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Incidence and Severity Of Elevated Transaminases With Methotrexate And Sulfasalazine In Rheumatoid Arthritis Patients

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Abstract

Aim of the Work: Methotrexate and Sulfasalazine are immunosuppressive drugs which are used to treat Rheumatoid arthritis (RA). But both these are hepatotoxic, so a need arises to evaluate their harm, benefits and efficacy.

Materials and Methods: In this retrospective cohort study the incidence of transaminase elevation among patients on Methotrexate and Sulfasalazine drug was calculated. The association between the categorical variables and incidence of transaminase elevation is tested using Pearson Chi-Square test for variables and Chi-Square for trend is used. All p- values reported were based on two-tailed test and set at 0.05.

Result: Out of the 180 RA patients in each group, 73% in Methotrexate and 66.7% in Sulfasalazine group were females. The mean age of Methotrexate group: 53.65 $\pm$ 1.341years and Sulfasalazine group: 49.44 $\pm$ 1.898years. The incidence of elevated transaminases with Methotrexate and Sulfasalazine was 19.1% and 7.2%. Mean elevation from baseline was 6.89U/L (AST), 6.03U/L (ALT) with Methotrexate and 5.71U/L (AST) , 5.01U/L (ALT) with Sulfasalazine. Minimum dosage above which elevated transaminases was observed was 10mg weekly for Methotrexate and 1g BD for Sulfasalazine. Male gender, habituation to smoking and obesity status were found to be risk factors for transaminase elevation ($p<0.05$). No signs or symptoms of hepatotoxicity were noted among the patients.

Conclusion: Elevated transaminases were found to be more with Methotrexate irrespective of gender and habituation to smoking. But for obese patients, this incidence was higher for those on Sulfasalazine. Male gender, smoking habituation and obesity status were found to be predilections for transaminase elevation.

Keywords: Elevated transaminases, Methotrexate, Sulfasalazine, Rheumatoid Arthritis

Introduction

Rheumatoid arthritis (RA) is a severely disabling chronic inflammatory disease characterized by inflammation, persistent synovitis, progressive joint destruction, systemic and extra articular manifestations. [1] RA is also related to an increased mortality, and the expected survival of RA patients is likely to decrease by 3–10 years. [2]

Methotrexate (MTX) and Sulfasalazine (SSZ) are Disease Modifying Anti Rheumatoid Drugs (DMARDS) which are used routinely to slow the progression of the disease as they have immunosuppressive effects. Methotrexate, formerly known as Amethopterin, is a folic acid antagonist. It inhibits dihydrofolate reductase enzyme. Methotrexate is highly effective for a range of diseases. However, Methotrexate toxicity remains a germane situation and is one of the main reasons for its discontinuation. [3] The most frequent adverse effects are gastrointestinal, however hepatotoxicity is the most feared. In 2015, ACR recommended the use of MTX monotherapy as principle treatment in early naïve RA irrespective of its severity [4] and in 2019 EULAR recommended MTX to be part of the first treatment strategy. [5]

Sulfasalazine is a sulfa type DMARD which can decrease pain and swelling of arthritis, prevent joint damage and reduce risk of long term disability. The ingested Sulfasalazine reaches the large bowel, where colonic bacteria break it into Sulfapyridine and 5-Aminosalicylic acid. Sulfapyridine is mostly absorbed, acetylated by N-acetyltransferase 2 (NAT2) and eliminated in the urine. Although the hepatic side effects of SSZ are relatively less as compared to MTX, its use has been linked with hepatotoxicity, which seems to be underaknowledged; hence intensive monitoring and vigilance are very important.

Hydrochloroquine (HCQ) is another drug used to treat RA. The incidence of transaminase elevation with the use of HCQ is relatively low according to current literature however the drug is metabolized in the liver and may alter the metabolism of other drugs. [6] Leflunamide is mostly used as an add on drug in the management of RA, and this is also hepatotoxic, the transaminase levels are brought down by either reducing the dosage or by discontinuing the treatment altogether. [7]

Transaminase elevation is the elevation of liver enzymes, alanine transaminase (ALT) and aspartate transaminase (AST), in blood. It is indicative of liver damage and in its initial phase, it may be asymptomatic. The elevation of these enzymes can be monitored easily with a Liver Function Test (LFT) which can be performed quickly and is relatively cheap.

Normal values are 8-40 U/l for each. The normal values vary slightly depending on the testing centre, for this study the values have been taken from the diagnostic laboratory at Amrita Institute of Medical Sciences, Kochi. The incidence of elevation of transaminases can be extrapolated so as to associate it with hepatotoxicity in long term, though they are not being used as synonyms here. Comparison of this incidence for the two drugs might indicate the injurious potential. Outcome might vary for each individual depending on their genetic makeup, age, co morbidities, etc.

