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ORIGINAL ARTICLE

Comparative evaluation of efficacy and safety of methotrexate either alone or in combination with hydroxychloroquine in patients suffering from rheumatoid arthritis

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ABSTRACT:

Background: Methotrexate (MTX) remains the foundation treatment for patients with rheumatoid arthritis (RA), with entrenched wellbeing and viability profiles and support in universal rules. Clinical and radiologic comes about show advantages of MTX monotherapy and blend with different specialists, yet patients may not get ideal dosing, span, or course of organization to augment their reaction to this medication. The primary goal of this investigation is to evaluate efficacy and safety of methotrexate either alone or in combination with hydroxychloroquine in patients with Rheumatoid arthritis**. Materials and Methods**: Patients with dynamic rheumatoid arthritis taking MTX for >3 months were incorporated into this investigation and were partitioned in two gatherings, Group-1 (n=30) patients got methotrexate (MTX) and Group-2 (n=30) patients got Methotrexate + Hydroxychloroquine (HCQ) twice every day. The patients were followed up for a time of 4 months. **Result:** The mean time of patients was 42.5 ± 5.6 years. 42 patients were females and 18 were males. 18 patients had positive family history of the ailment. The Rheumatoid factor was certain in 36 and anti-CCP was increased in a large portion of the patients. After 3 months, improvement noted in patients treated mix of methotrexate and hydroxychloroquine**. Conclusion:** The combination treatment was observed to be more effectual than MTX monotherapy in improving symptoms and personal satisfaction.

Keywords: Rheumatoid Arthritis(RA); Antirheumatic agents; Biological products, Methotrexate (MTX) Hydroxychloroquine (HCQ).

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Introduction:

Conventional sickness modifying anti-rheumatic medications (DMARDs), including methotrexate (MTX), sulfasalazine, and leflunomide, have been the foundation of the treatment of rheumatoid arthritis (RA). As of late biological operators (biologics), particularly tumor necrosis factor opponents (against TNFs, TNF-i), have shown considerable viability in treating patients with RA who don't react or demonstrate bigotry to conventional DMARDs.[1]

The expansive presentation of methotrexate (MTX) for the treatment of rheumatoid arthritis (RA) approximately 20 years back had much bigger outcomes from a pragmatic and monetary perspective.[2] This medication turned out to be exceptionally compelling, had a moderately quick beginning of activity, was all around endured much of the time, and could be recommended in a wide measurements go considering the requirements of every individual patient. These components prompted MTX turning into the most generally utilized DMARD around the world. In addition, MTX adds to the viability of tumor necrosis factor alpha (TNF-a) biologic specialists, which seem, by all accounts, to be shown in just a minority of patients experiencing serious RA regardless of traditional DMARDs.[3] MTX remains the "anchor drug" in the treatment of the majority of patients with RA.[4]

MTX is for the most part taken week after week by the oral or parenteral (iv,im,sc) course. Oral ingestion of dosages in the vicinity of 10 and 25 mg might be as low as 25% and as high as 100% (mean 70%).[5] With the higher dosages of 25-40 mg (median 30 mg) week by week, the bio-accessibility in RA patients extended from 20% - 95% (mean 65%) when

contrasted with subcutaneous application. On the off chance that adequacy is inadequate, parenteral dosing might be attempted. The ingestion rate stays steady after some time in a similar individual at the low measurements of 7.5 mg/week , however diminishes by 13.5% at an upkeep dosage of 17 mg.[6]

Combinations of various DMARDs give extra, or notwithstanding potentiating, impacts, and along these lines have turned out to be generally utilized. The mix of MTX with sulfasalazine (SAS) was just imperceptibly better than the individual medications. Triple mix treatment including MTX +SAS+ hydroxychloroquine exhibited high effectivenes.[7] The triple mix MTX + HCQ + SAS was more powerful than the mix MTX+SAS and the combination MTX +HCQ.[8] The present study was conducted to assess the efficacy and safety of methotrexate either alone or in combination with hydroxychloroquine in patients with RA.

