MEDICAL CHANNEL

Original Article

ASSESSING THERAPY RESPONSE IN RHEUMATOID ARTHRITIS BY RAPID3 SCORE AND GRIP STRENGTH TEST

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ABSTRACT

Objective: To evaluate usefulness of Rapid3 Score and Grip Strength Test in assessing therapy response in rheumatoid arthritis.

Material and Methods: A 24-week, single-blind, study was carried out on 274 patients, aged 29-69 years, diagnosed with rheumatoid arthritis. They were divided into two groups; one received tablet Methotrexate whereas the other received tablet Leflunomide. Rapid3 score and Grip Strength Test were recorded at initial visit and follow-ups.

Rapid3 score indicates degree of patients' impaired functional capacity, pain intensity and opinion of general well-being. Grip strength test shows the extent to which patients can compress a partially inflated, aneuroid, sphygmomanometer cuff in their palms.

Results: Rapid3 score improved from a baseline of 8.25 to 1.79 units in the Methotrexate group and from 8.35 to 1.63 units in the Leflunomide group at 24 weeks ($p < 0.001$). Remission was achieved in 26% of patients on Methotrexate and in 27% of patients using Leflunomide.

Grip Strength rose to 153.02 mm of Hg from a baseline of 69.70 in the right hand and to 151.10 mm of Hg from 68.62 in the left hand in patients using Methotrexate whereas it rose to 154.04 mm of Hg from a baseline of 71.10 in the right hand and to 151.53 mm of Hg from 70.58 in the left hand in patients using Leflunomide [$p < 0.001$].

Conclusion: Rapid3 score and Grip Strength test are credible, non-invasive, cost-effective, functional tools for assessing therapy response in rheumatoid arthritis.

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INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune, progressive, systemic, chronic

disease in which destruction of joints, with subsequent loss of function, is followed by deterioration in life quality. [1] There is a worldwide prevalence of 1%, the highest incidence being between 40 and 50 years and it affects women three to five times as often as men. [2] India and Pakistan have prevalence rates of 0.5% and 0.2-1% respectively. [3]

Genetic association with (HLA-DR4), cigarette smoking, use of decaffeinated coffee, presence of Herpes virus, Epstein-Barr virus and Human Herpes Virus-6 infections are risk factors that make a person susceptible to RA. [4, 5]

Patients present with joint inflammation, fever, malaise, anorexia, weight loss, pain, local edema, synovial thickening and joint erosion. They have painful, mostly symmetrical small joint involvement, initially of the hands, feet and cervical spine with subsequent involvement of the large joints. Morning stiffness is present whereas, the presence of rheumatoid nodules, usually seen in 20-30% of patients, is indicative of a poor prognosis. Disease progression leads to deformity and loss of function. Extra-articular manifestations are seen in 15% of individuals. [6]

Diagnosis rests upon physical examination, laboratory tests, x-rays and the American College of Rheumatology criteria (1987) [Table 1]. [7] Disease-modifying anti-rheumatic drugs (DMARDs) are the mainstay in the current treatment of RA. Of these Methotrexate, Leflunomide, Penicillamine, Cyclosporine, biologics along with NSAIDs and Corticosteroids (where and when needed) are the common choices.

RA, being a progressive disease, requires patients to come for regular follow-ups to assess response to therapy and the development of any untoward effects. In today's busy consultant practice a detailed physical examination, including assessment of different joints is sometimes not possible. Our patients are usually financially challenged and repeated follow-up visits, with laboratory tests, as well as the cost of drugs, prove to be a great financial burden, resulting in frequent drop-outs from therapy. Inadequate patient compliance thus leads to subsequent increase in morbidity. Present study was thus designed to evaluate the usefulness of Grip Strength Test and Rapid3 Score questionnaire; two simple, cost-free methods, as adjunctive tools in monitoring patients' response to therapy.