This study aims to compare the incidence of transaminase elevation with Methotrexate and Sulfasalazine in treatment of naive Rheumatoid Arthritis. This study also aims to identify the minimum drug dosage of Methotrexate and Sulfasalazine with which elevated transaminases has been observed. Further, the examination of the role of gender, habituation to smoking, obesity status in modifying the association with elevated transaminases will be assessed. There are few studies which compare these parameters between MTX and SSZ treated patients in association with transaminase elevation and no similar study has been conducted in the South Indian population

Methods:

This was a retrospective cohort study, conducted in a 1500 bed tertiary center in South India and had a total sample size of 360 subjects (180 for each drug). Patients who are/ were attending the rheumatology outpatient clinic with active RA but naïve to DMARD treatment initially were selected for this study. The serum transaminases levels were assessed in 4 stages- treatment naïve stage, at the end of first month after treatment initiation and at the end of second and then the third month.

The inclusion criteria were all patients over 18 years of age with active RA disease, fulfilling the

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American College of Rheumatology/ European League Against Rheumatism 2010 classification criteria for RA who were naïve to DMARDs before being referred here. Treatment was with either MTX or SSZ and no other drug associated with hepatotoxicity.

Exclusion criteria were patients with known pre-existing liver dysfunction, those consuming more than 14 units of alcohol per week alcohol (consuming less than 14 units of alcohol per week was found to be not associated with transaminitis in RA patients on DMARDs [10]) Patients with previously known systemic disorder involving the liver or any known genetic liver abnormality, patients with any other acquired cause which has predisposed the subject to hepatic damage prior to initiating the treatment, patients whose diagnosis is doubtful or controversial due to any cause or patients with baseline transaminase levels above 40 U/l. Computerized system which stores the history, records and reports of the patients which can be accessed for use by appropriate authority was utilized, the data was recorded. The data collected comprised of name, gender, age, occupation, BMI, co-morbidities, habituations (apart from alcohol consumption) transaminases levels in treatment naïve stage, and then for the subsequent 3 months along with dosage of the drug at the beginning of the respective month.

2.1 Ethical Clearance:

Ethical clearance was obtained prior to data collection from ethical clearance committee. The consent of all the patients who fulfilled the inclusion and exclusion criteria for the study was obtained.

2.2 Statistics:

Since no existing article related to 'Incidence and severity of transaminase elevation with Methotrexate and Sulfasalazine in Rheumatoid Arthritis patients' is available in literature so this study was preceded by a pilot study. 50 patients who fulfilled the inclusion and exclusion criteria, were selected. Of this, the number of patients on MTX and those on SSZ were noted. Transaminase elevation cases occurring with each was also noted down. Sample size was calculated using this data. The pilot study subjects were excluded from the main study.

The incidence of transaminase elevation among patients on MTX and SSZ drug was calculated. The association between the categorical variables and incidence of transaminase elevation is tested using Pearson Chi-Square test at 5% significance level for variables age and BMI Chi-Square for trend is used. All p- values reported were based on two-tailed test and the level of significance set at 0.05 (5%). All statistical analyses were performed using Statistical Package of Social Sciences (SPSS) version 23.0 (IBM SPSS statistics 23 for Windows, Version 18.0. Chicago: SPSS Inc.)

Result:

All the patients in this study were seropositive with active RA disease during the period of study. Out of the 180 Methotrexate treated RA patients the percentage of females was 73% and the rest were males. The mean age for this group was 53.65 ± 1.341years (the range of age 30-83 years). The BMI distribution of study population for Methotrexate group is given in Table I. Out of the 180 Sulfasalazine treated RA patients, the percentage of females was 66.7% and for males it was 33.3%. The age range was 25-72 years, the mean age being 49.44 ± 1.898 years. The BMI distribution of study population of Sulfasalazine group is given in Table I.

Table I: BMI distribution of MTX and SSZ treated RA patients

	Methotrexate		Sulfasalazine	
BMI category	**Frequency**	**Percentage**	**Frequency**	**Percentage**
Underweight	**19**	**10.1**	**11**	**6.1**
Normal	**36**	**20.2**	**41**	**22.8**

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BMI category	Methotrexate		Sulfasalazine	
	Frequency	Percentage	Frequency	Percentage
Overweight	46	25.3	43	23.9
Obese	79	44.4	85	47.2
TOTAL	180	100.0	180	100.0

