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ASSESSING THE IMPACT OF METHOTREXATE, HYDROXYCHLOROQUINE, AND THEIR COMBINATION IN RHEUMATOID ARTHRITIS: EFFICACY, SAFETY, AND COST ANALYSIS WITH VITAMIN D3 AND BMI

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ABSTRACT

Background: A chronic, symmetrical & inflammatory disease, which affects small joints and later progresses to involve large joints. To promote remission and control further joint destruction, disease modifying ant rheumatic drugs are used. The role of low Vitamin D3 and High BMI have been found in pathogenesis of RA. **Methodology:** The study was designed by Department of pharmacology and patients were enrolled from department of medicine. This was an open label; prospective study. After obtaining, informed written consent, the subjects were randomized in three groups, Group 1-Methotrexate 7.5-15mg once a week, Group 2 - Hydroxychloroquine 200mg BD and Group 3-Methotrexate 7.5mg once a week Plus HCQ 200mg OD. The Vitamin D3 levels and Body mass index was assessed at first visit. The quality of life was assessed using DAS-28/CRP, RAPID-3 Score. Average cost-effective ratio was also calculated. The adverse effects were also assessed using WHO-UMC causality assessment. The statistical analysis of the data Graph pad insta version 3.1 was used, p-value <0.05 was considered statistically significant. **Results:** The mean changes in DAS28/CRP and RAPID-3 between baseline & 16 weeks was highly significant (p<0.0001) in all groups. Vitamin D3 levels at baseline was 19.14±0.42, 19.86±0.67 and 19.52±0.98 in all groups respectively. **Conclusion:** The vitamin D3 levels were in the lower limit and BMI was raised in almost all the patients at first visit. The efficacy of combination therapy is found to be better when given at initial stages of RA patients.

INTRODUCTION

Rheumatoid Arthritis (RA) a disease, affecting smaller joints initially but slowly progressing to involve large joints, is a chronic, symmetrical and autoimmune inflammatory disease [1]. The disease usually affects people of 35 to 60 years of age group. In spite of many bio-molecular mechanisms underlying, the

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disease pathology has been proposed, yet the aetiology is yet not fully understood. The production of anti-citrullinated peptide antibodies is being considered as the newer hypothesis. Being a multi factorial disease, the genetics is estimated to play major contribution in its origin [2]. The path physiology of RA is not elucidated, though immunoglobulin G, Type 2 collagen and Vimentin, have been though to play a role in its origin. Other than this, many cytokines (TNF and Interleukin 1, 6), that get released at joint inflammation site can act as a triggering factor [2]. In a recent cross over study, a strong association between air pollutants and evolution of RA has been found in 888 RA patients, as the air pollution has been found to be associated in raising CRP levels in patients.3 RA has been associated with reduced Ultraviolet B radiation and gut micro bacteria [3, 4]. In 2010, American college of Rheumatology (ACR) and classification criteria given by EULAR (European league against rheumatism) evaluates a number of RA variables for example associated risk factors, joints involved, symptoms duration, for making the early detection of RA [5].

In recent studies to diagnose presymptomatic phase of RA, anti-Carp (Carbamylated proteins) presence in serum have been established [6]. RA factor (RF) is an IgM antibody with a specificity of 85% [7]. The sensitivity of anti-CCP being having more prognostic value in RA is 48-80% & specificity is 96-98% [7]. Another sensitive marker of RA is C - reactive protein (CRP) & is elevated in patients with RA [8]. Studies have reported strong association between acute phase reactants & disease activity [9-11]. RA is being linked to many co morbid conditions such as infections, cardiovascular diseases, cancers and lung diseases. Therefore, a patient with RA should be screened for any co morbid conditions and life style changes, exercise, diet balance should be the part of its management. As per Recommendations given by EULAR, a rheumatologist is the most authenticated person to identify and organise risk factor assessment and plan a proper care for RA patient [12]. It is used to quantify disease activity at each visit & to be used in subsequent visits for comparison. Anti-inflammatory drugs usually do not affect CRP levels; therefore, changes in CRP probably reflect a change in the underlying disease [13,14]. An important role in bone metabolism is played by Vitamin D and in addition by inhibiting the level of cytokines, Vitamin D can prevent the occurrence of RA [15], to relieve pain and also to decrease inflammation should be the major goal of treatment in RA. Major treatment approaches have been recognized as Non-pharmacological and Pharmacological. Non- pharmacological are further divided into rest, occupational therapy & lifestyle changes and use of Polyunsaturated fatty acids, as being linked to release anxiety and depression [16]. Moreover, occupational therapy has shown improvement in joint function in RA patients as per a systemic review [17]. A considerable progress has been made in the pharmacological approaches. As per ACR and EULAR recommendations, treatment with non-steroidal anti-inflammatory drugs, Glucocorticoids and disease modifying management has been established [18]. The suppression of autoimmune activity and joint degradation prevention has been contributed by DMARDs. The results are better, if they are implemented at an early stage of RA [18], it has been claimed by 2021 ACR, that MTx should be the first line as per of its efficacy and safety profile [18]. Many biologic agents have been developed, such as TNF-alpha inhibitors, Interleukin inhibitors, RankL Inhibitor, Granulocyte macrophage colony stimulating factor inhibitor, Janus kinase inhibitors. The present study was aimed to comparatively evaluate the efficacy, safety and cost of MTx, HCQ alone and in combination in RA.

