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Efficacy and Safety of Conventional Synthetic Disease Modifying Anti-Rheumatic Drugs (csDMARDs) on the treatment of Rheumatoid Arthritis

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ABSTRACT

Introduction: Rheumatoid arthritis is a systemic disease that can induce a wide range of extra- articular symptoms. CsDMARDs–methotrexate, hydrochloroquine, leflunomide, and sulfasalazine are a few beneficial remedies for RA. DMARDs are a mainstay in the management of rheumatoid arthritis. **Objective-** To assess the efficacy of Conventional Synthetic DMARDs on the treatment of Rheumatoid Arthritis. **Methodology:** A total 36 patients of Rheumatoid Arthritis fulfilling the inclusion criteria and having symptoms of RA were enrolled for this Interventional study from OPD of Department of Medicine, SS Hospital, Institute of Medical Sciences, BHU, Varanasi and were followed for three months. After the completion of the study, 32 patients completed all 3 follow-ups. **Result:** DMARDs has significantly improved the RA factor, Anti CCP, CRP and ESR values, as median values of these diagnostic tests have reduced over time (RA factor- 27.12 to 16.24, Anti CCP- 28.26 to 18.86, CRP – 7.65 to 4.23 and ESR- 34.50 to 23.50). After 3 months treatment with synthetic DMARDs, the mean SGOT, SGPT and Urea level decreased significantly from 36.43 ± 12.92 to 31.93 ± 10.92, 38.74 ± 12.15 to 34.01 ± 10.59 and 39.14 ± 12.34 to 34.51 ± 10.44 respectively. DMARDs was also effective in reducing the pain (joint pain, low back pain and neck pain),as median values of joint pain, low back pain and neck pain have reduced over time (Joint pain- 6 to 3, Low Back Pain- 6 to 2 and Neck Pain- 4.5 to 1). Adverse effects were observed in more than 30% of patients **Discussion:** The study showed that DMARDs was effective and safe for the treatment of Rheumatoid Arthritis according to the biochemical and clinical pain score finding over -90 day follow up. A long term follows up and histological examination, invasive or non – invasive, is required to give conclusive report.

Keywords: Rheumatoid Arthritis, Efficacy, DMARDs, Safety.

Introduction

A symmetric peripheral polyarthritis is a hallmark of Rheumatoid Arthritis (RA), a chronic inflammatory autoimmune illness with an unclear cause. It is the most prevalent type of long-term inflammatory arthritis and frequently causes physical impairment, joint deterioration, and loss of function. Rheumatoid arthritis is a systemic disease that can induce a wide range of extra-articular symptoms. There is considerable evidence of autoimmunity in these patients, despite the fact that the etio-pathogenesis of the disease is still unclear. [1, 2]

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The global prevalence of RA between 1980 and 2019 was 0.46% (95% CI, 0.39% to 0.54%) and women are affected approximately three times more than men. The prevalence increases with age and sex difference diminish in the older age group. [3] It is painful condition commonly involves synovial joints which lead to substantial loss of functioning and mobility, if not adequately treated. It is reported that in India, the prevalence of RA is 0.34%.[4] This suggests that, near about 4.1 million people in India are afflicted with this illness.

Since rheumatoid arthritis is a chronic, incurable, complicated, and morbid condition, it is one of the most difficult diseases for doctors to treat. Even after the best medications are administered, the illness tends to worsen; leading to incapacitation of patients. NSAIDs and DMARDs are the cornerstones of modern medicine's therapeutic regimen. Disease Modifying Anti-Rheumatic Drugs (DMARDs)–methotrexate, hydrochloroquine, azathioprine, leflunomide, glucocorticoids, and sulfasalazine are a few of the remedies that are beneficial for RA. Four DMARDs are primarily used in this study to treat rheumatoid arthritis: leflunomide, methotrexate, hydroxychloroquine, and sulfasalazine.

The drugs are usually used multiple times per day and may produce side effects such as vomiting, abnormal liver function, abdominal discomfort, lung infection, rashes, myopathy, neuropathy, cardiovascular effects, bone marrow suppression. Some of the observed side effects are seriously limiting for the treatment. Cost of treatment is another limiting factor. The problem gets compounded especially in the rural area, when the patient with low paying capacity and with chronic painful illness used to take cheap steroid without medical advice. In this way, RA continues to be a major therapeutic challenge despite several advances in modern medicine.

So, there is needed to look into the therapeutic effect and side effect of DMARDs, again, in a changed socioeconomic, climatic and cultural environment. We estimated the efficacy of DMARDs using a various statistical test and pain measurement score (Numerical Rating Scale). The findings of studies on the burden of disease can be utilized to establish health policy priorities and support the necessity for funding social interventions, disease management, and prevention.

