, the preparations seem worth a trial in patients of OA knees.^{22,23}

Radiosynovectomy in RA

Yttrium-90 has been injected intra-articularly to accomplish radiosynovectomy. A systematic review of the literature is reported by Liesbeth et al and come to the conclusion 'from the point of view of evidence-based medicine it should be seriously questioned whether yttrium synovectomy deserves a place in clinical practice.'²⁴ To advocate its use in OA is not correct.

Topical Agents for OA

A number of NSAIDs are marketed for topical application at times with tall claims. Are they useful? A recent review commented that the evidence is poor as most studies being short term. The authors found limited evidence that topical agents provide some pain relief for people with OA and that they are less toxic than systemic drug treatments.²⁵

Corticosteroids in RA (Cochrane Review)

Gotzsche and Johansen performed a systemic review of trials comparing corticosteroids with placebo or NSAIDs covering ten studies involving 320 patients. They concluded that 'Prednisolone in low doses (not exceeding 15 mg daily) may be used intermittently in patients with rheumatoid arthritis, particularly if the disease cannot be controlled by other means. Since prednisolone is highly effective, short-term placebo-controlled trials studying the clinical effect of low-dose prednisolone or other oral corticosteroids are no longer necessary.'²⁶

Thermotherapy for RA (Cochrane Review)

Heat and cold therapy are often used as adjuncts in the treatment of RA. The review has carried out extensive survey of the existing studies and literature and concluded 'since patients preferred thermotherapy to no therapy, thermotherapy can be used as a palliative therapy which can be applied at home as needed to relieve pain'. These results are limited by the poor methodological quality of the trials.²⁷

Balneotherapy for RA and OA (Cochrane Review)

Balneotherapy (hydrotherapy or spa therapy) is one of the oldest forms of therapy. How useful is this? A systematic review of ten trials of 607 patients came to a conclusion that one cannot ignore positive findings reported in most trials. But the scientific evidence is weak because of poor methodological quality. Further trials must avoid flaws found in the reviewed studies.²⁸

Role of Alternate Systems for Arthritis

Relevant but a controversial subject, this calls for an indepth systematic review in the style of Cochrane reviews. This is lacking. For that matter, quality studies are lacking in the first instance. Also there is lack of funding into research to confirm or reject claims of Ayurvedic/homeopathic preparations for arthritis. What is disturbing is that such preparations are marketed without any permission of authorities such

as Drugs Controller; also there is no quality control on such products. This makes alternate systems of medicine for arthritis circumspect due to lack of evidence. This serious anomaly emphasizes the importance of bringing out facts that stem out of EBM.

CONCLUSION

Rheumatology being largely a clinically oriented discipline, there are gray areas where there is lack of evidence to make clearcut diagnosis and recommend specific therapies. Therefore some therapeutic approaches have been empirical. Nonetheless, strengthening clinical research endeavour to address rheumatological problems with enhanced quality control of clinical problems seem the only answer towards generating EBM. In its absence there is a distinct possibility that with the commercial pressures we may be influenced by 'medicine-based evidence' rather than evidence-based medicine. The movement to practice evidence-based medicine in the realm of rheumatology is a welcome change even if it percolates gradually.

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