

To Study The Correlation Of First Line Antituberculosis Drugs Induced Peripheral Eosinophilia With Antituberculosis Drugs Induced Other Adverse Effects.

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Abstract: Antituberculosis drugs (ATT) results in adverse events leading to serious morbidity and discontinuation of drugs. Many ATT drugs cause eosinophilia but its correlation with adverse effects has not been well studied. **OBJECTIVES:** Primary: To study the correlation of first line ATT drugs induced peripheral eosinophilia with ATT induced other adverse effects. Secondary: To study the incidence of adverse effect and incidence of peripheral eosinophilia due to first line ATT drugs. **METHODS:** This is a prospective cohort study done at a tertiary care centre. Patients diagnosed with tuberculosis and started on first line ATT drugs were included in the study. Demographic details, history, physical examination, investigations like CBC, absolute eosinophil count, LFT, RFT, uric acid and fundoscopy were done. Patients were followed up at 2, 4, and 8 weeks. At each week they were monitored for adverse effects and blood samples for CBC, AEC, SGOT, SGPT, total bilirubin, uric acid, and creatinine were collected. **RESULTS:** The incidence of adverse effects was 66.12%. Significant adverse effects leading to change in treatment was seen in 37% cases. Eosinophilia was seen in 11.29 % cases. There was no correlation between eosinophilia and adverse effects. Eosinophilia was significantly associated with dermatological side effects (OR: 23.11, CI: 3.47 – 153.92). Adverse effects were more common in females (OR: 4.4, CI: 1.2 – 16.1). **CONCLUSION:** ATT induced side effects were not associated with eosinophilia except dermatological. Adverse effects were more often seen in female patients. Higher risk of hepatotoxicity due to ATT was noted. Pyrazinamide is mostly attributed drug leading to side effects leading to its discontinuation in one third cases. Adverse effects lead to modification of treatment in one third of cases.

Keywords: Antituberculosis drugs, adverse effects, peripheral eosinophilia

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I. Introduction

Tuberculosis is an infectious disease caused by Mycobacterium tuberculosis. In the present era, short course Antituberculosis treatment (ATT) with standard first line drugs, namely Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E) and Streptomycin (S) is the norm. These drugs constitute the essential components of DOTS (Directly observed treatment, short course) strategy for the control of TB as endorsed by World Health Organization (WHO)¹. ATT may result in adverse effects involving almost all systems in the body including gastrointestinal, liver, skin, nervous system, otovestibular apparatus and eyes. More than 25% of study patients on ATT report at least one type of reaction^{2,3,4}. There are several studies that have reported eosinophilia due to ATT^{5,6,7,8} but its incidence and correlation with adverse effects has not been well studied. Hence this study was planned to address this issue.

II. Material And Methods

Primary Objective: To study the correlation of first line ATT drugs induced peripheral eosinophilia with ATT induced other adverse effects. **Secondary Objectives:** To study the incidence of adverse effect of first line ATT drugs and to study the incidence of peripheral eosinophilia due to first line ATT drugs. **Primary outcome:** The correlation between occurrence of adverse effects and peripheral eosinophilia will be analyzed by an appropriate test for statistical analysis (Chi square test, Fisher exact test). **Secondary outcomes:** Incidence of adverse effect will be measured by the ratio of the number of patients with adverse events and total number of patients and Incidence of peripheral eosinophilia will be measured by the ratio of the number of patients with eosinophilia with total number of patients.

III. Definitions

Peripheral Eosinophilia: Peripheral eosinophilia will be defined as absolute eosinophilic count (AEC) of more than $0.5 \times 10^9/L^9$. **Tuberculosis:** The diagnosis of tuberculosis will be done on the basis of standard tests like Chest X-ray, Sputum studies (AFB smear and culture), Line probe assays like Genotype (Hains test, Germany) for rapid detection of Tuberculosis and Histopathology reports of extra pulmonary samples and confirmation will be done by expert chest physician. **Mild Transaminitis:** This is defined as rise in liver enzymes level (SGPT) > 45 IU but less than 135 IU¹⁰. **Significant Transaminitis:** Defined as SGPT more than 135 IU in presence of symptoms or >225 IU in absence of symptoms¹⁰. **Jaundice:** It is present when the bilirubin is more than 2 mg/dl or rise in TSB level 2 fold above the baseline¹⁰. **Hyperuricemia:** It is defined as the increase in uric acid level above 6.5 mg/dl¹¹.

IV. Methodology:

Study design: Prospective cohort study.