Materials and Methods:

This prospective investigation was directed between March 2013 and May 2014. The investigation convention was affirmed by an institutional survey board or ethics committee . All patients gave written,informed assent. Patients must be no less than 18 years old, have dynamic rheumatoid arthritis, have been accepting MTX >12.5 mg/week for at least 3 months at a steady measurement for no less than a month and a half at the season of study enrolment. All patients more likely than not been no less than 16 years old at the beginning of rheumatoid joint pain, must not have utilized any DMARDs other than MTX inside 12 weeks of screening, and probably had lacking control of rheumatoid joint inflammation side effects while on MTX treatment.

Patients who required simultaneous utilization of prednisone, 10 mg/day, or its comparable, were prohibited from study. Other exculsion criteria were presence of known significant simultaneous therapeutic infections, utilization of bolus corticosteroids inside a month and a half or intra-articular corticosteroid infusions inside a month of the screening visit, and past treatment with HCQ or whatever other organic treatment. Patients were arbitrarily relegated to get MTX alone or in mix with HCQ . Patients were partitioned into two gatherings as group 1 (n=30) got methotrexate 7.5-15mg/week and group 2 (n=30) got methotrexate 7.5mg once every week in addition to hydroxychloroquine 200mg twice day by day. The patients were followed every two weeks till one month and then monthly for 4 months. Scales utilized for clinical evaluation and change in personal satisfaction were disease activity score in 28 joints (DAS-28) and Routine assessment of patient index data-3 (RAPID-3) at baseline and at four months. Lab parameters as rheumatoid factor, anti-cyclic citrullinated peptide antibody (anti-CCP) and C-reactive protein (CRP) were assessed. Adverse drug reaction checked at each subsequent visit.

Result:

The mean time of patients was 42.5 ± 5.6 years. 42 patients were females and 18 were males. 18 patients had positive family history of the ailment. The Rheumatoid factor was certain in 36 and anti-CCP was increased in a large portion of the patients. After 3 months, improvement noted in patients treated mix of methotrexate and hydroxychloroquine**.**

Table 1: Baseline characteristics of subjects under study

Characteristic	Number
Age (years)	42.5 ± 5.6
Gender	
Male	18
Female	42
Total joint count	21.4 ± 4.7
Swollen joint count	9.5 ± 5.2
ESR (mm/hr)	41.29 ± 17.3
Pain assessment on VAS	71.23 ± 8.5
Raised anti-CCP	48
Positive RA Factor	36
Positive family history	18

Table 2: Comparison of disease activity score in both groups

	Group 1 (MTX)	Group 2 (MTX+ HCQ)
Baseline	5.4	5.5
After 4 month	1.85	1.41

Table 3: Comparison of RAPID-3 score in both groups

	Group 1 (MTX)	Group 2 (MTX+ HCQ)
Baseline	3.49	3.69
After 4 month	2.45	2.03

Table 4: Adverse drug reaction in both groups

ADR	Group 1 (MTX)	Group 2 (MTX+ HCQ)
Nausea	4	5
Gastrointestinal symptoms	4	7
Vomiting	3	2
Ulcers in mouth	3	5
Body pain	4	8
Bloating sensation	3	4

Discussion:

An improved understanding of the pathophysiology of rheumatoid arthritis has facilitated the development of new drugs specifically targeted at cytokines, which play a well defined role in
the inflammatory process. These "biologic agents" have been proven to be effective and well tolerated, but are very expensive. Methotrexate (MTX) remains the cornerstone therapy for patients with rheumatoid arthritis (RA), with well-established safety and efficacy profiles and support in international guidelines. Clinical and radiologic results indicate benefits of MTX monotherapy and combination with other agents, yet patients may not receive optimal dosing, duration, or route of administration to maximize their response to this drug.[9]

