Role of Risorine in the Treatment of Drug – Susceptible Pulmonary Tuberculosis: A Pilot Study

Agam Vora¹, Sanjay Patel², Kamlesh Patel²

Abstract

Objective: To study the efficacy and tolerability of Risorine Capsule (A fixed dose combination of Rifampicin 200 mg + INH 300 mg + Piperine 10 mg) therapy in the treatment of drug–susceptible pulmonary tuberculosis patients who developed GI intolerance with standard WHO anti TB regimen.

Methods: 33 patients with pulmonary tuberculosis were treated with one Risorine kit, daily consisting of one capsule of Risorine, one tablet of ethambutol (800 mg) and two tablets of Pyrazinamide 750 mg each, for first two months of therapy. All the patients received one capsule of Risorine daily for next four months. Symptomatic improvement, Sputum conversion and radiological improvement were monitored at regular intervals.

Results: Out of 27 patients who were sputum positive at baseline, 24 patients became sputum negative during the first two months of treatment. Out remaining three patients, one became sputum negative at the end of third month of treatment and the other two became sputum negative at the end of sixth month of treatment. Out of 33 patients, only two patients developed mild nausea, which subsided spontaneously. One patient who was HIV positive, developed hepatitis.

Conclusions: Risorine, a novel formulation of rifampicin 200 mg with bioenhancer piperine 10mg, is found to be highly effective and well tolerated in the treatment of drug – susceptible pulmonary tuberculosis.

Introduction

Every second someone in the world is infected with tuberculosis, with an estimated 9.6 million new cases each year. Approximately a third of the world’s population is currently infected with tuberculosis and up to 10% of these will go to develop active TB, leading to 1.6 million deaths per year.¹

TB was declared a “global emergency” by WHO in 1993 because of its toll on the health of individuals and its social as well as economic impact on the overall progress of a country. It is estimated that about 40% of the Indian population is infected with the tubercle bacilli and about 10% of them will develop active TB during their life time. There are over 8.5 million TB patients in India with an annual incidence of 1.9 million cases. It is estimated that about 170 million workdays are lost annually in India due to TB. The annual economic cost of TB to the Indian economy is atleast US $ 3 billion (more than Rs. 13,000 crores).

The current WHO recommended DOTS therapy is highly effective in the treatment of active, drug–susceptible TB, as long as patients complete the course. However poor patient’s compliance is very common. Non–adherence to drug regimen may be due to side effects, long duration of treatment, number of drug doses required and the cost of drugs. Adverse effects of anti-TB drugs is one of the most common reason for non – adherence, eventually contributing to treatment failure, relapse or the emergence of drug resistance.²

¹Asst. Hon. and In Charge, Dept. of Chest and TB, Dr. R. N. Cooper Muni. Gen. Hospital, Mumbai and Prof., Dept of Chest and TB, KJ Somaiya Medical College, Mumbai, Maharashtra; ²Medical Department, CPL, Ahmedabad, Gujarat

Received: 10.07.2016; Accepted: 25.07.2016
The most frequent adverse effects of Anti–TB drugs are hepatotoxicity, skin reactions, gastrointestinal disturbances and neurological disorders. Nausea, vomiting, upper abdominal discomfort and pain are the most commonly encountered adverse effects of first-line anti-TB drugs. A study conducted in India, in 1195 patients treated with DOTS under Revised National Tuberculosis Control Programme (RNTCP) during January 2002 to June 2003, reported that 53% of patients developed gastro-intestinal adverse effects, the commonest complaint being nausea and vomiting. Another study conducted in Hong Kong among 627 pulmonary tuberculosis patients reported that 38% of patients developed nausea and vomiting with four drug treatment, during first 2 months of treatment. Out of the four first-line drugs, Rifampicin is known to produce maximum gastro-intestinal adverse effects. These GI adverse effects may require additional medication or may lead to change or discontinuation of therapy. This may result in adverse treatment outcomes.

Hepatotoxicity is the most serious adverse reaction seen with Anti–TB drugs. There are differences in reported rate of hepatotoxicity induced by Anti–TB drugs in different studies. Studies have shown that the risk of hepatotoxicity in patients from India is higher than those reported in west (11.5% versus 4.3%). The incidence of Anti–TB drug – induced hepatotoxicity during standard multi – drug TB treatment has been variably reported as between 2% and 2.8%. Among the most widely accepted risk factors for hepatotoxicity are advanced age (above 60 years), female sex, malnutrition, low body mass index, prior liver disease, alcohol consumption, concurrent use of hepatotoxic drugs, genetic polymorphisms in drug – metabolizing enzymes, co-infection with HIV, HBV or HCV and dosing schedules. Several studies have shown that daily TB treatment in comparison with thrice weekly treatment, increases the risk of hepatotoxicity. Isoniazide, Rifampicin and Pyrazinamide are potentially hepatotoxic drugs. No hepatotoxicity has been described for Ethambutol or Streptomycin.

