SAFETY OF METHOTREXATE AND LEFLUNOMIDE AS A COMBINATION THERAPY IN PATIENTS OF RHEUMATOID ARTHRITIS

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ABSTRACT

Objective: To study the safety profile of MTX+LEF combination in patients with active RA at 03 and 06 months.
Study Design: Quasi-experimental study.
Place and Duration of Study: Rheumatology department, Fauji Foundation Hospital Rawalpindi, from Jun 2015 to Dec 2015.
Material and Methods: This quasi-experimental study was conducted at Rheumatology department, Fauji Foundation Hospital, Rawalpindi. Seventy two patients who had an active RA despite optimal dose (20-25mg/week) of MTX were enrolled and leflunomide 20mg/day was added. Patients underwent clinical and laboratory review at 0, 1, 3 and 6 months to note any adverse effects.
Results: Seventy two patients were enrolled with a mean age (years) ± SD of 51.5 ± 9.1 and a mean duration of disease (years) of 8.25 ± 6.1. Patients had active disease at baseline with a mean disease activity score (DAS28) of 6.2 ± 0.7. At 6 months the most frequent side effects (mostly mild); were abdominal pain and nausea. Fifty Seven patients (79.1%) continued with the combination therapy. Only 3 patients stopped the treatment temporarily (due to raised ALT and vomiting). Twelve patients discontinued treatment due to diarrhea, severe oral ulcers, markedly raised ALT; (Each affecting 2 patients) and severe vomiting, abscess, MTX Induced pneumonitis, severe chest infection (each affecting 1 patient).
Conclusion: MTX + LEF combination is safe to use in RA patients if vigilant clinical and laboratory monitoring is ensured.

Keywords: Methotrexate, Rheumatoid arthritis, Safety, Leflunomide.

INTRODUCTION

Rheumatoid arthritis (RA) is an inflammatory disorder characterized by progressive joint destruction leading to disability and increased mortality. RA not only affects the joints but has widespread effects on numerous organ systems including eyes, nerves and vessels[1]. Therefore earlier the treatment is initiated, lesser is the joint damage and resultant disability. Various disease modifying anti rheumatoid drugs (DMARDs) have to be employed for adequately ameliorating the clinical symptoms as well as halting the process of joint destruction[2].

Methotrexate (MTX) is a folic acid analogue and a competitive inhibitor of dihydrofolate reductase (DHFR)[3]. It is employed as first line agent while starting off the DMARD therapy in patients with RA. Various tools like disease activity score in 28 joints (DAS-28), simplified and clinical disease activity indices (SDAI, CDAI) are in common use to monitor treatment efficacy[4]. Despite the use of MTX monotherapy, many patients tend to have high disease activity and have to rely on either combination therapy employing conventional DMARDs or biologics[5,6].

MTX and Leflunomide (LEF) remain a plausible option in this aspect. This combination is still an under studied area as evidenced by sparsity of data and also contradictory results as far as safety profile is concerned. Kremer et al[7] and Curtis et al[8] report raised transaminases and increased risk of liver toxicity with the use of this combination. On the other hand another study reveals no such toxicity[9]. The major adverse effects attributable to the use of this combination therapy are nausea, vomiting,

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diarrhea, hepato-toxicity, infections, hypertension and menstrual disturbances. As far as local data is concerned, the safety of MTX + LEF has only been analyzed on a pool of 20 patients[10]. In Pakistan, it is difficult to use biologics for many patients with persistently active RA because of the sky high costs and have to rely on combination therapies of DMARDS. Moreover only few biologics are available in Pakistan. Hence further studies are needed to study the safety profile of synthetic DMARDs so that we employ this combination therapy frequently in our patients. This would not only benefit patients but would also strengthen the economics of health infrastructure.

