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Comparison of the Efficacy & Safety of Minocycline versus Hydroxychloroquine as an Add-On Therapy to Methotrexate in Treatment of Rheumatoid Arthritis

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ABSTRACT: Objective: This study was designed to compare the efficacy and safety of minocycline versus hydroxychloroquine (hcq) as an add on therapy to methotrexate in treatment of rheumatoid arthritis. **Methods**: This was a prospective open label, randomized, comparative, clinical study conducted in Pt. B. D Sharma, PGIMS, Rohtak. Fifty newly diagnosed rheumatoid arthritis patients were included in the study. These were randomly assigned to one of the following treatment protocols: group one was given oral methotrexate (7.5–25 mg orally in divided doses per week), hydroxychloroquine (200mg b.d) & etoricoxib (400mg o.d). In the other group oral methotrexate (7.5–25 mg orally in divided doses per week), minocycline (100mgb.d) & etoricoxib 400mg o.d) were given. Efficacy and safety assessmentwas done by evaluation of various parameters of rheumatoid arthritis at 2, 6 & 12 wks. Repeated measures ANOVA test was applied for intragroup analysis and independent 't' test was applied for intergroup analysis of various parameters. **Results**: In minocycline treated group, there was statistically significant improvement in most of the parameters at 12 weeks as compared to hydroxychloroquine (hcq) group except the three parameters i.e grip strength in right hand, erythrocyte sedimentation rate (esr) &health assessment questionnaire (HAQ). These three parameters although also show improvement but the difference was not statistically significant. Regarding the side effects, incidence of side effects was more with hcq group than minocycline group. **Conclusion**: Minocycline was found to be more efficacious and safer than hydroxychloroquine, as an add on therapy to methotrexate for the treatment of rheumatoid arthritis.

KEYWORDS: Rheumatoid arthritis (RA); Minocycline; Hydroxychloroquine; Methotrexate; Disease Activity Score -28 (DAS-28).

INTRODUCTION

Rheumatoid arthritis (RA) is the most common chronic inflammatory polyarthritis and it afflicts people of all ages and races. It's prevalence is 1% and is more common in females than males .It can begin at any age, but the higher incidences are seen in the 4th& 5th decade.[1]The cause of RA remains unknown. It might be due to the response to an infectious agent in a genetically susceptible host. A number of possible causative agents have been suggested, including mycoplasma, epstein-barr virus, cytomegalovirus, parvovirus, and rubella virus, but till now there is no clear evidence.[2]

Medical management of RA involves five general approaches. These include: nonsteroidal anti-inflammatory drugs

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(NSAIDs), glucocorticoids, conventional disease-modifying antirheumatic drugs (DMARDs), immunosuppressive drugs and biological DMARDs. DMARDs are needed for most patients in order to alter the disease progression. Essentially, all RA patients should be considered for DMARD therapy in an effort to halt joint damage and disease progression. The therapy should be started within the first 3 months (or as soon as possible) for patients with confirmed diagnosis and active disease.[3] DMARDs include methotrexate (MTX), sulfasalazine, hydroxychloroquine and leflunomide. Methotrexate is the mainstay of the treatment of RA and may be used as monotherapy or in combination with other agents.[4] It is frequently the first DMARD prescribed following the diagnosis of RA, and a significant percentage of patients respond favorably to MTX monotherapy. Hydroxychloroquine is commonly used in combination with other DMARDs, rarely used as monotherapy. It has proven efficacy in controlling the signs and symptoms of RA, but it is the DMARD which hardly shows retardness of radiographic progression when used in monotherapy.[5]

Minocycline is an effective treatment for RA, especially when used in early seropositive disease. It has been shown to have antibacterial, immunomodulatory, antiinflammatory, and chondroprotective effects.[6]Its mechanism of action in RA is clearly not known. Certain animal studies have clearly shown dramatic efficacy of metalloproteinases inhibitors like tetracyclines.[7]Other probable mechanisms are inhibition of production of tumor necrosis factor, depression of polymorphonuclear leukocyte chemiluminescence and generation of reactive oxygen species.[8]It also suppresses the erythrocyte sedimentation rate and C-reactive protein levels in RA.[9]