The BMI reference: Underweight - <18.5; Normal – 18.5-22.9; Overweight – 23-27.5; Obese – >27.5. 44% of the study population on Methotrexate and 47.2% of the study population on Sulfasalazine were obese. 19.1% of Methotrexate treated RA patients and 7.2% of Sulfasalazine treated RA patients developed transaminase elevation. The incidence rate of transaminase elevation with Methotrexate was 0.43 person year (0.04 person month) and that with Sulfasalazine was 0.16 person year (0.01 person month). The mean AST and ALT values for the two study populations at the treatment naive stage and after the commencement of treatment at the end of each month for the next 3 months is given in Table II. Mean transaminase elevation in the period of study for MTX group was 6.89IU/L (AST) and 6.03IU/L and for patients on SSZ it was found to be 5.71IU/L (AST) and 5.01IU/L (ALT). The incidence of transaminase elevation at the end of each month of treatment for Methotrexate and Sulfasalazine treated patients is given in Figure I and II respectively.

Table II: Mean AST and ALT levels at treatment naive and at the end of each month of treatment for MTX and SSZ mono therapy study population

	Methotrexate		Sulfasalazine	
	Mean		Mean	
	AST (IU/L)	ALT (IU/L)	AST (IU/L)	ALT (IU/L)
Rx naive stage	20.25	19.34	23.72	22.45
End of 1st month	21.88	23.31	23.92	25.23
End of 2nd month	24.13	24.77	26.09	27.35
End of 3rd month	27.14	25.37	29.43	27.46

Rx naive – Treatment naïve; AST – Aspartate aminotransferase; ALT- Alanine aminotransferase

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Figure I: Transaminitis with Methotrexate for Each Month

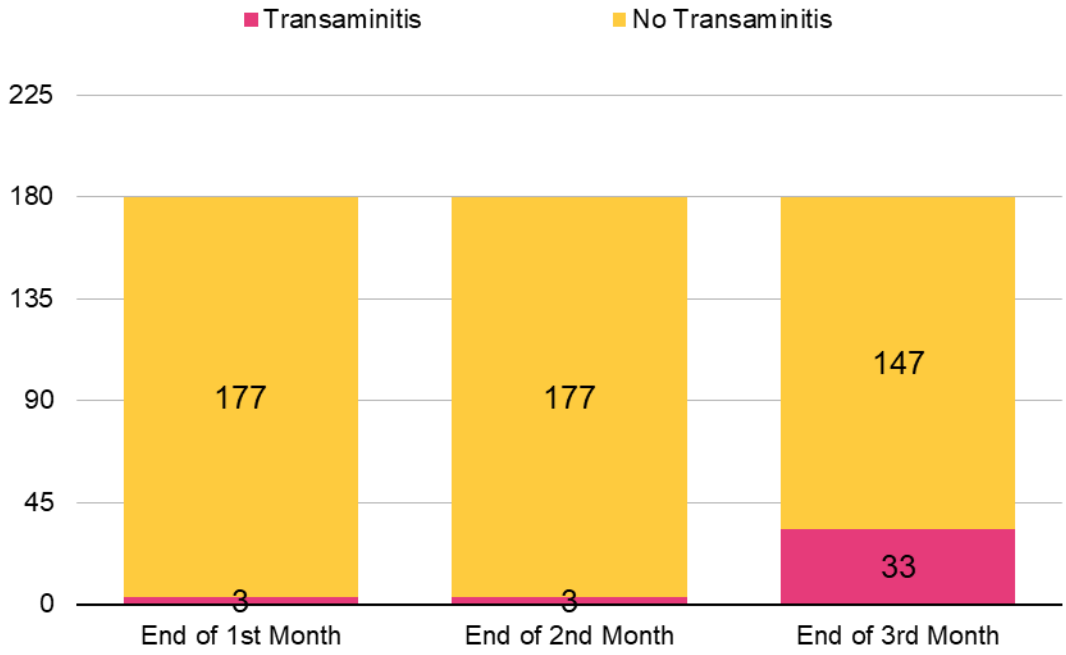
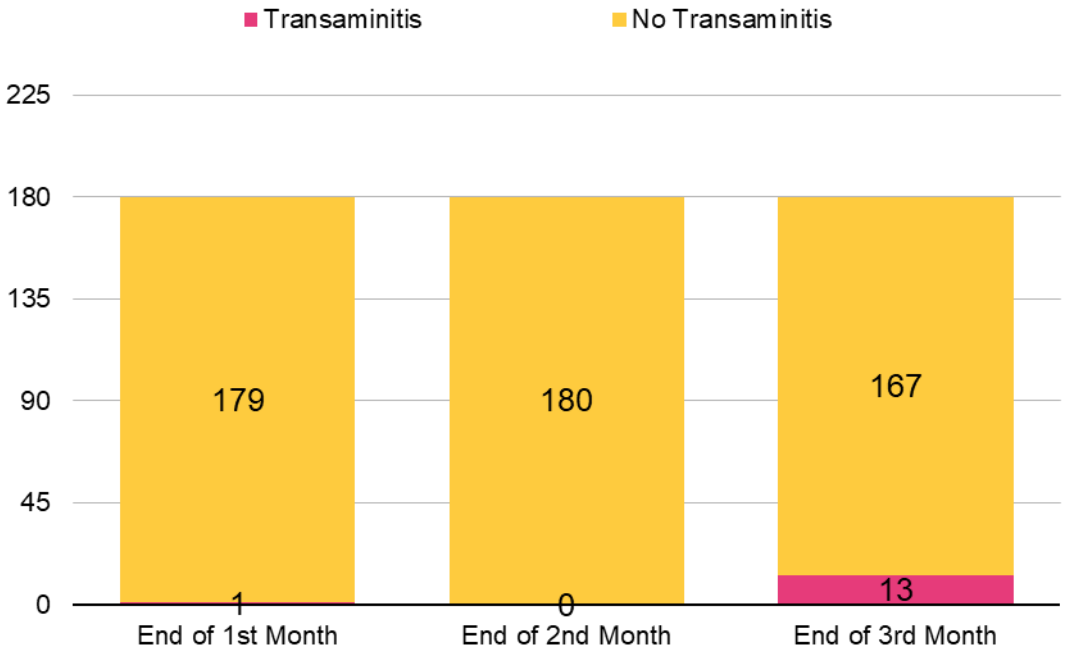