MATERIAL AND METHODS

This is a quasi-experimental study. Approval for this study was taken from Ethical review committee, Fauji foundation hospital, Rawalpindi. The sample was calculated by using WHO sample size calculator. Following are the calculations. Confidence interval: 95%, anticipated population proportion[7]: 16.2%. Absolute precision required: 9% Sample Size: 63 patients. Non probability consecutive sampling was used. To avoid any drop outs due to loss of follow-up, an arbitrary number of 73 patients was chosen. This study was carried out in the department of Rheumatology, Fauji Foundation Hospital; Rawalpindi. The mean duration of study was 06 months in which the patients were randomly selected from Jan 2015 to Dec 2015 from the outpatient department. A total of 72 patients (18 to 75 years of age) were included in the study. Patients with RA fulfilling the American College of Rheumatology (ACR) criteria 1987[11] and disease duration of at least six months were selected. Out of these, only those patients who had high disease activity (i.e. DAS 28 score >5.2)[12] despite optimal doses of methotrexate 20-25 mg/week were enrolled in the study.

Patients with liver disease, active hepatitis B and C, renal disease (creatinine clearance <30 ml/min), active serious infection and those with hypersensitivity to the study drugs were excluded from the study. For this purpose history of any drug hypersensitivity was taken and blood tests were drawn before enrolment. Female patients who were pregnant or were of child bearing age not using contraception were also excluded.

Patients with RA fulfilling the inclusion criteria were enrolled in the study and combination therapy with MTX and LEF started. Written consent from the patient was mandatory before enrollment. Patient's biodata was entered into a proforma along with contact number for follow up. Patient's biodata was recorded as age, gender, marital status and occupation. The duration of disease since the symptoms onset was also noted. The disease activity status of each patient was calculated by noting down the tender joint count, swollen joint count, patient's pain score on visual analogue scale (from 0 to 10) where 0 means no pain and 10 means maximum pain, along with ESR at the time of inclusion[12]. The dose of leflunomide was kept to 20 mg PO per day. After recording baseline profile, though patients were followed up at 1, 3 and 6 months; data was evaluated for the study at 3 and 6 months for study purpose. Blood samples were drawn at baseline for complete blood picture, alanine aminotransferase enzyme levels (ALT), random blood sugars; fasting lipid profile. Blood pressure was noted at baseline and thereafter at 3 and 6 months.

The adverse effects were documented as laid down in British National formulary (BNF)[13]. Any patient who developed the adverse effects was noted down. Adverse effect was defined as any sign, symptom, syndrome, or illness that appeared during the study period and that might have impaired well being of the subject. Any adverse effect considered life threatening or serious eventually lead to discontinuation of the therapy. The drug combination was with-held temporarily or discontinued depending upon the adverse effects experienced.

Hematology and blood chemistry were noted down as stated above. Clinically significant

ALT elevations subsided with temporary with holding whereas persistent elevation or ALT >5 × upper limits normal (ULN) lead to permanent discontinuation of combination therapy. The highest elevation of ALT [>2 ×ULN; > 2 to ≤3 ×ULN; and > 3×ULN] were also summarized.

Statistical analysis was performed using IBM SPSS Statistics 20. Mean ± standard deviation of quantitative variables like age and duration of disease was calculated. Paired t-test was used for quantitative variables to evaluate the level of significance. A *p*-value of <0.05 was considered significant. A confidence interval of 95% was used. Frequency and percentages were presented for categorical variables like gender, nausea, vomiting and other adverse events. Also percentages of patients who continued, temporarily stopped or discontinued the therapy were noted.

RESULTS

A total of 73 patients fulfilling the inclusion criteria were enrolled. One patient was loss to follow up after enrolment. The majority of patients were female (97.2%) with a mean age (years) ± SD of 51.5 ± 9.1 and a mean duration of disease (years) of 8.25 ± 6.1. The clinical and demographic characteristics at baseline are as shown in the table-I. A detailed safety analysis was conducted across 3 months and 6 months to document the various adverse events (AE) noticed.