MATERIAL AND METHODS

All the patients of more than 18 years diagnosed on the basis of EULAR-ACR criteria, included in study, underwent RA factor and Anti-ccp, CRP laboratory tests at the time of presentation to hospital. The study was conducted for a period of one year, after approved by Hospital Research and Ethics Committee, with reference number SGRR/REC/57/14. All the stable patients of Rheumatoid Arthritis were included in the study, only after obtaining informed written consent, at the time of enrolment in the study. Patients were stabilized on Non-steroidal Anti-inflammatory Drugs for a period of 1 week and simple randomization was done into the following 3 groups:

Group 1: Methotrexate (7.5-15mg once /week)

Group 2: Hydroxychloroquine (200mg BD)

Group 3: Combination therapy with Methotrexate (7.5mg once a week) + Hydroxychloroquine (200 mg OD)

Inclusion Criteria:

1. Both sexes (M & F) with new onset of RA
2. Age >18 years
3. Diagnosed on the basis of 2010 American College of Rheumatology (ACR) – European League against Rheumatism (EULAR) Classification Criteria for Rheumatoid Arthritis.

Exclusion Criteria:

1. Age <18 years
2. Pregnant or lactating women
3. Patients with impaired renal or hepatic function
4. Patients with RA complications

The follow up was done for every 2 weeks till one month then every 4 weeks up to 16 weeks. Body mass index using weight in Kilograms divided by height square in meters and Lab values of Vitamin D3 were assessed at first visit. ADRs were monitored at each visit and are assessed using WHO-UMC scale. To assess the quality-of-life disease activity score in 28 joints/ CRP was used. Direct medication cost was analysed & compared between each treatment group. ADRs were monitored at each visit and are assessed using WHO-UMC scale. Average cost-effective ratio (ACER) was estimated by dividing the total cost of the study drugs over the study period to that of the decrease or improvement in disease activity score in 28 joints in all the study groups. For statistical analysis, p-value <0.05 was considered statistically significant. Paired T test and ANOVA analysis was used for intragroup and intergroup comparisons respectively.

Table 1: Comparative Changes in DAS-28/CRP at baseline & at 16 weeks

Parameters	At Baseline	At 16 weeks	p-value intragroup	p-value intergroup (at 16 weeks)
Group-1 (n=29)	3.96±0.12	3.20±0.12	<0.0001	1vs.2>0.05
Group-2 (n=23)	3.94±0.11	3.30±0.11	<0.0001	2 vs. 3<0.001
Group-3 (n=23)	4.39±0.14	2.53±0.11	<0.0001	3 vs. 1<0.001
p-value intergroup at baseline	1 vs. 2>0.05	2 vs. 3 >0.05	3 vs. 1>0.05	

(All values are expressed in Mean ± SEM). The intergroup comparison using one way ANOVA analysis was highly significant (p<0.001) between group 2 and 3 and group 1 and 3, but not significant (p>0.05) in group 1 & 2 (Table 1).

