



Adverse Drug Reactions in Rheumatoid Arthritis Patients Taking Combination DMARDs

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Abstract

Aim - To ascertain the adverse drug reactions among RA patients taking combination DMARDs

Methods- It's a prospective single centre controlled study. Patients of Rheumatoid arthritis were divided into 2 study groups, Group-1 patients were given Methotrexate (MTX) oral weekly with Hydroxychloroquine oral daily. Group-2 patients were given Methotrexate (MTX) oral weekly with Sulfasalazine oral daily in divided doses. Apart from the study medications, all patients were also given concomitant medications. The data was obtained from suspected ADRs reporting forms, between January 2014 to January 2015 from the Rheumatology OPD, Medicine department to the ADRs monitoring centre attached to department of Pharmacology under the Pharmacovigilance programme of India (PvPi). The reported ADRs were assessed for causality using WHO causality assessment scale. The severity was assessed using Hartwig and Siegel scale.

Observations: 131 patients who entered the study, 68 were study assigned to receive Methotrexate and Hydroxychloroquine (Group 1) and 63 to receive Methotrexate and Sulfasalazine. In the study, in total 99 ADRs were reported from 53 ADR Forms. Most common occurring ADRs were nausea and vomiting in both the treatment groups. Different adverse drug reactions like nausea, blurring of vision, hyperpigmentation of skin, anaemia, epigastric pain, breathlessness were observed amongst patients in group-1. Whereas in group-2 patients the nausea, diarrhoea, headache, hepatotoxicity and leucopenia were seen.

Conclusions: DMARD's combination cause more but tolerable adverse effects. Combination DMARD regimens are safe for use in Rheumatoid arthritis to control disease activity with tolerable, transient and reversible adverse effects.

Keywords - Rheumatoid arthritis, DMARDs, Adverse drug reactions (ADR).

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease that typically affects the small joints of the hands and feet, often symmetrically. It is usually presented with constant pain, stiffness, progressive joint destruction and deformity with significant disability^[1]. It's a chronic condition which persists for years together and may be lifelong. Some patients may develop crippling disease because of deformities these patients have. If the disease is controlled in its initial stage the disease activity can be controlled and deformities can be prevented. For control of disease activity we have got conventional DMARDs and newer biological agents armamentarium.

The underlying pathogenic process of most rheumatic diseases start years before the clinical diagnosis is made and irreversible joint damage occurs and as the long-term morbidities decrease with prompt, responsible and aggressive treatment with disease-modifying therapy; both forming core challenges^[2]

The global prevalence of RA varies between 0.3-1.1%.^[3] The prevalence of rheumatoid arthritis in the adult Indian population is 0.75%.^[4] RA is more prevalent in females than in males (3:1) and its incidence rises with increasing age, plateauing after the age of 60. In the last decades, there was a decreasing trend in the incidence of RA; however this variation do appear cyclic as the latest findings again show an increase in the incidence of RA.^[5, 6, 7]

Now a days stress is on early aggressive approach so as to control disease in its initial stage to prevent joint damage later in the life. More aggressive the approach, more doses and more pharmacocetical agents are used in combination and there are more chances of adverse drug reactions.

Nausea and mucosal ulcers are the most common toxicities due to Methotrexate. Progressive dose-related hepatotoxicity in the form of hepatic enzyme elevation occurs frequently, but cirrhosis is rare (< 1%). The incidence of gastrointestinal and liver function test abnormalities can be

reduced by the use of daily folic acid.^[8] A rare "hypersensitivity" lung reaction with acute shortness of breath is documented, as are pseudolymphomatous reactions. This drug is contraindicated in pregnancy. Intramuscular or subcutaneous administration increases efficacy and reduces toxicity, especially gastrointestinal.^[9] Approximately 30% of patients using sulfasalazine discontinue the drug because of toxicity. Common adverse effects include nausea, vomiting, headache, and rash. Hemolytic anemia and methemoglobinemia also occur, but rarely. Neutropenia occurs in 1.4–4.4% of patients, while thrombocytopenia is very rare. Pulmonary toxicity and positive double-stranded DNA are occasionally seen, but drug-induced lupus is rare. Reversible infertility occurs in men, but sulfasalazine does not affect fertility in women. The drug does not appear to be teratogenic.^[10]