The laboratory profile at 0, 3 and 6 months is represented in table-II. The mean change in Hb and platelets at 6 months was not significant (*p*=0.97, 0.092 respectively) whereas the mean change in TLC was significant at 6 months of study (*p*=0.015), as mentioned in the table-II. Percentage of patients with Hb<10 mg/dl was 11, 19 and 11% at 0, 3 and 6 months respectively. A TLC falling below 4×10^3 was noted in only 3 patients at 3 months and 2 patients at 6 months.

The serum total cholesterol, serum LDL cholesterol and random blood sugars at 0, 3 and 6 months were noted. Results are stated in table-II as mean ± SD. The rise in serum total cholesterol, serum LDL cholesterol and random blood sugars was not significant at 6 months (table-II). Similarly the change in mean blood pressure at 6 months was also insignificant.

The risk of liver toxicity in the patients on the MTX+LEF combination was followed by observing serum ALT during the study period. The elevations in serum ALT from the baseline were noted as shown in table-III. The ALT levels

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

Variables	
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

in the patients that increased to >2 and >3 × ULN settled by temporarily stopping the combination therapy, except for one patient whose MTX+LEF was stopped permanently as the ALT levels didn't settle. Similarly only one patient had ALT rising up to five times the ULN and the combination therapy was stopped completely at the first instance. The change in mean ALT at 6 months was significant (p=<.000); as mentioned in table-II.

The frequency of oral ulcers, vomiting and diarrhea at 3 months was 22%, 18% and 11% respectively. The trend these adverse events followed by 6 months is as shown in fig-1 and 2. Similarly the frequency of nausea and abdominal pain at 3 and 6 months was 40%, 38.8% and 29.1%, 23.6% respectively. Even the milder abdominal complaints were noted. The gastro-intestinal tract related AE were the most frequent during first 12 weeks and decreased thereafter.

The frequency of upper respiratory infections at 3 and 6 months was 20.8% vs 11.1%. But serious chest infection was noted in only one patient at 3 months leading to permanent discontinuation of the combination therapy. Similarly no serious life threatening body infections were noted in any patient except for one who developed a large left sided sub mammary abscess and the combination therapy was discontinued permanently, incision and drainage was done by surgeons and appropriate antibiotics given according to culture results. The patient recovered fully afterwards.

Other infrequent AE to be noted down were skin discoloration, urticaria, alopecia and menstrual irregularities (16.6, 0.02, 0.19, 0.06% at 3 months and 13.2, 0.08, 0.13, 0.04% at 6 months respectively).

Skin discoloration was noticed in 4.2, 16.6, and 13.2% patient at 0, 3 and 6 months respectively. Similarly urticaria was observed in only 0.8, 0.02 and 0.08% whereas alopecia noted in 0.4, 0.19 and 0.94% patients at 0, 3and 6 months respectively. Menstrual irregularities were also

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 $(\times10)^3$ cells	8.45 ± 2.37	7.36 ± 2.19	0.000	7.43 ± 2.41	0.015
Platelet count $(\times10)^3$ 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

$p \leq 0.05$: Significant, *p*-value: Comparison between baseline (0 month) and 3 months, *p*-value*: Comparison between baseline (0 month) and 6 months respectively.

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

seen infrequently i.e. 1.8, 2.0 and 2.6% patients at 0, 3 and 6 months respectively.

Overall 57 patients (79.1%) continued with the combination therapy (fig-3). Patients who stopped the treatment regimen temporarily were mainly due to raised ALT and vomiting. Amongst the 12 patients whose treatment on

DISCUSSION

Rheumatoid arthritis is not only a deforming and disabling arthritis but also a source of considerable financial burden when it comes to treatment. Apart from following the clinical guidelines[14], treatment has to be rationalized from case to case due to the presence of