Figure II: Transaminitis with Sulfasalazine for Each Month



The minimum drug dose at which transaminase elevation is seen is 10mg weekly for Methotrexate and 1g BD for Sulfasalazine. Severity of elevated transaminases is given in Table III. It was found to be more with MTX than SSZ. For MTX patients who had moderate elevated transaminases the drug was stopped temporarily and for those who had mild elevation, either the dosage was decreased or it was kept the same and folic acid was added in their treatment. As the patients on SSZ had mild elevation, their treatment was either supplemented with folic acid or SSZ dosage was decreased.

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12% of females and 16% of males in the study population developed transaminase elevation at the end of 3 months. Among males the incidence of transaminase elevation was found to be 22.9% in Methotrexate treated population and 10% in Sulfasalazine group. Among females the incidence of transaminase elevation was found to be 17.7% in Methotrexate treated population and 6% in Sulfasalazine group.

Table III: Severity of transaminase elevation with MTX and SSZ

Severity of elevation	METHOTREXATE	SULFASALAZINE
No Elevated transaminases	81.1%	93.3%
Mild (1-2 times elevated)	16.9%	6.7%
Moderate (2-3 times elevated)	1.1%	0%
Severe (>3 times elevated)	0%	0%

1.1% of the study population on Methotrexate, with a minimum dosage of 10mg developed 2-3 times elevation in transaminase levels at some point in the duration of the study. 20.12% of obese patients in this study developed transaminase elevation. BMI distribution of transaminase elevation cases for MTX treated RA patients and for Sulfasalazine treated RA patients is given in Table IV and V respectively. 16.3% of people habituated to smoking developed transaminase elevation of which incidence of transaminase elevation among smokers on Methotrexate mono therapy was found to be 18% and for Sulfasalazine patients was 14%. Obesity ($x2=8.455$, $p<0.05$) and habituation to smoking ($x2=5.569$' $p<0.05$) were found to be factors associated with transaminase elevation among patients on MTX mono therapy. For patients on SSZ mono therapy, only habituation to smoking was found to be associated with transaminase elevation ($x2= 49.960$, $p<0.05$). The smoking habituations of RA cases who developed transaminase elevation on treatment with MTX and SSZ are given in Table VI and VII. The median Transaminase values for RA patients treated by MTX monotherapy and SSZ monotherapy are given in Figure III and IV. No signs or symptoms of elevated transaminases were reported among the patients during the period of study.

