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Clinico-epidemiological profile and treatment outcome (DAS28-ESR) in Adult Rheumatoid Arthritis: Early results of intensive treatment in a tertiary care institute from North-East India

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Abstract

Introduction: Although Rheumatoid arthritis (RA) is the most common type of autoimmune arthritis that can lead to chronic disability and deformities, the overall benefit of intensive treatment strategies in rheumatoid arthritis remains uncertain. RA often causes pain and swelling in the wrist and small joints of the hand and feet. DAS28 score in RA of greater than 5.1 implies active disease, less than 3.2 low disease activities, and less than 2.6 remissions. Adequate treatment not only controls the symptoms but also may prevent joint damage and deformities.

Objective/**Aim**: To understand clinic-epidemiology of RA and value of applying DAS28-ESR scores in monitoring disease activity in a "treat to target" strategy before, during and after treatment for making timely treatment decisions.

Materials and Method: We longitudinally studied confirmed cases of Adult RA (n = 44) in a tertiary care teaching hospital located in the North-eastern region of India ACR/EULAR (2010) classification criteria were used for case definition. Patients with advanced stage disease were excluded. Baseline DAS28- ESR score was calculated. The target was to achieve and maintain a target DAS28-ESR of 3.2 or improve score by at least 1.2 within 3-6 Months. Patient-centric physiotherapy and occupation therapy were added to the regime. After six months of intensive treatment targets with DMARDs and symptom modifying agents, final endpoint DAS28-ESR data were compared to baseline scores to measure treatment outcomes.

Results: The cohort was dominated by females between 30-55 years of age with M/F ratio 1.17: 4. Nearly 85% were seropositive RA. The average baseline DAS28-ESR score was 5 indicating aggressive RA cohort. The change in the average score by 2.27 after intensive treatments with DAS28-ESR targets was impressive for further treatment decisions. Thirty out of 44 had DAS28 <3.2. Indicating low disease activity and 27/44 had score <2.6 indicating remission.

Conclusion: Intensive treatment in RA with a treat to target strategy to bring objective change in DAS28 score was generally well-tolerated and it complemented well with the concept of early intensive treatment according to inverted pyramid model for timely optimization of appropriate regime and lower likelihood of joint damage and disease progression.

Keywords: Rheumatoid arthritis (RA), DAS28 (Disease activity score), ESR (Erythrocyte sedimentation rate), DMARDs (Disease modifying anti-rheumatoid drugs).

Introduction

The overall benefit of intensive treatment strategies in rheumatoid arthritis (RA) remains uncertain. ACR/EULAR (2010) Classification Criteria for RA formulated by collaboration of the American College of Rheumatology and EULAR (European League against Rheumatism*)* is now widely accepted globally.[(1)] Rheumatoid arthritis is the most common type of autoimmune arthritis that can lead to chronic disability and deformities. RA often causes pain and swelling in the wrist and small joints of the hand and feet. Proper treatments for RA can control symptoms of joint pain and swelling. Adequate treatment also can prevent joint damage and joint deformities. Early treatment is likely to give better long term results.[(2)] People who receive early treatment for RA have better quality of life, and are more likely to lead an active life.[(2)] They also are less likely to need joint replacement surgery due to joint damage. It is therefore important to monitor the overall disease activity by the treating physicians (rheumatologist, orthopaedicians etc.) using practical yet objective outcome measures like DAS28 scores to optimize therapy and deny disease progression. The National Rheumatoid Arthritis Society (NRSA), United Kingdom has succinctly summarized the role of DAS28 score for evaluation of Rheumatoid arthritis especially from the angle of monitoring effectiveness of treatment.[(3)]

Materials and Method

It is a prospective study involving data obtained between 2013-2016, on Adult Rheumatoid Arthritis (RA) from a 570 bedded tertiary care referral teaching hospital located in the North-eastern region of India. Between 2013-2016, we diagnosed a total of 79 patients of RA, based on ACR/EULAR (2010) Classification Criteria for case definition. We could follow up a smaller cohort compliant to DMARDs. Patients with joint space narrowing on radiograph, pre-existing deformities, past history of treatment with steroids or joint surgery were excluded. A much smaller cohort (n= 44) finally fulfilled our criteria to be analyzed in our study, that were on the attractive evolving principle of treating rheumatoid arthritis on 'treat to target' (TTT).