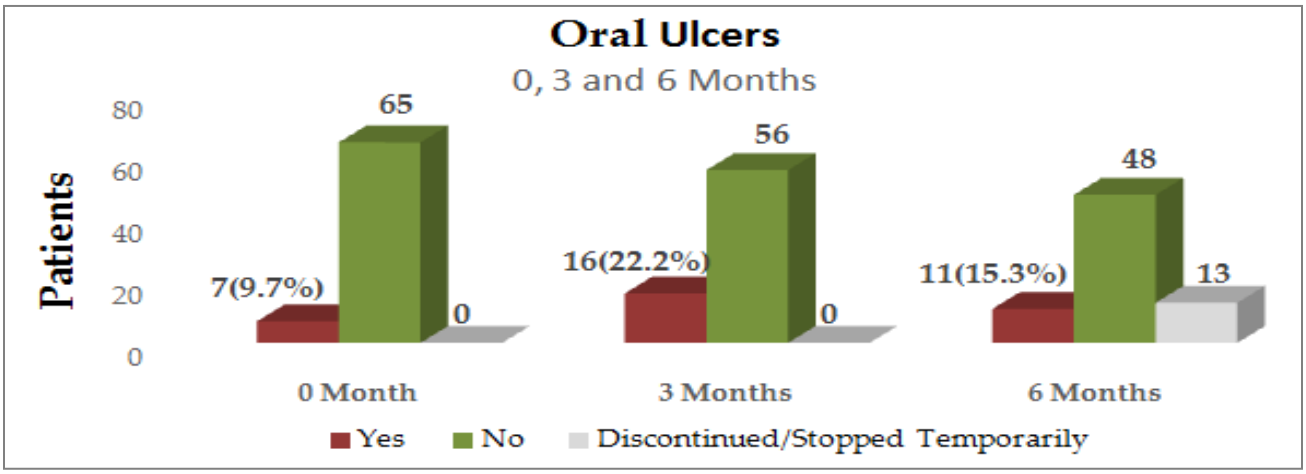

Figure-1: Patients presenting with oral ulcers at 0, 3 and 6 months.

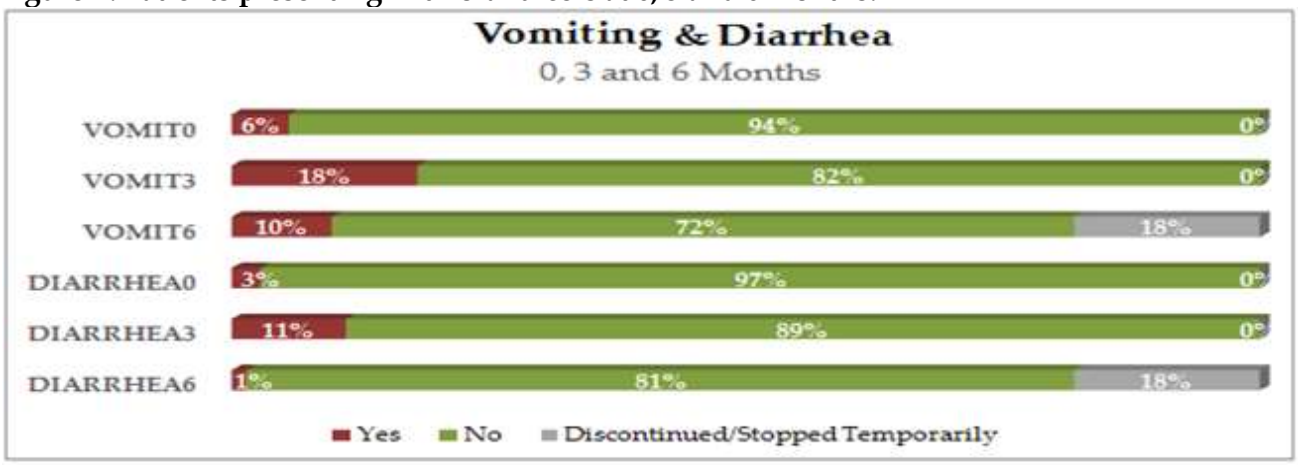

Figure-2: Frequency of vomiting and diarrhea at 0, 3 and 6 months.

