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Rheumatology

OUTCOME OF RHEUMATOID ARTHRITIS IN INDIAN PATIENTS: A RETROSPECTIVE STUDY

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ABSTRACT

Background and objective: Rheumatoid arthritis (RA) is a major burden in India. Factors determining remission have been studied in Western population but not in India. Hence, the objective was to find out the factors determining low disease activity (Disease activity Score 28 erythrocyte sedimentation score (DAS28) and the efficacy of biologics alone or as add on in RA patients.

Materials and methods: This was a descriptive study from a single centre, tertiary care hospital carried out in South Mumbai, India. Data was analyzed retrospectively between January 2014- June 2016 from hospital medical records department, lab records department, Outpatient department (OPD) register and pharmacy records. Patients with RA as per American college of Rheumatology (ACR) criteria were enrolled into the study.

DMARD failure patients were put on methotrexate (MTX) treatment along with Biologic response modifier (BRM) to or switched to another BRM. To monitor disease activity, DAS28 was obtained at baseline, and after three months and six months of therapy initiation. To predict the factors that would determine outcomes defined by DAS28<3.5 at six months, logistic regression was applied.

Results: A total of 135 RA patients with mean age of 44 years were subjected to either; MTX+ Hydroxychloroquine (HCQ) (n=73) or MTX+ Leflunomide (LEFT) (n=22) or HCQ/LEFT combination n=2, either LEFT or HCQ n=91 or MTX+ BRM (n=51) or MTX+ 2nd BRM (n=23). The mean duration of treatment was five months. The Rheumatoid factor (RF) titre values were positive for 90 patients and negative for 45 patients. The Anti-cyclic citrullinated peptide antibody (anti-CCP) titre values were positive for 86 patients and negative for 26 patients.

Initial DAS28 was 4.10±1.13 (mean ± standard deviation (SD)) which reduced to 3.58±0.98 at three months of treatment and further reduced to 3.11±0.69 at six months of treatment. About 48.1% and 70.4% of patients attained remission at three months and six months of treatment, respectively.

Patients who have received the biological treatment had statistically significant logistic regression, odds ratio of 2.77 (1.0, 7.62, 95% Confidence Interval (CI)) or approximately three times more pain relief as compared no biologic treatment. The data on regression of patients who were shifted from BRM to another BRM was poor due to less sample size for each biologic. Patients with remission at baseline (DAS28), had a lower chance of pain relief, 0.24 compared to who did not have remission, which was statistically significant.

Conclusion: Lower disease activity at baseline and use of BMRs were predictors of better outcomes in terms of DAS28 score at the end of six months. Patients with female sex, longer duration of illness and positive ACPAb were statistically found to have higher disease activity. Patients who did not respond to combination DMARD or first line BRM are less likely to respond to second BRM, although more study is required in this field.

KEYWORDS : Rheumatoid arthritis; Biologics; Disease activity, DAS 28, DMARD

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease with a worldwide prevalence of approximately 0.5% to 1% among adults.[1] Rheumatoid arthritis is a major burden in India and the prevalence ranging from 0.28% to 0.7%. This indicates that, in India there are more than 10 million patients affected with RA.[2,3] Remission is an ideal target in the management of RA.[4]

Factors determining remission have not been evaluated in Indian RA population, except for a recent study, which noted a remission of 20% among Indian patients.[5] Early treatment, escalating dose of disease-modifying anti-rheumatic drugs (DMARDs), and patient counseling are important contributing factors for attaining remission.[5]

Pharmacological therapies comprise several classes of agents, including nonsteroidal anti-inflammatory drugs (NSAIDs), nonbiol ogic and biologic disease-modifying antirheumatic drugs (DMARDs), immune-suppressants, and corticosteroids.[6] The contemporary recommended approach to treating RA is very aggressive. DMARDs that reduce disease activity and prevent joint deformity have become the standard of care and MTX has become the first treatment strategy and most commonly used in patients with active RA.[7,8]

In patients with established RA with moderate or high disease activity despite DMARD monotherapy, the recent ACR guidelines strongly recommend the use of combination of traditional DMARDs or addition of a Tumour necrosis factor inhibitor (TNFi) or a non-TNFi BRM .[9] The development of potent inhibitors of the inflammatory process, biological, revolutionized the treatment of RA. The BRMs (Abatacept (ABT), Adalimumab (ADA), Etanercept (ETN), Infliximab (INF), Rituximab (RTX), Tocilizumab (TCL), golimumab, and certolizumab pegol) are very effective in the inhibition of inflammation and several studies reported favorable actions of biologic therapies in RA management.[10,11] BRMs are not only effective with regard to symptom reduction their use is also associated with a decrease in mortality.[12]

With this background, we conducted this study to determine the factors determining low disease activity (DAS28<3.5) and the efficacy of BMRs alone or as add on in RA patients in India.

