Best Parameters for Assessment of Anti-Rheumatoid Arthritic Drugs is ECHO MODEL (Economical, Clinical and Humanistic Outcome)

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Abstract

Physicians are always in dilemma for selection of the right parameters to assess anti-rheumatoid arthritis drugs. Any single parameter is incapable to reveal the efficacy safety and cost-effectiveness of anti-rheumatoid arthritis drugs. Therefore a group of parameters are obligatory to assessment of anti-rheumatoid arthritis drugs. Here the best parameters are mentioned in ECHO model (Economical, Clinical and Humanistic outcome) for best assessment of anti-rheumatoid arthritis drugs.

Keywords: Rheumatiod Arthiritis, Economical analysis, Clinical analysis and Humanistic analysis or outcomes

Rheumatoid arthritis (RA) is a systemic auto-immune disease, with a main characteristic of persistent joint inflammation that results in joint damage and loss of function (Henk, 2005). The predominant symptoms are pain, stiffness, and swelling of peripheral joints. The clinical course of the disorder is extremely variable, ranging from mild, self-limiting arthritis to rapidly progressive multi-system inflammation with profound morbidity and mortality (David *et al.,* 2001).

Economics Outcome

Cost to society: The majority of cost associated with RA is the indirect cost associated with work disability, which increase the disease duration. The average annual indirect costs is US$ 9,700 and direct costs of RA amount to an average of US$ 5,400, per affected individual per year (Yelin, 2003) and are estimated to range from US$ 6,500 to more than US$ 1, 30,000 per affected individual over the course of a lifetime (Wong *et al.,* 2001). Over a lifetime, work disability cost range from US$ 2, 22,500 to US$ 3, 7000 per affected individual (Wong, Ramey, Singh,

Gabriel, Tugwell, O'Brien, Yelin, Drummond, Ruff, 1999).

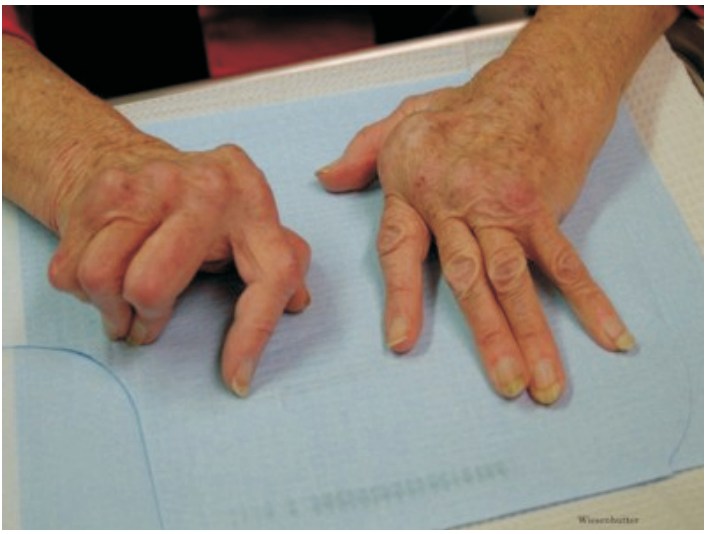

Fig. N. 1- Hand deformity of rheumatoid arthritis

The economic evaluation is to identify, measure, value and compare the cost and consequences of the alternatives being considered. The economic evaluation methods include cost-of-illness evaluation, cost-minimization, cost-benefit, cost-effectiveness, and cost-utility analyses. Each method, except cost-of –illness evaluation, is used to compare competing programs or treatment alternatives. The method are all similar in the way they measure cost (dollar/rupees) and different in their measurement of outcomes. Cost effectiveness analysis is therefore used in health economics to compare the financial cost of therapies whose outcome can be measured purely in terms of health effect. The common costs involved in economic outcomes are the following (Wong *et al.,* 2001).

Table 1. Common cost involved in economic outcomes.

Sr. No.	Cost –Category	Cost
1.	Direct medical cost	Drug, Supplies, Laboratory tests, Health care professional's time, Hospitalization
2.	Indirect non-medical cost	Transportation, Food, Family care, Home aids
3.	Direct non-medical cost	Lost wages [morbidity], Income forgone due to death
4.	Intangible cost	Pain, Suffering, Grief

Direct cost: Direct costs are those directly associated with detection, treatment, and prevention of disease (Eisenberg, 1989). These costs may be disease specific, a direct result of the condition, or disease associated, a consequence of the

primary disease or its treatment. Direct costs include costs of physician visits, diagnostic tests, prescription drugs, over-the-counter medication, hospital stay and procedures, aid and devices and outpatient procedures.