Study period: April 2013 to April 2014

Study Site: Department of Chest Medicine, Jaslok hospital and research centre, Mumbai, India.

Inclusion criteria:

Patients diagnosed with Tuberculosis (pulmonary or extra pulmonary) and started on first line ATT drugs. (Category 1 or 2 of RNTCP guideline)

Exclusion criteria:

1. Patients with peripheral eosinophilia at baseline.
2. Patients with Asthma and other atopic diseases.
3. Patients with any other significant cause for eosinophilia.
4. Patients on any drugs known to cause eosinophilia.

Methods

Patients fulfilling inclusion criteria with no exclusion criteria were invited to participate in the study. All patients were handed a patient participation information sheet either in English or in Marathi (Annexure 1, 3). They were explained about the study and their doubts were addressed satisfactorily. After obtaining informed written consent (Annexure 2, 4), patients were assessed according a structured proforma (Annexure 5). Demographic details, history and physical examination were recorded. Baseline investigations like CBC, absolute eosinophil count, LFT, RFT, uric acid and fundoscopy were done. Records were maintained in the proforma. Patients were followed up at 2, 4, and 8 weeks. At each week they were monitored for adverse effects and blood samples for CBC, AEC, SGOT, SGPT, Total Bilirubin, uric acid, and creatinine were collected. These data were recorded on follow up sheets. Standard laboratory technique was used for analysis of the test. AEC was done by manual count on a peripheral smear by a trained pathologist for better accuracy.

Ethical considerations

In the present study, patient with diagnosed tuberculosis and planned to start on ATT drugs were enrolled. The baseline investigations were done on the same day of enrollment and ATT was started without any delay. Regular follow up was ensured. The study protocol was submitted to Ethics committee of Jaslok Hospital and research institute. Study was started after obtaining clearance. Informed consent was taken from the parents/caretaker in English or Marathi. Three copies of the same were maintained for record.

Statistical methods

Sample size calculation:

With confidence limit of 95% and prevalence of adverse effects to be 25%, the sample size was calculated as $(3.814 \times p \times q) / d^2$ which came out to be 75.

During the entire study period, 70 patients were screened but only 62 patients were included in the study.

Statistical analysis:

All data was entered in MS Excel spreadsheet. Analysis was done using Epi info 7.1.1. Continuous variable are presented as mean (standard deviation) in case of well distributed data and median (Interquartile range) in skewed distribution respectively. Categorical data are presented as frequency (percentage). Analysis was done using 2×2 tables and the measures of association were analyzed by Odds ratio (confidence interval), Chi square or Fisher exact p value. P value below 0.05 was considered significant.

V. Result

A total of 70 patients were eligible for enrollment in the studies. But only 62 patients fulfilled the inclusion criteria. 7 patients were excluded due to history of allergic disorders like Asthma, allergic rhinitis, baseline eosinophilia or were on medication which can suppress eosinophilia like steroids. One patient did not give consent to participate in the study. There were no lost to follow up cases. Table 1 showing baseline characteristics of study population.

Table 1: Baseline Characteristics

Age (years)	34.27 (15.05)
Sex male	13 (20.97 %)
Female	49 (79.03 %)
Body mass index(kg/sqm)	21.73 (3.81)
Diabetes	6 (9.68 %)
Hypertension	3 (4.84 %)
Hypothyroidism	8 (12.9 %)
IHD	0

Continuous variables are shown as mean (standard deviation) and categorical variables are shown as frequency (percentages).

All 62 cases were enrolled after a diagnosis of tuberculosis was confirmed. Thirty cases had pulmonary tuberculosis out of which 26 were microbiologically confirmed and four patients were started ATT on clinic-radiological basis. Thirty two cases had extra pulmonary tuberculosis which included 19 patients of endometrial tuberculosis(endometrial biopsy PCR for Mtb positive), six with pleural effusion, six with cervical lymphadenopathy and one had spinal TB. All the cases were started on ATT. 56 cases received Category 1(HRZE) while 6 cases were started on Category 2(HRZES).

