A Randomized, Controlled, Phase III Clinical Trial to Evaluate the Efficacy and Tolerability of Risorine with Conventional Rifampicin in the Treatment of Newly Diagnosed Pulmonary Tuberculosis Patients

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Abstract

**Background:** The overall goals for treatment of Tuberculosis (TB) are to cure individual patient and to minimize the transmission of *Mycobacterium tuberculosis*. At the time of study conduction, the standard treatment for newly diagnosed tuberculosis patients consisted of an intensive phase for two months with four drugs (HRZE), followed by continuation phase for four months with two drugs (HR). Rifampicin, which is very effective against *Mycobacterium tuberculosis*, in both the phases of treatment, has certain concerns, which includes, decreased bioavailability with chronic use and hepatotoxicity. To overcome these concerns a new boosted formulation of Rifampicin (Risorine) with bio-enhancer Piperine was developed. Piperine has been found to increase bioavailability of several drugs including Amoxicillin, Cefotaxime, Theophylline and Propranolol. Risorine is a fixed dose combination that contains Rifampicin 200 mg + Isoniazid 300 mg + Piperine 10 mg.

**Aim and Objective:** The aim of the present study was to validate the therapeutic efficacy and tolerability of Risorine formulation containing regimen with a conventional regimen in the management of patients with newly diagnosed pulmonary tuberculosis.

**Methods:** Total 216 patients with sputum positive and treatment naïve pulmonary tuberculosis were enrolled in the study after fulfillment of inclusion / exclusion criteria. These patients were randomized to receive either a conventional anti-TB therapy (n = 117) or a similar regimen containing Risorine (n = 99) for 6 months. During the study period, symptomatic improvement, sputum conversion and radiological improvement were monitored at regular intervals.

**Results:** Of the 216 enrolled patients, 75% in the Risorine group and 79% in the control group completed the study. At 4 weeks the sputum conversion rate was significantly superior in Risorine group (93%) than

**Editorial Viewpoint**

- A new boosted formulation of Rifampicin (Risorine) with bio-enhancer Piperine is developed.
- Risorine is a fixed dose combination of Rifampicin 200 mg + Isoniazid 300 mg + Piperine 10 mg.
- In this study Risorine showed higher sputum conversion rate during the Intensive Phase which was maintained till the end of study.

**Introduction**

In India, more than 40% of population is infected with TB with very high mortality rate (2.2 lakhs compared to 1.1 million globally). The overall goal for TB treatment is to cure the individual patient, and to minimize the transmission. Earlier (at the time of study conduction), standard treatment approach for all adults with previously untreated TB consist of a 2-month initial phase of Rifampicin (R), Isoniazid (H),...
Pyrazinamide (Z), and Ethambutol (E) followed by a continuation phase with H and R for 4 months. Amongst all the first line anti-TB drugs; blood levels of Rifampicin are found to be most variable having evidences of sub-therapeutic serum levels too. Such sub-therapeutic serum levels lead to cases of therapeutic failure (non-conversion at 2 months of treatment) and relapse (reconversion at 6 months of treatment) as well as development of bacterial resistance. One of the pharmacokinetic study in pulmonary TB patients, after two months of daily therapy, it was found that 69% patients had $C_{\text{max}}$ below the reference range and 22% had very low $C_{\text{max}}$. Wide variation in $C_{\text{max}}$ (56%) and clearance (60%) of rifampicin was also reported by Israili ZH et al. The reasons for underlying decreased absorption of Rifampicin are:

a. Rifampicin induces its own metabolism

b. Rifampicin is potent inducer of mixed function oxidases as well as P-glycoprotein (P-gp)

Another area of concern is side effects; mainly hepatotoxicity, gastrointestinal disturbances (38% - 53%) and tolerance of Anti-TB drugs. The risk of hepatotoxicity in patients from India is higher than those reported in west (11.5 % versus 4.3%). Isolated Rifampicin-induced hepatic toxicity occurs in up to 2% patients whereas co-administered with INH and PZA, it is up to 28%. To overcome the limitations of conventional Rifampicin, AT - 3, Renowned formulation of Rifampicin with a bio-enhancer Piperine was developed by scientists at the Indian Institute of Integrative Medicine – IIIM, Jammu in collaboration with Cadila Pharmaceuticals Limited, Ahmedabad, which is currently marketed in India as “Risorine”. Risorine contains Rifampicin (200 mg), Piperine (10 mg) and Isoniazid (300 mg). Risorine was developed to provide more Rifampicin in blood compared to in Gastro-intestinal tract as well as maintaining the blood levels of Rifampicin on chronic therapy.