Indirect cost: Indirect costs are more difficult to measure. Some can be given a monetary value, although this is dependent on local systems of social support, sickness benefits and pension. Lost of work productivity is important in chronic musculoskeletal conditions but rarely is included in economic evaluations.

Intangible costs: Intangible costs are those associated with loss in function, increased pain and reduced quality of life of patients, families and careers. These include the costs of lost opportunities. These are very important for musculoskeletal conditions, because disability is a significant outcome with limitation in activities of daily living, reduction in leisure and community activities, chronic pain, psychologic problems including depression and anxiety and reduced general health.

Cost-Effectiveness Analysis: Cost Effectiveness Analysis (CEA) involves comparing programs or treatment alternatives with different safety and efficacy profiles. Cost is measured in rupees and outcomes are often expressed in efficacy unit, a natural unit, or non-rupees units (i.e. lives saved, cases cured, life expectancy, or drop in blood pressure in mm Hg, improved functional ability, disease activity etc) (Bootman, Larson, Mcghan, Townsend, 1989; Detsky, Nagiie, 1990). The results of Cost Effectiveness Analysis (CEA) are expressed as a ratio – either as an average cost effectiveness ratio (ACER) or as an incremental cost effectiveness ratio (ICER).

An Average CER represents the total cost of a program or treatment alternative divided by its clinical outcome to yield a ratio representing the rupees cost per specific clinical outcome gained, independent of comparators (Eisenberg, 1989; Detsky, Nagiie, 1990; Sanchez, Lee, 1994). ACER = health care cost / Clinical outcome.

An Incremental CEA may be used to determine the additional cost and the effectiveness gained when one treatment alternative (A) is compared with the next best treatment alternative (B).Thus, instead of comparing the average C/E ratio of each treatment alternative, one over another treatment is compared with the additional effect, benefit, or outcome it provides (Eisenberg, 1989).

ICER = cost A – cost B / effect A (%) – effect B (%).

Clinical Outcome

Clinical outcome are the medical events that occur as a result of disease or treatment (e.g. safety and efficacy end points). The measures of clinical effectiveness in RA are:

Disease Activity

Disease activity in RA is a complex phenomenon, impossible to define and discern. At the present time no single test of disease activity in RA is effective because RA may cause various kinds of symptoms and signs. Thus, the disease activity variables can be considered as surrogate markers for the in-self un-measurable process. Clinical symptoms of disease activity are e.g. morning stiffness, fatigue, pain, impaired function, and psychological and sleep disturbances. Clinical signs include joint swelling and deformity, reduced objective function, low-grade fever, osteoporosis and weight loss. Some of these symptoms and signs are used to assess disease activity, e.g. the number of swollen and tender joints (Prevoo, van't, Kuper, Van, Putte, Riel, 1995), graded, ungraded or weighted joint indices (Ritchie, Boyle, McInnes, Jasani, Dalakos, Grieveson, 1968; Thompson, Silman, Currey, 1987), pain and fatigue (Ferraz, Quaresma, Aquino, Atra, Tugwell, Goldsmith, 1990), duration of morning stiffness and different scores for functional decline (Fries, Pincus, Summey, Soraci, Wallston, Hummon, 1983). The patient's own global assessment of the disease activity is sometimes added. Laboratory markers of disease activity are for instance acute phase proteins and ESR. In some instances, clinical and laboratory markers for disease activity are combined, including the patient's global assessment of disease activity, into compound indices of disease activity, e.g. the disease activity score (DAS) (Van der, 1990), the Stoke index (Davis, 1990), Simplified Disease Activity Index (SDAI) and Rheumatoid Arthritis Disease Activity Index (RADAI). The first three instruments includes measurements of clinical and laboratory marker and the patient's and physician's global assessments of disease activity but the last one i.e. RADAI is self-administered questionnaire used by the patient to assess own disease activity.

Disease Activity Response Criterias: There are three standard response criteria being used widely in clinical trial of RA are (Gestel, 1996; Lipsky, 2000)

(i) American college of rheumatology (ACR) criteria (Felson, Anderson, Boers, Bombardier, 1993; Arnett, 1988)

(ii) European League Against rheumatism (EULAR) criteria (DAS-28 score) (Prevoo, Hof, Kuper, Van, Van de Putte, Van Riel, 1995; Gestel *et al.,* 1996)

(iii) Paulus criteria (Paulus, Egger, Ward, Williams, 1990)

(i) ***American college of Rheumatology (ACR) criteria****:* Overall patient's clinical response of therapy is assessed by ACR improvement criteria. The ACR20 criterion is developed to define improvement in rheumatoid arthritis. The primary efficacy variable is rate at which the intention to treat sample achieves 20% improvement in ACR core set variables (ACR20). To be considered an ACR20%

responder, a subject has to show a 20% improvement in tender and swollen joints count and 20% improvement in at least three of the following five criteria: patient global assessment, physician global assessment, pain intensity, physical function or disability (e.g. HAQ) and level of acute-phase reactant or erythrocyte sedimentation rate (Felson, Anderson, Boers, Bombardier, 1993).