Soon after the introduction of Rifampicin several reports suggested that hepatitis was more frequent and severe in patients receiving both INH and rifampicin than those receiving INH alone. In a meta-analysis, the presence of Rifampicin in a multi – drug treatment regimen increased the incidence of significant hepatotoxicity for adults from 1.6 to 2.55% and in children from 1% to 6.9%. Since administration of INH and Rifampicin together (Usually in association with other drugs) is now recommended for almost all cases of tuberculosis, this issue is an important one.

Piperine is an alkaloid obtained from plants belonging to the family Piperaceae, such as black pepper (Piper nigrum Linn) and long pepper (Piper longum Linn). 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.

One of the pilot study by Zutshi et al in 14 pulmonary tuberculosis patients, significant increase in Cmax (10.2 µg/ml from 8.15 µg/ml) and AUC (81 µg.h/ml from 47.49 µg.h/ml) of Rifampicin 450mg observed when co-administered with piperine as compared to Rifampicin 450mg alone. Risorine Capsule, a FDC of Rifampicin 200mg + Isoniazide 300mg + Piperine 10mg, got approval in India for the treatment of pulmonary tuberculosis in adult patients in 2008. In a randomized, 3-sequence, 3-period, 3-treatment, 3-way cross-over study in healthy volunteers, it was observed that Risorine Capsule is bio-equivalent to conventional Rifampicin 450mg. A multicentric, phase III clinical trial in 216 patients established efficacy of Risorine in category I pulmonary tuberculosis patients in comparison to standard WHO anti tubercular regimen. Low dose of Rifampicin in Risorine Capsule is associated with higher safety profile with equal or higher efficacy than conventional Rifampicin 450mg. Due to reduce dose of Rifampicin in Risorine, there could be less chances of side effect and equal efficacy compare to standard anti-tubercular regimen.
tolerability of Risorine capsule treatment in the treatment of drug susceptible category I pulmonary tuberculosis patients who develop GI intolerance with standard anti-tubercular therapy.

**Methods**

**Study Design**

This was an open–labeled, non–comparative, pilot study conducted in patients attending a TB clinic.

**Study population**

33 fresh cases of pulmonary tuberculosis of either sex, who developed GI intolerance (nausea, vomiting, upper abdominal discomfort) with a WHO recommended regimen containing standard doses of four first–line drugs (Rifampicin 450 mg + Isoniazid 300 mg + Ethambutol 800 mg + Pyrazinamide 1500 mg) were included in this study. Due to intolerable GI adverse effects, these patients were switched over to Risorine containing regimen. Eligibility of the patients was ascertained by following inclusion / exclusion criteria.

**Inclusion criteria**

- Category I pulmonary tuberculosis patients who developed GI intolerance with standard anti-tubercular treatment
- Age between 20 – 60 years
- Body weight 35 – 50 kg
- Normal liver functions (ALT <3 times ULN, Serum bilirubin <1.5 mg/dL)
- Normal renal function (Serum creatinine <1.5 mg/dL).

**Exclusion criteria**

- Pregnant women
- Children
- Seriously ill TB patients
- Retreatment and relapse cases
- Patients with significant disorders of the cardiovascular system
- Patients with psychiatric disorders

- Patients unwilling to give written informed consent.

**Demographic Data**

Demographic data of the patients enrolled in the study was summarized in Table 1.

Out of 33 patients, 27 patients were sputum positive and six were sputum – smear negative. Radiological examination showed that 26 patients were having unilateral lobar lesions of tuberculosis, while seven patients had bilateral lesions. Out of 33 patients with pulmonary TB, 5 patients were also having tuberculous cervical lymphadenitis. Out of 33 patients, three patients were having type 2 diabetes mellitus and one patient was HIV–positive. Written informed consent was obtained from all the study subjects.

**Baseline disease findings**

Table 2 showing base line disease findings of the enrolled patients.

**Study Treatment**

Thirty-two eligible patients received one Risorine kit, consisting of one capsule of Risorine (200 mg Rifampicin + 300 mg INH + 10 mg piperine) + one tablet of Ethambutol (800 mg) + two tablets of Pyrazinamide 750 mg each, daily for first two months of treatment. Only one patient, who was HIV – positive received one Risorine kit daily for 3 months.