MATERIAL AND METHODS

This twenty-four week, interventional, prospective, single-blind study was conducted from October, 2009 to March, 2011. It was approved by the Institutional Review Board (IRB) and Board of Advanced Studies and Research (BASR), Dow University of Health Sciences (DUHS). It was carried out on patients visiting the out-patients department of a private teaching hospital and a private consultant's clinic in Karachi.

317 patients, fulfilling the ACR criteria, were included after an informed, written consent. Each patient was asked to select a chit from a basket containing chits on which the alphabets "A" or "B" were written; "A" signifying tablet Methotrexate and "B" signifying tablet Leflunomide, this being known only to the Principal Investigator. Thus two groups of patients were obtained, one taking tablet Methotrexate (159) and the other taking tablet Leflunomide (158). 33 patients in group A and 10 patients in group B were lost to follow-up. The 274 patients who completed the study consisted of 126 patients on tablet Methotrexate, 10 mg weekly (4 tablets of 2.5 mg, orally) and 148 patients on tablet Leflunomide, 20 mg, orally daily. They were advised to continue with (or were prescribed) NSAIDs or corticosteroids (< 10 mg daily) which they had been taking when included into the study and were told to return for follow up at 6, 14 and 24 weeks. Baseline values of hemoglobin (Hb), total leucocyte count (TLC), erythrocyte sedimentation rate (ESR), platelet count (PC), C-reactive protein (CRP), serum creatinine and serum glutamic pyruvic transaminase (SGPT) were conducted as these parameters not only help guide the treating physician in tailoring the dose of medications but the drugs also adversely affect their levels. Financial aspects were mainly catered to by

TABLE 1

THE AMERICAN COLLEGE OF RHEUMATOLOGY CLASSIFICATION CRITERIA

S. No.	Parameter	Features
1	Morning stiffness	>1 hour most mornings
2	Arthritis and soft-tissue swelling	of >3 of 14 joints/joint groups
3	Arthritis of hand joints	Inflammation of joints of the hands
4	Symmetric arthritis	Arthritis of the same joints on both sides of the body.
5	Subcutaneous nodules	Usually found over body prominence that sustain repeated mechanical stress e.g Olecranon, Calcaneum.
6	Rheumatoid factor	present
7	Radiological changes	suggestive of joint erosion

Criteria 1-4 should have been present for at least 6 weeks.

At least 4 criteria have to be met for classification as Rheumatoid arthritis

TABLE 2
BASELINE PARAMETERS
N=274

	MTX (126)		LFN (148)		P value
	No of pts (%)	Mean (+ SD)	No of pts (%)	Mean (+ SD)	
Sex Female	89 (70)	————	118 (79.7)	————	
Rheumatoid Factor Present	77 (61.1)	————	109 (73.6)	————	
Age (years)	————	45.57 (10.32)	————	46.35 (9.68)	0.520 NS
Grip strength Right hand (mm Hg)	————	69.70 (16.93)	————	72.30 (16.07)	0.194 NS
Left hand (mm Hg)	————	68.62 (17.04)	————	72.26 (16.49)	0.074 NS
Rapid3 score (units)	————	8.25 (0.97)	————	8.35 (0.98)	0.379 NS

MTX = Methotrexate
No. of pts = Number of patients
NS= non-significant statistically
LFN = Leflunomide
_____ = Nil
Independent T-test utilized

TABLE 3
COMPARISON OF STUDY TOOL PARAMETERS at 24 weeks
N = 274

	MTX (126) Baseline Mean (+SD)	at 24 weeks Mean (+SD)	P value	LFN (148) Baseline Mean (+SD)	at 24 weeks Mean (+SD)	P value
Grip strength Right hand (mm Hg)	69.70 (16.93)	153.02 (20.51)	<0.001 ***	72.30 (16.07)	155.15 (19.14)	<0.001 ***
Left hand (mm Hg)	68.62 (17.04)	151.10 (17.76)	<0.001 ***	72.26 (16.49)	155.32 (16.60)	<0.001 ***
Rapid3 score (units)	8.25 (0.97)	1.79 (1.04)	<0.001 ***	8.35 (0.98)	1.63 (0.93)	<0.001 ***

