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STUDY OF EFFECT OF IMMUNOMODULATOR IN TREATMENT OF CATEGORY-I SPUTUM POSITIVE PULMONARY TUBERCULOSIS

Rabindra Kumar Panda[1], Archana Toppo[2]

ABSTRACT: BACKGROUND: Tuberculosis is amongst one of the major public health problems in the developing countries of the world today. Modern Chemotherapy kills most of the bacilli within days. WHO initiated DOTS for treating TB but still success rate of treatment is less. Immune response in most of the tuberculosis patients is inappropriate because of gross tissue destruction and progression of the disease. The nature of an effective immune response to TB is incompletely understood but the most effective vaccination strategies is to stimulate T- cell responses, both CD4 and CD8, to produce Th-1 associated cytokines. So rationale for TB immunotherapy is to replace immunopathology with protective antibacterial immunity. Mycobacterium w. have such immunogenic properties, so it was used in clinical trial as an injectable immunomodulator adjuvant to treatment of sputum positive new Pulmonary TB cases taking Cat-1 therapy. **AIMS AND OBJECTIVES:** To study the effect of Immunomodulator used as an adjuvant to treatment of newly diagnosed sputum positive cases of Pulmonary Tuberculosis taking Cat-I Therapy under RNTCP. **MATERIAL AND METHODS:** Patients were selected from OPD and IPD of TB & Chest Department V.S.S. Medical College Burla. It was a Double blind randomized placebo contolled study done during Jan. 2004 to Jan. 2006. Study was conducted in30 newly diagnosed cases of Pulmonary Tuberculosis of which 17 were in group A and 13 were in group B after taking informed consent. The study subjects were randomly assigned to one of the two groups (A&B).Group A was treated with Cat-I and injectable Immunomodulator and Group B received Cat-I with placebo. Analysis of sputum status was done at 15, 30, 45 and 60 days. Sputum conversion, side effects, weight gain and relief of symptoms between both the groups were analysed. **RESULTS:** The majority of patients of new sputum positive pulmonary tuberculosis were found in between the age group of 21 – 40 years, which constitute 51%. Most of the patients presented with symptoms of cough followed by fever, weight loss, chest pain and hemoptysis. It was observed that many patients have pleomorphic presentation as infiltration, cavity, fibrosis and consolidation on radiological investigations. The rate of sputum conversion was seen in 30-45 days in patients taking mycobacterium w. along with CAT I (RNTCP) whereas in the patient taking placebo along with CAT I (RNTCP) was 45- 60 days, so there was an increase in rate of sputum conversion by 15-30 days earlier in patient taking Mycobacterium w. was compared to placebo. The average gain in weight in the group with mycobacterium w. was 3.74 kg and in control group was 1.60 kg i.e, a gain of weight by 2.3 times more in patients taking Mycobacterium w. along with CAT I (RNTCP) than that of those taking placebo and CAT I (RNTCP) All the patients taking Mycobacterium w. had local reaction at the site of injection, which heals by scar formation after one month. Only 2 patients had extensive scar formation and one patient had abscess at the local site. There was no severe systemic side effect. Neither of the

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patients taking placebo had any reaction at the local site. **CONCLUSION:** It is clear from our study that there is definite increase in sputum conversion rate by 15-30 days and there is also weight gain in the Mycobacterium w. group as compared to the control group. It is clear that use of immunomodulator containing Mycobacterium w in tuberculosis fulfil the much desired therapy gap. It increases the rate of sputum conversion. So this decreases the duration of therapy for tuberculosis which may be helpful for controlling of tuberculosis.

KEYWORDS: DOTS- Directly Observed Therapy Short course, RNTCP-Revised National Tuberculosis Control Programme, TB-Tuberculosis.