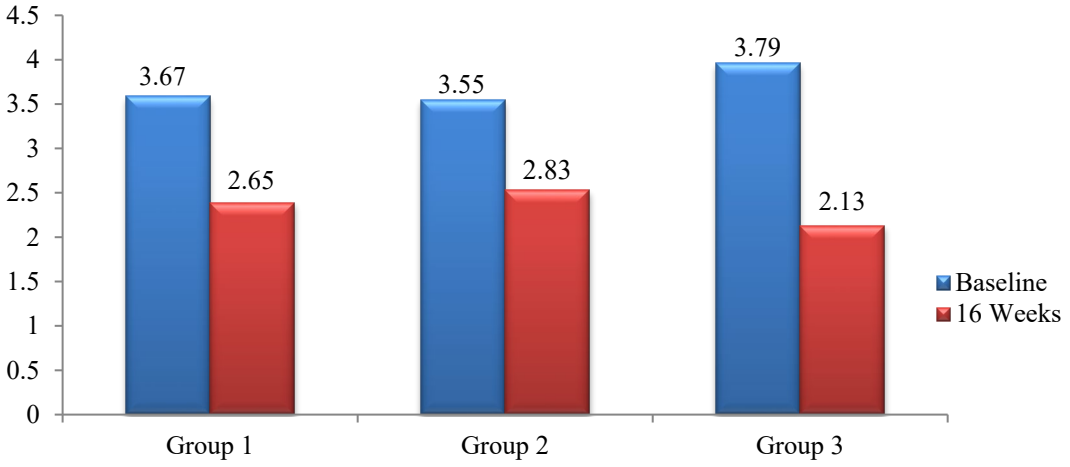

Figure 1: Comparison of RAPID-3 at baseline & at 16 weeks in three groups

Table 2: Comparison of Adverse effects amongst all study groups:

Adverse Effects	Group 1	Group 2	Group 3	Adverse Effects	Group 1	Group 2	Group 3
Nausea	4(3.36%)	4(3.36%)	7(5.88%)	**Decreased Vision**	-	3(2.52%)	4(3.36%)
Vomiting	2(1.68%)	2(1.68%)	4(3.36%)	**Constipation**	6(5.04%)	-	-
Epigastric Pain	4(3.36%)	7(5.88%)	7(5.88%)	**Loose stools**	3(2.52%)	-	-
Bloating sensation	9(7.56%)	4(3.36%)	6(5.04%)	**Hyper pigmentation of Lips**	1(0.8%)	-	1(0.8%)
Weakness	-	7(5.88%)	-	**Mouth Ulcers**	6(5.04%)	-	10(8.40%)
Generalized Body Pain	6(5.04%)	-	-	**Hoarseness of voice**	-	-	1(0.8%)
Diarrhea	1(0.8%)	1(0.8%)	3(2.52%)	**Dry Cough**	-	-	1(0.8%)
Hair Fall	-	4(3.36%)	1(0.8%)				

RESULTS

A total 75 patients were followed till 16 weeks. The most common RA presenting age group was in the age range of 46-60 (36%). The mean age of patients was 50.56±14.60 years. In the present study the positive family history was positive in 35% of the patients. The mean BMI calculated was 27.73±0.35, 27.52±0.86 and 28.07±0.69 in group 1, 2 and 3 respectively. Vitamin D3 levels at baseline were 19.14±0.42, 19.86±0.67 and 19.52±0.98 (ng/ml) in all three groups.

The mean changes in RAPID-3 between baseline & 16 weeks were highly significant ($p<0.0001$) in group 1, 2 & 3. The RAPID-3 Score was 3.67±0.06 in group 1, 3.55±0.08 group 2 & 3.79±0.09 group 3 at baseline, 2.65±0.09 in group 1, 2.83±0.09 in group 2 & 2.13±0.15 in group 3 at 16 weeks. The intergroup comparison was not significant ($p>0.05$) in group 1 & 2, was highly significant ($p<0.001$) in group 2 & 3 and group 3 & 1 (Figure 1).

All the patients were enquired for any adverse reactions due to study drugs throughout the study period of 16 weeks. Overall, 119 adverse events were reported 42 (35.29%) in Group 1, 32 (26.89%) in Group 2 & 45 (37.81%) in Group 3. The predominant side effects were gastrointestinal distress in 74 (62.18%), followed by weakness with generalized body pain in 13 (10.92%), mouth ulcers 16 (13.44%), decrease vision 7 (5.88%), hair fall 5 (4.20%), hyper pigmentation of lips 2 (1.68%), dry cough with hoarseness of voice 2 (1.68%) were reported. The side effects in all the groups were transient, mild & did not require any change in the treatment protocol. None of the patients opted out of the study due to adverse drug effects.

