Research Article

The safety, efficacy, and quality of life of methotrexate with hydroxychloroquine as a combination versus methotrexate as monotherapy in rheumatoid arthritis: A comparative single-blinded prospective study

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ABSTRACT

Objective: The objective of this investigation was to study and ascertain the effect of adjunct therapy in naïve rheumatoid arthritis (RA) patients by disease active index, quality of life (QoL), and hematological changes pre- and post-treatment. **Materials and Methods:** A comparative prospective study was carried out where the patients were divided into two groups, namely, combination and monotherapy groups of 30 patients each. The combination group was administered 2.5 mg and tab. hydroxychloroquine 200 mg, whereas the monotherapy was administered with tab. methotrexate (MTX) 5 mg. The hematological changes and QoL were noted during the commencement of the study and after 12 weeks of treatment. **Results:** The drug works together and produces synergic effect, thereby increasing the disease activity index and decreasing the disease activity score. There was statistically significant difference in the values of biomarkers in the naïve patients before and after the treatment with the combination group and monotherapy group. **Conclusion:** The study has significantly proved that even though MTX is the preferred drug of choice in RA, the efficacy and end results are better when given in combination with the hydroxychloroquine (disease-modifying antirheumatic drugs) making it safer and more potent.

KEY WORDS: Hydroxychloroquine, Methotrexate, Rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammation of the synovial tissue, lining the joint capsule that results in the proliferation of the tissue.[1] The pannus invades the cartilage and eventually the bone surface, resulting in erosions of bone and cartilage and leading to the destruction of the joint. The factors that are responsible for the inflammatory process are unknown.[2,3] The development of the RA takes place in four stages such as Phase 1: Antigen-presenting cell phagocytes antigen. Phase 2: Antigen is presented to a T lymphocyte. The T lymphocyte attaches to antigen at the major histocompatibility complex portion of the cell wall, causing activation. Phase 3: An activated T-cell stimulates T and B lymphocyte production, promoting inflammation. Phase 4: Activated T-cells and macrophages release factors that promote tissue destruction, increase blood flow, and result in the cellular invasion of synovial tissue and joint fluid.[4,5]

Methotrexate (MTX) is an antimetabolite which was formerly known as amethopterin which is a chemotherapeutic agent and immune system suppressant.[6] It is mainly used to treat certain types of cancer or to control severe psoriasis. Furthermore, MTX is widely used as the first choice of disease-modifying antirheumatic drug (DMARD) in the treatment of RA.[7] The mechanism of the action of MTX in RA might be more of anti-inflammatory in nature rather than its original immunosuppressive property.[8,9]

Hydroxychloroquine is an antimalarial which is used in the treatment of RA, lupus, and porphyria

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cutanea tarda.[10] When hydroxychloroquine is given as adjuvant therapy in combination with MTX, they produce synergistic effect and the disease activity index decreases and show more rapid response though MTX and hydroxychloroquine being a slow drug.[11,12]

Specific Objective of the Study Includes

- To study the disease activity index in the pre- and post-treatment in the RA patients
- To examine the quality of life (QoL) and the impact of drugs on them
- To understand the hematological changes, pre- and post-treatment using biomarkers in the patient.

MATERIALS AND METHODS

Study Site

The study was conducted in a tertiary care 1000-bedded multispecialty teaching hospital.

Study Period

This study was performed starting from August 2018 to a period of 6 months, ending February 2019.

Study Design

It is a comparative single-blinded prospective study. Patients selected were divided into combination and monotherapy groups. Naïve RA patients demographic data were collected. Then, 5 ml of blood were collected as samples from naïve patients to pre-check the biomarkers (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], anti-citrulline antibody, neutrophils lymphocyte ratio, and rheumatoid factor) levels. The patient was prescribed with MTX 2.5 mg/week for 3 months and hydroxychloroquine 200 mg/d for 3 months, p.o. The patients were asked to fill up a questionnaire regarding QoL. On follow-up after 3 months, repeat 5 ml blood were collected as samples to check the biomarker (ESR, CRP, anti-citrulline antibody, neutrophils lymphocyte ratio, and rheumatoid factor) levels. Moreover, again, the same questionnaire was asked to fill up by the patients. The collected biomarker data were analyzed and the reports are collected.