INTRODUCTION: Tuberculosis is one of the first secondary infections to be activated in human immunodeficiency virus (HIV) positive individuals.[1] It is believed that one third of the earth's population is 'latently' infected with Mycobacterium tuberculosis. Moreover the stress of poverty and malnutrition increase the rate of reactivation of tuberculosis. Pulmonary Tuberculosis is the most common form of Tuberculosis. Modern Chemotherapy kills most of the bacilli within days. WHO initiated DOTS for treating TB but still success rate of treatment is less. Immune response in most of the tuberculosis patients is inappropriate because of gross tissue destruction and progression of the disease.[2]

The nature of an effective immune response to TB is incompletely understood but the most effective vaccination strategies is to stimulate T- cell responses, both CD4 and CD8, to produce Th-1 associated cytokines. So rationale for TB immunotherapy is to replace immunopathology with protective antibacterial immunity. This could be achieved by switching off Th2 responses and enhancing Th1 mechanisms against antigens Mycobacterium w. a non-pathogenic environmental Mycobacterium has been shown to have such immunogenic properties.[3]

Some preliminary immunotherapy studies with killed suspensions of Mycobacterium w. for TB had reported benefits as symptom relief, weight gain, radiological resolution.[4] So with the considerable promise shown in treating the Pulmonary Tuberculosis with immunomodulator as an adjuvant to chemotherapy. A clinical trial taking Mycobacterium w. as an immunomodulator in adjuvant to ATT in treatment of sputum positive Pulmonary TB. This study presents findings and observations of the trial.

MATERIAL AND METHODS: Patients were selected from OPD and IPD of TB & Chest Department, V.S.S. Medical College Burla during Jan. 2004 to Jan.2006. Study was conducted in 30 newly diagnosed cases of sputum positive Pulmonary Tuberculosis. The study subjects were randomly assigned to one of the two groups (A&B) out of which 17 were in group A and 13 were in group B. Patients were included after giving informed consent.

Study Design: It was a Double blind randomized placebo controlled study.

Inclusion Criteria:
1. New sputum positive cases of Pulmonary Tuberculosis (under CAT-I per RNTCP).
2. Age 14-60 yrs.
3. Patient who gave consent.

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Exclusion Criteria:
1. Patients hypersensitive to drug.
2. Immunocompromised status e.g. HIV, DM
3. Patients on long term steroids e.g. Bronchial Asthma
4. Age group less than 14yrs. and more than 60 yrs.

Study Procedure:
Group A received;
   (i) ATT Cat-I as per RNTCP i.e. 2(HRZE) 3/4(HR) 3.
   (ii) Injectable Immunomodulator Mycobacterium w. 0.1ml every 15 days intradermally on deltoids at day 0, 15, 30, 45 and 60.

Group B received;
   (i) ATT Cat-I as per RNTCP i.e. 2(HRZE) 3/4(HR)3.
   (ii) With placebo (similar vial as like Immunomodulator but without Mycobacterium w.)

Analysis: Analysis of sputum was done at day 15, 30, 45 and 60 of both the groups (A & B).
Comparisons of following were done:
1. Sputum conversion at day 15, 30, 45 and 60 between Group A & B.
2. Comparison of side effects between Group A & B.
3. Comparing the weight gain and relief of symptoms between Group A & B.

OBSERVATION AND RESULTS: In the present study it is found that majority of the patients who were suffering from sputum positive pulmonary tuberculosis belongs to age group of 21- 30 years, which constituted 34% and there is again a rise in tuberculosis in the age group of 50 to 60 years which is 23%.

Type of lesion	Group A		Group B		Total (A+B)	
	No. of Pt.	%	No. of Pt.	%	No. of Pt.	%
Infiltrative	12	70.6	12	92.3	24	80
Cavitary	5	29.4	3	23.0	8	26.7
Consolidation	2	11.8	-	-	2	6.7
Fibrosis	6	35.3	1	7.7	7	23.3
Table 1: Distribution According to Type of Lesions in Group A and Group B						

In present study the most common lesion is infiltrative type (80%) followed by cavitary lesion (26.7%) and fibrosis (23%).