MATERIALS & METHODS

This was a prospective open, randomized, comparative, clinical study conducted by the Department of Pharmacology and Medicine, Pt B. D. Sharma PGIMS, Rohtak in 50 patients. An informed consent was obtained from all the patients enrolled for the study. The patients were screened according to the following inclusion and exclusion criteria. Inclusion Criteria included as per American College of Rheumatology (ACR) criteria (1987) , having mild to moderate DAS -28 score (3.6-5.1).Exclusion criteria were severely anemic patients, hypothyroid patients, patients having evidence of severe renal, cardiac, liver or pulmonary disease, pregnant ladies & lactating mothers, patients with history of allergy to any of the study medications. Patients who satisfied the inclusion criteria and gave informed consent, were randomly assigned to one of the two groups, A or B, of 25 patients each and received one of the following treatment protocols: Group A - treatment with oral methotrexate, hydroxychloroquine & etoricoxib, Group B - treatment with oral methotrexate, minocycline & etoricoxib. Methotrexate was given on a weekly schedule of 7.5–25 mg orally in divided doses, hydroxychloroquine was given as 200mg b.d for three months & minocycline was given as 100 mg twice daily. Etoricoxib was given as 400 mg hrs once daily. The patients were assessed for drug response at 2, 6 & 12 wks for the following parameters:28 joint count, pain assessment on visual analogue scale (VAS),morning stiffness duration ,patient disease global assessment (PDGA),evaluator disease global assessment (EDGA),disease activity score -28 (DAS-28),clinical disease activity index (CDAI) score, health assessment questionnaire (HAQ) score, grip strength, erythrocyte sedimentation rate (ESR)& side effect profile.

Statistical analysis: Both descriptive and analytical statistics was used in the study as was appropriate. In the descriptive analysis, mean and standard error of mean (SEM) of demographic and various clinical parameters were calculated. Among the analytical statistical technique, repeated measures analysis of variance test was applied for intragroup analysis and independent ‘t’ test was applied for intergroup analysis of various parameters. The significance of any difference between two groups was tested. A p- value < 0.05 was considered as statistically significant.

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RESULTS

A total of 70 patients of rheumatoid arthritis were screened for this study. 60 patients were found to be eligible as per the inclusion & exclusion criteria. Informed consent was taken from these patients; they were randomized & divided into two groups. Table 1 shows demographic characteristics for the two treatment groups. In group I, the age of the patients ranged from 30 years to 65 years of age (mean 47.52±2.36) and in group II this range was from 17 to 62years (mean 45.16±2.18). The difference between age of the patients was statistically insignificant ($p < 0.466$). All the patients were females in both the groups. Only 50 patients completed the study and the rest were lost to follow up. These were evaluated at the end of treatment.

On intragroup analysis, it was observed that there was statistically significant improvement in number of tender joints, pain assessment on VAS scale, morning stiffness duration, patient disease global assessment (PDGA), evaluator disease global assessment (EDGA), disease activity score -28 (DAS-28), clinical disease activity index (CDAI) score, grip strength of both hands at a period of 2 weeks after starting the treatment in both the groups & it continued over a period of 12 weeks. Regarding the other parameters, such as number of swollen joints & esr, statistically significant improvement was observed only with minocycline group at an early period of 2 weeks after starting the therapy. However with hcq, number of swollen joints improved after a period of 6 weeks while esr improvement was observed after a period of 12 weeks after starting the therapy.(Table 2)

Intergroup analysis showed that in minocycline treated group there was statistically significant decrease in number of tender joints, number of swollen joints, pain assessment on VAS scale, morning stiffness duration, patient disease global assessment (PDGA), evaluator disease global assessment (EDGA), disease activity score -28 (DAS-28), clinical disease activity index (CDAI) score & statistically significant increase in Grip strength in left hand at 12 weeks as compared to HCQ group. Although better response was seen in improvement of grip strength in right hand, reduction in erythrocyte sedimentation rate (esr) & health assessment questionnaire (haq) score with minocycline at 12 weeks as compared to hcq but this difference was not statistically significant(Table 2).Thus minocycline showed a better efficacy over hydroxychloroquine as an add on therapy to methotrexate in treatment of rheumatoid arthritis.

Comparing the safety profile of both groups, incidence of gastrointestinal side effects like nausea, vomiting, epigasrtric pain, anorexia was more with hcq group than minocycline group. Central nervous system side effects like headache was observed more in hcq group whereas dizziness was more in minocycline group. In minocycline group, side effects like abdominal bloating & taste disturbance were also observed but only in few patients whereas skin pigmentation & mucosal ulcers were seen only in one patient each.