MTX+ LEF combination was discontinued; 4 patients had diarrhea, 2 patients had severe oral ulcers, 2 had markedly raised ALT, 1 had severe vomiting, 1 patient developed abscess, 1 developed MTX Induced pneumonitis and another one had a severe chest infection. An overview of side effect profile at 6 months is as shown in fig-4.

comorbidities and adverse effects (AE) profile of these drugs. Hence choosing the optimal therapy while treating RA not only benefits patients but also the finances of the health department especially in developing countries. A treat to target approach[15,16] has to adopted while managing rheumatoid arthritis since it is associated with better long term outcomes[17].

It stays beyond doubt that MTX is the gold standard for initiation of therapy in patients with RA. But those patients who continue to have persistent high disease activity are candidates for either combination of conventional DMARDs (MTX+Sulfasalazine and/or hydroxychloroquine and/or Leflunomide)[18] or biologics[19]. This study continues to favor the rationale of combination MTX+LEF in RA.

The most frequent AE noted at three months of analysis was the presence of nausea (40%), abdominal pain (39%) followed by oral ulcers (22%) vomiting (18%) and diarrhea (11%). It remains noteworthy here that most of the adverse effects experienced by the patients were related to gastrointestinal system. Despite apparent high frequencies, most of these symptoms were mild and settled remarkably by 6 months. Similar results are replicated in other studies which show increased frequency of gastrointestinal adverse effects in the start off of combination therapy that subsequently improved over the following months[7,16].

This study also highlights the extent of liver toxicity observed in the Pakistani patients. There was a significant chance of having raised transaminases (considering milder elevations too) by the end of six months (p<0.05). In this study, more than half of the study population had normal LFTS by the end of the study period. It is reassuring that most of the patients with mild ALT elevations especially those with ALT>1×ULN improved spontaneously. In others, the levels subsided with temporary withholding the combination therapy. Only 2 patients had to discontinue MTX+LEF.

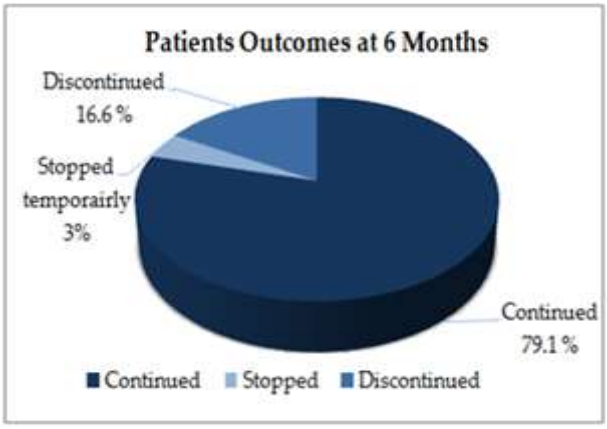

Figure-3: An overview of the side effect profile at 6 months.

Recent data examining toxicity of combination MTX + LEF are conflicting.