Although ocular toxicity might occur at dosages greater than 6.4 mg/kg/d hydroxychloroquine, it hardly ever occurs at lower doses. Yet, ophthalmologic monitoring every 6–12 months is advised. Other toxicities include dyspepsia, nausea, vomiting, abdominal pain, solar rashes, and nightmare.^[11]

Against the above background, an attempt was made in the current study to reveal the adverse drug reactions occurring in the RA patients taking combination non biological DMARDs along with changes in the dose of non fixed Mtx DMARD and together showing the pattern of lost to follow ups in the study done at tertiary care centre hospital in Kumaon region of Uttarakhand state. Also, the department of pharmacology of the GMC Haldwani runs pharmacovigilance programme to report about adverse drug reactions.

Objectives

- a) To ascertain about the adverse drug reactions among RA patients taking combination non biological DMARDs
- b) To find out the changes in the dose of non fixed drug i.e Methotrexate (Mtx)

Material and Methods

Study design: Prospective, single centered, Controlled Study

Study Place: Rheumatology clinic and Medicine OPD and Department of Pharmacology Susheela Tiwari Government Hospital of Government Medical College Haldwani

Study Period: 1 year (from Jan 2014 to Jan 2015)

Study subjects: Treatment naïve or chronic cases of RA in the age group 18-60 years of both sexes with RA duration \geq 6 months and Disease Activity score (DAS) $>$ 3.2

Total number of study subjects: n=131

Exclusion criteria

Patients of both sexes with clinical history of uncontrolled DM, severe CHF, interstitial lung diseases, active peptic ulcers, IBS, malignancies, abnormal RFT, abnormal hepatic functions, anaemia, leucopenia, thrombocytopenia, eye injury pathology were excluded from the study. Also, patients on biologic DMARD i.e etanercept & infliximab were not taken. And pregnant & lactating women were also not taken in the study.

Methodology

On following the exclusion criteria and on taking the written consent, the 131 patients of both sexes were divided into 2 study groups for taking of combination of DMARD drugs. Group-1 patients (n=68) were given tablet Methotrexate (Mtx) 0.3mg/kg/week (not a fixed dose to be adjusted according to clinical response & adverse effects) orally with hydroxychloroquine 200mg orally twice daily for first 3 months and 200mg daily afterwards. Group-2 patients (n=63) were given tablet Methotrexate 0.3mg/kg/week in fixed dose as in group-1 patients with tablet sulfasalazine 30mg/kg orally in divided doses.

Baseline investigations like Hb, TLC, DLC, Platelet counts, ESR, Rheumatoid factor (RF), serum creatinine, SGOT, SGPT, C-reactive protein (CRP), Chest Xray along with baseline DAS28 were done on all the patients in both the groups. Then, these patients were followed every month for 6 months with total 5 follow ups. In all

these follow ups, the baseline investigations & DAS28 were performed on all the patients. Apart from the study medications, all patients were also given folate supplements in the form of folic acid tablets; concomitant medications (eg NSAIDs, Proton pump inhibitors, antiemetic drugs, Calcium supplements, Vitamin D supplements) were given to the patients as and when required by the clinician decisions to curb down adverse effects.

Operational definitions used in the study

For treatment naïve RA patients, the new case of RA, the criteria of calling a patient, definite RA was based on 2010 ACR/EULAR criteria & ACR 1987 criteria was used for differentiating established RA from other rheumatic diseases. For the clinical response and severity of disease, the standard DAS28 score was used. **DAS28 is calculated from the formula given below**

$$\text{DAS28} = 0.56 \times \sqrt{\text{tender28}} + 0.28 \times \sqrt{\text{swollen28}} + 0.70 \times \ln(\text{ESR}) + 0.014 \times \text{VAS}$$

The 28 joints assessed were both sides shoulder, elbow, wrist & 1-5 metacarpal and 1-5 proximal interphalangeal joints and tender & swollen 28 joint count was calculated. ESR was measured using wester green method. Visual analogue scale was also used.^[12]

Study tool

ADR reporting form designed by centre for Drug standard Control organization (CDSCO) was used to collect data. The reported ADRs were assessed for causality using WHO causality assessment scale.^[13]

The severity was assessed using Hartwig and Siegel scale^[14].