According to WHO-UMC causality assessment 13 ADRs in group 1, 4 in group 2 & 24 in group 3 were in probable category, 29 in group 1, 28 in group 2 & 21 in group 3 were in possible category. The average cost per week (INR) was found to be Rs. 15.68/- in group 1, Rs. 88.2/- in group 2 & Rs. 56.8/- in group 3. The total direct cost (INR) per patient over 16 weeks was Rs. 251.03/- in group 1, Rs. 1411.2/- in group 2 & Rs. 908.8/- in group 3. The average cost-effective ratio as calculated by dividing the cost/mean decrease in disease activity score-28 joints was found to be 330.30 in group 1, 488.60 in group 3 & 2205 in group 2. The most cost-effective combination in the present study was combination of Methotrexate & Hydroxychloroquine.

Table 3: Assessment of Adverse effects using WHO-UMC Causality scale

WHO-UMC Causality Categories	Group 1	Group 2	Group 3
Certain	-	-	-
Probable	13	4	24
Possible	29	28	21
Unlikely	-	-	-
Unclassified	-	-	-
Unclassifiable	-	-	-

DISCUSSION

RA mainly affects the lining of joints and can lead to progressive disability and many economical burdens. The disease may present with exacerbations that are episodic and symptoms usually get worsen in the absence of proper treatment. The life expectancy of patients is expected to be reduced by complications and co-morbidities associated with RA. The disease has been considered a major public health issue. For the purpose of getting desirable results, an early diagnosis should be made. Therefore, joint disability can be reduced, functional disability can be controlled, and cost-effective treatment should be started [19, 20]. An important and prevalent co morbidity associated with RA is obesity, in the update dose response meta-analysis by Fen X et al, the increased risk of RA is linked to be associated with increased BMI [21].

The recently established criteria by EULAR (European League against Rheumatism) include Rheumatoid factor, ACPA (Anticitrullinated peptide antibody), ESR and CRP. Early diagnosis of disease and that should be focussed on achieving a low disease activity score. The composite scales being used for diagnosing the RA are Clinical disease assessment index, Simplified disease activity assessment index, DAS-28 joints [22]. To attenuate the activity of disease and to delay joint deformity, DMARDs should be started at the earliest [23]. Methotrexate being preferred as monotherapy as well as in combination therapy, due to its safety and efficacy. The anti-inflammatory properties of MTx are attributed to its role in purine synthesis inhibition, cytokine inhibition and adenosine receptors activation. Hydroxychloroquine, being having immune-modulatory properties, is usually considered as an alternative option for RA. Several biologic DMARDs have also emerged recently. In many newer therapies, Mesenchymal stem

cells and agents targeting toll like receptor 4 can be considered in future [24].

The efficacy is assessed in our study by using Disease Activity Score in 28 Joints (DAS28), Multidimensional Health Assessment Questionnaire (MDHAQ), C-reactive protein (CRP), which was done at the beginning & at the end (16 weeks) of the study. The safety was assessed at every visit by monitoring any adverse drug reactions to the medications given for the treatment of RA. The ADRs were assessed by using WHO Causality Assessment Scale & Naranjo Scale. Direct medication cost was analyzed & compared between each treatment groups. RA is commonly seen in the middle age group the most commonly presenting in 40-49 years [25]. In present study also the most common RA presenting age group was in the age range of 46-60 (36%). The mean age in our study was 50.56±14.60years, whereas in the study by Salaffi F et al. where the mean age was 43±12.45 years [25] & the study by Lee EB, et al, where the mean age was 48.8 [26]. In this study female out number males in the ratio of female: male 5.25:1. This finding is similar to previous studies which have shown high prevalence of RA among females. [25-28] The vitamin D3 levels analysed at 0 week were in the lower range in all groups, in meta-analysis by Guan Y et al, the lower serum levels of Vitamin –D3 are linked to be a predisposing factor for RA.

In the present study the positive family history was found in 35% of the patients. Various studies understanding the pathogenesis of RA have depicted concordance rate >30% among monozygotic twins for RA development & also strong association of HLA-DRB1 with RA so it suggests a strong genetic association of the disease [4, 29]. In the study the Disease Activity Score in 28 joints (DAS) has decreased by -0.76 in group 1 over duration of 4 months, though in study by LEE B et al, The DAS/ESR was higher in spite of using MTx and Tofacitinib. [29]. In group 3 the DAS score has reduced by -1.86, a significant improvement has been established in DAS-Score at 6 and 12 weeks, by using MTx and HCQ in combination by Shahshikumar N et al [30]. In a study by Pincus T et al, RAPID-3 Score was used as a tool to assess health quality [31]. In the present study the RAPID-3 score has been found to be decreased at 16 weeks by -1.02 (from 3.67±0.06 at baseline to 2.65±0.09 at 16 weeks), -0.72(from 3.55±0.08 at baseline to 2.83±0.09 at 16 weeks) & -1.66 (from 3.79±0.09 at baseline to 2.13±0.15 at 16 weeks) in group 1, group 2 & group 3. RF (RA factor) was positive in 70.66%, and higher percentage of positive RA factor (84.4%) in other study by Lee EB et al. [26]. The immunological marker Anti-CCP has been found to be more effective immunological marker of RA in earlier studies, in present study Anti-CCP was raised in 90.66% of the patients as in Lee EB et al where Anti-CCP levels were raised in 86.6% of patients [26].