Sputum AFB	Total No of Pt.	Day 15		Day 30		Day 45		Day 60	
		No. of Pt.	%	No. of Pt.	Cumulative %	No. of Pt.	Cumulative %	No. of Pt.	Cumulative %
3+	1	0	0	1	6	1	6	1	6
2+	7	2	12	5	29	7	41	7	41

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1+	9	2	12	9	53	9	53	9	53
Scanty	-	0	0	0	0	0	0	0	0
Total	**17**	**4**	**24**	**15**	**88**	**17**	**100**	**17**	**100**

Table 2: Sputum Conversion in Group A Patient

Sputum AFB	Total No of Pt.	Day 15		Day 30		Day 45		Day 60	
		No. of Pt.	%	No. of Pt.	Cumulative %	No. of Pt.	Cumulative %	No. of Pt.	Cumulative %
3+	3	0	0	0	0	1	8	3	23
2+	6	0	0	0	0	2	15	6	47
1+	2	1	8	1	8	2	15	2	15
Scanty	2	0	0	2	15	2	15	2	15
Total	**13**	**1**	**8**	**3**	**23**	**7**	**53**	**13**	**100**

Table 3: Sputum Conversion in Group B Patient

From the above table 2 & 3, it is clear that there was a reduction in sputum conversion rate in the group taking Mycobacterium w. compared to control group. At day 15 here is 24%, at day 30 its 88% and on day 45 its 100%.conversion with the mycobacterium w. whereas in control it's 8% on day 15, 23% on day 30, 53% on day 45 and on day 60 its 100%. So it can be seen that what is achieved on day 15 and day 45 with Mycobacterium w. Group, it takes about 30 day and 60days respectively in control group.so with Mycobacterium w. the sputum conversion is earlier by 15to 30 days compared to control group.

Group	Day 0	Day 15	Day 30	Day 45	Day 60
A	0	0.76	1.64	2.72	3.74
B	0	0.30	0.80	1.03	1.60

Table 4: Average Weight Gain in Group A and B During The course of Treatment

There is more increase in weight in the Mycobacterium w. group compared to that of the control group.

Adverse reaction	Group A	Group B
Pustule	17	None
Ulceration	17	None
Scar	17	None
Itching/ pain at local site	4	None
Abscess	1	None
Systemic reaction	None	None

Table 5: Adverse Reactions in Group A and B

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All patients taking Mycobacterium w. have a normal local reaction at the site of injection such as pustule, ulceration and scar formation. Some patients complained of itching at the local site and one patient had abscess at the local site. One of the patients had abscess formation at the local site. None of the patient had systemic side effect. In control group there was no adverse reaction.
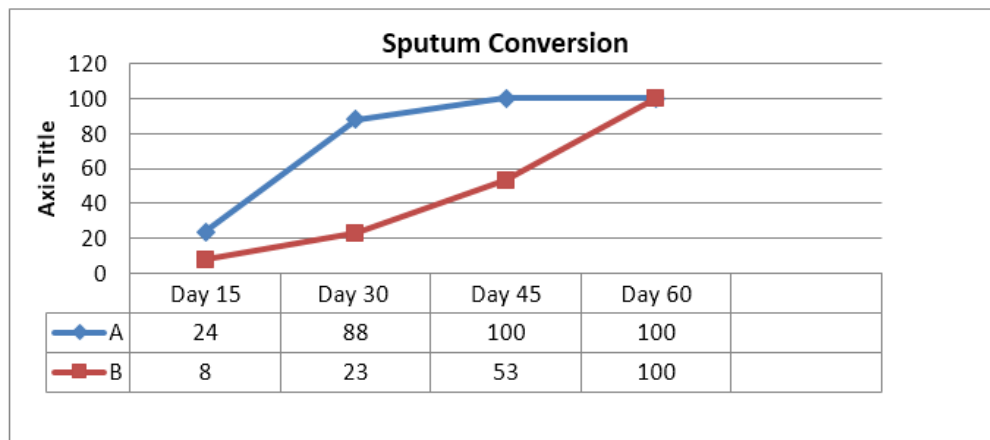