Objective: To assess the efficacy of Conventional Synthetic Disease Modifying Anti- Rheumatic Drugs (DMARDs) on the treatment of Rheumatoid Arthritis.

Methodology

Planning of the Study: A Hospital-based study was planned to determine the efficacy of DMARD son the treatment of Rheumatoid Arthritis patients in SS Hospital, IMS, BHU, Varanasi.

Research Strategy: Interventional Study

Research Setting: The study was hospital-based in the SS Hospital, IMS, BHU, Varanasi.

Diagnostic Criteria: The diagnosis of RA is based on clinical criteria, with laboratory and radiology findings helping to establish the diagnosis. The 2010 American College of Rheumatology/European League against Rheumatism (ACR/EULAR) diagnostic criteria was applied for diagnosis as well as assessment of the trial. A patient with a score of 6 or more points out of 10 can be classified as having RA.[5, 6]

Reference Population: Adult population of SS Hospital, IMS, BHU.

Study Population: Adult subjects attending the Medicine OPD of SS Hospital, IMS, BHU, Varanasi were diagnosed as a case of Rheumatoid Arthritis.

Inclusion Criteria:

1. Adult population of age group 18-60 years attending Rheumatology OPD, suffering from Rheumatoid Arthritis.
2. Patient with duration of disease not more than two years.
3. Patients with Rheumatoid Arthritis with mild to moderate.
4. Patients of Rheumatoid Arthritis without any systemic complications.

Exclusion Criteria:

1. Patient having co-morbidity like diabetes mellitus.
2. Patient having pregnancy.
3. The patient not giving consent to participate in the study.

Sample Size: Total Sample Size (N) =36

Study Design and Treatment Schedule: In the present study sample size was 36 but after the completion of the study, total 32 patients completed all follow - up, so we included 32 patients in this study. The cases were randomly allocated regardless of their age, sex, and religion. 36 clinically diagnosed and registered patients of RA were treated by-

DMARD's

(1)	Methotrexate	**:**	2.5 mg tab OD orally	- 90 days.
(2)	Hydroxychloroquine	**:**	200 mg tab BD orally	- 90 days.
(3)	Sulfasalazine	**:**	1000mg tab BD orally	- 90 days.
(4)	Leflunomide	**:**	10 mg OD tab orally	- 90 days

Data Analysis: [7, 8]

Intra-group (within the group) comparison: To test the significance of mean of difference of paired observations (BT versus AT) **Paired "t" tes**t was applied, wherever; the data did not satisfy the assumptions of parametric test, non-parametric test viz., **Wilcoxon Signed–Rank** test was applied. In case of repeated measurements of same subject for various follow-ups, **Repeated Measure ANOVA** (Analysis of Variance) was applicable whereas, a corresponding non-parametric test Friedman **Chi-square test** was applied**.**

Results

Figure –1 show, there is improvement in all test parameters in majority of patients. The improvement in number of beneficiary after treatment with DMARDs is also reflected when we take the median value of test result. Table-1 shows significant improvement in RA Factor, Anti CCP and Creatinine value. These three tests are important in the diagnosis in RA.

Table-1: Changes in Diagnostic Test values over a 90-day period (Before treatment and after treatment)**.**

Diagnostic Parameter	Q1:Q3	Median	Within group Comparison For Paired Observation (Wilcoxon Signed Ranks Test)
RA Factor (D1)	18.20 : 100.75	27.12	z = - 4.97
RA Factor (D90)	12.05 : 66.05	16.24	p = 0.00
Anti CCP (D1)	18.56 : 108.05	28.26	z = - 4.93
Anti CCP (D90)	13.61 : 75.08	18.86	p = 0.01
Creatinine (D1)	0.80 : 1.27	0.90	z = -3.67
Creatinine (D90)	0.70 : 1.07	0.80	p = 0.00