Table IV: BMI of patients who developed elevated transaminases after taking MTX

BMI percentage distribution	Elevated Transaminases Yes	No	Total	Chi Square value	P value
Underweight (<18.5) 3%	1 5%	19 95%	20 100%	9.719	0.021
Normal (BMI 18.5-22.9) 12%	4 11.1%	32 88.9%	36 100%		

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BMI percentage distribution	Elevated Transaminases Yes	No	Total	Chi Square value	P value
Overweight (BMI 23-27.5) 18%	6 13.3%	39 86.7%	45 100%		
Obese (BMI>27.5) 67%	23 29.1%	56 70.9%	79 100%		
Total	34 18.8%	146 81.2%	180 100%		

29.1% of obese patients developed elevated transaminases as compared to 11.1% of patients with normal BMI. Since p value is less than 0.05, it is significant

Table V: BMI of patients who developed elevated transaminases after taking SSZ

BMI	Elevated Transaminases Yes	No	Total	Chi Square value	P value
Underweight	1 9.1%	10 90.9%	11 100%	6.291	0.098
Normal	0 0%	41 100%	41 100%		
Overweight	2 4.7%	41 95.3%	43 100%		
Obese	10 11.8%	75 88.2%	85 100%		
Total	13 7.2%	167 92.8%	180 100%		

11.8% of obese patients developed elevated transaminases as compared to 0% of patients with normal BMI. Since p value is less than 0.05, it is significant

Table VI: Smoking habituations of patients who developed elevated Transaminases after using MTX

	Elevated Transaminases Yes	No		Chi Square value	P Value

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	Elevated Transaminases Yes	No		Chi Square value	P Value
Smoker	3 60%	2 40%	5 100%	5.569	0.018
Non-Smoker	31 17.7%	144 82.3%	175 100%		
Total	34 18.8%	146 81.2%	180 100%		

60% of smokers developed elevated transaminases as compared to 17.1% of non smokers who were treated using Methotrexate. Since p value is less than 0.05, it is significant

Table VII: Smoking habituations of patients who developed elevated Transaminases after using SSZ

	Elevated Transaminases Yes	No		Chi Square value	P Value
Smoker	6 66.7%	3 33.3%	9 100%	7.876	0.082
Non-Smoker	7 4.1%	164 95.9%	171 100%		
Total	13 7.2%	167 92.8%	180 100%		

66.7% of smokers developed elevated transaminases as compared to 4.1% of non smokers who were treated using Sulfasalazine. Since p value is less than 0.05, it is significant.