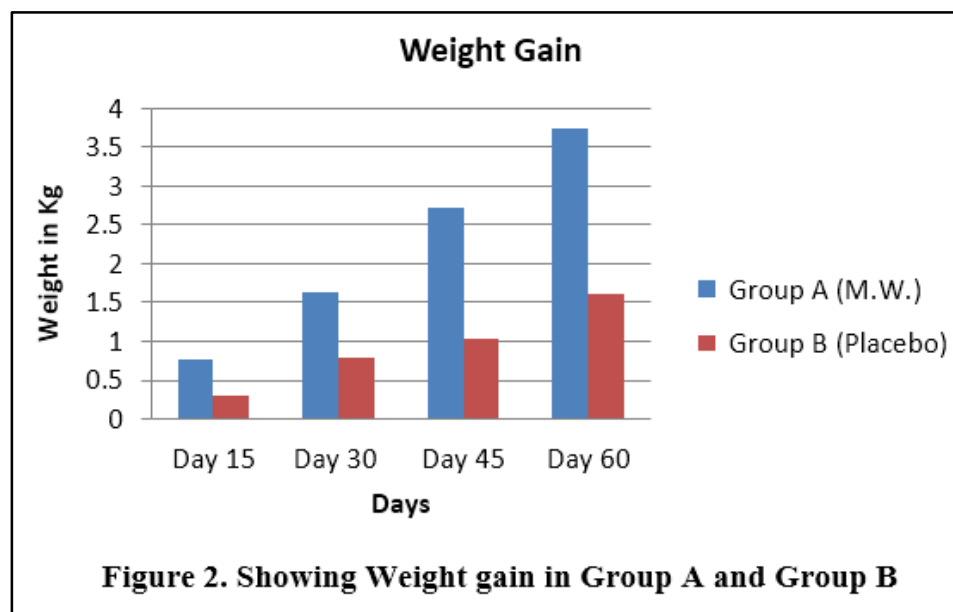**Figure 1. Sputum Conversion Graph of Group A and Group B**

Figure 2. Showing Weight gain in Group A and Group B

DISCUSSION: Age and Sex Variation in Patients of Pulmonary Tuberculosis: Increase rates of tuberculosis seen in young adults (20-45 years of age) suggest tuberculosis as a result of recent infection among this age group and a sharp rise after 65 years of age suggests an additional burden of reactivation disease may be due to probably immunodeficiency associated disease may be like HIV, diabetes mellitus, environmental pollution, malnutrition, stress and strain etc.

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In the present study maximum number of cases was from the age group 21-40 years (51%) the next more commonly involved group is 50-60 years, which coincides with the study by Raj Narain et al 1963 that is 55.9% in below 45 years age group.[5]

In present study the prevalence of tuberculosis was observed higher in males (67%)with males to female ratio2.08: 1 and similar result were found in studies by Frimodt –Moller 1960 ratio was 1.75:1[6] Pamra et al 1973 observed ratio of1.08:1,[7] Raj Narain et al 1963 got a ratio of 2:1.[5]

Occupation: In our study tuberculosis was less in group of employess and businessmen showing less prevalence in economically better groups hence indirectly more prevalent in the low socio – economic status. Pamra et al,1968 found that the incidence in the low –income is nearly 3 times more than in the middle –income group.[7] In another study by Cantwell et al 1998 significant association between increase risk of tuberculosis and increase levels of crowding,poverty and decreasing levels of education was seen.[8]

Symptoms: In the present study cough was 97%, fever in 63%, loss of weight in 47%, chest pain in 33%, hemoptysis in 23%, loss of appetite in 10%. Similarly in a study by Branes et al 1988 (209)found cough in 78%,weight loss in 74%,fatigue in 68%,fever in 60% and hemoptysis in 37% of cases.[9] In another study by Miller et al 2000 found cough in 76%, fever in 51 %, fatigue in 59%, weight loss in 43% and hemoptysis in 24% cases.[10]