The target was to attain a DAS28 (ESR) <3.2 (low disease activity) at 6 months in all included cases. All 44 such confirmed cases of both seropositive and seronegative but clinically active Adult Rheumatoid Arthritis were evaluated at treatment entry level (baseline) before commencement of DMARDs using DAS 28 scoring using ESR and such data were maintained in excel sheet by the treating physicians. ACR/EULAR (2010) Classification Criteria were used for case definition for a diagnosis of RA. DAS28 was calculated with erythrocyte sedimentation rate (ESR) by senior physician only (Author-2) to avoid misinterpretation and inter-observer variability to assess disease activity.

DAS 28-ESR scoring involved obtaining the critical range of measures of disease activity by 1) Counting the number of painful/tender joints, 2) Counting the number of swollen joints, assessing the global scores of pain and overall status: No symptoms (0) to sever symptoms(100) and 4) Blood markers of inflammation (ESR). The DAS28-ESR is a composite score derived from four of these measures. Obtained data are then entered to online calculator and get the composite DAS28-ESR score.

All these 44 cases were treated for at least 6 months with DMARDs, occupational therapy, physical therapy in a multidisciplinary rehab-centric approach involving orthopaedics and general medicine specialist with interest and exposure to management of joint disorders. DMARDS used were combination of oral Methotrexate (5-15 mg/week), HCQS (100-400 mg/day) and Salfasalazine (500 BD/TDS when no past H/O sulfa drug allergy) based on severity of disease and BMI. Loflunamide was not used in any case. All patients received COX 2 inhibiting NSAID (Aceclofenac/ Etoricoxib) in the first one and a half months. All patients with high RA disease activity (DAS28 >5) initially received corticosteroids in tapering doses. All patients received folic acid 5 mg supplement weekly. Diabetic and hypothyroid cases did not receive steroids, but received oral Atorvastatin in 10-20 mg daily at night-time instead. Patient centric physiotherapy and occupation therapy (including wax bath and night splinting whenever appropriate) were added to the treatment regime in all cases. Lastly, DXA (Dual X-ray Absorptiometry) scan was performed in 16/44 cases due to multiple risk factors and any low BMD (Bone Mineral density) status detected was treated with biphosphonate, calcium and vitamin D supplements whenever indicated according to BMI (Body Mass Index) and T scores. After 6 months of completion of DMARDs repeat DAS28-ESR score was done to analyses treatment response. Finally, baseline and final endpoint data for DAS28-ESR were compared.

Results

Between 2013-2016, we diagnosed a total of 79 patients of RA, but could follow up a much smaller cohort (n= 44) compliant to DMARDs for over six months. Notably, 29/44 patients (66%) were indigenous to Meghalaya and a small numbers were from other North Eastern states. Out of 44 patients, 34 cases (73.3%) were female (**Table 1, Fig. 1**). All patients presented with symmetrical polyarthralgia and no patient had mono-articular disease pattern at baseline. The average age of our patients was 42.6 years (Range 22-70 years). Most patients were 30-55 years of age (**Table 1**). The average BMI was 23.9 (Range 36.5-15.9). BMI was within normal range in most (23/44) cases (**Table 2**). The spectrum of disease activity is summarized **(Table 3).** There was high prevalence (86.4%) of sero-positive RA **(Table 3).** In 21/44 patients where Anti CCP antibody values were available, the average value was 178.6 (Range 341-0). Twelve cases had values between above 200. Although statistical analysis is not yet performed, the patients with co-morbidities of hypothyroidism and diabetes and high SUA and Anti CCP antibody appears to have more severe diseases.