Selection of Patients

Inclusion criteria

All Naive RA patients are included. Patient should be in the age group of 30–65 years and outpatients and inpatients were included in the study.

Exclusion criteria

High total cholesterol and triglycerides levels, newly married, pregnant and lactating women, history of cardiovascular disease, undergone treatment elsewhere for RA, and chronic hypertensive patients who are hypersensitive to DMARDs were excluded from the study.

An informed consent has been obtained from all the patients involved in this study. The study has been approved by the Institutional Ethics Committee vide no. SPS/IEC/V/2018/03.

Statistical Analysis

Continuous data were summarized as mean ± deviation. *t*-test was used to analyze the data and significance was found out by comparing the calculating *t* value with tabulated *t* value at 95% confidence interval ($P = 0.005$). $P < 0.001$ was considered to be statistically significant.

RESULTS AND DISCUSSION

The study evaluated the impact of the combination group with DMARDs and monotherapy group without the DMARDs. Out of 60 patients included in this study, 24 (41.25%) were male and 36 (59.65%) were female. Here, in this study, the female population outweighed the male population because the females are more prone to the RA. The number of patients between the age group of 45 and 55 was more than the age group of 30–44 and 56–65 which were found to be less. The baseline characteristics of the patient are shown in Table 1.

Biomarker Intervention

The efficacy of the drugs was tested based on the biomarker value. The biomarkers were selected in such a way that they are very precise and restricted to RA. Table 2 shows the pre- and post-treatment for the biomarker rheumatoid factor. This factor is restricted only to RA and it shows the amount of damage to the bone. Table 3 shows the pre- and post-treatment for the biomarker CRP. This biomarker shows the amount of inflammation in and around the bone. Table 4 shows the pre- and post-treatment for the biomarker anti-citrulline antibody. This biomarker helps to diagnose the severity of symptoms in the RA patient. Table 5 shows the pre- and post-treatment for the

Table 1: Baseline characteristics

Characteristics	Combination group (MTX and hydroxychloroquine)	Monotherapy (MTX)	*P* value
Age	51.6±13.0	45.6±12.6	0.742
Male	13 (41%)	12 (38%)	0.886
Number of joints	6.56±2.10	6.32±1.69	0.929
Alcohol	12 (38%)	11 (35%)	0.975
Smoker	10 (32%)	9 (29%)	0.965
DM	6 (19%)	4 (12%)	0.772

MTX: Methotrexate

Table 2: Effect of biomarker pre- and post-treatment: Rheumatoid factor

Group	Pre-treatment	Post-treatment
Combination group	29.6±2.72	12.4±1.6
Monotherapy group	28.6±1.94	19.7±2.17

Table 3: Effect of biomarker pre- and post-treatment: CRP

Group	Pre-treatment	Post-treatment
Combination group	10.6±3.2	2.3±0.6
Monotherapy group	11.2±2.6	7.34±2.1

CRP: C-reactive protein

Table 4: Effect of biomarker pre- and post-treatment: Anti-citrulline antibody

Group	Pre-treatment	Post-treatment
Combination group	46.3±11.4	19.6±6.2
Monotherapy group	45.2±10.2	23.4±10.4

Table 5: Effect of biomarker pre- and post-treatment: ESR

Group	Pre-treatment	Post-treatment
Combination group	39.6±9.6	16.2±3.2
Monotherapy group	40.2±8.4	29.6±7.4

ESR: Erythrocyte sedimentation rate

biomarker ESR. This biomarker shows the amount of inflammation. Table 6 shows the pre- and post-treatment for the biomarker neutrophils lymphocyte ratio. This biomarker shows the subclinical inflammation, which is one of the drawbacks of RA. When analyzed with the above-mentioned biomarkers, there was a significant difference between the pre- and post-treatment in both the groups, but the combination group outweighed the monotherapy group in all compared aspects. Table 7 shows the adverse drug reaction (ADR) reported and was less severe in both the groups. Anemia being the major adverse effect of MTX was reduced to a greater extent in the combination group.[13]

