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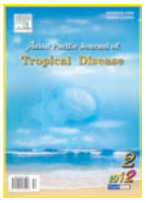

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Determination of clinical outcome and pharmacoeconomics of anti-rheumatoid arthritis therapy using CDAI, EQ-5D-3L and EQ-VAS as indices of disease amelioration

Pinaki Ghosh, Amit Dattatray Kandhare, V. Shiva Kumar, Anuchandra Ramchandra Rajmane,

Mohammad Adil, Subhash Laxman Bodhankar*

Department of Pharmacology, Poona College of Pharmacy,Bharati Vidyapeeth Deemed University,Pune, Maharashtra, 411038. India

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ABSTRACT

Objective: Arthritis is a severe debilitating chronic disease. The objective of the present investigation was to evaluate the clinical outcome and cost effectiveness of anti-rheumatoid arthritis regimen for the treatment of arthritis.**Methods:** The patients were classified into three treatment cohorts on the basis of the treatment regimens prescribed by the physicians. These were group I consisting of patients treated with monotherapy of non-steroidal anti- inflammatory drugs alone, group II consisting of patients treated with disease modifying anti rheumatoid drugs + non-steroidal anti- inflammatory drugs and group III consisting of patients treated with disease modifying anti rheumatoid drugs along with oral Corticosteroids. The patient reported outcome was measured using European questionnaire 5 dimension 3 levels (EQ-5D-3L) and European questionnaire visual analogue scale (EQ-VAS) before and after the treatment regimen. Clinical outcome was measured using Clinical disease activity index (CDAI). The details of costs were recorded by interviewing the patients. **Results:** The patient reported outcome measured by EQ-5D-3L and EQ-VAS was significantly improved in patients belonging to group III when compared to group II ($P < 0.05$) and I ($P < 0.001$) respectively. The outcomes of CDAI scores demonstrate that the mean change in CDAI levels was 7.04, 12.01 and 16.98 in group I, II and III respectively. Total cost incurred per patient was found to be equal to Rs. 1120 ($19.6) in group I, Rs. 1685 ($29.49) in group II and Rs. 2465 ($43.14) in group III. The ACER was determined as 159.09 in group I, 140.299 in group II and 145.17 in group III.**Conclusion:**Amelioration of arthritis in clinics can be effectively measured by validated instruments (EQ-5D-3L, EQ-VAS, CDAI) and DMARDs along with NSAIDs are the most cost effective therapy for treatment of arthritis.

1. Introduction

Rheumatoid arthritis (RA) is a severe debilitating chronic disease affecting various joints in the body [1, 2]. The term arthritis literally means "joint inflammation," but it usually refers to an umbrella of more than 100 varied pathobiological conditions encompassing joints, muscles and connective tissues [3]. It largely affects synovial joints, which are lined with a specialized tissue called synovium. RA is typified by the inflammation in small joints of the hands and the feet, and usually both sides equally and symmetrically, although any synovial joint can be affected. It is a systemic disease and hence can affect the entire body, including the heart, lungs and eyes [4, 5]. An array of modern diagnostic tests like Doppler, magnetic resonance imaging and echo radiographic analysis are required to determine the extent and severity of arthritis [6, 7]. These techniques possess immense clinical value and are objective indicators of disease progression. But these facilities are not available in most of the clinics in developing and transitional economies like India [8].

In a developing country like India, the prevalence of rheumatoid arthritis has elevated but the diagnostic options

*Corresponding author: Dr. S. L. Bodhankar,㊀Dept. of Pharmacology,Poona College of Pharmacy,Bharati Vidyapeeth Deemed University,Erandwane.Pune - 411038㊀Maharashtra.
Tel: +91-20-25437237, +91-20-25437229
Facsimile numbers: +91-20-25439383
E-mail: sbodh@yahoo.com

are costly and involve specialized infrastructure. This forms a basic hurdle in management of the disease from the societal perspective [9]. The variety of scales which are available clinically can be applied in the primary health care centers across the country where specialized dedicated high end infrastructure is not available to assist the physician to assess and grade the clinical condition of the arthritic patients [10]. They include DAS (disease activity score), HAQ (health assessment questionnaire) and AIMS (Arthritis impact measurement scale -2) [11]. AIMS has been recently used to measure the disease intensity in India [12, 13]. On the other hand, clinical classification of the disease condition is an indispensable step in the management and judicious prescription of medications. The recent surge in the medical and allied costs has changed the face of therapeutic management of arthritis [14, 15].