Materials and methods:

This was a single centre, tertiary care hospital study carried out in South Mumbai, India. Data was analyzed retrospectively between January 2014 to June 2016 from hospital medical records department, lab records department, OPD register and pharmacy records. Adult subjects fulfilling the 2010 ACR classification criteria for RA were enrolled into the study. Patients with Lupus, cancer or HIV infection were excluded.

RA patients who showed continued disease activity despite on therapy with DMARD for at least six months disease activity score 28-erythrocyte sedimentation rate (DAS28>4.6) were declared as DMARD failure cases and were put on either MTX+ HCQ or MTX+ LEFT or HCQ+LEFT or MTX+ BRMs or MTX+ 2nd type of BRM. The biologic used in the study were ABT, ADA, ETN, INF, RTX, TCL,

switch from INF to ABT (INF-ABT), switch from INF to RXT (INF-RXT), switch from ETN to INF (ETN-INF) and switch from ETN to RTX (ETN-RTX). Patients who were not able to maintain DAS28 score of <3.6 after six months of treatment with DMARDs were given BRMs. The study design in this study been descriptive all patients were included and no sample size calculation was required.

Randomization was not performed for treatment allocation in either DMARD failure patients or Anti-TNFi failure patients. Further, since this was not a clinical trial but a compilation of experience with different agents, informed consent waiver was obtained from the Institutional Ethics Committee.

Patients' demographic data, initial therapy used by patients, their duration of disease, baseline values of RF titers and ACPAb titers were collected. In this study, normal reference values for RF and ACPAb titers were <15 IU/ml and <20 IU/ml, respectively. To measure disease severity, DAS28 was obtained at baseline, and after three months and six months of therapy initiation. A reduction in DAS28 score by more than two points from initial score, or DAS28<3.5 was considered to be significant.

All data were recorded electronically and analyzed using IBM Statistical Package for the Social Sciences version 21.0; P<0.05 was considered to be statistically significant for all tests applied.

Results:

Patient disposition is summarized in Figure 1.

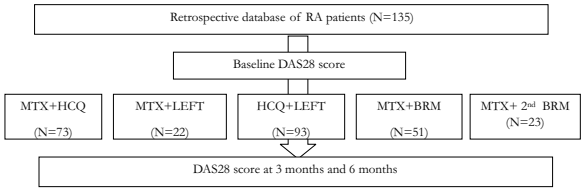

Table 1: Patient baseline characteristics (N=135)		
Parameter	**Category**	**N(%)**
Age(years) Mean± SD	<44	65 (48.1)
	>44	70(51.9)
Gender	Male	35 (25.9)
	Female	100 (74.1)
Duration of treatment (months)	<5	53 (39.3)
	>5	82 (60.7)
RF titre	Positive	90 (66.7)
ACPAb titre	Positive	86 (63.7)
HCQ	Yes	73 (54.1)
LEFT	Yes	22 (16.3)
Add-on with HCQ and LEFT	Dual	2 (1.5)
	Single	91 (67.4)
	No intervention	42 (31.1)
Types of BRMs	ABT	11 (8.1)
	ADA	1 (0.7)
	ETN	3 (2.2)
	INF	10 (17.4)
	RTX	14 (10.4)
	TCL	5 (3.7)
	INF-ABT	1 (0.7)
	INF-RXT	2 (1.5)
	ETN-INF	2 (1.5)
	ETN-RTX	2 (1.5)
	No intervention	84 (62.2)
BRM	Yes	51 (37.8)
BRM or as add on	Add-on	23 (17.0)
	Single	28 (20.7

Patient baseline characteristics are as summarized in Table 1. Patient data was categorized into five treatment groups. A total of 135 RA patients (female=100, male=35) with mean age of 44 years were subjected to either; HCQ (n=73) at a dose of 200 mg once daily or LEFT (n=22) at a dose of 10 mg OD or HCQ+LEFT (dual n=2, single n=91) or BRM (n=51) or 2nd BRM (n=23). All patients were treated with standard MTX at a dose of 15 mg/week. Patients not responding to DMARDs or their combination were treated with biologics. The mean duration of treatment was five months. The RF titre values were positive for 90 patients and negative for 45 patients. The ACPAb titre values were positive for 86 patients and negative for 49 patients.