QoL

SF-12 questionnaire contains a total of 12 questions, of which 6 are for physical component score (PCS) and 6 are for mental component summary (MCS). The questionnaire was given at the 0th week and then again in the 12th week. Table 8 shows the score for PCS and there was a significant change in the patient physical state after the treatment in the combination group compared to the monotherapy group. Table 9 shows the score for MCS and there was a significant change in the patient mental status after the treatment in the combination group compared to the monotherapy group.[14]

The numbers of female patients (59%) were more than the male patient (41%) in the study because the females are more prone to the RA than male.

Table 6: Effect of biomarker pre- and post-treatment: Neutrophil lymphocyte ratio

Group	Pre-treatment	Post-treatment
Combination group	11.2±0.9	5.6±2.1
Monotherapy group	10.6±0.8	7.23±3.1

Table 7: ADR reported

ADR	Combination group	Monotherapy group	*P* value
Anemia	3	12	0.0032
Vomiting	4	5	0.0013
Nausea	7	6	0.0023
Weight loss	1	2	0.0027
Skin rash	2	3	0.0031
Headache	3	2	0.0014

ADR: Adverse drug reaction

Table 8: QoL-PCS score

Weeks	Combination group	Monotherapy group	*P* value
0th week	35.4±10.6	37.16±12.1	0.4961
12th week	49.3±7.6	41.16±10.6	0.001*

P<0.05* is considered significant. QoL: Quality of life, PCS: Physical component score

Table 9: QoL-MCS score

Weeks	Combination group	Monotherapy group	*P* value
0th week	31.2±10.4	29.6±11.4	0.5659
12th week	42.6±4.6	34.6±7.2	0.0101*

P<0.05* is considered significant. QoL: Quality of life, MCS: Mental component summary

Table 2 shows that there were significant differences in both the groups after the treatment, but the combination group (12.4 ± 1.6) outweighed the monotherapy group (19.7 ± 2.17).

Table 3 shows that there were significant differences in both the groups after the treatment, but the combination group (2.3 ± 0.6) outweighed the monotherapy group (7.34 ± 2.1).

Table 4 shows that there were significant differences in both the groups after the treatment, but the combination group (19.6 ± 6.2) outweighed the monotherapy group (23.4 ± 10.4).

Table 5 shows that there were significant differences in both the groups after the treatment, but the combination group (16.2 ± 3.2) outweighed the monotherapy group (29.6 ± 7.4).

Table 6 shows that there were significant differences in both the groups after the treatment, but the combination group (10.6 ± 0.8) outweighed the monotherapy group (7.23 ± 3.1).

Table 7 shows the adverse events reported in this study. Development of anemia is the most significant

ADR in MTX group while the combination group showed a comparatively lesser development of anemia.[13]

Table 8 shows among the combination group in the 0th week 35.4 ± 10.6 in the mean PCS level while the 12th week showed 49.3 ± 7.6 and among the monotherapy group in the 0th week 37.16 ± 12.1 in the mean PCS level while the 12th week showed 41.16 ± 10.6. $P < 0.05$* is considered significant.

Table 9 shows among the combination group in the 0th week 31.2 ± 10.4 in the mean MCS level while the 12th week showed 42.6 ± 4.6 and among the monotherapy group in the 0th week 29.6 ± 11.4.1 in the mean MCS level while the 12th week showed 34.6 ± 7.2. $P < 0.05$* is considered significant.

CONCLUSION

There was a statistically significant difference in the values of biomarkers in the naïve patients before and after the treatment with the combination group and monotherapy group. The MTX and hydroxychloroquine showed good safety and tolerability in RA. Although MTX is the preferred drug of choice for RA, it works better when given in combination with the hydroxychloroquine (DMARDs) making it safer and potent. The drug works together and produces synergistic effect, thereby increasing the disease activity index and decreasing the disease activity score.