Piperine is very well studied bio-enhancer of various drugs, including Rifampicin. During the initial studies by scientist at IIIM revealed the bioavailability enhancing behavior of pepper. Various studies on active principle of peppers i.e. Piperine, revealed the potential of use as a bio-enhancer which demonstrated that Piperine enhances bioavailability of several drugs including Amoxicillin, Cefotaxime, Cycloserine A, Theophylline, Propranolol, Nevirapine etc. Zutshi et al had demonstrated significant increase in blood levels of Rifampicin when co-administered with Piperine as compared to Rifampicin 450mg alone in 14 pulmonary TB patients. Piperine enhances the bioavailability of drugs by:

- Inhibiting drug metabolizing enzymes in enterocytes, including cytochrome P-450 enzymes and uridine diphosphate-glucuronyl transferase, thus decreasing first-pass metabolism of drugs
- Inhibiting P-gp in enterocytes and thus inhibiting efflux of absorbed drugs from enterocytes

During pre-clinical studies, piperine was not associated with any abnormalities related to growth, organ weight ratio or blood chemistry even at higher dose (500 mg/kg). The same were not found even during autopsy and microscopic examination. Piperine 10 mg was found optimum with rifampicin 200 mg during Phase I pharmacokinetic (PK) study. During Phase I studies, PK profile of Risorine (Rifampicin 200 mg and Piperine 10 mg) was identical with Rifampicin 450 mg alone on first day; while reduced blood levels were observed in Rifampicin 450mg on day 14, but not with Risorine. Pharmacokinetics of other anti TB drugs like, Isoniazid and Pyrazinamide, were also unaffected with concomitant administration of Risorine.

In a phase II randomized, double blind, comparative clinical trial was conducted in Category I, sputum smear-positive and radiologically confirmed pulmonary TB patients, Risorine containing regimen was shown to be as efficacious as the standard WHO anti-TB regimen without any additional adverse effects. Also Rifampicin blood levels were found to be reduced over 6 month’s treatment with rifampicin 450mg but not with Risorine formulation.
To confirm the above findings and to validate the therapeutic efficacy and tolerability of Risorine containing regimen against conventional regimen in patients with newly diagnosed pulmonary TB, this Phase III study was planned. Upon positive outcome it may result in considerable dose reduction and consequently the cost of active drug i.e. Rifampicin.

Later on, Vora et al had demonstrated efficacy of Risorine in drug susceptible pulmonary TB patients. Risorine was found highly effective and well tolerated in the treatment of drug – susceptible pulmonary TB patients who developed GI intolerance with standard WHO anti TB treatment.¹⁰

**Material and Methods**

**Study Design**

The present study was a randomized, triple-blind, parallel-group, multicenter, comparative clinical trial of experimental treatment (AT-3, Ethambutol and Pyrazinamide) versus WHO standard treatment. With regard to blinding, patients, investigators, as well as other study personnel were completely blinded of treatment allocations. This study consisted of two phases – an intensive phase of 2 months followed by a continuation phase of another 4 months. The study was carried out at 3 centers in India. The detailed regarding the study design and study medication administration was described in below Figure 1.

**Patient population**

Two hundred and sixteen (216) newly diagnosed pulmonary tuberculosis patients were enrolled at 3 centers in India, namely, Jammu, Bangalore and Ahmedabad. Having read, all patients signed informed consent form, which was duly approved by Institutional Ethics Committees. Eligibility criteria for enrollment in the study included:

- Patients of either sex
- An age of 15 to 50 years
- Weight not less than 30 Kg
- Only newly diagnosed, sputum positive case (fresh case) of pulmonary tuberculosis
- Patients with minimal to extensive severity of disease were included with confirming radiological diagnosis
- A serum aspartate transaminase (AST or SGOT) and serum alanine transaminase (ALT or SGPT) level less than 3 times the upper limit of normal (ULN)
- A serum total bilirubin level of less than 2 times the ULN
- A serum creatinine of less than 3 times the ULN

Patients were retained indoor for at least one month of the initial period. Although, patients were encouraged to stay in the study throughout the initial and continuation phases, however, all withdrawals were completely voluntary.