In India, the diagnostic options are scarce and the burden of arthritis is rising day by day. In the wake of such circumstances, cost effectiveness of the generally administered medication strategies at the outpatient departments and a typical tertiary care hospital need to be investigated [2, 16-20]. The diagnostic utility of the patient reported outcome research instruments also need to be deciphered. A wide spectrum of preclinical and clinical investigations have been directed to develop therapeutic strategies from herbal and synthetic moieties to treat arthritis but the paucity of optimum treatment regimen remains elusive [21-25]. Various pharmacoeconomic studies to evaluate the cost effect relation of anti-arthritic drugs have been carried out across the globe [26, 27] but only one such study has been carried out in India [28].

The aim of the present investigation was to elucidate and establish the comparative clinical applicability of the European questionnaire 5 dimension 3 levels (EQ5D3L); European questionnaire visual analogue scale (EQ-VAS); Clinical disease assessment index (CDAI) and determine the cost effectiveness of three most common treatment strategies namely DMARDs (disease modifying anti rheumatoid drugs), DMARDs along with NSAIDs (non-steroidal anti-inflammatory drugs) and DMARDs and NSAIDs along with corticosteroids.

2. Material and methods

2.1. Study design and Patient recruitment

The investigation was designed as a prospective, longitudinal, open label study. Patients suffering from rheumatoid arthritis attending the outpatient departments and being prescribed anti-arthritic drug regimen by the physician were included in the study. Clinical assessment of arthritis was performed by a qualified physician. Patients were prescribed therapeutic regimens as per the discretion of the physician. Thereafter, the patients could be majorly classified into three treatment cohorts namely group I (NSAIDs alone), group II (DMARDs + NSAIDs) and group III (DMARDs + oral Corticosteroids). 30 patients from each treatment cohort were included in the study and the total number of patients initially recruited into the study was 90.

The patient reported outcome was measured using EQ-5D-3L and EQ-VAS before and after the treatment regimen. Clinical symptomatology was recorded using Clinical disease activity index (CDAI). The details of direct and indirect costs were recorded by interviewing the patients.

The study protocol was approved by scientific and institutional human ethics committee and a formal written permission was obtained from the governing authorities of Tirupati Hospital and Physiotherapy clinic, Khenat Hospital, Agarwal Hospital and Research Centre, Dhekane Clinic for the recruitment of arthritic patients from the outpatient departments of these hospitals. The study was carried out in strict adherence to laws and guidelines laid down by international health authorities and organizations (The Code of Ethics of the World Medical Association for experiments involving humans).

Inclusion criteria include age 18 years or older and a diagnosis of RA made by the physician. The inclusion criteria were i) Patients who were diagnosed to have RA according to the guidelines laid down by American Rheumatism Association 1987 revised criteria [29] ii) age greater than or equal to 20 years and iii) patients with pain and arthritis suggestive symptoms for more than 3 months. The patients belonging to following groups were excluded from the study i) Patients with psychological disorders ii) Age below 20 years, iii) Women who were pregnant or lactating. The patients who were prescribed biological drugs like Tumor Necrosis Factor-α and Interlukin-1β antagonists were not included in the study [30-32]. The patients were interviewed by an experienced outcomes research analyst or pharmacist and the baseline characteristics were carefully recorded.

