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COMBINATION THERAPY OF LEFLUNOMIDE AND METHOTRXATE IN RHEUMATOID ARTHRITIS PATIENTS

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Abstract:

Objective*: The objective of the research was to study the profile of safety of (LEF + MTX) in a combined form in patients along with active (R.A) at the time duration of three & six months.*

Material and Methods: *Duration of the research was from January, 18 to April, 18 at Nishtar Hospital, Multan. A Total of 72 patients with active (R.A) in spite of the maximum medicine which was 20 to 25 mg per week of (MTX) were enrolled & leflunomide at 20 mg per day was also added. Both the clinical & laboratory reviews were taken at zero, one, three & six months to check any of the side effects.*

Results: *A total of 72 subjects were included with an average age of ± SD (51.5 ± 9.1) years & a mean disease time as (8.25 ± 6.1) years. All the subjects have baseline active disease having mean activity of disease score as DAS-28 of (6.2 ± 0.7). At a time after six months, most of the side effects were nausea & abdominal pain. Total 57 subjects at 79.1 percent were continued with combination therapy. Due to raised (ALT) & vomiting, just three ceased treatment temporarily & 12 discontinued treatment because of diarrhoea, intensive oral ulcers, evidently increased (ALT) which affected two patients, abscess, vomiting, chest infection, (MTX) induced pneumonitis which affected one patient.*

Conclusion: *If vigilant clinical & laboratory monitoring is confirmed then (MTX + LEF) combination is very safe in using in all R.A. patients.*

Keywords: *Safety, Leflunomide, Methotrexate, Rheumatoid arthritis.*

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INTRODUCTION:

The (RA) i.e. rheumatoid arthritis is an inflammatory disorder known by progressive joint destruction resulting in increased mortality & disability. It affects numerous organ systems like vessels, eyes & nerves [1]. Many (DMARDs) i.e. disease modifying anti-rheumatoid drugs must be used for reducing clinical symptoms & stopping joint destruction [2]. The methotrexate is folic acid analogue & competitive inhibitor of (DHRF) dihydrofolate reductase [3] and used as 1st agent when starting (DMARD) therapy in the patients with R.A. Many techniques as (DAS) i.e. disease activity score in twenty-eight joints, (CDAI) i.e. clinical disease activity indices & simplified are in usual practice to monitor treatment efficacy [4]. In spite of the use of (MTX) mono-therapy, several patients have to depend on combination therapy using traditional (DMARDs) or biologics [5, 6].

The (LEF) i.e. MTX & Leflunomide has remained a reasonable choice in this regard. The area is still under research proved by contradictory results & scarcity of data and as for safety is concerned. The Curtis et al8 & Kremer et al7 report highlighted enhanced danger of liver toxicity along with use of this combination & transaminases but another research shows not any such toxicity [9].

The main side effects attached with the use of such combination therapy following: Menstrual disturbances, hypertension, infections, nausea, vomiting, diarrhoea, & hepato-toxicity. The safety of (MTX + LEF) has just analysed on a pool of twenty affected persons [10]. It is not easy to use biologics for number of patients along with consistently active (RA) due to large prices & dependence on combination therapies of (DMARDS) in Pakistan. A few biologics are there in Pakistan & it will be beneficial both for patients & will strengthen finance of health infrastructure.

MATERIAL AND METHODS:

It was type of quasi experimental research approved by ethical review committee at Rawalpindi in Fauji foundation hospital. The WHO sample size calculator was used to measure the sample size with the calculations like absolute precision required: 9 percent, sample size: 63 patients, confidence interval: 95 percent, anticipated population proportion7: 16.2 percent. The method of non-probability consecutive sampling was used. An arbitrary number of seventy-three patients was selected to save from any of the drop outs because of the loss of the follow up. The research was performed in department of Rheumatology at Rawalpindi in the Fauji foundation hospital. The duration of research was six months and patients were selected randomly from January, 15 to December, 15 in the outpatient department. Total of seventy-two patients of age from 18 to 75 years were made part of research. The patients of RA & coming on (ACR) criteria as 198711 & duration of disease of 6 months were selected. The patients having greater (DAS 28 score > 5.2) in spite of maximum doses of methotrexate as (20-25) mg per week were included.