To improve the response to oral MTX, a high initial dose should be administered followed by rapid titration. Importantly, this approach does not appear to compromise safety or tolerability for patients. Treatment with oral MTX, with appropriate dose titration, then should be continued for at least 6 months (as long as the patient experiences some response to treatment within 3 months) to achieve an accurate assessment of treatment efficacy. If oral MTX treatment
fails due to intolerability or inadequate response, the patient may be “rescued” by switching to
subcutaneous delivery of MTX.[10] Consideration should also be given to starting with subcutaneousMTX given its favorable bioavailability and pharmacodynamic profile over oral delivery. Either initiation of subcutaneous MTX therapy or switching from oral to subcutaneous administration improves persistence with treatment.This study was designed to evaluate efficacy and safety of methotrexate either alone or in combination with hydroxychloroquine in patients with Rheumatoid arthritis.**[11]**

The mean age in our investigation was 42.5 ± 5.6 years which was similar with the past examinations by Bajraktari IH et al, and Lee EB et al, where mean age of the patients were 48.30 and 45.80 years respectively.[12,13] In exhibit contemplate the females exceeds the males this is like past examinations which indicated high pervasiveness of RA among females than males.6-9 Our examination demonstrated 30% patients had positive family history and this finding is like the case control study by Koumantaki Y et al, which proposes critical relationship of creating RA among first degree relatives.[14]

A significant change in disease activity score was seen in both the groups at baseline and after 4 months after initiating therapy with the investigative drugs. The study has highlighted the improvement in disease activity score in group-1 and group-2 respectively. The study showed that the combination of methotrexate and hydroxychloroquine is more effective as compared to methotrexate alone in improving the disease activity. We conclude that methotrexate in combination with hydroxychloroquine is higher efficacy as compared to methotrexate alone as an initial therapy in active rheumatoid arthritis.

An examination by Song Y et al, on RA has demonstrated that clinical ailment action as evaluated by Routine Assessment of Patient Index Data (RAPID) enhanced personal satisfaction by enhancing physical capacity, torment and overall wellbeing status.[15] In the present investigation the RAPID-3 score has been observed to be diminished at 4 months by 3.49 at pattern to 2.45 at 4 months in group 1 and , from 3.69 at baseline to 2.03 at 4 months in group 2 separately. In the examination by Pincus T et al, RAPID-3 score was observed to be successful as a manual for evaluate persistent quality of life.[16]

The ADRs revealed in the present examination were, 18.3% were suffering from gastrointestinal symptoms 13 % were mouth ulcers, 20 % were body pain and comparative ADRs have been accounted for in the past investigations by Bathon JM et al, which additionally detailed the event of nausea (15%), bloating sensation (11.6%), and with the utilization of methotrexate either alone or in combination.[17]

T This is like the investigation by O'Dell JR et al, additionally detailed the gastrointestinal symptoms in patients taking methotrexate and Hydroxychloroquine in combination treatment in the examination time of two years.[18]

The primary confinement of this investigation was little example estimate which may not be sufficiently adequate to

exhibit the intergroup distinction in viability of study drugs. Longer span of catch up with bigger specimen estimate expected to additionally assess the adequacy and wellbeing of DMARDs.

Conclusion:

The combination treatment was observed to be more strong than MTX monotherapy in enhancing manifestations and personal satisfaction. The adverse drug responses were mellow, more in mix treatment and none of the patients required withdrawal of treatment.

References:

1. Herman RA, Furst DE: Pharmacokinetics of low dose methotrexate in rheumatoid arthritis patients. J Pharm Sci 1989; 78: 165-71
2. Jarrier I, LE-Levier F et al.: Comparative bioavailability of methotrexate given orally or intramuscularly in rheumatoid arthritis. Presse Med 1992; 21: 822.
3. Oguey D, Gerber NJ, : Effect of food on the bioavailability of low-dose methotrexate in patients with rheumatoid arthritis. Arthritis Rheum 1992; 35: 611-4.
4. Korber H, Iven H, Gross WL: Bioavailability and pharmacokinetics of methotrexate and its metabolite 7-hydroxy-MTX after lowdose MTX (25 mg) in patients with chronic rheumatoid diseases. Arthritis Rheum 1992; 35: S142 (abstract).
5. Hoekstra M, Haagsma C, Neef C et al.: Bioavailability of higher dose methotrexate comparing oral and subcutaneous administration in patients with rheumatoid arthritis. J Rheumatol 2004; 31: 645-48.
6. Anaya JM, Fabre D, Bressolle F et al.: Unchanged methotrexate pharmacokinetics\ upon initial therapy compared with prolonged therapy in rheumatoid arthritis. Arthritis Rheum 1992; 35: 142
7. Hamilton RA, Kremer JM: Why intramuscular methotrexate may be more efficacious than oral dosing in patients with rheumatoid arthritis. Br J Rheumatol 1997; 36: 86-90.
8. Turkstra E, Ng SK, Scuffham PA. A mixed treatment comparison of the short-term efficacy of biologic disease modifying anti-rheumatic drugs in established rheumatoid arthritis. Curr Med Res Opin 2011;27:1885-1897.
9. Graudal N, Jurgens G. Similar effects of disease-modifying antirheumatic drugs, glucocorticoids, and biologic agents on radiographic progression in rheumatoid arthritis: meta-analysis of 70 randomized placebo-controlled or drug-controlled studies, including 112 comparisons. Arthritis Rheum 2010;62:2852-2863.
10. Genovese MC, Han C, Keystone EC, et al. Effect of golimumab on patient-reported outcomes in rheumatoid arthritis: results from the GO-FORWARD study. J Rheumatol 2012;39:1185-1191.
11. Huang J, Xie B, Li Q, et al. Infliximab reduces CD147, MMP-3, and MMP-9 expression in peripheral blood monocytes in patients with active rheumatoid arthritis. Eur J Pharmacol 2013;698:429-434. 6. Bajrakatri IH, Cico TB, Meka VS, Bajrataki H, Saiti V, Krasniqi B et al. Demographic Features of patients with rheumatoid arthritis in Kosovo. Med Arh. 2014;68(6):407-10.
12. Lee EB, Fleischmann R, Hall S, Wilkinson B, Bradley JD, Gruben D, et al. Tofacitinib versus methotrexate in rheumatoid arthritis. NEJM. 2014;370:2377-86.
13. O' Dell JR, Mikuls TR, Taylor TH, Ahluwalia V, Brophy M, Warren SR, et al. Therapies for active rheumatoid arthritis after methotrexate failure. NEJM 2013;369:307-18.
14. Koumantaki Y, Giziaki E, Linos A, Kontomerkos A, Kaklamanis P, Vaiopoulous G, et al. Family History as a risk factor for rheumatoid arthritis. J Rheumatol. 1997;24(8):1522-6.
15. Song Y, Li-an Zhu, Wang SL, Leng L, Bucala R, Lu LG. Multi dimensional Health Assessment Questionnaire in China: Reliability, Validity and Clinical Value in Patients with Rheumatoid Arthritis. 2014;9(5):1-9.
16. Pincus T, Callahan LF, Sale WG, Brooks AL, Payne LE, Vaughn WK. Severe functional declines, work disability, and increased mortality in seventy-five rheumatoid arthritis patients studied over nine years. Arthritis Rheum. 1984;27:864-72.
17. Bathon JM, Marthin RW, Fleischmann RM, Tesser JR, Keystone E, Schiff MH, et al. A comparison of Etanercept and Methotrexate in patients with early rheumatoid arthritis. NEJM. 2000;343(22):1586-93.
18. O'Dell JR, Claire E, Haire RN, Erikson N, Drymalski W, Plamer W, et al. Treatment of rheumatoid arthritis with methotrexate alone, Sulfasalazine and hydroxychloroquine, or a combination of all three medications. NEJM. 1996;334:1287-91.

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