Figure-1: Number of patients in normal range, before and after treatment

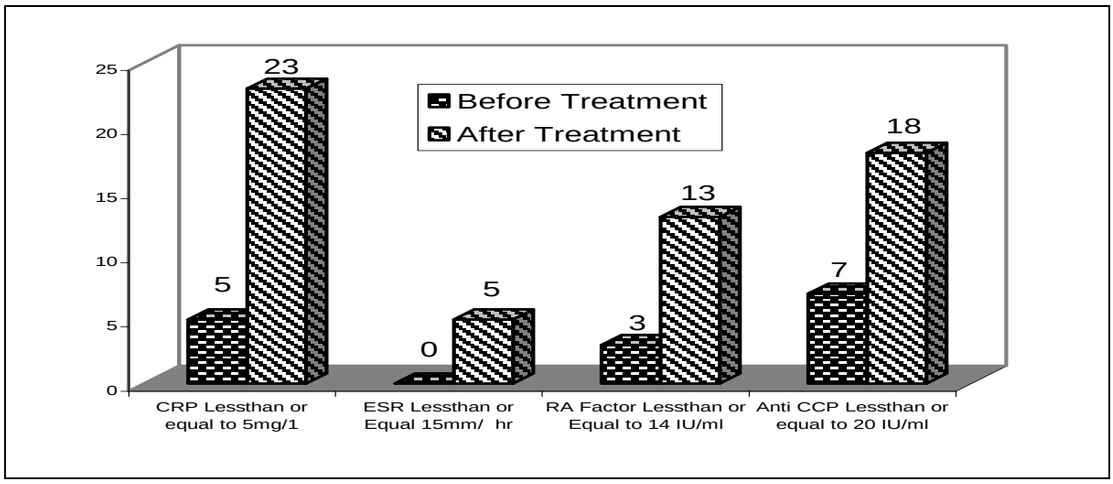


Table -2 shows the descriptive statistics of pre and post- test scores. The p- value of the *Paired t-* test (For SGOT) is *0.01*, which is highly significant. We, therefore, conclude that DMARDs has significantly improved the SGOT level of RA patients. The p- value of the *Paired t- test is* (For SGPT) is *0.00*, which is highly significant.

We, therefore, conclude that DMARDs has significantly improved the SGPT level of RA patients. The p- value of the *Paired t- test* (For Blood Urea) *is 0.01*, which is highly significant. We, therefore, conclude DMARDs has significantly improved the Urea level of RA patients.

Table-2: Changes in Diagnostic Test values over a 90-day period (Before treatment and after treatment)

Diagnostic Parameter	Mean ± SD	Within group Comparison for Paired Observation (Paired t Test)
SGOT (D1)	36.43 ± 12.92	t = 5.15 p = 0.01
SGOT (D90)	31.93 ± 10.92	
SGPT (D1)	38.74 ± 12.15	t = 6.05 p = 0.00
SGPT (D90)	34.01 ± 10.59	
Blood Urea (D1)	39.14 ± 12.34	t = 6.17 p = 0.01
Blood Urea (D90)	34.51 ± 10.44	

Figure-2: Changes in Diagnostic Test values at each level of treatment (i.e., D1, D30 and D90)

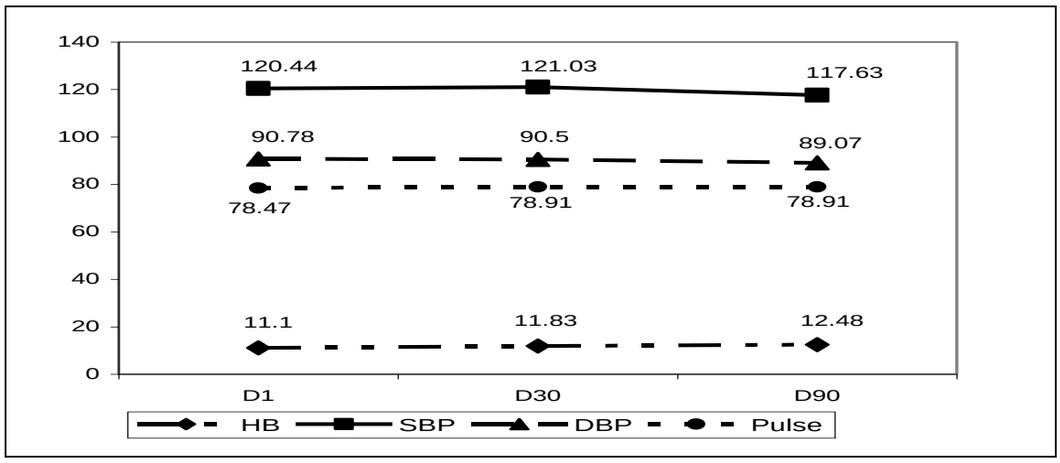


Figure – 2 shows, DMARDs has significantly improved the Haemoglobin level of RA patients. It can be said on the basis of p value <0.05 on applying repeated measurement ANOVA. On the other hand, DMARDs has no significant

effect on the Systolic Blood Pressure, Diastolic Blood Pressure, Pulse Rate of RA patients. On the safety point of view desirable findings were seen over 90- day period.