The following were the dosages of BRM used; RTX four doses of 1g, INF six doses of 200 mg for two months, ADA 40 mg monthly for six to nine months, ETN 24 inj – 50 mg weekly for first three months/50 mg x fortnightly for next three months/50 mg x monthly for next three months, ABT eight doses of 500 mg/month and TCL six doses of 8 mg/kg/month.

Efficacy of BRMs alone or after switch

- Patients who were treated with single BRM, the DAS28 score changed from 4.49 to 3.47 at the end of 6 months.
- Patients who were treated with two BRM (Switched from one BRM to another), the DAS28 score changed from 4.33 to 4.17 at the end of 6 months.

Overall, the improvement in disease, as evidenced by reduction in the mean DAS28 scores over six months of treatment was significant in all treatment groups. The mean DAS28 scores at baseline, three months, and six months is summarized in table 2. Initial DAS28 was 4.10±1.13 (mean±SD) which reduced to 3.58±0.98 at three months of treatment and further reduced to 3.11±0.69 at six months of treatment. About 48.1% and 70.4% of patients attained remission at three months and six months of treatment, respectively (see Table 2).

Patients who have received the biologic treatment had statistically significant logistic regression, odds ratio of 2.77(1.0, 7.62, 95% CI) or approximately three times more pain relief as compared to no biologic treatment. The data on regression of patients who were shifted from one biologic to another biologics was poor due to less sample size for each biologic.

A total of 51 patients were who have failed to DMARDs in the study population were treated with BRM only according to dosage mentioned earlier; in these patients, the baseline DAS28 score was 4.5 (SD 1.06) which progressively declined to 4.00 (SD 1.01) at three months of treatment to further 3.45 (SD 0.70) at six months of treatment. A total of 23 patients were treated with two types of BRM; in these patients, the baseline DAS28 score was 4.6 (SD 1.03) which progressively declined to 3.89 (SD 1.2) at three months of treatment to further 3.43 (SD 0.69) at six months of treatment.

	Table 2: Mean DAS28 scores at baseline, 3 months and 6 months	
Parameter	score	Remission (%)
DAS28 at baseline	4.1	27.4
DAS28 at 3 months	3.58	48.1
DAS28 at 6 months	3.1	70.4

Table 3: Factors determining low disease activity (odd ratio)			
	Odds ratio	**95% C.I**	
		Lower	**Upper**
Age	.680	.239	1.934
Sex	1.709	.507	5.766
Duration of illness	1.296	.394	4.255
RF titres	.712	.192	2.638
ACPAb	1.617	.461	5.669
Baseline DAS28 score	.190	.039	.934

Table4. Effect of different treatments on DAS28 score					
	Baseline DAS28 score	**DAS28 score at 3 months**	**DAS28 score at 6 months**	**Decrease in DAS28 score at 6 months (%)**	**Patients who achieved remission at 6 months (%)**
HCQ	4.02	3.50	3.08	23.4	71.2
LEFT	3.92	3.20	2.83	27.8	77.2
HCQ+LEFT	4.00	3.44	3.01	24.7	74.1
BRM	4.56	4.00	3.45	24.3	52.9
Add on BRM	4.64	3.89	3.43	26.0	47.8

Factors determining low disease activity

Variables predicting response/non-response to treatment (overall and by sub group [DMARDs and biologicals]) where response is defined as: a) low disease activity DAS28 < 3.5, b) DAS28 reduction of at least 1.2 units, c) a reduction in DAS28-ESR score by more than two points from initial score, d) Improvement as per physician's global asses sment.