Fig 1: Diagnosis of patients enrolled in the study

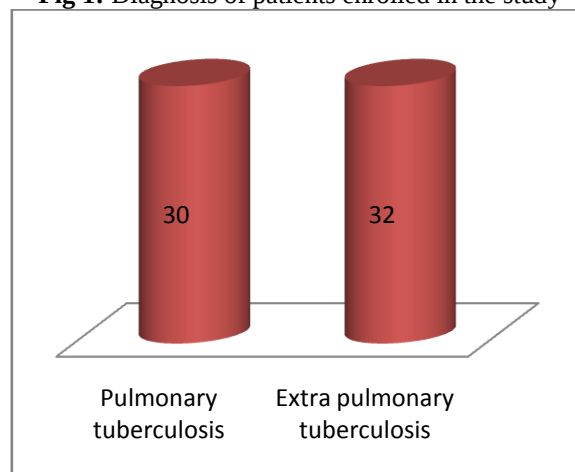


Table 2: Effect of Antituberculosis treatment on Hematology and biochemical parameters

Anemia	0
Leucopenia	0
thrombocytopenia	1
Eosinophilia	7 (11.29 %)
Mild transaminitis	11 (17.74 %)
Significant transaminitis	7 (11.29 %)
Hyperbilirubinemia	5 (8.07 %)
Hyperuricemia (n=58)	7 (12.07 %)
Renal dysfunction	0

Among 62 cases, eosinophilia was noted in 7 cases. **Incidence of eosinophilia was 11.29%.** Liver enzymes were mildly elevated in 11 cases (17.74%). Significant transaminitis was seen in 7 cases (11.29%). Hyperbilirubinemia was present in 5 cases. Uric acid was mildly elevated in 7 cases. No renal dysfunction was seen.

Table 3: Common clinical adverse effects due to Antituberculosis drugs (n=62)

Nausea	17 (27.42 %)
vomiting	18 (29.03 %)
Itching	9 (14.52 %)
Heartburn	8 (12.90 %)
Skin rashes	7 (11.29 %)
Joint pain	6 (9.68 %)
Vision problems	3 (4.84 %)
Pain in abdomen	2 (3.23 %)
Acne	2 (3.23 %)
urticaria	2 (3.23 %)

Forty one patients developed adverse effects due to ATT. **The incidence of adverse effects was 66.13%.** Nausea, vomiting and heart burn were the common symptoms after starting ATT. Itching and skin rashes were noted in 9 cases. Six cases developed joint pains. Few patients developed acne, urticaria and vision problems. In 23 cases the adverse effects were severe leading to modification of treatment regime.

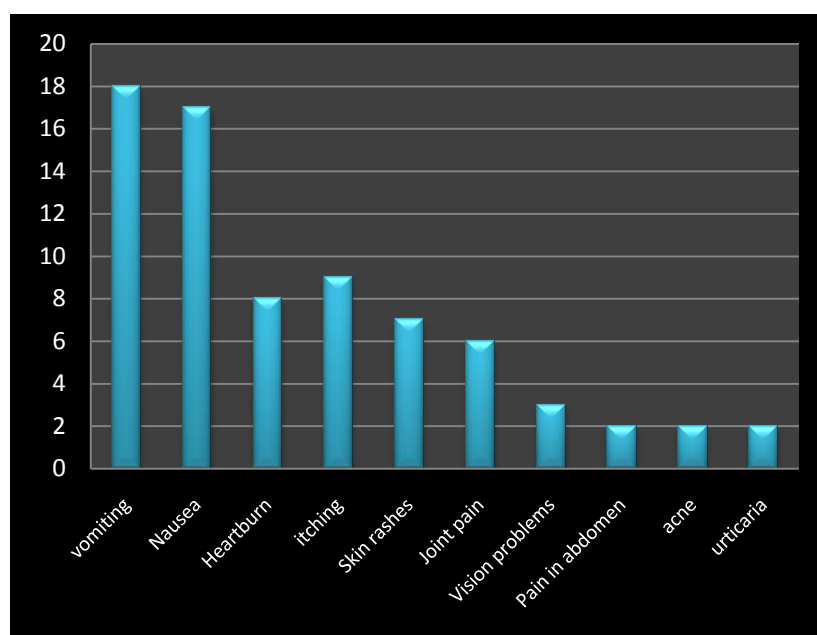


Fig 2: Common adverse effects noted on Anti tuberculosis treatment

Table 4: Uncommon clinical adverse effects due to Antituberculosis drugs (n=62)

Adverse effects	Frequency
burning sensation in soles	1
constipation	1
dizziness	1
drowsiness	1
eye heaviness, headache and facial swelling	1
Giddiness	1
heaviness of eye and pain	1
tinnitus	1