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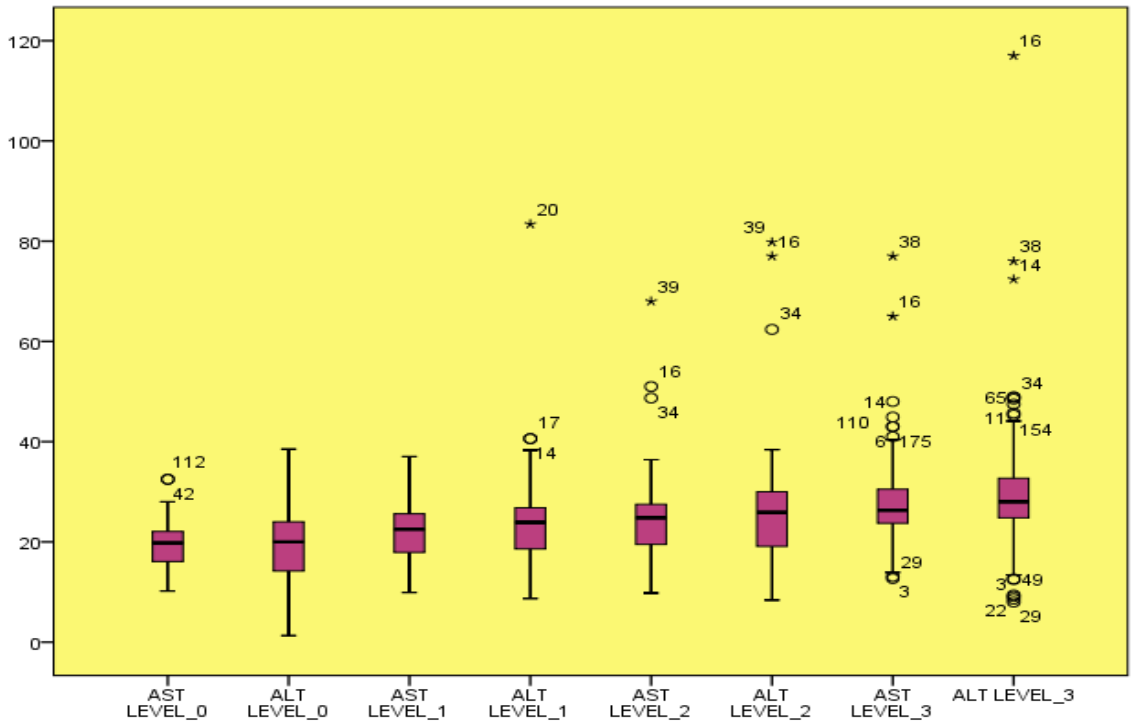
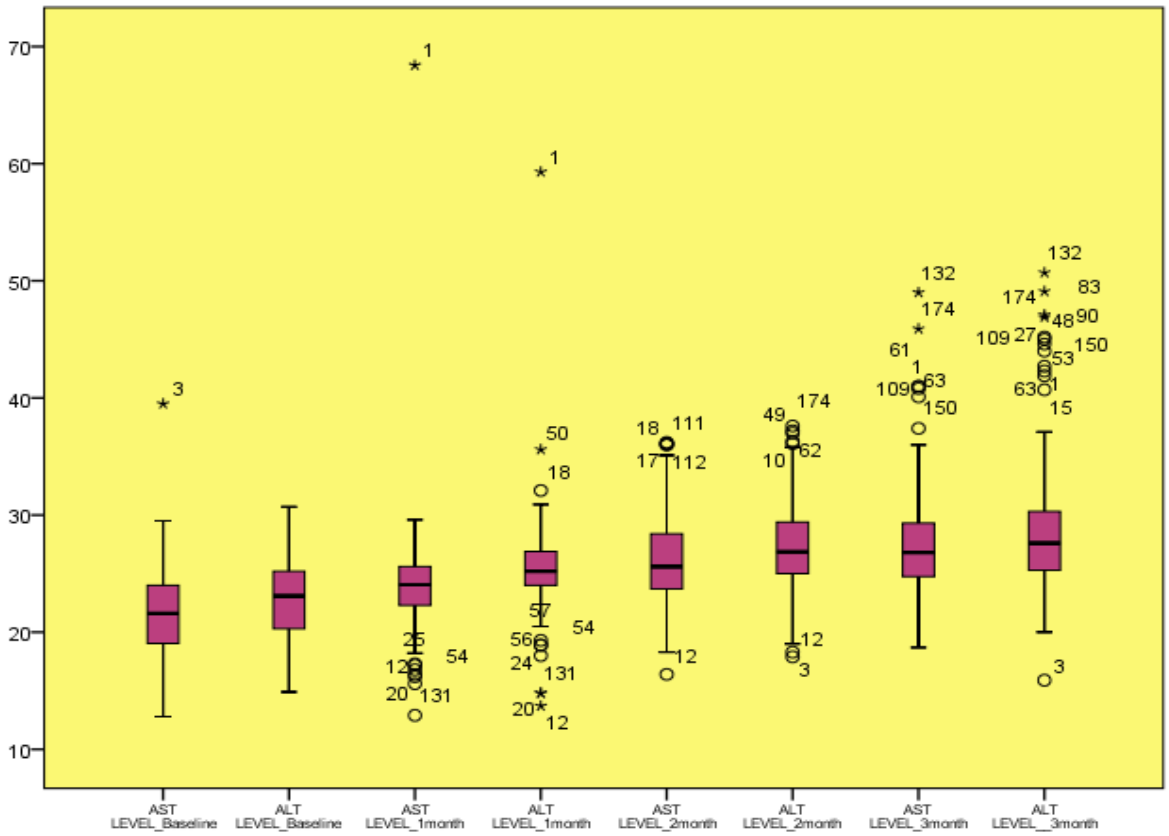
Figure III: Median transaminase values for Methotrexate mono therapy RA patients



The median Transaminase values for RA patients treated by MTX monotherapy are given in Figure III

Figure IV: *Median transaminase values for Sulfasalazine mono therapy RA patients*



The median Transaminase values for RA patients treated by SSZ monotherapy are given in Figure IV.

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Discussion:

This study reports on and compares the incidence of transaminase elevation with Methotrexate and Sulfasalazine in treatment naive Rheumatoid Arthritis patients in a Rheumatology outpatient department of a tertiary care hospital in Kerala and it tries to identify the safe dosage of Methotrexate and Sulfasalazine, the maximum dosage up to which transaminase values don't exceed 40 IU/L. Also it examines the role of gender, age, obesity status and smoking in modifying the association with transaminase elevation.

The incidence of transaminase elevation was found to be lower for SSZ as compared to MTX, though both are hepatotoxic drugs. The level of hepatotoxicity caused by each cannot be directly assessed. Transaminases level at treatment naïve stage and after 3 months of treatment with drug can indirectly indicate the injury to liver if transaminases value has increased. Mean transaminases value at the end of 3rd month of treatment had risen for both but it was net higher for MTX as compared to SSZ. It can be deduced that degree of transaminase elevation will be more with MTX. Hence transaminase elevation was found to be higher and more frequent with MTX than with SSZ. Paired T test was used to compare AST level and ALT level at treatment naïve stage and after 3 months of treatment and it was found to be statistically significant with $p<0.05$ for both MTX and SSZ. The difference of the means for AST and ALT each was found to be higher for MTX than for SSZ.