The following patients were excluded: with hypersensitivity to study drugs, active serious infection, with liver disease, active hepatitis B & C, pregnant females or of child bearing age not using contraception and renal disease as creatinine clearance < 30 ml per minute. To ensure it, blood tests were drawn & history of any drug hypersensitivity was taken before enrolment. All the patients along with R.A meeting the criteria were enrolled & combination therapy along with (MTX & LEF) was initiated and consent was necessary before enrolment. The particulars of patients like age, gender, marital status & occupation were written in a form with contacts for the aim of follow-up. The duration was also recorded from the start. DAS of each subject was calculated by the pain score of patient on VAS in the range of (0 – 10), for noting down the tender joint count & swollen joint count. In it zero means no pain & ten relates highest observed pain with (ESR) on inclusion time [12].

Leflunomide medicine was taken as twenty mg (PO)/day. The data was assessed for research at three & six months after recording baseline profile while patients were reviewed at one, three & six months. All the blood samples were taken on baseline for entire blood picture, fasting lipid profile, random blood sugars & (ALT) alanine aminotransferase enzyme levels. The B.P was recorded at the start & then after three and six months' intervals. All the side effects were noted as mentioned in (BNF) British national formulary [13]. All the side effects were thought to be threatening and serious which may result to stop the therapy. Drug combination was done for the time being and stopped when adverse effects were shown. The blood chemistry & haematology were also recorded. All the important (ALT) elevations were minimized along with temporary treatment and enhancement as {(ALT > 5 × normal upper limit i.e. (ULN)} may cause therapy discontinuation permanently. Moreover, highest increase ALT as [> 2 × ULN, > 2 to ≤ 3 × ULN, & > 3 × ULN] were briefly explained. The (IBM) SPSS was used for analysis. Both age & duration of disease were calculated in mean and ± standard deviation.

Significant assessment rate was assessed through (paired T – test) (P under 0.05) and CI as 95 %. Many variables such as percentage & frequency were also shown as nausea, gender & vomiting.

RESULTS:

The total number of 73 patients fulfilling the criteria were under study in which 1 patient was loss to follow-up. Most of the patients were female as 97.2 percent along with an average age ± SD of 51.5 ± 9.1 years & (8.25 ± 6.1) years as mean time duration of disease. All the demographic & clinical characteristics at baseline are as demonstrated in table No. I and then safety analysis was also done in three & six months to record many adverse events. In table No-2, laboratory profile at zero, three & six months is demonstrated. An average change in the (TLC) was clear at six months of research as p = 0.015 and mean change in the platelets & (Hb) at six months was not important as p = 0.97, 0.092 respectively as shown in the table No-2.

The percentage of the patients having (Hb<10 mg/dl) was observed as 11, 11 & 19 percent at 0, 6 & 3 months respectively. The value of (TLC) going below (4×103) was observed just in three patients at three months & only two patients at six months' duration. The random blood sugars, serum LDL cholesterol & serum total cholesterol at 0, three & six 6 months were observed as results are shown in table-2 in terms of mean ± SD. The increase in random blood sugars, serum total cholesterol & serum (LDL) cholesterol was not clear at six months as in table-2. In the same way, change in average blood pressure at six months was found not clear. The danger of liver toxicity in subjects on (MTX+LEF) combination was resulted by observing serum (ALT) during research.

All elevations in the serum (ALT) from the start were demonstrated as table-3. (ALT) levels in all patients which enhanced to > 2 & >3 × ULN were made by timely stopping combination therapy. Only 1 patient whose (MTX+LEF) was ceased permanently because (ALT) stages never settled. Just 1 patient has (ALT) raising to 5 times as compare to (ULN).