Count of tender joints is based on 68 joints assessments by pressure and joint manipulation on physical examination, and count of swollen joint is based on 66 joint assessments. Percentage changes in the tender joint and swollen joint counts are based on the number of evaluable joints at a visit. Physician and patient assessment of global RA disease activity is based on a ten-point (10 cm line) non-anchored horizontal visual analogue scale (VAS) ranging from 1(very good) to 10 (very poor) and pain intensity assessment is based on a visual analogue scale (VAS), made up of a 10 cm line which also ranges from 0 (no pain) to 10 (severe pain) point scale.

Sixty-Eight Joint counts: Sixty eight joint are Metacarpophallenges (MCP-10), Metatarsophallenges (MTP-10), Distalinterphallenges (DIP-8), Proximalinterphallenges (PIP-20), wrist (2), elbow (2), shoulder (2), knee (2), Hip (2), ankle (2), Subtalar (2), Temporomandibular (2), Sternoclavicular (2) and Acromioclavicular (2)

Secondary outcome included in ACR are ACR50 and ACR 70 responder rates. The ACR50 and ACR70 are defined as at least 50% and 70% improvement, respectively, assessed by the same criteria used to calculate ACR20 response (Van der *et al.,* Felson, Anderson, Boers, Bombardier, 1993).

(ii) ***European League of Association against Rheumatism (EULAR)*****:** The EULAR criteria is based on both an improvement and the achievement of a low disease activity state, as measured by the DAS-28 (Prevoo, van't Hof, Kuper, Van, Van de Putte, Van Riel, 1995). Disease Activity Score involving 28 joints (DAS28). It is a linear sum of four outcome parameters: tender joint count, swollen joint count, Patients' global assessment of disease activity and a level of C – reactive proteins or Erythrocyte sedimentation rate (ESR) (Gestel *et al.,* 1990).

$DAS\text{-}28 = 0.56\sqrt{TJC} + 0.28\sqrt{SJC} + 0.70[\ln ESR] + 0.014\ (VASGH)$
TJC = Tender joint Count
SJC = Swollen Joint Count
ESR = Erythrocyte Sedimentation Rate in mm first hour.
VASGH = Patient global assessment of general health.

Disease activity by DAS scores is interpreted as:

DAS < 3.2 = mild disease activity.
DAS 3.2-5.1 = moderate disease activity
DAS > 5.1 = severe disease activity

Twenty-Eight Joint counts: Twenty-eight joints are MCP (10), PIP (10), wrist (2), elbow (2), shoulder (2) and knee (2) joints are examined for the presence or absence of tenderness or pain on motion, swelling, or deformity (Smollen *et al.,*1995).

Patient's global assessment of disease activity: It represents patients overall assessment of how the arthritis is doing. Patients are asked to mark a cross on a 0 to 10 cm scale (Visual analogue scale) for how well he/she is doing by considering all the ways the arthritis affect the life.

Change of DAS score from Baseline is categorized as good improvement if DAS change ≥ 1.2, moderate > 0.6 but ≤ 1.2, and no improvement ≤ 0.6 (Van Gestel *et al.,* 1998). The Disease Activity Score is widely used to quantify disease activity and gauge the response to treatment. A rather complex calculation conceals the relative contribution of each measure to the composite score.

(iii) Paulus: The Paulus response criteria is based on 20% improvement in 4 of 6 measures: Joint tenderness score, joint swelling scores, physician's global assessment, patient's global assessment, ESR, and morning stiffness (Paulus *et al.,* 1990).

The current standards of disease activity indices for clinical trials are the EULAR Disease Activity score (DAS) and the ACR 20% response criteria.

Disability

Disability in RA is associated with the extent of joint damage, and influenced by factor such as age, female gender, low socio economic status, income and educational level, and pain and depression (Fries, Spitz, Youg, 1982). The effects of disability have a substantial impact on individuals and their role, and on their families. Disability influences psychosocial function and can lead to anxiety, depression and fatigue. Health assessment Questionnaire- Disability index (HAQ-DI) (Chopra, 2004) and Global function performance (GPF) (Agustin, Roy, Rincon, 2004) is expressed as measure of disability.