DISCUSSION

Rheumatoid arthritis (RA) is the most common chronic inflammatory polyarthritis. Major problem with rheumatoid arthritis is that its etiology is poorly understood & it is a life long process. Patient has to take drugs for long period, which result in increase in their adverse effects & moreover tolerance to their effects. So there is always a need of good alternative drugs for substitution. Four broad categories of medical therapies are used for the treatment of RA: nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, conventional disease-modifying antirheumatic drugs (DMARDs), and biological DMARDs. Methotrexate (MTX) is considered to be the crucial drug for the treatment of RA and may be used as monotherapy or in combination with other agents.[4]Hydroxychloroquine is frequently used for the treatment of RA, usually in combination with methotrexate. It has proven efficacy in controlling the signs and symptoms of RA, but it doesn't affect the radiographic progression when used in monotherapy.[5]

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	HCQ group	Minocycline group
Number of patients	30	30
Mean age*	47.52±2.36	45.16±2.18
Female / Male	25/0	25/0

Table 1 Showing patient characteristics for the two treatment groups* All values are expressed in Mean ± SEM

	Pretreatment values		P values	At 2 weeks		P values	At 12 weeks		P values
	HCQ	Minocycline		HCQ	minocycline		HCQ	minocycline	
Tender joints	13.24 ±0.78	13.16±0.83	0.94	11 ±0.64	7.36±0.47	<0.001	7.72 ±0.49	2.48±0.25	<0.001
Swollen joints	1.48 ±0.32	1.44±0.36	0.93	1.08 ±0.34	0.64±0.19	0.27	0.64 ±0.19	0.16±0.07	<0.05
Pain assessment on visual analogue scale (VAS)	8.64 ±0.11	8.72±0.12	0.62	5.96 ±0.21	4.52±0.20	<0.001	4.36 ±0.12	2.24±0.23	<0.001
Morning stiffness duration	134.4 ±9.96	136.8±9.17	0.86	56.6 ±7.38	62.4±9.63	0.63	28.6 ±3.76	13.8±3.13	<0.001
Patient disease global assessment (PDGA)	8.36 ± 0.12	8.36± 0.11	1	5.76 ± 0.11	4.68± 0.17	<0.001	4.2 ±0.17	1.68±0.25	<0.01
Evaluator disease global assessment (EDGA)	7.44 ± 0.14	7.6 ±0.12	0.38	5.04 ± 0.15	3.92± 0.17	<0.001	3.60 ±0.11	1.44±0.19	<0.001
Disease activity score -28 (DAS-28)	4.9 ±0.04	4.93±0.05	0.64	4.63 ±0.05	4.18±0.06	<0.001	4.15 ±0.05	3.35±0.05	<0.001
Clinical disease activity index (CDAI) score	30.4 ±0.69	30.28±0.80	0.91	22.8 ±0.74	16.28 ±0.69	<0.001	16.24 ±0.54	5.6±0.64	<0.001
Health assessment questionnaire (HAQ) score	22.92 ±0.39	23.64±0.73	0.38	19.4 ±0.48	18.16 ±0.45	0.06	15.2 ±0.28	14.76 ±0.25	0.25
Grip strength(Left hand)	57.6 ±3.38	58±4.16	0.94	75.6 ±3.56	94.4±3.19	<0.001	94.24 ±3.20	109.2 ±3.55	<0.001
Grip strength(Righthand)	54.2 ±3.97	55.6±3.56	0.79	77.2 ±3.62	82.4±3.42	0.3	92±3.41	98.4±3.14	0.17
Erythrocyte sedimentation rate (ESR)	39.16±1.51	41.04±1.56	0.39	38.52±1.23	35.76±1.20	0.11	32.88±1.45	32.2±1.24	0.72

Table 2 Showing the comparison of different parameters with p valuesin two groups at pretreatment ,2 weeks and 12 weeks.All values are expressed as Mean ± SEM

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Minocycline is an effective treatment for RA, especially when used in early disease. The mechanism of action in RA is uncertain, possibly there is inhibition of matrix metalloproteinases (MMP), which are important mediators of joint damage. To the best of our knowledge, no such study has been done on Asian population & the present study has therefore been done, to compare the efficacy & safety profile of minocycline with hydroxychloroquine as an add on therapy to methotrexate for the treatment of rheumatoid arthritis.