Incidence of transaminase elevation was found to be more among males than females. On comparing the incidence of transaminase elevation among males of the two drug groups, it was found to be greater for males on MTX than males on SSZ. On comparing incidence of transaminase elevation among females of the two drug groups, it was found to be more for MTX group.

Smoking and obesity status were found to be risk factors for developing transaminase elevation. Among those habituated to smoking, the incidence of transaminase elevation was found to be greater in patients on MTX mono therapy than those on SSZ. Transaminase elevation was found to be positively associated with increasing BMI. Among obese patients of the two groups, those on SSZ had a greater incidence of transaminase elevation than those on MTX.

The minimum dosage of drug with which transaminase elevation is seen was found to be 10mg weekly for MTX and 1g BD for SSZ. Above this dose transaminase elevation is seen but below this dose, the drug might not be efficacious enough, hence further research in this topic is required.

The incidence of transaminase elevation with MTX in this study was found to be higher than that of a study by Lindsay Tilling et al on incidence of transaminase elevation with MTX in RA and psoriatic arthritis patients (7.5%). [9] It was found to be comparable to a study done by Curtis et al, in which it was 22% [10] but it was found to be lower than a study by Hersh EM, et al 48.9%. [11] This might be due to the short period of observation (3 months) for this study as compared to the others. Also all the patients in our study were prescribed folate as a prophylactic measure, as this has shown to reduce the hepatic injury in some studies [12] which might have contributed to lesser cases of transaminase elevation in our study. Demographic and genetic constitution might also have had a role to play.

The incidence of transaminase elevation with SSZ in this study was higher than that of a study done by Jobanputra et al for which it was 0.4%. [13] Various factors like demographic, racial, genetic, different time periods, etc. might have been reasons for this discrepancy. Also, a study showed that the majority of transaminase elevation cases occurred within the first month of starting Sulfasalazine therapy, and these could present either as a hepatocellular or cholestatic pattern of liver injury. [14] In this study, the majority of cases of transaminase elevation were observed after the 3rd month of continuing with the treatment. This might have been because this dose was higher than the first month and also the duration of exposure to SSZ was longer, thereby having a cumulative effect. Both of these might have culminated in damage to the liver and hence resulting in more number of transaminase elevation cases after the 3rd month of treatment. Other factors like study population and its demographics might have had a role.

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Transaminase elevation among females on MTX (17.7%) was higher than SSZ (5.8%). A similar scenario was observed in case of males where 29.2% of males on MTX developed transaminase elevation as compared to 10% of males on SSZ.

Transaminase elevation was found to occur more among people belonging to obese category (in Asian BMI classification) on MTX as compared to those on SSZ. For MTX it was found that obese (67.6%) people have a higher incidence of transaminase elevation as compared to overweight (17.6%), normal (11.8%),and underweight (2.9%) people. The result shows that the incidence of transaminase elevation is positively associated with the increasing body mass index (BMI) of the subjects and the result was found to be statistically significant ($p<0.05$).

Although liver biopsy provides the most reliable information regarding organ damage, it is not without risk, and has cost implications. [15] Liver biopsy was not undertaken during the course of our study. Serum transaminases were used as an indication of liver injury. Our study has several limitations, some of which have been mentioned above. Potential confounding factors in this study include obesity, increasing age, diabetes, usage of NSAIDs, and co-existent diseases such as congestive heart failure and Sjögren's syndrome. This was a retrospective cohort study. We studied a small number of subjects, which may account for differences in incidence of transaminase elevation between our study and others, and which limits the generalisability of our findings. The level of disease activity and genetic constitution will be different in different subjects hence the dose given and toxicity due to it will vary. Also the treatment duration taken into consideration for this study was of three months and this might have also resulted in discrepancy between the observations from this study and those of others.

Limitations:

Serum transaminase elevation was used as an indicator of liver injury in this study but the gold standard is liver biopsy. The incidence of transaminase elevation in this study was found to be lower than certain other studies [9, 13, 14, 16] due to the shorter period of observation and folate prescription (reduces hepatic injury). [12] Demographic and genetic constitution might also have had a role to play.

Potential confounding factors in this study include obesity, increasing age, diabetes, usage of NSAIDs, and co-existent diseases such as congestive heart failure and Sjögren's syndrome. Further research needs to be done on this, which is for a longer duration of time and encompassing more subjects, which couldn't be done for this study due to time and resource constrain.