The values of the various scales were determined and the patient reported and physician reported patient related data was captured. No biochemical, radiographic, echographic or imaging analysis was carried out to determine the disease intensity. The drug regimen or strategy that was prescribed encompassed three regimens namely NSAIDs, DMARDs along with NSAIDs and DMARDs along with oral corticosteroids but the discretion of the prescription lay with the physician. The authors were involved only in recording the treatment regimen of a particular treatment option and grouping them into respective cohorts. Permission from office of EuroQoL group, The Netherlands, was obtained to use EQ-5D-3L and EQ-VAS instruments for academic research. The instructions and methodology mentioned for the use of these instruments were strictly adhered [33, 34]. Permission to use CDAI was granted by Dr. Smolen and Dr. Alteha, Austria and the operational methodology laid down for the use of CDAI instrument was followed during

the investigation. CDAI score of each patient was calculated by summation of the number of tender and swollen joints and the global health score reported by the patient and determined by the physician on a scale of 0 to 10. The maximum possible score of CDAI has been reported to be equal to 76 [35-37]. The side effect profile was determined after the completion of the treatment regimen of six months. The patients were interviewed and the side effects recorded in the follow up forms.

2.2. Determination of the clinical outcome

A trained pharmacist interviewed each patient and completed a detailed questionnaire. The individuals were questioned regarding the state of arthritis, quality of life and physically examined by the physician to determine the information about the swollen joints and other non-invasive parameters [38, 39]. Patients themselves filled up EQ-5D-3L, EQ-VAS in Marathi (local language). The physical examination (joint count), interview and interaction were focused to determine the details pertaining to the questions and parameters of the CDAI. In many cases the questions were translated by the physician into local language and explained to the patients.

2.3. Statistical methods

The outcomes values of EQ-5D-3L and EQ-VAS were compared using ANOVA. The statistical analysis was performed using Graph Pad Prism 5.0.

3. Results

3.1. Baseline Characters

The baseline characters of the pool of patients included in the study was recorded and 58 % (64.44) patients were males and 32 % (35.66) females. The mean age of the patients was 51.31 ± 2.12.

3.2. Measurement of Clinical Outcome

The study was initiated with 90 patients but punctuated with dropouts. After the completion of the treatment regimen, 27 patients in group I, 29 in group II and 23 in group III could be contacted for follow up. These patients were contacted and they returned to the hospital premises for re-examination and re-evaluation of quality of life by filling of questionnaires. The clinical outcome was depicted in terms of mean change in the initial and final scores of EQ-5D-3L, EQ-VAS and CDAI.

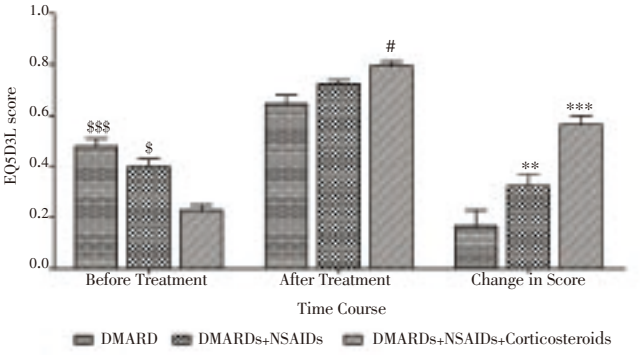

Figure 1. The statistical analysis of EQ5D3L utility scores of group I, II and III patients before and after the treatment regimen. All data analyzed using one way ANOVA. $$$P < 0.01$, $$$P < 0.001$ when the EQ5D3L scores before the treatment in the three cohorts were compared with each other. #$P < 0.05$ when the EQ5D3L scores after the treatment in the three cohorts were compared with each other. **$P < 0.01$, ***$P < 0.001$ when the change in score in all the experimental groups were compared with each other.

It is evident from the findings that before the beginning of

Table 1.
The details of the adverse effects reported by the patients after follow up (figures in parenthesis indicate percentage).

Characteristics	Group I (n = 27)	Group II (n = 29)	Group III (n = 23)
Weight fluctuations	1 (3.70%)	1 (3.45%)	9 (39.13%)
Excessive sweating	1 (3.70%)	1 (3.45%)	7 (30.43%)
Nausea	1 (3.70%)	1 (3.45%)	8 (34.78%)
Abdominal/Epigastric Pain	8 (29.63%)	12 (41.38%)	13 (56.52%)
Stool Abnormality	1 (3.70%)	1 (3.45%)	2 (8.69%)
Dizziness	1 (3.70%)	4 (13.79%)	5 (21.74%)

Table 2.
The details of the patients regarding costs, change in CDAI scores and ACER. The costs are indicated in Rs and figures in parenthesis indicate costs in US dollars.