MTX = Methotrexate
*** = very highly significant
LFN = Leflunomide
Paired T-test utilized

the researcher with minimal burden on the study participants.
Population of interest: Patients presenting to the clinic were from different strata of society and consisted of daily-wage earners, roadside workers, students, office workers, housewives and some business executives.
Study tools: Different measurement tools are used to assess RA patients viz, DAS (disease activity score), DAS28, (twenty eight joints) ACR20, ACR50, ACR70. However in today's busy clinical practice almost no quantitative measurements are taken due to a shortage of time and the necessity of the same person performing the joint examination to avoid variation.
The routine assessment of patient index data 3 [Rapid3] score was thus introduced to facilitate numerical assessment in clinical rheumatology practice. [8] It consists of three, patient-reported, outcome measures which estimate the

TABLE 4
MTX v/s LFN
REMISSION
RAPID3 SCORE 24 WEEKS
N=274

DRUG		Rapid 3 Score				TOTAL	P VALUE
		1.00	2.00	3.00	4.00		
MTX	No of patients	**33**	41	49	3	126	
	% within drugs	**26.2**	32.5	38.9	2.4	100.0	
LFN	No of patients	**40**	61	44	3	148	
	% within drugs	**27.0**	41.2	29.7	2.0	100.0	
Total	No of patients	**73**	102	93	6	274	
	% within drugs	**26.6**	37.2	33.9	2.2	100.0	**0.374** NS

(MTX) = Methotrexate
(LFN) = Leflunomide
No of patients = number of patients
NS = non-significant statistically
Chi square test utilized

Rapid 3 score is now one of the six measures recommended by the acr for measuring ra diseases activity status Kelly JC, 6 New Ways to Measure RA Disease Activity: ACR Recommendations. Arthritis Care Res. 2012; 64:640-57

Medina JE, Ballesteros G, Londoño JD, Giraldo R, Santos AM, Valle RR et al. EULAR 2014: Scientific Abstracts, THU0271?High Correlation of RAPID-3 with DAS-28 Score as a Measure of Disease Activity in a Cohort of Colombian Patients with Rheumatoid Arthritis at Hospital Militar Central. Bogot?, Colombia. Ann Rheum Dis 2014; 73:277 doi:10.1136/annrheumdis-2014-eular.5733

In order to facilitate and overcome this, Grip Strength Test, an effective, non-invasive assessment tool, was used to assess therapy response. Furthermore, in today's busy clinical practice a consultant is usually pressed for time when examining patients and this process often falls short. Rapid3 score was thus introduced to facilitate quantitative measurement in rheumatology clinical care. [8]

Grip strength depends on the ability of the patient's fingers to exert maximum pressure on a rolled-up cuff of a mercury sphygmomanometer inflated to 20 mm of mercury. RA leads to inflammation and subsequent swelling and stiffness of the fingers along with pain, which thus interferes with the patient's ability to compress the cuff.

potential of patients to carry out day-to-day activities, their perception of the effect of the disease on their body and the intensity of pain felt by the patient. It can be carried out easily, calculated in a very short time, does not need any joint count and gives results which are comparable to other measurement tools. [9] The **physical function** part asks the patient to score 13 questions about activities of daily living on a 0-3 level. This score is then averaged and multiplied by 3.33 to give a value ranging from 1-10. The second component is the **visual analogue scale rating of pain** experienced over the past weeks. This is graded on a 1-10 scale. The third and final component is the **global estimate** (also on a visual analogue scale from 1-10) regarding the patients assessment of how he/she is doing, considering the effects of the illness and health conditions affecting him/her. A higher score in all categories indicates a worse state. The sum of these three scores is then divided by three to give final Rapid 3 score ranging from 1-10. [10] Rapid 3 score is now one of six measures recommended by the ACR for measuring RA activity status. [11]

The interpretation of the final score, regarding **disease activity**, is as follows:
Near remission————score of < 1.00 (clinically regarded as remission)
Low severity———— score b/w 1.01 and 2.00
Moderate severity——score b/w 2.01 and 4.00
High severity————score > 4.01