It was confirmed that all patients included in this study were free from other diseases and disorders, such as HIV infection, seizure disorder, diabetes mellitus, congestive cardiac failure, hypertension, malignancy, chronic lung disease, abnormal hepatic, renal or hematologic functions, and retinopathy. Patients were ineligible if they had a history of MDR-TB or close contact with an MDR TB patient, >3 weeks of continuous ant-TB treatment immediately prior to enrollment, >2 months of anti-TB therapy in

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**Figure 1: Study Design and Flow Chart**

- **Total patients enrolled = 216**
- **Randomization**
  - **Experimental Group (n = 99)**
    - One capsule of AT-3 + Ethambutol 15mg/kg + Pyrazinamide 25 mg/kg
    - Withdrawals (n = 24)
      - 1 HIV Positive
      - 1 Death due to excessive hemoptysis
      - 22 Defaulters
    - 75 patients completed Intensive Phase
    - One capsule of AT-3
      - 01 Defaulter
    - 74 patients completed the study
  - **Control Group (n = 117)**
    - One capsule of Rifampicin 450mg and Isoniazid 300mg + Ethambutol 15mg/kg + Pyrazinamide 25 mg/kg
    - Withdrawals (n = 18)
      - 18 Defaulters
    - 99 patients completed Intensive Phase
    - One capsule of Rifampicin 450mg and Isoniazid 300mg
    - Withdrawals (n = 07)
      - 07 Defaulters
    - 92 patients completed the study

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the past 2 years, pregnancy, or exclusively extrapulmonary TB. Patients were also excluded if they had hypersensitivity to any of the study drugs or the excipients used in their formulation; were seriously ill; had undergone organ transplantation and/or were receiving immunosuppressive drugs; received systemic corticosteroids for more than 7 days within the past one month; had a history of alcohol or drug abuse; were non-compliant to the protocol requirements. Pregnant or lactating females or women of child bearing age not following barrier contraception or on oral contraceptives were not included in the study.

Pulmonary TB disease was classified based on intensity of disease as +1 (minimal lesions: infiltration not more than one zone, without cavity), +2 (moderate disease: total extent of disease more than one zone but less than total volume of one lung; cavity size less than 4 cm), +3 (advanced diseases: area involvement more than one lung with cavitation) and +4 (far advanced disease: bilateral involvement with cavities – size more than 4 cm).

**Study Outcome Measures**

In the initial phase, the primary outcome measure was sputum conversion. If a patient could not induce or produce sputum, then it was considered a negative sputum culture. The secondary outcome measures included sputum smear conversion, clinical response, survival, and adverse events.

In the continuous phase (the 16 weeks period after the 8 weeks of intensive phase with 4 drugs), the primary outcome of the study was treatment failure (during therapy) or relapse (within 4 months after completion of therapy). Treatment failure was defined as two or more positive *M. tuberculosis* cultures at least 1 month apart, with no intervening negative cultures, after the patient completed at least 2 months in the study and was still receiving anti-TB therapy. Relapse was defined two ways: (1) a positive *M. tuberculosis* culture (of sputum or another specimen) after the patient’s sputum culture had converted to negative and the patient had completed treatment or (2) a positive culture after the patient’s symptoms/signs of clinical pulmonary tuberculosis resolved and the patient completed treatment.

Secondary endpoints of the continuation phase of the study included adverse events or death. Adverse events that occurred during receipt of study medication and for 8 weeks after its discontinuation were graded on a 5-point scale.

In this study, “cure” has been defined as a patient who is sputum smear-negative in the last month of treatment and on at least one previous occasion. Definition of treatment completed refers to a patient who has completed treatment but who does not meet the criteria to be classified as a cure or a failure. Treatment success is defined as the sum of patients cured and those who have completed treatment.

**Evaluation and Follow-up**

Study visits were scheduled at weeks 2, 4, 6, and 8 during the initial phase and months 1, 2, 4, 6, 8, and 10 and every 4 weeks thereafter during the continuation phase.

The Baseline (screening) visit included laboratory tests involving blood, sputum (for consecutive days) and urine, physical examination including vitals, chest X-ray (PA view), pregnancy test for female patients and medical history for the patients. Laboratory examinations [blood and sputum (for two consecutive days) analysis], physical examination including vitals, concomitant illness, concomitant illness and medications were performed for each patient for all the visits after randomization. Chest X-ray (PA view) was performed at the end of initial phase and continuous phase.