All patients received one capsule of Risorine daily for next 4 months.

**Follow – up**

All patients were followed-up at the end of 2nd, 4th, 6th and 8th week of treatment during intensive phase and then at the completion of 3rd, 4th, 5th and 6th month of treatment. During each follow–up visit, apart from clinical assessment sputum examination for AFB was carried out during first two months. Chest X-rays were taken at the end of 2nd month and 6th month of treatment.

**Study Objectives**

The primary objective of the study was to measure the clinical cure rate and treatment failure rate with Risorine therapy. “Clinical Cure” was defined as a patient who is sputum smear – negative at the end of six months of treatment, with resolution of radiological lesions and without clinical signs and symptoms suggestive of active pulmonary tuberculosis.

“Treatment failure” was defined as a patient who is sputum smear – positive at the end of six months of treatment with clinical signs and symptoms suggestive of active pulmonary tuberculosis.

Secondary objective of the study was to evaluate the tolerability and safety of Risorine therapy.

**Results**

**Primary Objective**

Out of 27 patients who were sputum smear–positive at the beginning of Risorine therapy, 24 patients became sputum negative during the first two months of therapy. Out of remaining three patients, one patient became sputum smear – negative at the end of 3rd month and the other two became sputum smear – negative at the end of 6th month. The radiological lesions of tuberculosis had resolved in all the 33 patients at the end of 6th month. None of the patients were having any clinical signs or symptoms of active pulmonary tuberculosis at the end of 6th month. All patients were declared cured at the end of the study. There were no cases of treatment failure.

**Secondary Objective**

Out of 33 patients, only three patients developed adverse reactions during the study; presumably due to the study drug. Two patients developed mild nausea, which subsided spontaneously. One HIV patient developed hepatitis during the study.

**Discussion**

As every second one person is infected with tuberculosis across the globe, Tuberculosis now ranks
alongside HIV as a leading cause of death worldwide. With an estimated 9.6 million new cases each year, out of that, 2.2 million cases were from India, which is the highest TB burden country accounting for nearly one fifth of the global incidence. In 2014, 6 million new cases of TB were reported to World Health Organization (WHO). The year 2015 was a watershed moment in the battle against TB, with the major advances like fall down of TB mortality to 47% since 1990 and incidence has fallen by an average of 1.5% per year since 2000 and is now 18% lower than the level of 2000. Despite these advances and despite the fact that nearly all cases can be cured, TB remains one of the world’s biggest threats.1,18

The current WHO guideline for TB treatment emphasize on DOTS therapy which is highly effective in TB management including MDR TB. But poor patient compliance is a really an issue for successful TB treatment. Poor compliance may be due to long treatment duration, side effects of anti TB drugs and of course cost associated with treatment. The most common side effect of anti TB drugs are hepatotoxicity. Nausea and vomiting are most commonly observed side effects of first line anti TB drugs. Various study reported incidences of nausea and vomiting from 30% to 53%, nearly half of the patients receiving first line anti TB drugs reported nausea and vomiting.2,3,19

Hepatitis is one of the adverse effects of Rifampicin and Isoniazid. Isoniazid + Rifampicin and Rifampicin + Pyrazinamide appear to have synergistic effects in causing hepatitis. Isolated Rifampicin-induced hepatic toxicity occurs in up to 2% patients. When co-administered with INH and PZA, hepatic toxicity is reported in up to 28% patients.19 Some studies from India reported incidence of hepatotoxicity higher than western countries, 11.5% versus 4.3%.7

Though no new therapy has emerged for the management of TB in recent times, success of short-course chemotherapy has improved after implementation of DOTS under RNTCP in India since 1997. The success rate of treating TB under the RNTCP is now over 85%. In spite of this success, as per 2003 statistics, 28% of patients with active tuberculosis need retreatment.20 Further WHO’s End TB Strategy envisages a world of “zero deaths, disease, and suffering due to tuberculosis”. The 2035 target is a 95% reduction in deaths and a 90% reduction in incidence relative to 2015 levels. And to fulfill that, newer approaches are needed to address the current therapeutic gaps in tuberculosis management. Risorine Capsule, a fixed dose combination of Rifampicin 200 mg + Isoniazide 300 mg + Piperine 10 mg, could be one of the options to fill the current need gap in treatment of pulmonary tuberculosis.