The WHO causality assessment scale determines the causal relationship of a suspected drug to the ADR in question and categorize into “Certain”, “probable”, “possible”, “unlikely”, “conditional”, / “unclassified” and “unassessable” / “unclassifiable”.

The modified Hartwig and Siegel scale classifies severity as “mild”, “moderate”, and “severe”.

For statistical analysis, all the data was filled in Microsoft Excel (Office 2010), which was then transferred to SPSS version 21 for analysis.

Ethical clearance

Institutional ethical clearance was taken for the study.

Results

131 patients who entered the trial, 68 were assigned to receive Methotrexate and Hydroxychloroquine (Group I) and 63 to receive Methotrexate and Sulfasalazine. Out of 131 patients, 100 patients completed the study. 31 patients did not complete the study due to intolerance to study drugs. In the study, in total 99 ADRs were reported from 53 ADR Forms.

Among the patients completing study, baseline description of patients shows that equal number of patients (n=18) are present in the age group 51-60 years in both the groups. While n=16 patients and n=13 patients were present in the group-1 & group-2 respectively in the age group of 31-40 years. Age group, 41-50 years had 14 patients in group -1 and 15 patients in group-2. Remaining were of age-group 21-30years with 2 patients in group-1 & 3patients in group-2 and also only in group-2 there was n=1 patient having age < 20years Majority of the studied patients were females being 88% in group-1 & 86% in group-2. The mean duration of disease was also similar in the 2 groups i.e almost 4 years.

Table 1: Changes in the non fixed DMARD i.e Methotrexate in the 2 groups of patients

Methotrexate taken	Group-1	Group-2
Oral	50	48
Parental (IM/subcutaneously)	0	2
Mean dose of Mtx (mg)	14.65 ± 2.85	15.15 ± 2.34
Dose of Mtx to control the disease	Group-1	Group-2
10mg	12	5
15mg	31	37
17.5mg	1	3
20mg	6	5
Need to increase the dose of Mtx during follow up	Group-1	Group-2
No increase	8	3
Increased to 15mg	41	42
Increased to 17.5mg	0	1
Increased to 20mg	1	4

Only in 2 patients in group II were given parental form of MTX. The mean dose of MTX administered to the patients in the 2 groups was almost similar being 14.65 ± 2.85 mg in group I and 15.15 ± 2.34 mg in group II respectively with no significant difference (p value = 0.196) (table 1). As MTX is a non fixed DMARD there were maximum patients who required 15mg total dose of MTX and their number is respectively with 31 patients in group I and 37 patients in group II with no significant difference statistically (p value = 0.212) . Also, in majority of the patients with 41 in group I and 42 in group II it was observed that there is increase the dose of MTX to 15 mg.

Result safety profile

The adverse drug reaction reports were obtained by regular questioning of patients by the investigator in the OPD. Among the 131 patients observed, 99 ADRs were reported from 53 ADR Formsto the DMARDS regimen over 1 year study period. This included 51 ADR'sfrom group I, receiving Methotrexate and Hydroxychloroquine and 48 ADR's from group II receiving Methotrexate and Sulfasalazine.

Table 2: Adverse Drug Reactions in both treatment Groups.

	Group I (number of ADR)(n=68)	Group II (number of ADR)(n=63)
NAUSEA	12	8
VOMITING	5	3
DIARRHOEA	5	4
BLURRING OF VISION	2	0
HEADACHE	0	5
HEPATOTOXICITY	6	10
HYPERPIGMENTATION OF SKIN	7	0
ANAEMIA	5	4
LEUCOPENIA	2	3
THROMBOCYTOPENIA	2	4
EPIGASTRIC PAIN	4	7
BREATHLESSNESS	1	0
TOTAL	51 (29 patients)	48(24 patients)