Patients were provided with a ‘Study Diary’ that contains a calendar to record medication intake, visit dates for her/his duration of the study, and names and telephone numbers of the study site personnel to report problems or adverse events.

Specific adverse events (AEs) and adverse drug reactions (ADRs) were recorded at all times throughout the study. Routine examinations for AEs and ADRs related to sensitivity reactions (including cutaneous hypersensitivity), gastrointestinal, hepatic, renal or ophthalmic systems, drug fever, breast tenderness, and any other were performed and recorded during the study.

**Withdrawal Criteria**

Patients were withdrawn in case of a serious adverse event; non-compliance with protocol specifications, including non-intake of study medication for more than 15 days during the Intensive Phase or for more than 1 month during the Continuation Phase; if diagnosed as MDR-TB; were sputum smear positive at the end of 3 months and if AST, ALT and ALP levels are more than 5 times the upper limit of normal or serum bilirubin is >2mg/dl.

**Sample Size Calculation**

A sample size of the study was calculated based on an effect size and variation experienced in previous Phase-II studies with the same experimental and control administrations. The level of significance and statistical power were fixed at 0.05 (two tailed) and 80%, respectively. The sample size was calculated to be a total of 220 patients needed to complete the study. In fact, it was decided to enroll 300 patients to account for a relatively high dropout rate.

**Statistical Methods**

Comparisons of treatment groups were made by means of the Fisher’s exact test, Student’s *t*-test, and Wilcoxon rank-sum test,
Table 1: Baseline characteristics of evaluable subjects in experimental (E) and control (C) groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Across all centers</th>
<th>E</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>74</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>Age 29.14±9.57</td>
<td>30.05±11.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight 42.07±6.03</td>
<td>42.77±6.96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extent of disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal (+)</td>
<td>4 (05.41%)</td>
<td>2 (02.17%)</td>
<td></td>
</tr>
<tr>
<td>Moderate (++)</td>
<td>42 (56.76%)</td>
<td>41 (44.57%)</td>
<td></td>
</tr>
<tr>
<td>Advanced (++++)</td>
<td>14 (18.92%)</td>
<td>18 (19.57%)</td>
<td></td>
</tr>
<tr>
<td>Far advance (++++)</td>
<td>14 (18.92%)</td>
<td>31 (33.70%)</td>
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</tr>
</tbody>
</table>

Table 2: Change in weight (Mean ± SD) in evaluable patients in both, Experimental (E) and Control (C), groups

<table>
<thead>
<tr>
<th>Treatment duration</th>
<th>All patient</th>
<th>Experimental group (E)</th>
<th>Control group (C)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
<td>Weight gain from baseline to 4 week</td>
</tr>
<tr>
<td></td>
<td></td>
<td>42.46±6.64</td>
<td>1.84±6.59 (p = 0.0115)</td>
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<tr>
<td></td>
<td></td>
<td>44.30±6.53</td>
<td>45.70±6.59</td>
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<tr>
<td></td>
<td></td>
<td>44.05±6.15</td>
<td>1.99±6.1 (p = 0.0492)</td>
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<tr>
<td></td>
<td></td>
<td>45.43±6.3</td>
<td>45.91±6.84*</td>
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<td></td>
<td></td>
<td>44.92±6.84</td>
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<td></td>
<td></td>
<td>47.77±6.53</td>
<td>2.07±6.65 (p = 0.0051)</td>
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<tr>
<td></td>
<td></td>
<td>47.77±6.99</td>
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<tr>
<td></td>
<td></td>
<td>1.86±6.69 (p = 0.0644)</td>
<td></td>
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<tr>
<td>Overall weight gain from baseline to 24 weeks</td>
<td>5.70±6.63 (p &lt; 0.0001)**</td>
<td>4.99±6.83 (p &lt; 0.0001)**</td>
<td></td>
</tr>
</tbody>
</table>

Results

A total of 216 patients were enrolled in the study across three centers; Jammu (n=60), Ahmedabad (n=91) and Bangalore (n=65). Of these 216 patients, 99 patients were assigned in the experimental group (AT-3), whereas 117 patients were allocated in the control group. Seventy four (74.75%) and ninety two (78.63%) patients completed the 24 week of therapy among the experimental and control group, respectively.

