

## Review Article



## “Outcomes Research in Rheumatoid arthritis ” – Ushering in a new era

\*Suseem<sup>1</sup>, Emily James<sup>1,2</sup>, Mathew George<sup>2</sup>

\* Assistant Professor Senior, School of Advanced Sciences (SAS), Vellore Institute of Technology(VIT), Vellore, TN, India.

<sup>1</sup>Assistant Professor, Pushpagiri College of Pharmacy, Tiruvalla, Kerala, India.

<sup>2</sup>Principal, Pushpagiri College of Pharmacy, Tiruvalla, Kerala, India.

\*Corresponding author's E-mail: [srsuseem@vit.ac.in](mailto:srsuseem@vit.ac.in)

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### ABSTRACT

Rheumatoid arthritis is an autoimmune disorder which mainly affects the joints. Patients with rheumatoid arthritis suffer from joint pain, immobility, fatigue, functional disability, etc. Patient reported outcomes (PROs) in rheumatoid arthritis can generate useful information which can determine the further course of the disease and can also be used in assessment of therapy. Clinician reported outcomes (CROs) and PROs should however be seen as complementary tools in patient therapy. In modern rheumatology the challenge is how to unify the efficacy/outcome together with patient's need and, in particular, improve his 'quality of life'. In this review an attempt has been made to compile the various quality of life instruments as well as outcome measurement tools used in rheumatoid arthritis. Application of Information Technology (IT) in Outcome Measures may simplify the entire process and one may soon have individualised outcome measures data available to the patient and the physician at the click of a mouse.

**Keywords:** Outcome Measures, Rheumatoid arthritis, quality of life, disease activity index, global assessment, patient reported outcomes, clinician reported outcomes, disability scale, PROMIS.

### INTRODUCTION

Rheumatoid arthritis is an autoimmune disorder which mainly affects the joints. It can also produce systemic symptoms and is associated with significant morbidity, mortality and decreased quality of life. Patients with rheumatoid arthritis suffer from joint pain, immobility, fatigue, functional disability, etc.

Physicians have since long occupied the role of singlehandedly determining the outcomes in medicine. The patient's response to therapy or future prognosis have traditionally been measured by physical examination and sometimes laboratory tests to determine the patient status. For many decades in the past century, the lack of drugs specifically designed to treat rheumatic diseases kept rheumatology in a long 'lethargy', where the doctor was more like a 'thaumaturgus' - miracle worker - with limited therapeutic possibilities.<sup>1</sup>

Rheumatoid arthritis was earlier managed with traditional painkillers like nonsteroidal anti-inflammatory drugs (NSAIDs) which do not contribute to arrest the progression of the illness. However with the advent of DMARDs (Disease Modifying Anti Rheumatoid Drugs) there has been a more promising outlook in the pharmacological management of the disease.

#### Patient Reported Outcomes

In the 20<sup>th</sup> century the assessment of rheumatoid arthritis shifted to the "biomedical model" wherein physical examination, core laboratory tests as well as radiographic

examination were primarily the hallmarks of patient assessment.



**Figure 1:** Symptoms in rheumatoid arthritis and effect on quality of life of the patient.

#### “Shared” Clinical Management

The idea of assessing the patient from his/her own point of view is a relatively new one. The inflammatory responses in arthritis lead to symptoms either directly (such as pain) or more indirectly (such as fatigue, emotional and social consequences), long term joint damage causing pain and disability which can directly be described by the patient himself. Fig1. Patient reported outcomes (PROs) in rheumatoid arthritis can generate useful information which can determine the further course of the disease and can also be used in assessment of therapy.<sup>2</sup>

Thus a new era has been ushered in - of shared clinical management with the patient occupying a significant role in his own therapy.



Such a global trend towards shared clinical management including the patient is picking up in many areas of medicine. Clinical trials have been designed in rheumatology incorporating patient reported outcomes to provide accurate, reliable and reproducible results of drug efficacy.

Such patient reported outcome measurement should reach the average patient rather than serving only as a part of clinical trials.

#### PRO's v/s CRO's

Awareness of the patient's needs and the heavy burden of rheumatoid arthritis (RA) for the society, for the patient and his family have led the rheumatologists to develop more precise measures to allow a correct evaluation of their treatments, with the inclusion of both patient's and doctor's point of view.

Patient's and physician's point of view sometimes do not completely match: physicians give great value to activity indices of the disease like laboratory values of ESR, CRP etc, while patients are more troubled with symptoms like pain, fatigue Table 2.