The final score also gives us the number of patients falling in different **response categories**:

- **good response**; a decrease of more than 3.6 units and

a final score < 6

- **moderate response**; a decrease of 1.8-3.6 units and a final score of < 12
- **poor response**; a decrease of less than 1.8 units and a final score > 12 (this refers to maximum Rapid3 score of 30 but this can be converted to a maximum of 10 by dividing it by 3). [12]

Grip Strength Test

Grip Strength Test is used to assess and monitor patient response to therapy. [13] It involves the measurement of the force or power exerted by a person while compressing a rolled-up, sphygmomanometer cuff. Values taken at baseline and after therapy enable one to compare the effect of therapy.The grip strength in normal subjects lies mostly between 300 and 600 mm. of Hg. Disability in RA patients has been associated with compromised function and reduction in the power of hand grip. In patients with rheumatoid arthritis the grip strength was seen to be less than 200 mm. of Hg, depending on the severity of the involvement of hand joints. To assess grip strength a pneumatic type of apparatus was used in which an aneuroid, adult, sphygmomanometer cuff was evenly rolled to conform to a normal, functional, hand position for grip. A rubber band was placed around each end of the cuff to hold it in position. The cuff was then inflated to 20 mm of Hg, which was the starting position for measurement of each subject.

Pre-requisites

The American Society of Hand Therapists (ASHT) has recommended an approved, standard, testing position for patients. This requires that the patient sit in a straight-backed chair with feet flat on the floor, shoulders adducted in a neutral position and arms unsupported. Elbows should be flexed at 90 degrees with forearm and wrist rotated in a neutral position and fingers flexed, as needed for maximal contraction. The patient should breathe in through the nose and blow out through pursed lips as a maximum grip effort is made for 3 seconds. [14] A prior demonstration of how to perform the procedure should be given.

STATISTICAL ANALYSIS

Statistical analysis was done on SPSS version 18.0 with paired T-test and Chi-squared tests. The results are shown as mean along with standard deviation.

RESULTS

The results of the 274 patients were as follows. The 126 patients in Methotrexate group consisted of 89 (70.6 %) females with 77 (61.1%) patients positive for Rheumatoid factor. They had a mean age of 45.57 + 10.32 years, ranging between 29 to 70 years. The mean baseline Grip strength was 69.70 + 16.93 millimeter (mm) of mercury (Hg) in the right hand, 68.62 + 17.04 mm of Hg in the left hand, while the mean Rapid3 score was 8.25 + 0.97 (Table 2).

At the end of 24 weeks, Grip strength in the right hand rose to 153.02 + 20.51 mm of Hg while that in the left hand rose to 151.10 + 17.76 mm of Hg. Rapid3 score fell to 1.79 +1.04 units (Table 3). All values were highly significant statistically ($p < 0.001$).

The 148 patients on Leflunomide consisted of 118 (79.7 %) females with 109 (73.6 %) patients positive for Rheumatoid factor. They had a mean age of 46.35 + 9.68 years, mean baseline Grip strength was 72.30 + 16.07 mm of Hg in the right hand, with 72.26 + 16.49 mm of Hg in the left hand and a mean Rapid3 score of 8.35 + 0.98 (Table 2).

Grip strength rose to 155.10 + 19.14 mm of Hg in the right hand at 24 weeks while it rose to 155.32 + 16.60 mm of Hg in the left hand. Similarly the Rapid3 score fell to 1.63 + 0.93 units (Table 3). All values were highly significant statistically ($p < 0.001$).

A total of 73 (26.6%) patients achieved near remission at the end of the study with 33 (26.2 %) patients in the Methotrexate group and 40 (27.0 %) patients in the Leflunomide group (Table 4).

DISCUSSION

Therapy today is aimed at achieving a high rate of remission. Patients scoring < 1.00 unit in the ***Rapd3 score*** were said to be in near remission, considered as remission clinically. Rapid3 score changes in our study were statistically very highly significant when 24-week values were compared to their baseline values ($p<0.001$). The reduction in Rapid3 score indicated that there had been a substantial improvement in the patients functional status brought about by a decrease in the level of pain and stiffness which was thus manifested by their ability to perform the various activities of daily living with ease.