Table-3: Changes in Diagnostic Test values at each level of treatment (i.e., D1, D30 and D90)

Diagnostic Parameter	Q1:Q3	Median	Within group Comparison More than two measurements (Friedman Test)
CRP (D1)	5.51 : 13.62	7.65	$\chi^2 = 41.06$; p = 0.001
CRP (D30)	4.25 : 10.36	6.11	
CRP(D90)	2.21 : 5.24	4.23	
ESR (D1)	28.00 : 57.50	34.50	$\chi^2 = 45.56$; p = 0.01
ESR (D30)	22.00 : 50.75	29.00	
ESR (D90)	18.00 : 32.00	23.50	

Table -3 and 4 shows the descriptive statistics at each level of treatment. The p-value of the *Friedman Test* (For CRP) is 0.00, which is highly significant. It is therefore conclude that DMARDs has significantly improved the CRP level of RA patients.

The p-value of the *Friedman Test* (For ESR) is 0.01, which is highly significant and therefore, conclude that DMARDs has significantly improved the ESR level of RA patients. The p- value of the *Friedman Test* (For Joint Pain) is 0.01, which is highly significant. We, therefore, conclude that DMARDs is effective in reducing joint pain, as median joint pain value has reduced over time. The p-value of the *Friedman Test* (For Low Back Pain) is 0.01, which is highly significant. We, therefore, conclude that DMARDs is effective in reducing Low Back Pain, as median Low Back pain value has reduced over time. The p- value of the *Friedman Test* (For Neck Pain) is 0.00, which is highly significant. We, therefore, conclude that DMARDs are effective in reducing neck pain, as median neck pain values have reduced over time.

Table -4: Changes in Pain Score at each level of treatment (i.e., D1, D30 and D90)

Diagnostic Parameter	Q1:Q	Median	Within group Comparison More than two measurements (Friedman Test)
Joint Pain (D1)	5.00 : 6.00	6.00	$\chi^2 = 52.51$; p = 0.01
Joint Pain (D30)	3.25 : 5.00	4.50	
Joint Pain (D90)	2.00 : 3.00	3.00	$\chi^2 = 45.06$; p = 0.01
Low Back Pain (D1)	0.75 : 6.00	6.00	
Low Back Pain (D30)	0.00 : 5.00	4.00	
Low Back Pain (D90)	0.00 : 3.75	2.00	$\chi^2 = 36.07$; p = 0.001
Neck Pain (D1)	0.00 : 6.00	4.50	
Neck Pain (D30)	0.00 : 4.00	3.00	
Neck Pain (D90)	0.00 : 2.75	1.00	

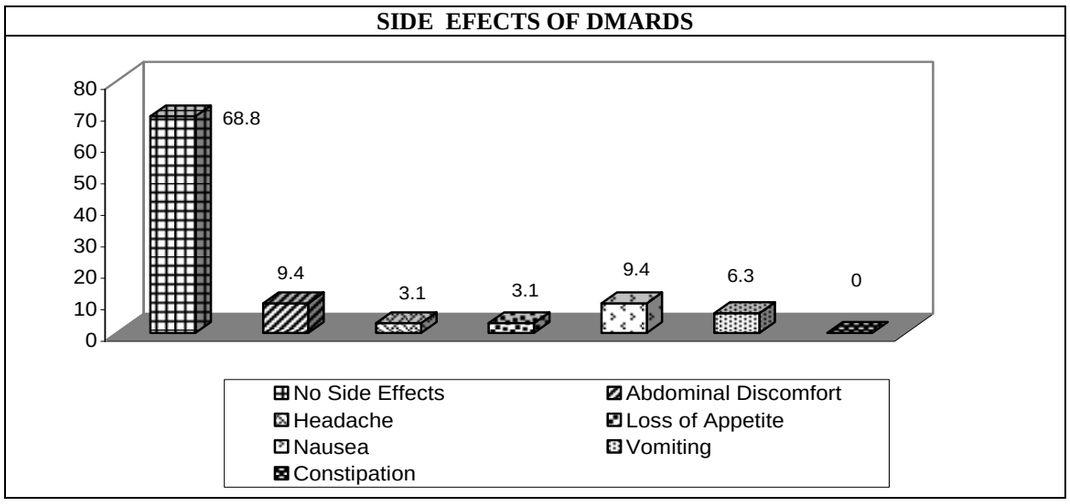
Table-5: Percentage effect in diagnostic parameters, after the treatment

Parameter	Treatment		
Diagnostic Parameter	Before Treatment Mean ±SD	After Treatment Mean ±SD	Percentage Effect
RA Factor	27.12 (M)*	16.24 (M)	- 40.11
Anti CCP	28.25 (M)	18.86 (M)	-33.23
CRP	7.65 (M)	4.23 (M)	- 44.70
ESR	34.50 (M)	23.50 (M)	- 31.88

*M – Median

The table provides a detailed comparison of various diagnostic parameters before and after treatment with Ginger and Castor Oil in the interventional group. The data includes mean values and standard deviations (SD) for some parameters, and median (M) values for others, along with the percentage effect observed post-treatment. There is a significant reduction in RA Factor, indicating a positive effect of the treatment. A notable decrease in Anti CCP levels, suggesting improvement in this parameter. CRP levels dropped significantly, indicating a strong anti-inflammatory effect. ESR values decreased, showing a positive response to the treatment.