Clinician reported outcomes (CROs) and PRO should however be seen as complementary.

In modern rheumatology the challenge is how to unify the efficacy/outcome together with patient's need and, in particular, his 'quality of life'.

**Table 1:** The "Core Set" in RA

Painful joint count
Synovial joint count
Acute phase reactants
Global assessment (doctor)
Pain (assessed by patient)
Global assessment (patient)
Functional capacity (patient)

**Table 2:** Patient v/s Physician perspective

Patient Perspective	Physician perspective
Pain	Synovitis
Function	Acute Phase Reactants
Fatigue	Structure

#### Outcome Measurement in RA

A close monitoring of rheumatoid arthritis is required after the diagnosis to ensure adequate response to therapy, surveillance of drug toxicity as well as for early detection of any complications.

This has been supported by studies like the TICORA4 and Best5 (Dutch acronym for Behandel-Strategieën, "treatment strategies"). However, this awareness stands in contrast to what is practiced in the "real world."<sup>3</sup>

Experts from various organizations like American College of Rheumatology (ACR), the European League against

Rheumatism (EULAR) and Outcome Measures in Rheumatology (OMERACT) have arrived at a consensus of "core set of symptoms" inclusive of 3 PRO's viz pain, patient global assessment and functional capacity as the dominating complaints in Rheumatoid arthritis. Table 1.

However fatigue, well being, sleep, psychological distress, ability to cope, and final consequences of disease impact the ability to work and to Have a satisfying family and social life.<sup>4</sup>

The Health Assessment Questionnaire (HAQ) and its derivatives have been shown to be the best predictors of functional and work disability, cost, joint replacement surgery, and mortality.

The American College of Rheumatology (ACR) Core Data Set was developed to provide a consistent group of outcome measures for RA. ACR20, 50, and 70 responses have been used and are good tools, with some differing opinions as to which one is more clinically relevant.

The Disease Activity Score (DAS) and its derivatives, DAS28 (a 28-joint count) and DAS-CRP (using CRP in place of ESR), are widely used in RCTs.

The Simplified Disease Activity Index (SDAI), The RAPID instrument (Routine Assessment of Patient Index Data), the Clinical Disease Activity Index (CDAI) are a few more. The Global Arthritis Score (GAS) is a sum of three measures, patient pain, the raw mHAQ score, and tender joint count, and is closely correlated with both the SDAI and DAS.

The table 3 below gives a summary of these measures and the dominant domains each covers.<sup>5,11-16</sup>

#### Quality of Life (QOL) Instruments in Rheumatoid Arthritis

Measurement of health or health related quality of life can be thought of within the WHO's definition of health as "the state of complete physical, mental and social well being". In rheumatoid arthritis in the absence of a cure the goal of medical care is to improve the quality of life of the patient. Quality of life can vary dramatically between patients with the same clinical status measured by traditional methods. Hence in rheumatoid arthritis health related quality of life occupies a prominent position.

The most widely used questionnaires in QOL studies in RA are HAQ, AIMS, MHAQ and MACTAR. The health assessment questionnaire (HAQ) includes disability, discomfort, therapeutic toxicity and cost as the primary domains. AIMS includes psychological status of the patient by evaluation of anxiety and depression scales. The MHAQ is a modified form of the earlier health assessment questionnaire by including patient satisfaction as one of the domains. Social health domains have been incorporated in AIMS (Arthritis Impact Measurement Scale). A brief summary of these quality of life questionnaires has been provided in table 4.



**Table 3:** Outcome measurement tools in rheumatoid arthritis

Clinical Feature	ACR 20/50/70	DAS28	SDAI	CDAI	GAS	ERAM	RADAI	RADARA	RAPID
Patient function	+	+			+			+	+
Patient Pain	+	+			+				+
Patient global	+	+	+	+		+	+		
Physician Global	+		+	+					
No. of tender joints	+	+	+	+	+		+	+	
No. of swollen joints	+	+	+	+		+		+	
ESR or CRP	+	+	+						

**DAS**-Disease Activity Score; **SDAI**-Simplified Disease Activity Score; **RAPID**-Routine Assessment of Patient Index Data

**RADAI**-Rheumatoid Arthritis Disease Activity Index; **RADARA**-Real-time Assessment of Disease Activity in Rheumatoid Arthritis

**ERAM**-Easy Rheumatoid Arthritis Measure; **CDAI**-Clinical Disease Activity Index

**GAS**-Global Arthritis Score; **HAQ**-Health Assessment Questionnaire

Cush JJ. Presented at: 2005 ACR Annual Scientific Meeting. November 12-17, 2005. San Diego, CA. Abstract 1854; Sesin CA. *Semin Arthritis Rheum.* 2005;35:185-196; Makinen H. *Clin Exp Rheumatol.* 2006; 24:22-28; Yazici Y. *Bull NYU Hosp Jt Dis.* 2007;65(suppl 1):25-28; Call S Presented at: 2007 ACR Annual Scientific Meeting. Boston, MA. Abstract 425. Fransen J; *Rheumatol.* 2000;39:321-327.