There was no significant association in any of the demographic variables like age, sex, duration of disease, RF titres, ACPAB with DAS28 score. However, there is a significant association with DAS 28 at baseline variable. Patients who had remission at baseline (DAS28), their chance of pain relief was less, 0.24 compared to who did not have remission, which was statistically significant. The odds ratio is 0.190; 95% CI is 0.039 to 0.934 (see Table 3).

Use of BRM was one of the factors determining DAS28<3.5. Patients who have received the biologic treatment had statistically significant logistic regression, odds ratio of 2.77(1.0, 7.62, 95% CI) as compared to no biologic treatment.

The data on regression of patients who were shifted from one BRM to 2nd BRM was poor due to less sample size for each biologic.

Discussion

Rheumatoid arthritis remains a major clinical problem and the development of new therapies such as BRMs have revolutionized its management.[13] The recent ACR guidelines recommend the use of DMARD or a TNFi or with a Non-TNFi BRM (with or without MTX) therapy in patients with established RA with moderate or high disease activity despite DMARD therapy. In case, the disease activity is moderate to high despite a single TNFi BRM therapy, the non-TNFi biologics are recommended. However, no details are mentioned about the sequence of choice of TNFi BRMs and the Non-TNFi BRMs.[14]

The initial trials of biologics in RA focused on patients with active disease which had failed to respond to methotrexate and other DMARDs. Summarizing the risk of remission in various trials, overall, biologics have shown to increase the frequency of remission and are highly cost-effective in RA.[15] Since the efficacy of each BRM agent is not similar in all patients, there is an underlying need for switch between BRM agents. It is reasonable to switch from one anti-TNFi agent to a second one, possibly with a different mechanism of action. This could also be necessary because of the presence of driving cytokines other than TNFα.[16]

In the present study, patients who were on BRM treatment had statistically significant logistic regression as compared to no BRM treatment. However, comparison was not possible in patients who were shifted from one BRM to another BRM due to less sample size for each BRM.

In my recently published study, over six months of treatment of in DMARD failure RA patients with ENT or INF, and TNFi failure RA patients on RTX or ABT or TCL showed reduction in disease activity based on reduction in the mean DAS28 scores. This was statistically significant for all patients when considered together, as well as when individual biologics were considered separately. But there was no statistically significant difference in the magnitude of reduction in the mean DAS28 scores between patients who received ETN and INF in DMARD failure RA patients or between patients who received RTX, ABT, and TCL in TNFi failure patients. Therefore, the researchers concluded that different biologic agents showed similar efficacy in patients with RA.[17] Previous studies that have compared the efficacy of different BRMs in RA, mostly concluded that the efficacy of BRMs is similar.18-20 In one of the study, the estimated difference in DAS28 improvement between those who switched from one TNFi to another and those who switched from a TNFi to RTX was −0.63 (95% CI: −1.14, −0.12). This shows that response rates after sequential TNFi use were lower than for first-time use.[21]

Factors that determine remission have been studied extensively in Western population; however data pertaining to Indian population is very limited. Therefore, in our study we determined factors that predict low disease activity (DAS28 < 3.5) during RA treatment. According to our results, logistic regression analysis showed that the baseline dependent variables predictive of remission was higher disease activity. Patients with higher disease activity at baseline showed higher remission at the end of six months. Similarly, patients on biologics showed significantly better treatment outcome. Therefore, higher baseline disease activity and use of BRM were predictors of better outcomes in terms of DAS28 score at the end of six months of treatment.

The recent Karnataka rheumatoid arthritis comorbidity (KRAC) study intended to estimate the effect of various treatment strategies in achieving remission (DAS28< 2.6) among Indian RA patients. According to the authors, around 20% of the study subjects achieved remission and early treatment and escalating dose of DMARDs were some of important contributing factors for attaining remission.[22] In another study by Gossec, et al., baseline prognostic factors for remission in early RA were mainly clinical markers of disease activity and radiological scores.[23]

Limitation of Study:

The study design is descriptive observational study, so we cannot assume causality from this study. Also individual DMARD and BRM are not compared for treatment compliance or outcome in this study.

Conclusion:

Lower disease activity at baseline and use of biologics were predictors of better outcomes in terms of DAS28 score at the end of six months. Patients with female sex, longer duration of illness and positive ACPAb were statistically found to have higher disease activity. Patients who did not respond to combination DMARD or first line BRM are less likely to respond to second BRM, although more study is required in this field.

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