Anaemia: In our study all the patients were anaemia with mild (63%), moderate (33%) and severe (4%). This may be due to the fact that the majority of the patients are tribal were malnutrition, parasitic infestation, early marriage and multiple children prevails. Lee SW et al, studied 898 patients out of which 32.7% of patients had anaemia.[11]

Radiological Lesions: In our study the infilteration is 77% of the cases and cavitation in 23% of cases. In addition to this we found that patients may have multiple lesions, infilteration only (56%), infilteration and cavity (13%), fibrosis only (10%), infilteration and fibrosis (3.3%) fibrosis and consolidation (6.7%), cavity only (6.7%) and infilteration and cavity (3.3%). So about half of the patient with pulmonary tuberculosis has pleomorphic presentation. In a study by Miller et al, Woodring et al observed that pulmonary infilteration in 80% of the cases and tubercular cavity is present in between 19% to 50% of all tuberculosis patients.[10],[12]

Sputum Conversion Rate: According to Patel N et al in 2002 studied that sputum conversion was found to be faster when Mycobacterium w. was added to category I sputum positive cases. They found that the effect of Mycobacterium w. begins early and were found to be significant from day 15 as compared to 45-60 days in chemotherapy. Thus Mycobacterium w's effect was more pronounced when bacterial load was highest. Use of Mycobacterium w. containing immuno-modulator resulted in preponing the sputum conversion by 30 days. This was found irrespective of bacterial load. The overall sputum conversion irrespective of sputum status or category the following are the sputum conversion rate in M.W. group 20% (15 days), 45% (30 days), 49% (45

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days), 58% (60days) but in control group the sputum conversion rate was 12% (15days), 25% (35 days), 32% (45 days) and 45% (60 days).[13]

According to Luhadia s. et al, in 2004 (196) sputum conversion in CAT I was 97% in 15 days and 30 days and 100% in Mycobacterium w. group compared to 42%, 75% & 90 % in control group respectively.

As patel N et al in 2004 (210) found sputum conversion in CAT I taking Mycobacterium w. to be 97% at day 15, 100% at day 30 as compared to control (taking CAT I) only to be 42% at day 15, 75% at day 30 and 93.5% at the end of 2 months.

In our study patients taking CAT- I overall sputum conversion rate irrespective of gradation of sputum positivity was 24% in 15 days, 88% in 30 days, 100% in 45 days in patients taking Mycobacterium w. as compared to 8% in 15days, 23% in 30 days and 53% in 45 days and 100% at day 60 in control group. This clearly shows at day 15 the sputum conversion is three times in M.W. group to that of the control group.at day 30 at was four times and at day 45 twice in M.W. group as compared to the control group.

By comparing the above study we found that Patel N et al 2002, Luhadia et al 2004 and Patel et al 2004 observed that at day 15 the sputum conversion was 57%, 97%, and 97% respectively in patients with Mycobacterium w. But we had a sputum conversion of 24% which is quite less than the above cited study the reasons may be that the majority of the patients are tribal where malnutrition, parasitic infestation, early marriage and multiple children prevails.

On 30 days Patel Net al 2002(18), Luhadia et al 2004 (196) and Patel et al 2004 (210) observed sputum conversion was 78%, 97% and 100% respectively in patients with Mycobacterium w. In our study we found a conversion rate of about 88% at the end of 30 days, which is almost similar to the above study.

On day 45, Patel N et al 2002 and observed sputum conversion was 92% whereas in our study it was 100% in patients with Mycobacterium w.

So in Mycobacterium w. group there is clearly a early sputum conversion i.e 15-30 days earlier as compared to the controlled group.

Weight Gain: Luhadia et al found that there was a definite increase in weight of about two times by day 60 with Mycobacterium w. compared to the control group.[14]

In our study we have found there is definitely more weight gain by about 2.3 times in patients with Mycobacterium w. vaccine as compared to the control group i.e average weight weight gain was 3.74 kg in group taking Mycobacterium w. compared to the control group.