Sr. No.	Drug	Physician Consultation per patient	App. cost of drugs for 6 months	Drugs to treat side effects per patient	Average cost of Travelling to hospital (per patient)	Average expense on hospital enrollment and physiotherapy personells (per patient)	Total Cost of 6 months regimen (per patient)	Mean Change in CDAI after Treatment	ACER
1.	NSAID monotherapy	75	835	10	50	150	1120 (19.6)	7.04	(1120/ 7.04)= 159.09
2.	DMARD+ NSAID	75	1380	25	50	150	1685 (29.49)	12.01	(1685/ 12.01) = 140.299
3.	DMARD +Corticosteroids	75	1780	410	50	150	2465 (43.14)	16.98	(2465/ 16.98) = 145.17

the treatment, EQ-5D-3L levels were significantly low in the group II and group III patients ($P < 0.05$ and $P < 0.001$) when intergroup statistical analysis was employed among the three cohorts. After the completion of the treatment regimen, EQ-5D-3L levels were significantly high in the group III patients ($P < 0.05$) when intergroup statistical analysis was employed among the three cohorts. The findings depict that the changes in the EQ-5D-3L levels was significantly high in the group III patients ($P < 0.05$ and $P < 0.001$) when the three cohorts were statistically analyzed with respect to each other (Figure 1).

The findings depict that before the beginning of the treatment, EQ-VAS levels were significantly low in the group II and group III patients ($P < 0.05$ and $P < 0.001$) whereas after the completion of the treatment regimen, EQ-VAS levels were significantly high in the group III patients ($P < 0.05$). The results demonstrate that the changes in the EQ-VAS levels were significantly high in the group III patients ($P < 0.05$ and $P < 0.001$) when the three cohorts were statistically analyzed (Figure 2).

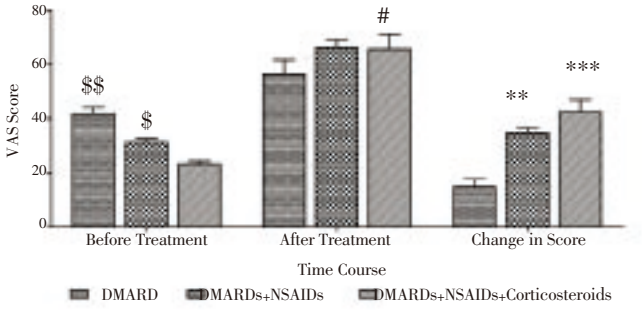

Figure 2. The statistical analysis of EQ-VAS utility scores of group I, II and III patients before and after the treatment regimen. All data analyzed using one way ANOVA. $\$\$P < 0.01$, $\$P < 0.05$ when the EQ5D3L scores before the treatment in the three cohorts were compared with each other. $\#P < 0.05$ when the EQ5D3L scores after the treatment in the three cohorts were compared with each other. $**P < 0.01$, $***P < 0.001$ when the change in score in all the experimental groups were compared with each other.

The outcomes of CDAI scores demonstrate that the mean change in CDAI levels was 7.04, 12.01 and 16.98 in group I, II and III respectively (Table 2).

3.3. Average cost effectiveness ratio

The costs involved in various facets of treatment for one patient for a period of six months have been depicted in Table 1. ACER was computed by dividing the total costs involved in a treatment strategy for one patient by the change in the average CDAI score. Total cost incurred per patient was found to be equal to Rs. 1120 ($19.6) in group I, Rs. 1685 ($29.49) in group II and Rs. 2465(43.14) in group III. The ACER was determined as 159.09 in group I, 140.299 in group II and 145.17 in group III (Table 2).