Conclusion:

Methotrexate had higher incidence of elevated transaminases than Sulfasalazine irrespective of gender and habituation to smoking. However this incidence in obese patients was more for those on Sulfasalazine. Male gender, habituation to smoking and obesity status were found to be associated with elevated transminases (more than 40U/L)

Reference:

1. Benowitz NL. Nicotine addiction. N Engl J Med. 2010 Jun 17;362(24):2295-303. doi: 10.1056/NEJMra0809890. PMID: 20554984; PMCID: PMC2928221.
2. Alamanos Y, Drosos AA. Epidemiology of adult rheumatoid arthritis. Autoimmun Rev. 2005 Mar;4(3):130-6. doi: 10.1016/j.autrev.2004.09.002. PMID: 15823498.
3. Weinblatt ME, Kaplan H, Germain BF, Block S, Solomon SD, Merriman RC, Wolfe F, Wall B, Anderson L, Gall E, et al. Methotrexate in rheumatoid arthritis. A five-year prospective multicenter study. Arthritis Rheum. 1994 Oct;37(10):1492-8. doi: 10.1002/art.1780371013. PMID: 7945475.
4. Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, Vaysbrot E, McNaughton C, Osani M, Shmerling RH, Curtis JR, Furst DE, Parks D, Kavanaugh A, O'Dell J, King C, Leong A, Matteson EL, Schousboe JT, Drevlow B, Ginsberg S, Grober J, St Clair EW, Tindall E, Miller AS, McAlindon T. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol. 2016 Jan;68(1):1-26. doi: 10.1002/art.39480. Epub 2015 Nov 6. PMID: 26545940.
5. Smolen JS, Landewé RBM, Bijlsma JWJ, et al EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic

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drugs: 2019 update Annals of the Rheumatic Diseases 2020;79:685-699.
6. Cheema B, Triplett D, Krishnamurthy P. Hydroxychloroquine-Induced Acute Liver Injury: 2306. American Journal of Gastroenterology. 2019 Oct 1;114(2019 ACG Annual Meeting Abstracts):S1286.
7. Gupta R, Bhatia J, Gupta SK. Risk of hepatotoxicity with add-on leflunomide in rheumatoid arthritis patients. Arzneimittelforschung. 2011;61(5):312-6. doi: 10.1055/s-0031-1296204. PMID: 21755815.
8. Humphreys JH, Warner A, Costello R, Lunt M, Verstappen SM, Dixon WG. Quantifying the hepatotoxic risk of alcohol consumption in patients with rheumatoid arthritis taking methotrexate. Annals of the rheumatic diseases. 2017 Sep 1;76(9):1509-14.
9. Tilling L, Townsend S, David J. Methotrexate and hepatic toxicity in rheumatoid arthritis and psoriatic arthritis. Clin Drug Investig. 2006;26(2):55-62. doi:
10. Curtis J, Beukelman T, Onofrei A, Cassell S, Greenberg J, Kavanaugh A et al. Elevated liver enzyme tests among patients with rheumatoid arthritis or psoriatic arthritis treated with methotrexate and/or leflunomide. Annals of the Rheumatic Diseases. 2009;69(01):43-47.
11. Hersh EM, Wong VG, Henderson ES, Freireich EJ. Hepatotoxic effects of methotrexate. Cancer. 1966 Apr;19(4):600-6. doi: 10.1002/1097-0142(196604)19:4<600::aid-cncr2820190420>3.0.co;2-3. PMID: 5933584.
12. Whittle SL, Hughes RA. Folate supplementation and methotrexate treatment in rheumatoid arthritis: a review. Rheumatology (Oxford). 2004 Mar;43(3):267-71. doi: 10.1093/rheumatology/keh088. Epub 2004 Jan 6. PMID: 14963199.
13. Jobanputra P, Amarasena R, Maggs F, Homer D, Bowman S, Rankin E, Filer A, Raza K, Jubb R. Hepatotoxicity associated with sulfasalazine in inflammatory arthritis: A case series from a local surveillance of serious adverse events. BMC Musculoskelet Disord. 2008 Apr 11;9:48. doi: 10.1186/1471-2474-9-48. PMID: 18405372; PMCID: PMC2329632.
14. Aithal GP. Hepatotoxicity related to antirheumatic drugs. Nat Rev Rheumatol. 2011 Mar;7(3):139-50. doi: 10.1038/nrrheum.2010.214. Epub 2011 Jan 25. PMID: 21263458.
15. Bridges SL Jr, Alarcón GS, Koopman WJ. Methotrexate-induced liver abnormalities in rheumatoid arthritis. J Rheumatol. 1989 Sep;16(9):1180-3. PMID: 2681761.
16. Björnsson ES. Hepatotoxicity by Drugs: The Most Common Implicated Agents. Int J Mol Sci. 2016 Feb 6;17(2):224. doi: 10.3390/ijms17020224. PMID: 26861310; PMCID: PMC4783956.

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