Table 1: Age and Gender distribution of RA cohort (n=44)

Age (yrs)	Male	Female	Total	%
20- 30	2	7	9	20.4
30-45	3	10	13	29.5
45-55	5	10	15	34.0
>55	0	7	7	15.9
Total	10	34	44	100

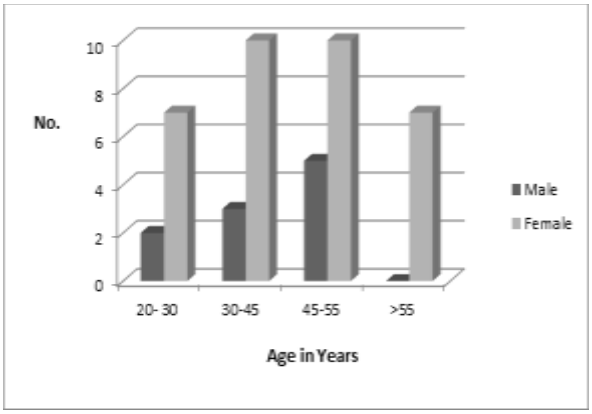

Fig. 1: Age & gender distribution of Adult RA: North-East India

Table 2: Body weight and BMI of the RA cohort

Weight/ BMI	Underweight < 18.5		Normal 18.5-25		Overweight 25-30		Clearly Obese >30	
RA cohort (n=44)	**No**	**%**	**No**	**%**	**No**	**%**	**No**	**%**
	1	2.6	23	52.6	15	34.1	5	11.4

Table 3: Clinico-epidemiology and disease activity of the RA cohort

RA Cohort Parameters	No	%	Total	Ratio/Average
Male	10	22.7	N= 44	M/F ratio 1.17: 4
Female	34	73.3		
Seropositive	38	86.4%	100%	Sero +ve to Sero-ve ratio 7: 1.1
Seronegative	6	13.6		
Anti CCP* level (n= 21): Unit/ml				
<100	5	N= 21		Average: 178
100-200	3			
>200 & <300	7			
>300	4			
*** Anti CCP: Anti-citrullinated citric peptide**				

The average baseline ESR was high at 51 mm/hr (Range 18-117mm/Hr) suggesting high disease activity**.** Eleven cases had ESR above 60 at presentation. The average serum uric Acid level was 5.0 mg% (Range 2.1mg% -14.1mg %). Three patients had SUA >7 mg% needing low purine diet followed by oral Febuxostat 40 mg daily until SUA was 6 mg%.

The average baseline DAS28-ESR score was 5.0, signifying significant disability before initiating treatment. Twenty one cases had DAS28 score above 5 and fourteen had score below 4 (Table 4). After 6 months of intensive treatment and rehabilitation the final average DAS28-ESR score has come down to 2.72 (Range 1.68-4.62) i.e. 2.28 lesser than earlier pre-treatment average of 5, suggesting significant clinical improvements and lowering of overall disease activity (Table 5). Notably, 41 out of 44 (93%) had a score below 4. But three patients still have a score above 4 signifying poorer response and these patients are now being considered for treatment with biologics for steroid sparing therapy.

There is significant delay in seeking proper treatment in this cohort. Only 14/44 presented to us in less than a year, The average time taken to come for regular treatment and follow up was as late as 3.9 years (Range 6 months to 10 years) suggesting likelihood of subclinical joint damage. There was low awareness about availability of good treatment for RA, importance of early treatment with DMARDs and compliance issues.

Table 4: Baseline DAS 28–ESR (A)

DAS 28	Disease activity	No	%	Total	Average value	Range
>6	High	7	15.8	N=44	5.0	8.24-2.45
6-5.1	High	14	31.7			
5-4	Moderate	10	22.7			
<4->3.2	Low - Moderate	8	18.2			
<3.2	Target value (Remission)	6	13.6			
ESR						
<40 mm	Low	15	34.1	N=44	51mm/hr	18-117 mm
40-60 mm	Moderate	18	40.9			
>60 mm	High	11	25			

Table 5: Final DAS 28–ESR after 6 months of intensive treatment (B)

DAS 28	No	%	Total	Average value	Range	Average improvement in DAS 28-ESR (B-A)
>6	0	0	N= 44	2.7	1.68- 4.62*	2.3

6-5.1	0	0				
5-4	3	6.8				
<4->3.2	11	25				
<3.2	30	68.2				
ESR						
<40 mm	41	93	N=44	25 mm	07-56 mm	26 mm
40-60 mm	3	07				
>60 mm	0	-				

Seventeen patients out of 44 had undergone DXA scan and about 64 % were osteoporotic, 24% osteopenic and 11.7% had a normal T score in DXA scan of hip and lumbar spine at presentation. Results showed patients with rheumatoid arthritis had high prevalence of osteoporosis at the measured sites. However none developed symptomatic fragility fracture.