Health Assessment Questionnaire (HAQ): A new approach to assess disability in RA was introduced by Fries *et al.,* 1980, the Stanford Health Assessment Questionnaire (HAQ). They developed a structure of patient outcome measurement representing five separate dimensions: Death, Disability, Discomfort, Drug (therapeutic) toxicity and Dollar cost. The Full HAQ assesses all the above mentioned five dimensions of health outcome. The Short HAQ questionnaire that only assesses disability (HAQ Disability Index, HAQ-DI) is often used by itself, and is here referred to as HAQ. The HAQ-DI was originally developed and validated for English speaking populations in the United States and Canada, and has since been translated or culturally adapted into more than 60 different

languages or dialects, often with only minor changes (Bruce, Fries, 2003). HAQ is a self administered questionnaire, with one or more specific questions on each of eight dimensions of activities of daily life (dressing and grooming, arising, eating, walking, hygiene, reach, grip and outdoor activities).

Global Function Performance (GFP): Measurement of physical functional limitations in patients with rheumatoid arthritis (RA) is a time-honored strategy to assess the disease's outcome. Performance based tests of physical function such as grip strength and walking velocity over 50 feet; and the timed shirt button test provide reproducible, quantitative information about a patient's current status and about the prognosis (Agustin, Roy, Rincon, 2004).

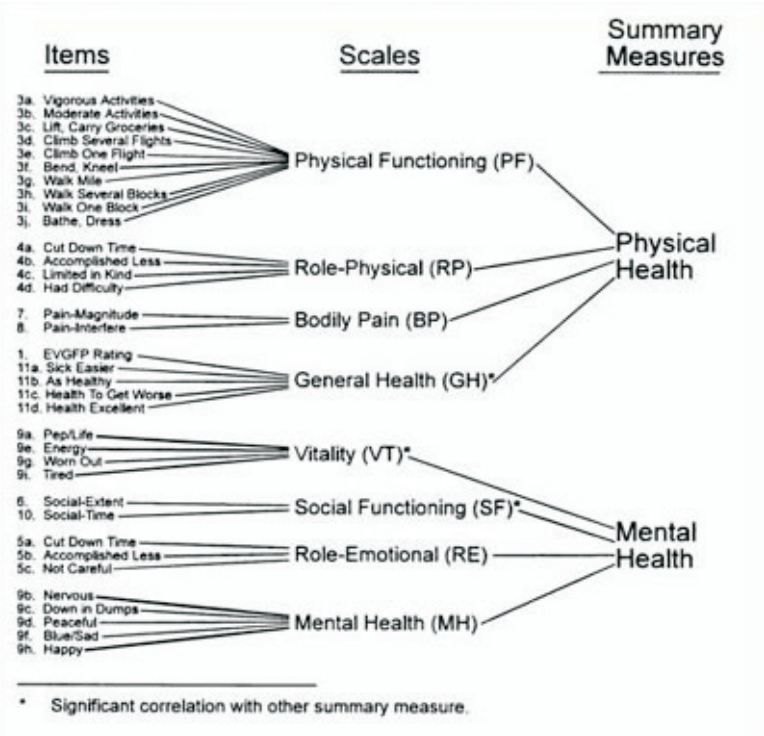

Figure 2. Diagrammatic overview of Short form-36 (Eight areas of general health

Humanistic Outcome

Humanistic outcome are the consequences of disease or treatment on patient functional status or quality of life. Quality of life is a descriptive term that refers to people's emotion, social and physical well being and their ability to function in the ordinary tasks of living. Several instruments such as Nottingham Health Profile (NHP), Sickness Impact Profile (SIP), Health Assessment questionnaire (HAQ),

European Quality of life (EuroQoL) and Short Form (SF)-36 have been designed in an attempt to go beyond measurement of physical impairment and disability by addressing more emotional and social aspect of a condition.

Short Form-36 (SF-36) –Short Form-36 (Eight Dimensions)

Area	Dimension	No of Question
Functional status	Physical functioning	10
	Social functioning	2
	Physical problem	4
	Emotional problem	3
Wellbeing	Mental health	5
	Vitality	4
	Pain	2
Overall evaluation	General health perception	5
	Health change*	1

This item is not included in the eight dimensions nor is it scored

Conclusion

The acceptance of any anti-rheumatoid arthritis drug in population is higher if the drug is of lower in cost as well as higher in effect against disease and the anti-rheumatoid arthritis effect is well shown by clinical outcomes via sign- symptom and humanistic outcome is measured via HAQ and SF-36. So the ECHO model is best to measure individual anti-rheumatoid arthritis drug effect on disease and its cost involve in treatment. ECHO model also provides the easy way to compare two different drugs or therapy regarding their cost and efficacy.

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