Fig 3: frequency of adverse effects as per drug

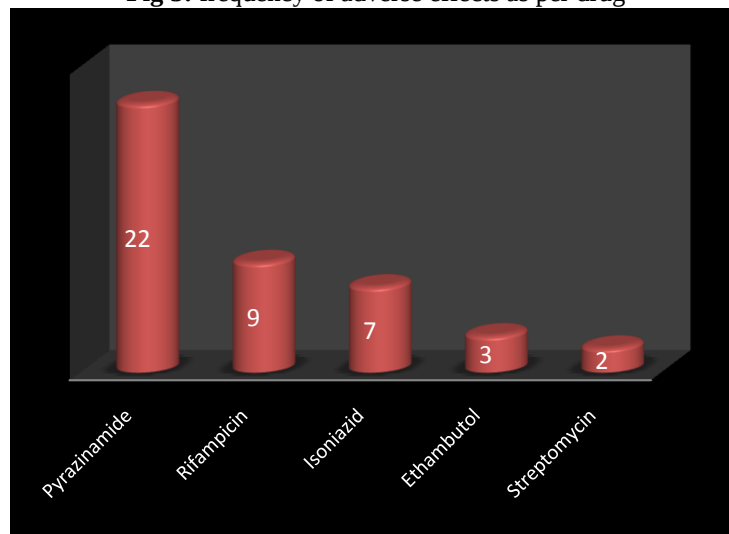


Table 5: Adverse effects due to individual drugs

Drug	Adverse effects
Pyrazinamide	Nausea, vomiting, heartburn (dyspepsia), joint pains, transaminitis, jaundice, hyperuricemia,
Rifampicin	Nausea, vomiting, transaminitis, jaundice
Isoniazid	Nausea, vomiting, transaminitis, jaundice, fever
Ethambutol	Vision disturbance, eye pain and heaviness
Streptomycin	Giddiness (vestibular toxicity)

Side effects were encountered in 41 patients (66.13%). In 18 cases, the side effects were mild and required no modification of the ATT regime. In 9 cases, the adverse events were serious enough to stop Category 1 and start on Modified ATT which included Ethambutol, Streptomycin and Levofloxacin. In 14 cases, the side effects were moderate which required discontinuation of at least one first line drug.

Table 6: Association of eosinophilia and adverse effects due to ATT

adverse effects			
Eosinophilia	1	0	Total
1	6	1	7
0	35	20	55
	41	21	62

	Point	95% Confidence Interval	
	Estimate	Lower	Upper
PARAMETERS: Odds-based			
Odds Ratio (cross product)	3.4	0.45	30.55(T)
Odds Ratio (MLE)	3.37	0.5315	83.16 (M)

STATISTICAL TESTS	Chi-square	1-tailed p	2-tailed p
Chi-square - uncorrected	1.35		0.24
Chi-square - Mantel-Haenszel	1.32		0.24
Chi-square - corrected (Yates)	0.54		0.46
Mid-p exact		0.14	
Fisher exact 1-tailed		0.23	0.40

No association was found between presence of eosinophilia and occurrence of side effects. Odds Ratio was 1.66 (CI: 0.29-9.36). p value by Fisher exact was 0.44 which is not significant.

Table 7: Association of eosinophilia with skin rashes

Eosinophilia			
skin rashes	1	0	Total
1	4	3	7
0	3	52	55
Total	7	55	62

Point		95% Confidence Interval	
Estimate		Lower	Upper
PARAMETERS: Odds-based			
Odds Ratio (cross product)	23.1111	3.4701	153.9230 (T)
Odds Ratio (MLE)	20.6181	3.0482	165.9838 (M)

STATISTICAL TESTS	Chi-square	1-tailed p	2-tailed p
Chi-square uncorrected	- 16.5644		4.81941E-05
Chi-square - Mantel-Haenszel	16.2973		5.53114E-05
Chi-square - corrected (Yates)	11.8056		0.000591691
Mid-p exact		0.000997738	
Fisher exact 1-tailed		0.00193128	0.00193128

Significant association was seen between eosinophilia and occurrence of skin side effects. The odds ratio was 23.11 (CI: 3.47 – 153.92). P value by Fisher exact test was 0.001 which was significant.

Table 8: Association of ATT induced side effects with sex

side effects			
female	1	0	Total
1	36	13	49
0	5	8	13
Total	41	21	62

Point		95% Confidence Interval	
Estimate		Lower	Upper
PARAMETERS: Odds-based			
Odds Ratio (cross product)	4.4	1.21	16.18 (T)
Odds Ratio (MLE)	4.25	1.20	18.14 (M)

STATISTICAL TESTS	Chi-square	1-tailed p	2-tailed p
Chi-square - uncorrected	6.4584		0.01
Chi-square - Mantel-Haenszel	6.3543		0.01
Chi-square - corrected (Yates)	4.9333		0.02
Fisher exact 1-tailed		0.019	0.022

Significant association was seen between female patients and occurrence of side effects. The odds ratio was 4.4 (CI: 1.2 – 16.1). p value by Fisher exact test was 0.02 which was significant.