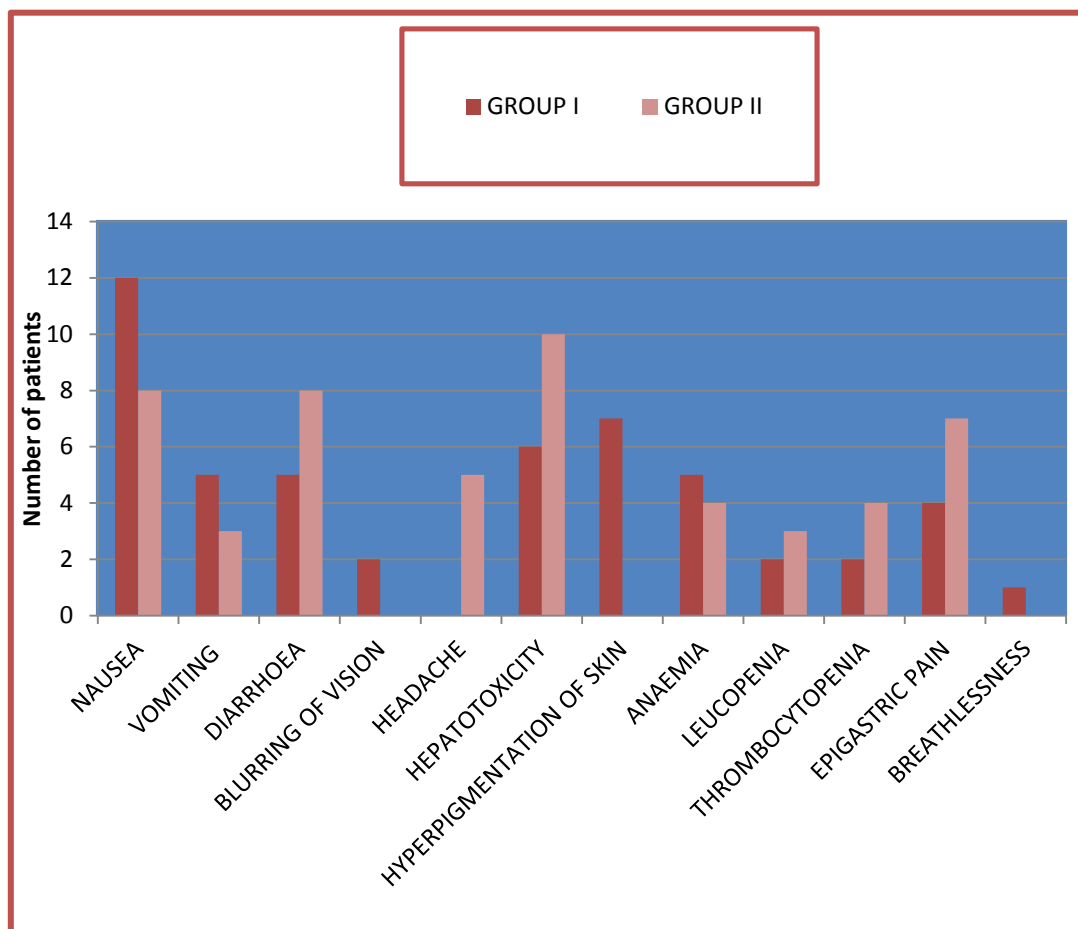


Figure 1: Adverse Drug Reactions in both treatment Groups.

Different adverse drug reactions like nausea, blurring of vision, hyperpigmentation of skin, anaemia, epigastric pain, breathlessness were observed amongst patients in group-1. Whereas in group-2 patients the nausea, diarrhoea, headache, hepatotoxicity and leucopenia were seen.

As per WHO-UMC causality assessment system, there were 17 (33.33%) ADR's in group I and 12 (25%) ADR's in group II that were termed "certain" reactions as patients took the drugs multiple times (rechallenge) and complained of

nausea with and without vomiting, and the reaction was controlled by self medications like anti-emetic drugs (Domperidone). However, the grade of causality for most ADR remained low due to presence of co-administered drugs. 11 (21.57%) of the ADRs in group I and 8 (16.67%) of the ADR's in group II were categorized as "probable". 23 (45.10%) of the ADRs in group I and 28 (58.33%) of the ADR's in group II were categorized as "possible".