3.4. Adverse drug reactions

The adverse drug reactions were determined by interviewing the patients and have been mentioned in Table 1. It is evident that the adverse reactions like weight fluctuations abdominal discomfort and excessive sweating were associated with patients of group III whereas the major side effect reported in group II was abdominal discomfort.

4. Discussion

Rheumatoid arthritis is a chronic inflammatory condition affecting symmetrically distributed diarthroidal joints [40]. Continuous clinical assessment of the disease in an important facet of the treatment of arthritis [41-44]. It may involve the usage of modern biomedical tools and biochemical tests accompanied by the radiographic techniques [6, 45]. But it is worth considering the utility of such strategies in Indian scenario. In India, there is a dearth of basic medical care and the cost of the clinical assessment of the disease has to be borne by the patient [46-49]. In such a scenario, if the physician has access to noninvasive accurate quality of life instruments, which reveal a true picture of the disease of the patient, it will be a boon to him. The present investigation involves the usage of three such instruments namely EQ-5D-3L, EQ-VAS and CDAI.

EQ-5D-3L is a European quality of life instrument that has been developed to gauge the health related quality of life of a patient. EQ-5D-3L is a standardized measure of health status developed by the EuroQoL Group, in order to provide a simple, generic measure of health for clinical and economic appraisal. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status which have been employed in the clinical and economic evaluation of health care as well as in population health surveys [50-52]. EQ-5D-3L is designed for self-completion by patients and is suited for use in postal surveys, in clinics, and in face-to-face interviews. It is cognitively undemanding, and takes only a few minutes to fill. Guidelines and cues are included in the questionnaire. EQ-5D-3L consists of 3 pages - the EQ-5D-3L descriptive system (page 2) and the EQ visual analogue scale (EQ-VAS) (page 3) along with a cover page. The EQ-5D-3L descriptive system consists of the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension consists of 3 levels: no problems, some problems, extreme problems. The respondent is asked to indicate his/her health state by marking a tick and cross in the box against the most appropriate statement in each of the 5 dimensions. The EQ-VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labeled 'best imaginable health state' and 'worst imaginable health state'. This information can be used as a quantitative measure of

health outcome as judged by the individual respondents.

The EQ-5D-3L has been translated into more than 150 languages across the globe. It has been translated and validated in many Indian languages including the local language Marathi. It is a five dimension three level questionnaire and is available in the local language Marathi. It was filled up by the patient at the beginning and at end of the treatment regimen. The differences in the scores depict the improvement in the HRQoL related brought about by the anti-arthritic regimen. It bears the utility values which have been formulated by team expert outcomes research analysts. EQ-VAS is a visual analogue scale which is also a patient reported outcome. It records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labeled 'Best imaginable health state' and 'worst imaginable health state' at the top and bottom of the scale. It bears a 100 cm long line and the patient strikes at the line at certain length conveying his/her health state at that moment. It was also recorded before and after the treatment regimen and mirrored the comparative efficacy of the three treatment regimens [33, 34, 53].

Evaluations of the psychometric properties of the EQ-5D-3L and EQ-VAS have provided consistent and substantial demonstrations of both its reliability and validity across many disease applications and in different patient populations [54-57]. In the present investigation, it was possible to segregate the patients into discrete cohorts on the basis of the utility scores EQ-5D-3L and EQ-VAS as the patients who had mild symptoms and prescribed only NSAIDs were included in Group I, followed by patients possessing more severe symptoms and prescribed DMARDs and NSAIDs, who were grouped into Group II and the patients possessing serious symptoms and prescribed DMARDs along with corticosteroids, who were included into Group III. The physician's diagnosis of arthritis and process of filling up of HRQoL questionnaires were independent of each other. It reflects the ability of EQ-5D- 3L and EQ-VAS to measure and quantify the health state in arthritis.

Scales and instruments for typification of arthritis based on numerical count of the swollen and tender joints has been advocated by various workers [57].