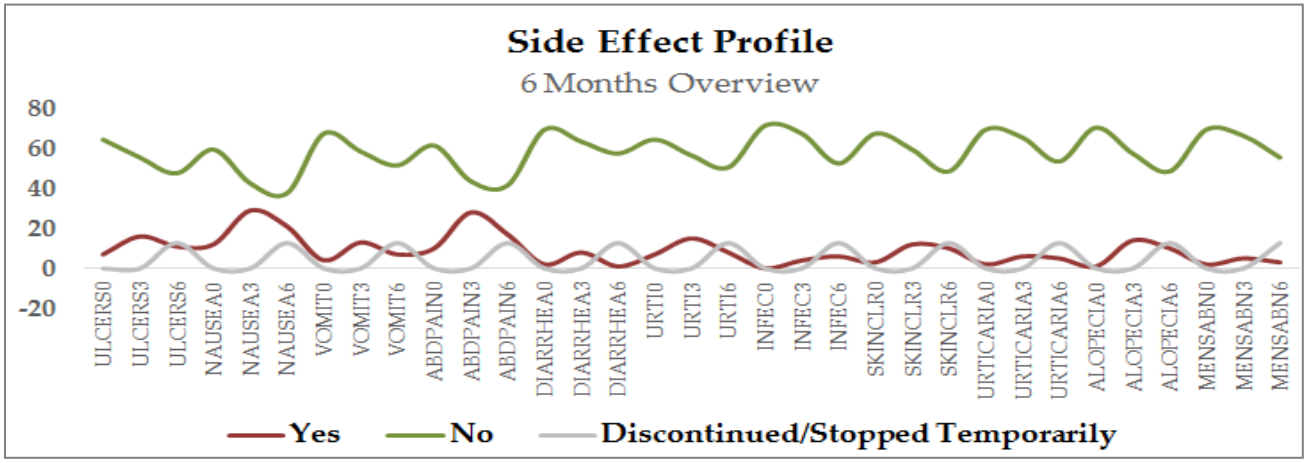

Figure-4: An overview of the side effect profile at 6 months.

Hensley[21] and Cubides et al[22] described their experience with combination MTX + LEF and reported no significant risk of elevated transaminases, hematologic disorders, or gastro-intestinal complaints. On the contrary, in the results of the corrona study done on North American population[8] which included patients with RA and psoriatic arthritis, up till 5 times increased risk of raised transaminases are documented. In our study, population performed

better than other study groups with only 2 permanent discontinuations of the combination therapy because of raised transaminases. Hence, a large sample size study is further needed in our setup to appreciate if any significant difference exists between Pakistani and North American population. There could be some protective influences of ethnicity on the degree of deranged ALT but that needs to be further explored.

In this study only one patient reported with MTX induced pneumonitis leading to discontinuation of the therapy. This patient was ultimately switched to alternate DMARD therapy. The risk of developing diabetes and dyslipidemias at the end of 6 months was not significant (p>0.05). Similarly, the risk of developing anemia or leukopenia secondary to the combination therapy was also insignificant (p>0.05). The frequencies of other adverse effects (rashes/urticaria, hair loss and menstrual abnormalities) observed were more or less similar to the data available from other studies[7,20].

At the completion of study, almost 80% patients continued the MTX+LEF combination therapy. Only 3% stopped temporarily whereas 16.6% had to stop the combination therapy completely. The main reasons for the discontinuations were diarrhea, severe oral ulcers, markedly raised ALT; each affecting 2 patients and severe vomiting, abscess, MTX Induced pneumonitis, severe chest infection; each in 1 patient. No life threatening opportunistic infection was noted. No death was reported.

The main limitation of this study was that the predominant study group was female so the applicability of the same adverse effect profile in male gender cannot be said for sure. Another limitation was that the duration of study is only six months, hence focusing only on short term safety profile. The long term side effects resulting from the use of MTX+LEF combination cannot be extrapolated and needs further extension of this primary study till atleast 24 months.

This study clearly represents the safety profile of MTX+LEF combination in RA patients in Pakistan at 6 months. The potential for liver toxicity cannot be ignored. Hence, careful patient selection is of paramount importance compounded with regular and vigilant monitoring. According to American College of Rheumatology (ACR) 2015 guidelines[14] for the management of RA, adverse effects should be monitored at 2–4 weeks for first 3 months, 8–12 weekly for 3-6 months and at every 12 weeks thereafter. Hence, this combination can be safely employed if one ensures vigilant and close monitoring of side effects as needed with other DMARD combinations. Utilizing this combination in developing countries would not only benefit patients but also save the costs of biologic therapy.

CONCLUSION

Methotrexate and leflunomide can be safely employed to treat patients with RA failing MTX monotherapy provided clinical and laboratory monitoring is ensured. Patients should be carefully selected before starting the combination therapy.

Disclosure

The preliminary results of partial research were presented as a poster presentation at 20th International Conference of Pakistan Society for Rheumatology, 2016 held in Karachi.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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