Table 3: WHO-UMC causality assessment system

	Group I (number of ADR)(n=68)	Group II (number of ADR)(n=63)
Certain	17 (33.33%)	12 (25%)
Probable	11 (21.57%)	8 (16.67%)
Possible	23 (45.10%)	28 (58.33%)
Unlikely	0	0
Conditional/ Unclassified	0	0
Unassessable / Unclassifiable	0	0

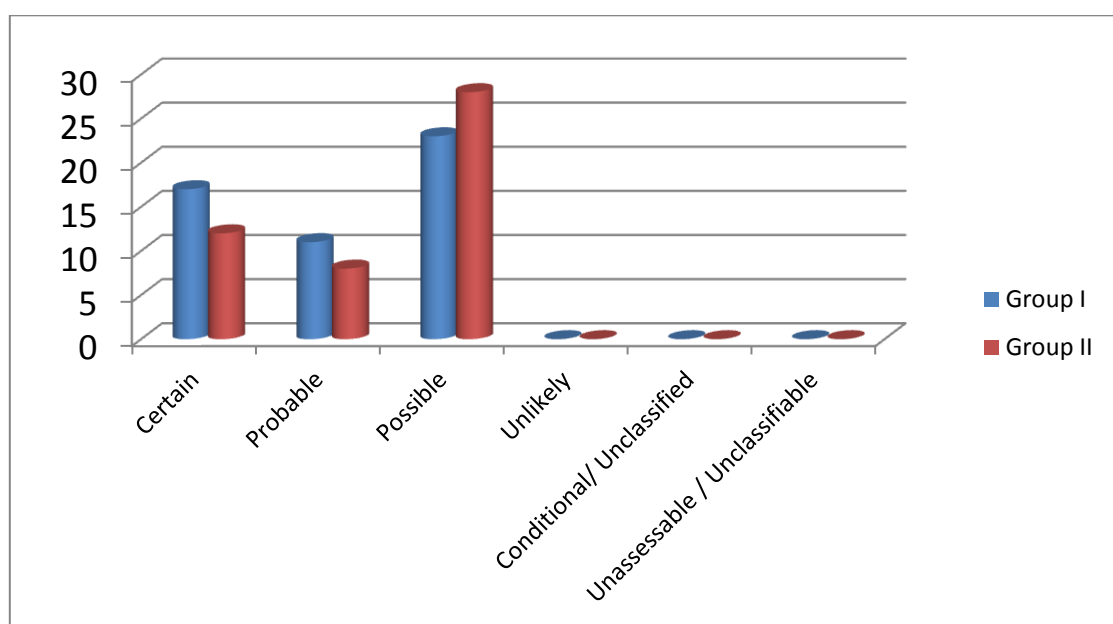


Figure 1: WHO-UMC causality assessment of two treatment groups

The Severity of the reported ADRs was assessed by modified Hartwig and Siegel scale. 33 (64.7%) ADR's in group I and 27 (56.25%) ADR's in group II were termed "mild" and 18 (35.29%)

ADR's in group I and 21 (43.75%) ADR's in group II were termed "moderate" 34.75% on modified Hartwig and Siegel scale.

Table 4: Severity of ADR'S assessed by modified Hartwig and Siegel scale.

	Group I (number of ADR)(n=68)	Group II (number of ADR)(n=63)
Mild	33 (64.7%)	27 (56.25%)
Moderate	18 (35.29%)	21 (43.75%)
Severe	0	0
Lethal	0	0