Graph- 3: Adverse effects of DMARDs, after the treatment (90 days)



Out of 32 patients, 10 (32.2%) patients complained for adverse effects. Abdominal discomfort and nausea were reported by 3 (9.4%) patients. Vomiting was reported by 2 (6.3%) patients.

Discussion

According to this study, after treatment (90 Days), DMARDs has significantly improved the RA factor, Anti CCP, CRP and ESR values, as median values of these diagnostic tests have reduced over time (RA factor- 27.12 to 16.24, Anti CCP- 28.26 to 18.86, CRP – 7.65 to 4.23 and ESR- 34.50 to 23.50). A study conducted in Chandigarh, India, has shown that after 3months of treatment with synthetic DMARDs, the mean ESR and CRP level decreased significantly from 36.10 ± 15.20 to 25.55 ± 10.04, $p<0.001$ and ,15.48 ± 11.74 to 8.26 ± 6.22, $p=0.001$, respectively, which is almost similar to our study. [9] After 3 months of treatment, the CRP levels of 18 (56.27%) patients returned to the normal range, ESR levels of 5 (15.62%) patients returned to the normal range. RA Factor levels of 10 (31.25%) patients returned to the normal range, Anti CCP levels of 11 (34.38%) patients returned to the normal range.

LFT, RFT and Urea test done for Safety point of view, after 3 months treatment with synthetic DMARDs, the mean SGOT, SGPT and Urea level decreased significantly from 36.43±12.92 to 31.93±10.92, 38.74±12.15 to 34.01± 10.59 and 39.14±12.34 to 34.51±10.44 respectively. DMARDs has significantly improved the haemoglobin level of RA patients (11.10±1.24 to 12.48±1.42). We, therefore conclude that DMARDs was safe for the treatment of Rheumatoid Arthritis.

DMARDs was also effective in reducing the pain (joint pain, low back pain and neck pain). Joint pain included- Shoulders, elbows, hips, knees and ankles. As median values of joint pain, low back pain and neck pain have reduced over time (Joint pain- 6 to 3, Low Back Pain- 6 to 2 and Neck Pain- 4.5 to 1). We, therefore, conclude that Disease Modifying anti – rheumatic drugs were effective to improve the joint pain, low back pain and neck pain. Morning stiffness was the most important symptom, after treatment, ‘morning stiffness’ improved in 6.3% of patients. ‘Joint

swelling' in 25.00 % patients. In this study more common side effects of DMARDs was abdominal discomfort and Nausea 3 (9.4%), followed by Vomiting 2 (6.3%).The side effects, which can include nausea, vomiting, irregular liver function, lung infection, mouth sores, rash, diarrhea, renal problem, hepatic problem, and stomach discomfort, are typically experienced after numerous daily doses.[10] Although, there was desirable biochemical findings and there was improvement in pain score, too; but more than 30% patients were having the adverse effect only during a short duration of treatment. In other studies, several other limiting adverse effects like, bone marrow suppression was seen on long term treatment.

This study has several limitations. First, a limited number of patients were included in the study and for a short duration. The study focuses exclusively on Conventional Synthetic DMARDs for RA treatment instead Biologic DMARDs and Targeted Synthetic DMARDs. Considering the duration of treatment for Rheumatoid Arthritis and the burden of this disease in Indian community, a long term follow up study is required. Histological examination of liver, either invasive or non – invasive, is required to give conclusive report. Future studies should explore the long – term efficacy and safety of DMARDs in larger more diverse patient populations. According to WHO data published in 2018, RA deaths in India reached 27000 (0.30 %) of total deaths (8.93 million). Morbidity pattern of RA is painful for rest of its life and gradually crippling leading to death; if left untreated. Major fund of health sector are now being directed towards the management of non-communicable diseases. Ayushman Bharat is an ambitious programme to address the ailing health condition of the society. RA may put an extra economic burden on the Indian society. Also, there is needed to go to look for the alternative therapy of the short-term curative regimen.

Ethical Approval -Yes

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