The reason for withdrawal were a) non-compliance with protocol or lost to follow up (48 patients); b) HIV positive patient (01 patient); and c) death (01 patient in experimental arm due to excessive hemoptysis during intensive phase).

Patients Demographics and Baseline Characteristics

Overall mean age of all participants was 29.6 (± 10.6) years and mean baseline weight was 42.5 (± 6.6) Kg. Similarly, 80.7% and 19.3% of patients were male and female among both the groups. The baseline patient characteristics of age and weight were statistically insignificant and comparable among the two treatment groups. Baseline characteristics of patients along with the extent of disease were shown in Table 1.

There was no significant difference in either the number of patients or the number of doses administered between the groups. Patient’s compliance to treatment regimen was similar for both daily and intermittent doses.

Clinical Efficacy

Experimental arm shown higher sputum conversion at 4 weeks, i.e. in 93.22% patients, while in control group sputum conversion was observed in 83.75% patients. The clinical improvement in all the patients appears almost equivalent at 4 weeks in both the treatment arms. But a striking difference was observed in experimental arm with AT – 3 at 8 weeks where 10 patients got complete cure. On other hand none of the patients in control group showed such improvement. Even at the end of 24 weeks of treatment, striking difference was maintained. The cure rate observed at the end of 24 weeks was 91.89% in the experimental group and 81.52% in the standard therapy group (Figure 2).

Effect on Weight Gain

Average weight of all patients was 42.07±6.03 in experimental group and 42.77±6.96 in control group. The difference between two groups is not statistically significant at baseline. Weight gain observed from baseline to 4 weeks of treatment and from 8 weeks to 24 weeks of treatment to end of treatment was statistically significant in experimental group while it was non-significant in control group. At the end of 24 weeks the weight gained was 5.70±6.63 Kg in experimental group and 4.99±6.83 kg in control group which is statistically significant (Table 2).

Safety and Tolerability

Both regimens were very well tolerated during the entire study period. However, in control group, total 9 patients reported with elevated liver function tests, which include 7 patients having elevated SGOT, 1 patient having elevated
SGOT and Bilirubin and 1 patient having elevated all three liver parameters. While in experimental group only 3 patients reported SGOT elevation. Out of these 12 patients, 1 patient from the control group with elevated all three liver parameters was discontinued from the trial whereas rest 11 were continued till end of study.

**Discussion**

Rifampicin along with Isoniazid form the backbone of anti-tubercular therapy. Rifampicin, while very effective against *M. tuberculosis*, in both initial and continuous phases of therapy has certain concerns. The bioavailability of Rifampicin is reduced on chronic therapy. Rifampicin clearance increases during multiple dose therapy due to its known induction of hepatic enzymes, which leads to auto-induction of its own metabolism. Another area of concern is hepatotoxicity. The treatment often produces severe hepatotoxicity and potentiates the same problem caused by Isoniazid. This may lead to discontinuation of therapy. To overcome these concerns a boosted formulation of Rifampicin with a bio-enhancer Piperine was developed. Piperine has been found to increase bioavailability of several drugs including Amoxicillin, Cefotaxime, Cycloserine A, Theophylline, Propranolol, Nevirapine etc. To the best of our knowledge, there are no previous attempts of increasing the bioavailability of Rifampicin to demonstrate its utility in a reduced dose for efficacy for the treatment of new TB patients.

In previous preclinical studies, different doses of piperine ranging from 1 mg to 40 mg were experimented with Rifampicin (40 mg/kg) in rats. The plasma Rifampicin levels were determined at possible peak timings of 2 and 4 hours post-dosing. It was revealed that though the bioavailability enhancing effect of piperine commences from 1 mg dose itself but the maximum effect becomes noticeable from 3 mg onwards. It stabilizes at 5 mg and is maintained up to 20 mg dose where after a decline in its effect is observed. In yet another unpublished study in rats, it was found that addition of piperine reduces the ED_{50} of Rifampicin in these animals by 50%. This was later on used to formulate AT-3 wherein only 200mg of Rifampicin was used together with 300 mg Isoniazid to replace 450 mg Rifampicin and 300 mg Isoniazid.