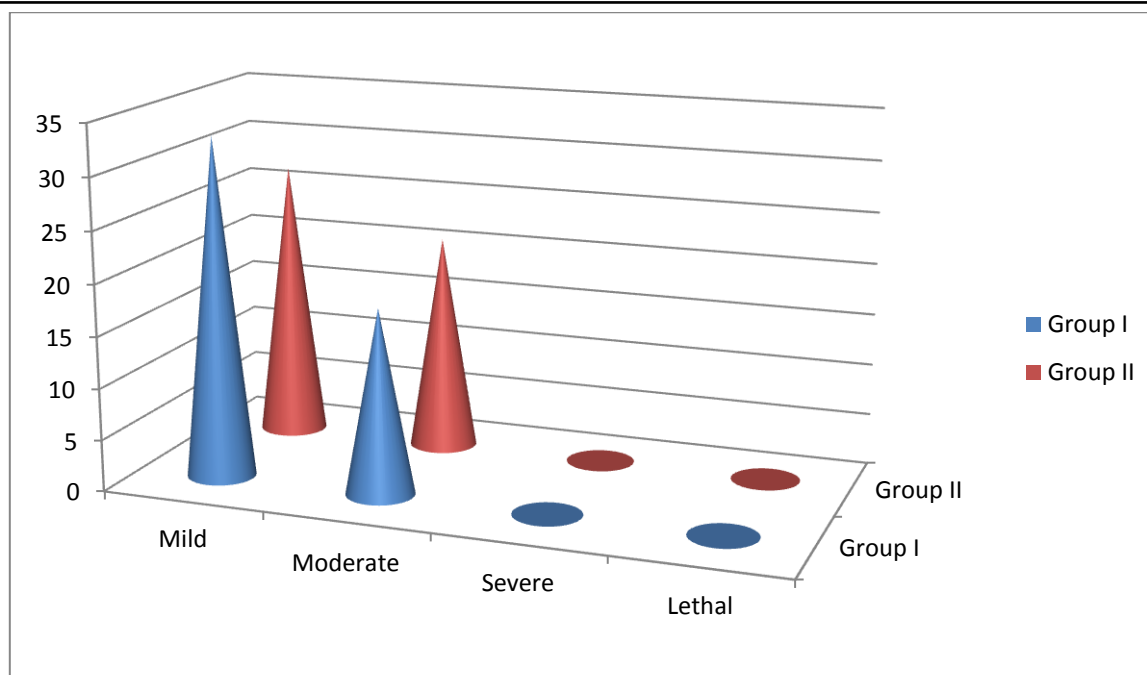


Figure 2: Severity of ADR'S assessed by modified Hartwig and Siegel scale.

Discussion

Methotrexate is now considered the first DMARD of choice in the treatment of Rheumatoid Arthritis. It is active in this condition at much lower doses than those needed in cancer chemotherapy. Methotrexate principal mechanism of action at the low doses used in the rheumatic diseases probably relates to inhibition of aminoimidazole-carboxamide (AICAR) transformylase and thymidylatesynthetase, with secondary effects on polymorphonuclearchemotaxis. While there is some effect on dihydrofolatereductase—and this effects lymphocyte and macrophage function, it is more likely its effect on AICAR transformylase that accounts for the major portion of its action in autoimmune disease.^[10]

Hydroxychloroquine anti-inflammatory action in rheumatic diseases is unclear. The following mechanisms have been proposed: suppression of T lymphocyte responses to mitogens, decreased leukocyte chemotaxis, stabilization of lysosomal enzymes inhibition of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) synthesis and the trapping of free radicals.^[10]

Sulfasalazine is metabolized to sulfapyridine and 5-aminosalicylic acid, and it is thought that the sulfapyridine is probably the active moiety when

treating rheumatoid arthritis. In treated arthritis patients, IgA and IgM rheumatoid factor production are decreased. Suppression of T cell responses to concanavalin and inhibition of in vitro B cell proliferation have also been documented.^[12]

Less number of patients' withdrawal from combination therapy when compared with monotherapy. Combinations of Methotrexate with tumor necrosis factor (TNF) inhibitors and Methotrexate with Sulfasalazine and/or Hydroxychloroquine are most effective.^[15]

The adverse drug reaction reports were obtained by regular questioning of patients by the investigator in the OPD. Among the 131 patients observed, a total of 99 ADRs were reported from 53 ADR Forms. This included 51ADR's from group I, receiving MTX and HCQ and 48ADR's from group II receiving MTX and SSZ over the study period of one year.