Table 6: DXA results of RA cohort with high risk of low BMD

WHO classification	BMD in T score	No	%	Total
Normal	- 1 or higher	2	11.7	
Oseopenia	- 1 to -2.5	4	2.6	N= 17
Osteoporosis	- 2.5 or lower	11	64.7	

Lastly, most patients seem to have tolerated DMARDs well. Despite some patients are on maintenance corticosteroid, none developed avascular necrosis of hip joint, possibly due to minimal dosing. Two female patients discontinued HCQS due to side effects after 3-4 months of treatment due to Tinnitus and dark facial pigmentation. One patient had deranged liver enzymes after 15 mg methotrexate dose escalation needing dose reduction to 7.5 mg. Patients with diabetes and hypothyroidism as co-morbidity responded poorly. A small number of cases (four) required single intra-articular steroid to improve function in one or two persistently swollen painful knee, elbow or finger joints even after 3-4 months of treatment. One case required unilateral total hip replacement for progression of his hip disease.

Discussion

The standardized prevalence of RA from population based survey of the North-Eastern states of India was estimated by ICMR using ACR criteria (1987) as 0.19% (Dibrugarh, Assam).[4] WHO-ILAR COPCORD Study estimated prevalence as 0.2% (Guwahati, Assam) and 0.4% (Manipur).[5] There is no dedicated rheumatology service in any medical colleges in this region.

Early diagnosis and prompt treatment can improve outcomes in rheumatoid arthritis (RA) because significant joint damage occurs early in the course of the disease, when RA is most aggressive. Aggressive treatment after the first 3–4 months of symptoms, with either disease modifying anti-rheumatic drugs or newer biologic response modifiers may reduce the rate of disease progression and may even switch off the disease.[6] Intensive strategy with inverted pyramid approach is now the standard of therapy; in which treatment with disease-modifying antirheumatic drugs is initiated the moment diagnosis is confirmed. Functional disability is the most important factor affecting quality of life (QOL) in RA and adequate attention is required to improve QOL during treatment.[7] An attractive evolving principle of treating rheumatoid arthritis is called 'treat to target' (TTT).[8] Accordingly our target was to attain or maintain a DAS28 (ESR) <3.2 (low disease activity) at 6 months to titrate correct regime for each case. This treat to target approach involved monthly assessment of RA disease activity followed by a change in treatment (higher doses or new drugs) until disease activity is brought down to an agreed target. One such target can be a DAS28 score of less than 2.6 (indicating remission) or less than 3.2 (low disease activity). Other targets might be a low CRP or ESR.[2,3]

The DAS score was originally developed for the purpose of standardizing and comparing results in clinical trials of new drugs for RA. Since then DAS 28 score is increasingly used for monitoring rheumatoid arthritis activity. Study by Inoue et al[9] showed that DAS28-ESR and DAS28-CRP were generally well correlated. NRSA, UK has succinctly summarized the role of DAS28 score for evaluation of Rheumatoid arthritis.[3] DAS28 of greater than 5.1 implies active disease, less than 3.2 low disease activities, and less than 2.6 remissions. We had DAS28-ESR in <2.6 in 27/44 (61.4%) and 30/44 (68%.2%) had score <3.2 indicating low RA activity. Notably, 14/44 (32%) continued to have disease activity with an average score of 3.6 although none had score >5.1 after treatment.

Whilst it is appealing to measure a composite scale like DAS28 to indicate how active or well controlled RA is; in day-to-day practice has it has not been routinely adopted by orthopaedicians/rheumatologists in India. There are some pitfalls in the interpretation of the score; for example if RA case affects the feet (these