Our study showed that in minocycline treated group there was statistically significant decrease in number of tender joints, number of swollen joints, pain assessment on VAS scale, morning stiffness duration, patient disease global assessment (PDGA), evaluator disease global assessment (EDGA), disease Activity Score -28 (DAS-28), clinical disease activity index (CDAI) score as compared to hcq group. Although minocycline showed better response in improvement of grip strength in right hand, reduction in ESR & HAQ score at 12 weeks as compared to hcq but this difference was not statistically significant. Thus minocycline exhibit better efficacy over hydroxychloroquine as an add on therapy to methotrexate in treatment of rheumatoid arthritis.(Table 2)

The study conducted by O'dell et al also showed a decrease in pain assessment on VAS in both minocycline as well as hcq group. The decrease in pain assessment on VAS in HCQ treated patients was from 5 to 3.8 whereas the decrease in minocycline treated patients was from 5.13 to 2.5, thus showing better response with minocycline.[10] The findings of our study are quite similar to the findings of this study. MIRA trial also showed more decrease in morning stiffness duration (in hrs) in minocycline as compared to placebo group. The decrease in morning stiffness duration in minocycline treated patients was from 6.3 to 3.6 whereas in placebo treated patients was from 6.1 to 4.1, thus showing better response with minocycline.[11] Our study also shows good response with minocycline group in decreasing morning stiffness duration. The present study revealed that both the groups showed significant decrease in DAS-28 at 2, 6 & 12 weeks as compared to baseline values. The average of DAS-28 in hcq treated patients at 0, 2, 6 and 12 weeks were 4.9, 4.63, 4.34 & 4.15 respectively while in minocycline treated patients were 4.93, 4.18, 3.67 & 3.35 respectively. In both the groups there was improvement from pretreatment values. On comparing the two groups, it was seen that decrease in DAS-28 was more in minocycline group as compared to hcq group over a period of 12 weeks and this difference was statistically significant. Minocycline therapy can now be added to the list of options available as initial therapy for patients with RA. The comparison between the two groups revealed that decrease in CDAI score was more in minocycline group as compared to HCQ group over a 12 week period and this difference was statistically significant. MIRA trial also showed more increase in grip strength (left hand) in minocycline as compared to placebo group. The increase in grip strength (left hand) in minocycline treated patients was from 100.7 to 129.8 whereas in placebo treated patients was from 101.7 to 119.5, thus showing better response with minocycline.[11] Our study also shows good response with minocycline group by increasing the grip strength (left hand). The study conducted by O'dell et al also showed a decrease in HAQ & ESR in both minocycline as well as HCQ group. The decrease in HAQ score in HCQ treated patients was from 1.32 to 0.74 whereas the decrease in minocycline treated patients was from 1.06 to 0.58, thus showing no significant difference in response between the two groups.[10] The decrease in ESR in HCQ treated patients was from 5.43 to 3.3 whereas the decrease in minocycline treated patients was from 5.03 to 2.2, thus showing better response with minocycline.[10] The findings of our study are quite similar to the findings of this study. Incidence of gastrointestinal side effects like nausea, vomiting, epigasrtric pain, anorexia was more with HCQ group than minocycline group. Central nervous system side effects like headache was observed more in HCQ group whereas dizziness was more in minocycline group. In minocycline group, side effects like abdominal bloating & taste disturbance were also observed but only in few patients whereas skin pigmentation & mucosal ulcers

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were seen only in one patient each. The study conducted by Patricia Clark et al also reported more incidence of headache than dizziness in HCQ group in a placebo compared trial.[12]The study conducted by O'dell et al also showed dizziness in minocycline group.[10] Thus the CNS side effect profile observed in our study was similar to that of these studies.

CONCLUSION

Both the groups were found to be efficacious in improving the parameters of rheumatoid arthritis over a period of 12 weeks. However, Minocycline was found to be more efficacious than hydroxychloroquine, as an add on therapy to methotrexate for the treatment of rheumatoid arthritis & regarding the safety profile, gastrointestinal side effects were more with hydroxychloroquine whereas central nervous system side effects were seen in both the groups.

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