Risorine has been approved in India for use as an anti-tubercular drug in place of rifampicin 450 mg plus isoniazid 300 mg. Piperine being an active alkaloid obtained from black pepper (Piper nigrum Linn) and long pepper (Piper longum Linn), has been added to increase the bioavailability of rifampicin. A number of in vitro and in vivo animal and human studies have demonstrated that piperine enhances the bioavailability of various drugs, including that of rifampicin, by inhibiting mixed-function oxidases, UDP-glucuronyl transferase and P-glycoprotein in the enterocytes and hepatocytes.12-15 Zutshi et al.16 have demonstrated a significant increase in Cmax (10.2 µg/ml from 8.15 µg/ml) and AUC (81 µg.hr/ml from 47.49 µg.hr/ml) of rifampicin when co-administered with piperine compared to rifampicin alone.

After evaluating Risorine in animal studies, clinical studies in human performed including bioavailability as well as safety and efficacy clinical studies including phase I, phase II and phase III before obtaining marketing approval. The pharmacokinetics of single dose of rifampicin 200 mg + piperine 10 mg or rifampicin 450 mg or rifampicin 200 mg were evaluated in a randomized, 3-sequence, 3-period, 3-treatment, 3-way cross-over study in healthy volunteer and it was observed that Rifampicin 200 mg + piperine 10 mg is bioequivalent to rifampicin 450 mg. Clinical safety and efficacy was established during phase III clinical trial involving 216 category I pulmonary tuberculosis patients. It was multicentric, randomized, active control, double-blind, parallel group clinical trial in which efficacy and safety of Risorine was compared with that of standard WHO anti-tubercular regimen in patients with Category I pulmonary tuberculosis. The observed sputum conversion rate was 92.75% with Risorine treatment and 85.39% in standard therapy group at four weeks. The cure rate observed at the end of 24 weeks was 92% in the Risorine arm while 81.5% in the standard therapy arm. No additional adverse effects were observed with Risorine treatment.17

Since during the development phase, the drug was evaluated in limited number of patients in standard clinical trial setup, to gain more experience with the drug in clinical care set up, the current study was designed with an objective of comparing the efficacy and tolerability of Risorine capsule therapy in the treatment of drug susceptible pulmonary tuberculosis who are GI intolerant to standard anti tubercular treatment.

In our study, total 33 patients were enrolled who initially develop GI intolerance on standard WHO recommended anti TB treatment and switched over to Risorine treatment. Out of that 33 patients, 27 patients who were sputum positive at the beginning of the study, 24 of them became sputum negative during first 2 months of after Risorine therapy, two patients became sputum negative after 3 months of therapy and one patient
became sputum negative at the end of 6th month of therapy. At the end of Risorine therapy, all patients had radiological lesions resolved and declared as clinical cured. Apart from efficacy, safety point of view, Risorine showed better tolerability and safety profile as out of 33 patients, only three patients were developed adverse reactions, which were mild nausea in two patients and hepatitis in one HIV positive patient. Occurrence of nausea was mild in nature, which was subsided spontaneously.

From the results of the study, Risorine can be established as a good alternative in treatment of category I pulmonary tuberculosis. But considering limitations of the study like un-blinded design and smaller sample size, larger post marketing studies are needed to established further safety and efficacy of Risorine in treatment of patients with category I pulmonary tuberculosis, especially in those patients who cannot tolerate conventional dose of Rifampicin or having higher chances of hepatic impairment associated.

Conclusion

The aim of the present study was to evaluate the clinical efficacy and tolerability of Risorine therapy in patients who developed gastro-intestinal side effects with conventional Anti-TB treatment.

All the patients treated with Risorine in this study were cured of tuberculosis and all the patients completed six months of therapy. There were no cases of default or treatment failure. No patient discontinued therapy due to adverse effects.

Present study proves that a lower 200 mg dose of rifampicin, when given along with bioenhancer Piperine 10 mg, provides clinical cure rates which are comparable to those obtained with 450 mg dose of rifampicin.

Better GI tolerability observed with Risorine therapy would be of help in improving patient compliance and minimizing the risk of non-adherence due to side effects. This may result in better cure rates and lower relapse rates.

Although the present study is un-blinded and has a small sample size, the results are promising and will provide impetus to initiate further studies. Larger studies are therefore needed to further establish efficacy and safety of Risorine therapy in patients who develop intolerable nausea and vomiting with regimen containing 450mg dose of Rifampicin.

Acknowledgements

We acknowledge the invaluable support provided by Cadila Pharmaceuticals Limited, Ahmedabad for this study. We thank all of the patients who participated in this study.

Source of Funding

This study is an independent, investigator-initiated trial

References

1. WHO Global Tuberculosis Report, 2015
2. Wares DF, Singh S et al. Non – adherence to TB treatment