**Table 4:** Summary of some quality of life instruments used in RA<sup>(7,17-24)</sup>

Instrument	Mode of administration	Administration time (mins)
HAQ	Interviewer/self report	3-5 mins
MHAQ	Interviewer/self report	5-8 mins
AIMS	Self report	20 mins
MACTAR	Interviewer	10-20 mins
MHIQ	Interviewer	20-40 min
QWB	Interviewer	10-15 mins
SIP	Interviewer/self report	20-30min
NHP	Self report	5 min

**HAQ**- Health Assessment Questionnaire; **MHAQ**-Modified Health Assessment Questionnaire

**AIMS**- Arthritis Impact Measurement Scale; **MACTAR**- McMaster –Toronto arthritis questionnaire

**MHIQ**- McMaster health index questionnaire; **QWB**- Quality of well being

**SIP**- Sickness Impact Scale; **NHP**- Nottingham Health Profile;

#### 'PROMIS' - a promising tool

The National Institutes of Health (NIH) Patient-Reported Outcomes Measurement Information System (PROMIS) Roadmap initiative ([www.nihpromis.org](http://www.nihpromis.org)) is a cooperative research program designed to develop, evaluate, and standardize item banks.

These are IT generated applications used to measure patient-reported outcomes (PROs) across different

medical conditions including rheumatoid arthritis across the US population.

The goal of PROMIS is to develop reliable and valid item banks using item response theory (IRT) that can be administered in a variety of formats including short forms and computerized adaptive tests (CAT)<sup>8</sup>.

PROMIS explores the idea of being able to administer a questionnaire application on disease activity by providing



a choice of fatigue, pain interference, physical function, or depression measures, among many other options, in the waiting room either on a Tablet, laptop, PC, and potentially a Smart Phone. Instant scoring, calibration to population norms and ready to share with the patient and physician at point of care is the goal of such an IT application. The item banks can be administered and assessed by the clinician at each visit. Current work is ongoing to assess the feasibility of incorporating such customised PROMIS item banks in generating patient reports in routine clinical practice. This would overcome the handicap of excessive time consumption and paperwork that one overcomes in the use of traditional questionnaire and appears promising indeed!

### Outcome of Outcome measures

Rheumatoid arthritis is a condition which affects the quality of life of the patient and especially the health related quality of life. It brings with it pain, functional disability, decline in work performance all of which decrease the quality of life of the person experiencing these. The patients perspective in reporting of his level of handicap will help the physician determine the efficacy of the therapy and charter alternate plans if necessary.

PROs are also essential in proving drug efficacy in obtaining the drug licensure from the FDA. The PROs have been proven to be at par with other tests like radiographic examination, joint counts etc in determining efficacy, prognosis in the illness.<sup>9</sup> It can also give the patient a sense of participation in his therapy rather than being a mute spectator.

This may improve adherence to therapy and have a positive impact on prognosis. Data from studies on outcome measures can be utilized in the development of standards of care (SOC) in RA. Such studies have been carried out under the eumusc.net project in Europe and found to be successful.<sup>10</sup>

### Limitations

PROs clearly play an important role in assessing symptoms but their role in assessing inflammation and damage is not well defined. This could well be a limitation in their role in disease assessment.

The time factor in completing the questionnaires may be a hindrance for many. In the United States, fewer than 10% of rheumatologists give patients questionnaires in routine clinical care, and fewer than 15% perform a formal joint count at each visit. Busy physicians and especially rheumatologist may not be able to supervise the conduct of these assessments. The questionnaires themselves vary in length and may require being regionally and culturally adapted before administration for it to be effective.

Patients should be educated regarding the importance of completing the questionnaires honestly and its role in their disease management. Research funding in PRO development varies from country to country. In a

developing country like India, research priorities presently resting elsewhere should be directed towards this field which has already found prominence in developed countries.

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