Sokka et al carried out a study on 5,848 patients (which were a part of the Questionnaires in Standard Monitoring of Patients with RA (QUEST-RA) database) in which various, available, remission definitions were applied and obtained a mean Rapid3 score remission rate of 14.3% (range 0-35%). [15] Breedveld et al obtained a much better remission rate with their patients, ranging between 21%-25%. [16] We achieved a remission rate of 26.6% in our patients which was almost in accordance with the above figures.

Cohen et al had 55% patients showing a good response with Leflunomide while Donahue et al reported a response rate of 82% with Leflunomide. [17, 18] Strand et al using Leflunomide in active RA obtained a good response rate of 52% while Moreland et al using Leflunomide obtained a rate of 56%. [19, 20] In our study we had 64% of patients falling in the good response bracket, a figure in accordance with the above two.

A 48-week, double-blind, randomized, multi-center, placebo-controlled trial was conducted by Tilley et al to determine

the efficacy and safety of Minocycline (mean age + S.D. 55 + 12.8 y, 76% women, n=109) and placebo (53.5 + 13.5 y, 80% women, n=110) in treating patients of rheumatoid arthritis. They utilized grip strength test and their patients showed significant changes in grip strength levels ($p < 0.03$) from baseline to the end of the study. [21] Whereas Eberhardt studied 183 patients with recent-onset RA who were participating in a study started at Lund in 1985. There were 116 females (64%) with a mean age ± S.D. of 51.4 ± 12.4 years and grip strength was measured by a sphygmomanometer. They received either of D-Penicillamine, Anti-malarials or Methotrexate. Grip strength values at the end of two years showed significant changes with p values of < 0.07. [22]

Clark et al studied 126 patients with early RA, in a double-blind, randomized trial over 24 weeks, who randomly received Hydroxychloroquine, 400 mg/d, or placebo. Grip strength was assessed using a sphygmomanometer with a standard grip bag. The patients showed a 22% greater mean improvement with a p value of 0.01. [23]

A trial conducted to study the efficacy of Flurbiprofen, given at different times and at varying frequencies during the day, utilized grip strength test measured with an inflatable, grip bag, attached to an aneuroid sphygmomanometer, that was inflated to an initial pressure of 20 mm of Hg. Minimal values for grip strength were achieved in the morning along with high scores for subjective pain and stiffness and the former further reduced with an increase in pain and stiffness, thus showing that it is a valid indicator of the severity of the patient's symptoms. [24] Ferraz and colleagues evaluated the degree of morning variation in assessment of grip strength in patients with RA and their results also showed significant changes. [25]

All the above mentioned studies were carried out on diagnosed patients of RA with the Grip Strength Test being a common denominator. The changes seen in the grip strength test in these studies are comparable to those seen in our study and indicate the effectiveness of the grip strength test in monitoring the patients' response to therapy in RA.

Wessel conducted a systematic review of related articles to evaluate the efficacy of hand exercises for persons with rheumatoid arthritis by searching the databases of Medline, Cumulative Index to Nursing and Allied Health Literature (CINAHL), EMBASE, PEDro, and Cochrane. He concluded that grip strength should be used along with other parameters in patient assessment as it is an easy-to-perform, reliable, reproducible, non-invasive test which does not cost the patient anything. [26] Appropriate key words and phrases were put into PubMed, Medline, Google Search etc. and the authors have not found any study against the grip strength test. This again emphasizes the effectiveness of this simple test.

CONCLUSION

Rapid3 score questionnaire is an easy-to-perform, time-saving, cost-effective measure that provides credible results. Similarly Grip strength test is a simple, cost-free, non-invasive effective, functional, adjunct tool for assessing RA patients' response to therapy. Both these assessment tools are suitable for use in clinical settings of a resource-poor country like Pakistan. Multi-center studies with large sample size are open horizons for future research.

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