Risorine was underwent the various stage of development before conducting Phase III clinical trial. Pre-clinical studies demonstrated that Risorine did not cause any abnormalities in general growth, body to organ weight ratio or blood biochemistry. During clinical phase I and phase II studies, pharmacokinetic profile was found to be similar as conventional Rifampicin 450 mg on day 1 while no change was observed in serum level with Risorine as compared to reduce levels with Rifampicin 450mg on chronic therapy, while no effect on co-administered other anti TB drugs. Also during Phase II study, it was found that Risorine containing regimen was as efficacious as the standard WHO anti-TB regimen without any additional adverse effect. Based on the results of Phase II study, Phase III study was planned to confirm the findings of Phase II study.

We assessed the efficacy and safety of a regimen containing AT-3 in comparison to the standard WHO regimen among newly diagnosed pulmonary TB patients. The study treatment included initial phase of 8-week treatment with either AT-3 plus Ethambutol and Pyrazinamide in experimental group or standard WHO regimen of Rifampicin, Isoniazid, Ethambutol and Pyrazinamide in control group. This was followed by continuation phase of 16-week treatment with either AT-3 in experimental group or standard WHO regimen (Rifampicin + Isoniazid) in control group.

A total of 216 patients were enrolled in the study across three centers; 99 patients in the experimental group (AT-3), whereas 117 patients in the control group (Standard WHO dose). The proportion of patients withdrawn or missing at the end of 24-week of treatment, the corresponding rates were 25.25% and 21.37%, respectively. The observed sputum conversion rate was 92.75% in the experimental group and 85.39% in standard therapy group at four weeks. The cure rate observed at the end of 24 weeks was 91.89% in the experimental group and 81.52% in the standard therapy group. Early sputum conversion was found in Risorine group which was maintained throughout the study period. At the end of the study, cure rate was found to be higher with Risorine group.

Both regimens were well tolerated with gastrointestinal side effects being the most common. Adverse events were of mostly mild to moderate severity. Elevations in SGOT, SGPT and total bilirubin were observed among 09 patients at the end 4th week of treatments in control group which was significant when compared to 03 patients in experimental group. Also 01 patient having elevated levels of all three parameters was discontinued from the study.

Later on, role of Risorine in the treatment of drug susceptible pulmonary TB was assessed by Vora et al. In that study, 33 pulmonary TB patients who could tolerated the conventional treatment with Rifampicin 450mg were given Risorine treatment. Out of 27 patients who were sputum positive at beginning of treatment, 24 of them became sputum negative at two months, one at three month and remaining two became sputum negative at six month of treatment. Out of 33 patients, only two patients developed nausea which was subside spontaneously and
one HIV positive patient developed hepatitis.

**Conclusion**

Rifampicin is key drug in drug susceptible TB management, simultaneously associated with low blood levels and adverse effects. These short falls associated with non-conversion and non-compliance leads to treatment failure and development of drug resistance TB. Risorine provides more Rifampicin in blood compared to GI tract as well as maintaining higher blood levels on chronic therapy compared to conventional Rifampicin. Further Risorine does not affect the pharmacokinetics of other co-administered anti TB drugs. Risorine provided higher sputum conversion during intensive phase and better cure rate at the end of treatment than conventional Rifampicin with better safety profile. Also Risorine was found to be highly efficacious and safe even in the drug susceptible pulmonary TB patients who cannot tolerated conventional Rifampicin. In conclusion, Risorine appears to be an effective and useful alternative to Rifampicin 450mg and Isoniazid 300mg in multi-drug regimens for drug susceptible pulmonary TB treatment.

**Acknowledgement**

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**Conflicts of Interest**

Laxaman Y, Shah Kusumben, Zutshi RK and Singh Rajinder all had contributed to the conduction of the study. Patel Naresh, K Jagannath, Vora Agam, Patel Mukesh and Patel Anand had contributed towards data analysis and manuscript preparation / revision and final approval of the manuscript.

**Key Highlights**

- Rifampicin, a key drug in the treatment of Tuberculosis, associated with decreased bioavailability with chronic use and associated hepatotoxicity, specifically when used with Isoniazid and Pyrazinamide
- Risorine, a Novel formulation of Rifampicin that contains Rifampicin 200mg + Isoniazid 300mg + Piperine 10mg
- **Risorine, the boosted Rifampicin**, having advantage of better tolerability, better treatment compliance and better response
- Clinical cure rate is better with Risorine treatment than conventional treatment, 91.89% Vs. 81.52%
- Only 03 patients developed liver function abnormality with Risorine, while 07 patients developed liver function abnormality with conventional treatment
- DCGI approved Rifampicin formulation undergone through regulatory trials including Pre-clinical to Phase IV

**References**