CDAI is a recent and evolved questionnaire designed to gauge the state of arthritis in the patients. It has been developed based on previous quality of life instruments like SDAI by Dr. Smolen and Dr. Aletaha, Austria [35-37]. It involves uncomplicated measurement of arthritis in the clinics without any need for the invasive biochemical tests to determine the severity of arthritis in a patient. It provides noninvasive and rapid quantification of the disease activity assessment for every patient. It has been used in India by various authors to measure the intensity of arthritis in various patient cohorts [58-60]. It involves a rapid count of the swollen and tender joints along with assessment of the patient's disease intensity on the global scale. It is a simple summation of these scores and does not involve any complex calculation or biochemical test. Various ranges of clinical values have been assigned which demonstrate the degree of intensity of arthritis [58]. Recently it has been correlated with other sensitive arthritis specific instruments like DAS [60]. CDAI has been advocated to be of immense value to measure and categorize the patient's intensity of arthritis in the clinics where the specific infrastructure is unavailable but the burden of patients is high. Various recommendations have been put forth for treatment strategies for the remission of arthritis in the clinics [61-63]. However, in India the prescription of a particular anti-arthritic drug regimen is up to the discretion of the physician. Various medicaments which were prescribed change the quantifications of the scales and depict amelioration of arthritis by improvement in the cumulative scores [64-66]. It is also worth noting that the scales vary in a similar pattern. In the present investigation, abrogation of disease was measured using outcomes scales only and correlated with the cost incurred to the patient to calculate the ACER. It also provides credence to the applicability and utility of noninvasive scales which seem to be suitable to the Indian clinics with scarce infrastructure. The present investigation is a pioneer approach to measure the HRQoL of arthritic patients using EQ-5D-3L and EQ-VAS in India. It was also clear from the findings that the patients in the group III experienced higher episodes of side effects like excessive sweating, weight fluctuations and abdominal discomfort but the remission of arthritis provided relief to patients of this group. In spite of the side effects, the quality of life scores were not diminished. However, these patients had to bear the cost of medications to counter act the adverse events instigated by corticosteroid therapy. The patients who were treated with only NSAIDs did not experience remission of arthritis although the expenses incurred were less as compared to group II and III. The patients of group II indicated a better quality of life and disease remission. These findings re iterate DMARD + NSAID therapy as regimen of choice for amelioration of arthritis.

Previous studies carried out in India were directed at evaluating the comparative cost effectiveness of various DMARDs and the outcome was measured using (HAQ-DI) [28]. However, in this study it was discernible that CDAI is a sensitive instrument able to determine the improvements in health state after treatment with various anti-arthritic strategies. It has been found that CDAI can be effectively used to diagnose the disease intensity in patients of arthritis in eastern India [13]. The present investigation provides credence the previous studies and depicts the clinical applicability of CDAI in a developing economy like India where state of the art diagnostic facilities are not available. The investigation supports the findings that CDAI can be used in the clinical practice to objectively monitor arthritis during chronic anti-arthritic treatment regimen [13]. It is evident from the findings that addition of the corticosteroids to the treatment regimen provides an option to produce excellent clinical outcomes [67, 68]. But the remission of

the disease is accompanied by a plethora of side effects of the steroid therapy which need to be managed by the patient. Hence, the expenses of the patients who are put on the steroid therapy rise up [69-73]. The expenses on the management of the side effects meant that DMARDs accompanied by NSAIDs is the most cost effective treatment option available to the physician. The present investigation shows that the therapeutic strategy involving oral corticosteroids which has the best outcome measure may not be the most cost effective strategy for the amelioration of arthritis. Another facet that is evident from the investigation is that determination of quality of life questionnaires like EQ-5D-3L and EQ-VAS should be accompanied by disease specific questionnaires like CDAI to put forth a complete picture of disease severity or abrogation. Studies akin to this investigation are warranted across a plethora of patient populations and geographical regions in India and across the globe to establish the clinical applicability of CDAI in outcome and economic evaluations of RA.

Amelioration of arthritis in clinics can be measured by sensitive noninvasive scales and DMARDs along with NSAIDs are the most cost effective therapy for treatment of arthritis.

Conflict of interest statement

We declare that we have no conflict of interest.

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