A significant change in the average (ALT) at six months was clear and p = <.000 shown in table-2. The rate of diarrhoea, vomiting & oral ulcers at three months was observed as 11 percent, 18 percent & 22 percent respectively. This is shown in adverse events. In the same way, rate of nausea & abdominal pain after three & six months was seen as 40 percent, 38.8 percent, 29.1 percent and 23.6 percent respectively. Moreover, gastrointestinal tract related (AE) have been frequently observed during 1st twelve weeks which were minimized after it. The rate of upper respiratory infections was on three & six months was 20.8 percent against 11.1 percent. Chest infection was observed 1 patient at three months resulting in permanent stop of therapy. There was no observation of life threatening body infections except only 1 patient who has a large sub mammary abscess on left side. The drainage & incision was performed by the surgeons with suitable antibiotics given & patients became healthy soon.

Many of the infrequent (AE) to be observed were urticarial, alopecia, skin discoloration & menstrual abnormalities (16.6%; 0.02%; 0.19% and 0.06%) after a time of three months & 13.2, 0.08, 0.13, 0.04 percent after six-month time respectively. A type of skin discoloration was also observed in 13.2, 4.2, 16.6 percent, and patient at six, three & zero-month time respectively. Another observation was about urticarial in just 0.8, 0.02 & 0.08 percent, alopecia observed in 0.4, 0.19 & 0.94 percent and menstrual irregularities were observed infrequently in 1.8, 2.0 and 2.6 percent in subjects after zero, three & six-month time respectively.

A total of 57 subjects at 79.1 percent have undergone combination therapy. In twelve subjects whose treatment on (MTX+ LEF) combination was stopped, four have diarrhoea, 1 has a severe chest infection, 1 developed MTX Induced pneumonitis, two subjects have severe oral ulcers, two had markedly elevated (ALT), 1 had severe vomiting & one patient has shown abscess.

Table-I: Baseline clinical and demographic features of patients enrolled for MTX+LEF combination therapy.

Variables	Values
Total patient	72 (100%)
Age mean ± SD (years)	51.5 ± 9.1
Gender m/f	1/71
Duration of disease Mean ± SD (years)	8.3 ± 6.1
Married (%)	95.8%
Tender joint count, TJ mean ± SD	14.8 ± 6.5
Swollen joint count, SJ mean ± SD	4.4 ± 2.3
Pain score, VAS mean ± SD	7.4 ± 1.9
Mean disease activity score, DAS28	6.2 ± 0.7

Table-II: Biochemistry profile across 0, 3 and 6 months

Variables	0 months	3 months	*p*-value	6 months	*p*-value*
Hemoglobin (Hb) mg/dl	11.3 ± 1.47	10.8 ± 1.48	0.019	11.2 ± 1.44	0.97
Total leukocyte count $(\times 10)^3$ cells	8.45 ± 2.37	7.36 ± 2.19	0.000	7.43 ± 2.41	0.015
Platelet count $(\times 10)^3$ cells	291 ± 99	274 ± 97	0.095	267 ± 98	0.092
Total serum cholesterol (mg/dl)	4.85 ± 0.70	4.85 ± 0.68	0.942	4.75 ± .09	0.523
LDL cholesterol (mg/dl)	2.42 ± .55	2.53 ± 0.47	0.072	2.58 ± 0.51	0.091
Random blood sugars (mmol)	6.58 ± 3.12	6.46 ± 1.96	0.662	6.90 ± 2.47	0.195
Systolic BP (mmHg)	117 ± 15.6	123 ± 14.3	0.001	123 ± 14.8	0.000
ALT (mg/dl)	34.1 ± 7.6	47.2 ± 34.8	0.001	39.7 ± 10.7	0.000

Table-III: Trend of serum ALT elevations at 0, 3 and 6 months

ALT	0 Month	3 Months	6 Months
Normal	68	47	42
> 1 X ULN	4	20	16
> 2 X ULN	0	1	0
> 3 X ULN	0	2	0
> 5 X ULN	0	1	0

DISCUSSION:

(R.A) is both deforming & disabling arthritis and also a financial pressure for treatment. The clinical guidelines must be followed and treatment differs in each case because of comorbidities & (AE) adverse effects profile of such medicines [14]. So the optimal therapy for dealing (RA) is beneficial for patients.