are not included in the standard 28 joint count) the score may be misleadingly low. Alternatively if any patient regularly suffers many tender joints but markers of inflammation are low, the score may be misleadingly high.[3] It is difficult at times to ascertain clinically whether an individual joint is swollen, and this uncertainty may lead to wrong score. When DAS28 result seems problematic, such as a discrepancy between the ESR and joint counts, it is possible to use musculoskeletal (MSK) ultrasound to document joint inflammation and decide if any change in treatment is required.[3] We were unable to do so in our study. Wiles et al compared five year outcome of rheumatoid arthritis using much more extensive tools: pain in visual analogue scale (VAS), the Health Assessment Questionnaire (HAQ), and the Short Form-36 (SF-36) in community and clinic based samples to infer that more comprehensive outcome assessment tools like SF 36 scorings in RA should be used for comparison and to set targets for improvement.[10] Nevertheless as the DAS28 score is one of the best measures we have for RA disease activity, it is desirable that orthopaedic/ rheumatology department measure DAS28, and use this to recommend a change in treatment regime. This can apply to either an increase or a decrease in therapy in the light of a high or low score respectively since persistently high score has been found to increase the likelihood of progressive joint damage, even in patients who appear to be doing well. Therefore, although not a perfect measure of disease activity, it is logical, useful and desirable do a DAS28 score to monitor the overall disease activity in RA as a practical outcome tools to optimize therapy that may prevent disease progression.

Improvement of DAS28 >1.2 means good to moderate improvement depending on baseline DAS 28 score.[3] After 6 months of intensive treatment and rehabilitation the final average DAS28-ESR score in our patients has come down to 2.72 (Range 1.68-4.62) i.e. 2.28 less than earlier pre-treatment average of 5, suggesting significant clinical improvements and lowering of overall disease activity after intensive treatment strategy in the majority. Since functional disability is important factor affecting QOL in RA[7] predicting outcome of therapy is welcome that may guide early better regime. Aramaki et al[11] reported such possible paradigm where DAS 28-C reactive protein (DAS28-CRP) was proposed as a potential predictor of outcome or remission at 6 months. It was found that good outcome in RA patients treated (with tacrolimus) may be predictive by some baseline variables. By logistic regression analysis they showed that male gender (first) and moderate disease activity at baseline (second) may be independent predictors toward achieving DAS28-CRP remission at 6 months. We had more female patients than male and CRP values of all 44 cases were unavailable to draw a comparison.

The overall benefit of intensive treatment strategies in rheumatoid arthritis (RA) remains uncertain.[12] In the United Kingdom a DAS28 score equal or greater than 5.1 is one of the mandatory criteria required to be eligible for NHS funded treatment with biologic (including anti-tumour necrosis factor) therapies. Miriovsky et al studied 826 veterans with RA, 75% tested positive for anti-CCP antibody and 80% were positive for rheumatoid factor and found that high anti-CCP antibody titer was associated with increased disease activity and inversely correlated with remission, especially in those also positive for rheumatoid factor.[13]

The incidence of osteoporosis among patients with rheumatoid arthritis is 15-20% at the hip and spine. Haugeberg et al elegantly showed[14] a twofold increase in osteoporosis in women with RA and a twofold increase of reduced bone mass in men with RA, compared with patients without RA in a population based study. In our cohort of sixteen RA patients out of 44 had undergone DXA scan and about 64% were osteoporotic, 24% osteopenic and 11.7% had a normal T score in DXA scan of hip and lumbar spine at presentation. Results showed that patients with rheumatoid arthritis had high prevalence of osteoporosis at the measured sites. Geraci et al studied patients with established RA and reported disease-related factors, such as long disease duration, high disease activity, joint damage, functional disability and corticosteroid use, as determinants of osteoporosis or reduced BMD.[15] Hence, patients with long-standing RA with destructive disease, functional disability or immobilisation, or who are on long-term corticosteroid treatment are at high risk for osteoporosis.[15,16] This could be explained by the fact that generalised osteoporosis is more associated with long-standing, destructive and disabling RA, whereas early RA is associated with periarticular osteoporosis. This is further supported by the fact that longer symptom duration is independently associated with more generalized osteoporosis in studies.[17]

In summary DAS28-ESR is a sound tool to assess, document and monitor disease activity for our Adult RA patients while they are on treatment with DMARDs to understand treatment response and need for any modification in the treatment regime. Six months of DMARDs and short term corticosteroids were generally well tolerated and effectively reduced DAS28-ESR in the majority to remission or low diseases activity. An intensive strategy with treat to target (TTT) approach to achieve and maintain a DAS 28-ESR of >3.2 or a change of score >1.2 reduced the existing ambiguities in choosing clinical decisions from the available treatment modalities beyond DMARDs. Those not responding may be candidates for arthroscopic synovectomy or advanced high end biologics to slow down disease progression.[18]

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