VI. Discussion

The study has been done in a private healthcare setting catering mainly to urban population. Majority of the enrolled patients were female (79.03%). This disproportionate representation was mainly due to several cases of endometrial tuberculosis being referred from Obstetrics OPD for Antituberculosis treatment. These patients were treated for infertility, multiple abortions and ectopic pregnancy. The diagnosis of tuberculosis was based on endometrial biopsy being positive for TB-PCR.

Multiple case reports have reported incidence of eosinophilia with ATT drugs^{1-4,12-14}. There has been no previous study which studied the association of eosinophilia with side effects. We attempted to study the incidence and analyze the association of eosinophilia with different adverse effects. In the present study, eosinophilia was present in 7 cases i.e. incidence of 11.29%. There was no significant association of occurrence of side effects with onset of eosinophilia. Among 7 cases of eosinophilia, one case was asymptomatic, 4 cases presented with skin adverse events like rashes or itching or urticaria. In one case the rashes were severe enough to stop all the first line drugs and start on second line drugs. One case had joint pain attributed to Pyrazinamide requiring discontinuation of the drug. One patient manifested with mild transaminitis with significant symptoms requiring modified ATT. Eosinophilia was significantly associated with skin rashes. The reason for the association may be drug induced eosinophilia leading to skin manifestation. We did not find any case with DRESS (Drug induced eosinophilia with systemic symptoms). Only in two cases the side effects associated with eosinophilia were severe enough for modification of ATT.

Various studies have highlighted the adverse events with ATT^{15,16}. These side effects are many times trivial and do not lead to discontinuation of the treatment course. But in some cases can lead to discontinuation of one drug or stopping of all the drugs. In our study, adverse effects were noted in 41 cases (66%). In one third cases some modification was required. The incidence of side effects was higher compared to what has been reported in other studies^{15,16}. But the profile of side effects was similar to the observations made in these studies. The common adverse events were hepatotoxicity, GI upset, skin rashes and joint pain. In our study, the average mean of onset of adverse events was 16.3 days (SD: 14.53)

Hepatotoxicity is a serious adverse effect of ATT drugs¹⁰. In few cases it can lead to mortality due to liver failure. Close monitoring of the patient symptoms and timely investigations can help identify hepatitis at early stage and the physician can stop the culprit drug. As it is difficult to determine the exact drug which has caused hepatitis, the physician has to stop all the drugs, and then reintroduce one after another on weekly basis with careful monitoring of the liver enzymes. The incidence of hepatitis in our study was 29.03 %. It was significant only in 11.29 %. The incidence is much higher than compared to western data. But it is similar to incidence reported in other Indian studies^{17,18,19,20}. The high incidence in Indian population is probably due to higher prevalence of viral hepatitis. This is also relevant to other developing countries. Risk factors like past history of hepatitis, alcohol intake, older age, Hepatitis B infection, HIV infection should be assessed before starting treatment. In our study we did not analyze all the risk factors for drug induced hepatitis.

Koumbaniou C¹¹ reported the association between hyperuricemia and Pyrazinamide therapy. The author concluded that in all 20 cases, hyperuricemia was present but only one patient had presented with severe joint pain (arthritis). Our results showed less incidence of hyperuricemia. But all the patients were asymptomatic as shown in their study. This concludes that uric acid may not be monitored in all cases receiving Pyrazinamide except in patients with gout. Pyrazinamide should not be discontinued in cases that develop hyperuricemia.

Limitation of the study: Study population consisted more of female patients leading to gender bias.

VII. Conclusion

Multiple adverse effects are noted in Indian population on ATT drugs. The incidence is much higher than reported in western literature. Adverse effects leads to modification of treatment in one third of cases. It leads to significant morbidity. The side effects are not associated with eosinophilia; hence it cannot be used as a marker to predict the onset of adverse events. Dermatological side effects are associated with eosinophilia. Side effects are more often seen in female patients. Indian population is at higher risk of hepatotoxicity due to ATT. Pyrazinamide is mostly attributed drug leading to side effects leading to its discontinuation in one third cases.

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