As it is linked with better results, a treat to target approach [15, 16] need to be used when dealing (RA) [17]. MTX is standard for starting the therapy in all the patients of (RA). Those subjects continuing to

have consistent (high disease activity) are candidates for the combination of traditional (DMARDs) (MTX + Sulfasalazine), (hydroxychloroquine) & (Leflunomide) [18] or it may be the biologics [19]. Our research favours the rationale of combination (MTX+LEF) in (RA).

The (AE) observed after 3 months of analysis was with abdominal pain 39 percent & nausea 40 percent followed by oral ulcers 22 percent, diarrhoea 11 percent and vomiting 18 percent. Many adverse effects felt by subjects were of gastrointestinal system. Many of the symptoms were soft & solved truly in six months. Same outcomes are shown in other researches that demonstrated enhanced rate of gastrointestinal adverse effects which later developed in following months [7, 16].

Our research shows the range of liver toxicity in Pakistani patients and there may be raised transaminases after 6 months as $p < 0.05$. More than half of subjects have normal (LFTS) till end of research. All patients with mild (ALT) elevations & those with (ALT > 1 × ULN) have also recovered spontaneously. Just 2 subjects have discontinued (MTX+LEF). Current data checking toxicity of combination (MTX + LEF) are more conflicting, Hensley 21 & Cubides et al22 shared their findings of combination (MTX + LEF). They never showed any danger of gastrointestinal complaints, elevated transaminases and hematologic disorders.

Five times enhanced danger of elevated transaminases are shown contrarily in the outcomes of corona research performed in North American population [8]. It included subjects with (RA) & psoriatic arthritis. A much bigger sample is needed in our set-up to appreciate if any clear difference is found among both Pakistani & North American people. Few protective influences relating to ethnicity are there on the level of deranged (ALT) but it requires to be worked upon further.

In this research only 1 subject was reported with (MTX) induced pneumonitis & therapy was stopped. This subject was then switched to the alternate therapy i.e. (DMARD). There was no danger of having (dyslipidaemias) & (diabetes) after six months as $p > 0.05$. The risk of having (leukopenia) or (anaemia) which was second option to combination therapy was not clear as $p > 0.05$. The rates of side effects like urticarial, rashes, menstrual abnormalities & hair loss observed were almost same as found in other researches [7, 20]. Almost 80 percent subjects continued (MTX+LEF) combination therapy and three percent ceased temporarily while 16.6 percent have to stop this therapy entirely.

There was no death reported and no life threatening opportunistic infection was found. The major drawback of research was that mostly study group was female and applicability of similar side effect profile in the male may not confirmed. It is also a study of 6-month duration so it focused just on safety profile for a short term duration. All side effects of long term by using (MTX+LEF) therapy can never be extrapolated & needs extension of this primary research up to minimum 2 years. It also demonstrates the safety profile of (MTX+LEF) in all the (R.A) subjects in Pakistan after six-month time. Potential for the liver toxicity may not be overlooked so patient selection is important along with vigilant & regular monitoring. In the view of (ACR) i.e. American College of Rheumatology, 2015 guidelines [14] in dealing with (RA), side effects must be examined at two to four weeks for 1st three months, eight to twelve weekly for three to six months & after every twelve weeks. So, this is effective therapy and can be safely used if ensuring vigilant & close monitoring of side effects as required with all the other (DMARD) therapies. If we use it in developing countries, it will both benefit the patients & will save expenses of biologic therapy as well.

CONCLUSION:

If vigilant clinical & laboratory monitoring is confirmed, then (MTX + LEF) combination is very safe in using in all R.A patient. The subjects must be selected carefully before initiating this combination therapy.

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