The above mentioned ADRs can be explained via methotrexate's most common side effects which include stomach pain, nausea, diarrhoea, leucopenia, anaemia and thrombocytopenia. Or less common side effects like headaches, a fall in the number of other blood cells, damage to the lungs (breathlessness). MTX can cause other side

effects including: Liver damage, blurred vision, gastrointestinal ulcers.^[10] The above mentioned ADRs can also be explained via SSZ leading to diarrhoea, nausea or vomiting, headache and upset stomach. The above mentioned ADRs can also be explained via hydroxychloroquine's very common ADR list nausea, stomach pain, stomach cramps; Common ADR like, diarrhoea. Less common ADRs like blurred vision and headache. Uncommon ADRs like increase skin pigmentation (bluish black color).^[10] Two Patients of the first group (MTX + HCQ) developed adverse events like blurring of vision. This adverse reaction may be due to accumulation of HCQ in cornea or retina. Blurred vision occurs in up to 3% of patients (usually due to corneal deposits), and may be is reversible. The retinal deposition of HCQ is a concern because this is more common in older patients on longer-term treatment, is irreversible and may worsen with time.^[16] That is why in this study patients of more than 60 years were excluded from the study, to avoid HCQ induced blurring of vision. Analysis of results of visual screening of large numbers of patients taking HCQ in various studies showed similar results^[16, 17]

In the present study, 7 patients developed hyper pigmentation on various parts of the body (face, back, legs etc). Hydroxychloroquine-induced pigmentation is not a rare adverse effect. Use of antimalarials (ie, quinacrine, chloroquine, HCQ) can induce tissue pigmentation in a variety of organs, including skin, joint tissue, trachea, and cartilage in the nose and ears, result from various studies adds up that, skin biopsies performed on patients showed that the median concentration of iron was significantly higher in biopsy specimens of pigmented lesions compared with normal skin. So it was hypothesis that HCQ induced pigmentation is secondary to ecchymosis or bruising.^[18, 19]

Patients of the first group (MTX + HCQ) also developed gastrointestinal adverse events like epigastric pain (4 patient), nausea (12 patient), vomiting (5 patients) and diarrhea (5 patients).

Studies have found an association of elevated blood HCQ concentration and gastrointestinal adverse events^[20]

Majority of side-effects with SSZ occur early, and most reverse completely on cessation of therapy. Frequent monitoring, therefore, is necessary only in the first six months. No cumulative or unexpected long term toxicity is known.^[21] One of the similar study presented similar data, MTX and SSZ group, 5 patients were withdrawn due to toxicity, 1 each because of headaches, rash, and pneumonia and 2 because of gastrointestinal distress. In the MTX and HCQ group, 5 patients were withdrawn, 1 each because of weight loss, gastrointestinal distress, possible HCQ-related changes in the eye, myocardial infarction, and lobar pneumonia.^[17]

Besides the comorbidities related to the disease itself, the treatments used in RA pose distinct problems, most of which are transitory. Nevertheless, immunosuppressive medications increase the risk of serious infections, and glucocorticoids additionally predispose the patients to osteoporosis, hypertension, diabetes mellitus, and cataract. However, all of these are features of high-dose glucocorticoid treatment and rare when small doses are used.^[22]

The mean dose of MTX administered to the patients in the groups was similar, 14.65 mg in group I and 15.15 mg in group II respectively. Maximum patients required 15mg total dose of MTX i.e. 31 patients in group I and 37 patients in group II. Various studies concur with the study data that the usual dose of Methotrexate in Rheumatoid arthritis patients is in the range of 15 to 17.5 mg/week.^[23]

At present as no curative therapy is available for Rheumatoidarthritis, With the perfect, curing, therapy of RA still lacking, the current treatment of RA should remove the inflammatory symptoms rapidly and safely, prevent permanent damage, and be financially available to all patients. Furthermore, as RA is a chronic, lifelong disease, all of these prerequisites should be met even in long-term.

Limitation

The study being done on less number of patients. Attrition bias is there.

Conclusion

DMARD's combination cause more but tolerable adverse effects. In both the treatment group, maximum patients required 15mg dose of MTX to control the disease activity. Combination DMARD regimens are safe for use in Rheumatoid arthritis to control disease activity with tolerable, transient and reversible adverse effects.

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