The QoL in patients also showed a significant difference in both PCS and MCS after the treatment.

All the ADRs were reported less in the combination group when compared with the monotherapy group and more severe ADR of MTX, anemia which was controlled to a larger extent in the combination group. Hence, the combination group showed better safety and efficacy as compared to the monotherapy group.

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REFERENCES

1. Mousavi M, Karimzadeh H, Pakzad B, Mirrokni F. Comparison of the effect of disease: Modifying antirheumatic drugs alone or in combination with biologic drugs in the outcome of patients with rheumatoid arthritis. Adv Biomed Res 2019;8:32.
2. Alivernini S, Tolusso B, Gigante MR, Petricca L, Bui L, Fedele AL, *et al.* Overweight/obesity affects histological features and inflammatory gene signature of synovial membrane of rheumatoid arthritis. Nature 2019;18:10420.
3. Mao IC, Lin CY, Wu CL, Kor CT, Chang CC. Hydroxychloroquine and risk of development of cancers: A nationwide population-based cohort study. Ther Clin Risk Manag 2018;14:1435-43.
4. Dalkilic E, Coskun BN, Yağız B, Tufan AN, Ermurat S, Pehlivan Y. Methotrexate intoxication: Beyond the adverse events. Int J Rheum Dis 2018;21:1557-62.
5. Qiu Q, Huang J, Shu X, Fan H, Zhou Y, Xiao C. Polymorphisms and pharmacogenomics for the clinical efficacy of methotrexate in patients with rheumatoid arthritis: A systematic review and meta-analysis. Sci Rep 2017;7:44015.
6. Dahiya A, Kalra BS, Saini A, Tekur U. Prescription pattern in patients with rheumatoid arthritis in a teaching tertiary care hospital. Indian J Pharmacol 2016;2:33-7.
7. Bonafede MM, Curtis JR, Mc Morrow D, Mahajan P, Chen C. Treatment effectiveness and treatment patterns among rheumatoid arthritis patients after switching from a tumor necrosis factor inhibitor to another medication. Clinicoecon Outcomes Res 2016;8:707-15.
8. Shinde CG, Venkatesh MP, Kumar TM, Shivakumar HG. Methotrexate: A gold standard treatment for rheumatoid arthritis. J Pain Palliat Care Pharmacother 2014;28:351-8.
9. Cipriani P, Ruscitti P, Carubbi F, Liakouli V, Giacomelli R. Methotrexate in rheumatoid arthritis: Optimizing therapy among different formulations current and emerging paradigms. Clin Ther 2014;36:427-35.
10. Shashikumar NS, Shivamurthy MC, Chandrashekara S. Evaluation of efficacy of combination of methotrexate and hydroxychloroquine with leflunomide in active rheumatoid arthritis. Indian J Pharmacol 2014;42:358-61.
11. Karlsson JA, Neovius M, Nilsson JA, Petersson IF, Bratt J, van Vollenhoven RF, *et al.* Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in early rheumatoid arthritis: 2-year quality-of-life results of the randomised, controlled, SWEFOT trial. Ann Rheum Dis 2013;72:1927-33.
12. Alam MK, Sutradhar SR, Pandit H, Ahmed S, Bhattacharjee M, Miah AH, *et al.* Comparative study on methotrexate and hydroxychloroquine in the treatment of rheumatoid arthritis. Mymensingh Med J 2012;21:391-8.
13. Morris SJ, Wasko MC, Antohe JL, Sartorius JA, Kirchner HL, Dancea S, *et al.* Hydroxychloroquine use associated with improvement in lipid profiles in rheumatoid arthritis patients. Arthritis Care Res 2011;63:530-4.
14. Lie E, van der Heijde D, Uhlig T, Mikkelsen K, Kalstad S, Kaufmann C, *et al.* Treatment strategies in patients with rheumatoid arthritis for whom methotrexate monotherapy has failed: Data from the NOR-DMARD register. Ann Rheum Dis 2011;70:2103-10.

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