The improvement in the C-reactive protein (CRP) was significant in all the patients during the study period. The mean levels in CRP were 16.37±0.91 in group 1, 18.25±0.81 in group 2 and 18.40±1.42 in group 3 at baseline, these findings are consistent with many previous studies where CRP was found to be elevated in RA patients [26,32]. At 16 weeks CRP was reduced by 7.23±0.53 in group 1 & in the study by Lipsky PE et al, a significant decline in CRP with Methotrexate alone at a dose of 12.5mg once a week has been observed [33]. Mean decrease in CRP was 12.76±0.58 in group 2 at 16 weeks which is similar to the study by Pavelka K. JR et al which showed significant decline in CRP over 1 year of study with Hydroxychloroquine 200mg OD & 400mg OD [34]. The mean changes in CRP have reduced to 3.87±0.40 at 16 weeks in group 3, however no study has been found in relation to this. In formulating, clinical decision, the knowledge of physician is must along with quantitative measures. The health assessment questionnaire cannot replace the need of careful and detailed history as well as the physical examination.

In the present study the patients have found to have no significant joint changes or no significant joint space narrowing in plain radiographs over the study of 16 weeks which is in co-relation with the study by Bathon JM et al which showed that the patients receiving Methotrexate have delayed progression to joint damage [35], however various studies suggest radiographic progression of the disease in 1st three years the study and that the study should be conducted for a longer duration for significant assessment of radiographic changes [35-37]. It has been recommended that the patients taking Hydroxychloroquine should undergo Fundoscopic examination every 12 monthly because of ocular toxicities concerned with the drug. In the present study the Fundoscopic examination at 16 weeks did not reveal any ocular toxicity to the patients. For Ocular toxicities to be assessed a longer duration of study is required [38, 39]. Drugs were well tolerated and none of the patient withdrawn due to the side effects. The most common adverse drug reactions reported in all the study groups over the study period were gastrointestinal

distress 62.18%, mouth ulcers 13.44%, body ache with weakness 10.92%, decreased vision 5.88%, alopecia 4.20%, dry cough 1.68% and hoarseness of voice 1.68%.

The cost in present study has been calculated by taking in account the cost of drugs over one week and for the duration of sixteen weeks and is found to be least with the Methotrexate alone and the cost effectiveness found to be most effective with the combination of Methotrexate and Hydroxychloroquine which is in co-relation with the study by Krishnan S et al in to which the cost has been calculated by adding the cost of drugs, monitoring costs & consultation cost and the Average cost effective ratio in the present study found to be most effective with the combination therapy as with the previous study [40].

Limitation of the study

The patients would have been prescribed Vitamin D3 in order to evaluate its effects in RA patients, as the low Vitamin D3 has been found in almost all of the study participants.

CONCLUSION

The study has revealed significant results in terms of assessing quality of life as assessed by DAS-28 and RAPID-3 Score. The adverse effects were also analysed using Naranjo scale and WHO-UMC SCALE. The result would have been more significant if a large number of patients would have been involved. Though, the findings will definitely be helpful in studying the effects of conventional DMARDs on early diagnosed RA patients. The present study will be helpful in understanding the DAS-28 score in RA patients. The importance of conventional DMARDs in managing the disease. Moreover, the impact of Vitamin D3 and BMI have been assessed in disease. Though, it would have been studied more specifically by looking into their effects on RA progression, with supplementation of vitamin D3 and calcium.

FINANCIAL ASSISTANCE

Nil

CONFLICT OF INTEREST

The authors declare no conflict of interest

AUTHOR CONTRIBUTION

Amandeep Singh and Amit Varma contributed in conception of work and study design. Amanjot Kaur performed experimental work, collected data and performed statistical analysis and interpretation. All the authors helped in proofreading and reviewing the final manuscript

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