Adverse Reaction: Luhadia et al (196), Patel et al (18) found that after giving mycobacterium w. there was no severe systemic reaction or death. But there were normal local reaction similar to BCG like pustules after 4-5 days, ulcer after 7-10 days & scar formation after 1 month.[14]

Similarly in our study we found that all the patients taking mycobacterium w. had local reactions at the site of injection like pustules after 4-5 days, ulcer after 7-10 days and scar formation after 1 month. There was no severe systemic reaction or death.

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SUMMARY:

1. The majority of patients of new sputum positive pulmonary tuberculosis were found in between the age group of 21 – 40 years, which constitute 51%. There was also increase in incidence after the age group of 50 years which constitute 23%.

2. The disease were more common in males than in females M:F ratio equal to2.08: 1. Majority of patient were labourer, farmer and housewife, which constituted 73%.

3. The patients presented with symptoms of cough (97%), fever (63%), weight loss (37%), chest pain (33%) and hemoptysis (23%).

4. The types of distribution of lesions were pleomorphic in nature,which is infiltration in 80% of cases, cavity in 27% cases and fibrosis in 23% of cases. We found that many patients have pleomorphic presentation, infiltration only (56%), infiltration and cavity (13%),fibrosis only (10%), infiltration and fidrosis (3.3%),fibrosis and consolidation (6.7%), cavity only (6.7%), and infiltration plus consolidation and cavity (3.3%). So about half of the patients with pulmonary tuberculosis have pleomorphic presentation.

5. The radiological presentation of majority of cases were far advanced to moderately advanced which makes 70%.

6. All the patients were anaemic and most were of mild variety (64%).

7. The rate of sputum conversion was high within 30-45 days in patients taking mycobacterium w. along with CAT I (RNTCP) whereas in the patient taking placebo along with CAT I (RNTCP) was 45- 60 days, so there was an increase in rate of sputum conversion by 15-30 days earlier in patient taking Mycobacterium w. was compared to placebo.

8. The average gain in weight in the group with mycobacterium w. was 3.74 kg and in control group was 1.60 kg i.e, a gain of weight by 2.3 times more in patients taking Mycobacterium w. along with CAT I (RNTCP) than that of those taking placebo and CAT -I (RNTCP).

9. All the patients taking Mycobacterium w. had local reaction at the site of injection, which heals by scar formation after one month. Only 2 patients had extensive scar formation and one patient had abscess at the local site. There was no severe systemic side effect. Neither of the patients taking placebo had any reaction at the local site.

CONCLUSION: It is clear from our study that there is definite increase in sputum conversion rate by 15-30 days and there is also weight gain in the Mycobacterium w. group as compared to the control group. Early sputum conversion with less frequent administration of drug is a cherished dream. After Rifampicin, Mycobacterium w. is the first immunotherapy, which shows further reduction in sputum conversion time. This result can be attributed to pure Th 1 response enhancement without Th 2 enhancement due to Mycobacterium w.

Currently short course chemotherapy is a popular, with this therapy the duration of treatment ranges from 6-9 months. The reduction in duration of treatment is attributed to Rifampicin, which hastens the sputum conversion. So faster sputum conversion rate is helpful in reducing duration of therapy, also decreases the spread of infection and helps in early rehabilitation of the patients. An immunomodulator intervention is required to shorten the duration of therapy even further, which can enhance the host immune system, so that the persister organism will be killed faster.

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It is clear that use of immunomodulator containing mycobacterium w. in tuberculosis fulfil the much desired therapy gap. It increases the rate of sputum conversion thereby can decrease the duration of therapy for tuberculosis which may be helpful for controlling tuberculosis.

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AUTHORS:
1. Rabindra Kumar Panda
2. Archana Toppo

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor & HOD, Department of Tuberculosis & Respiratory Disease, Pt. J. N. M. Medical College, Raipur, Chhattisgarh.
2. Assistant Professor & HOD, Department of Medicine, Pt. J. N. M. Medical College, Raipur, Chhattisgarh.

NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Rabindra Kumar Panda,
Assistant Professor & HOD,
Department of Tuberculosis & Respiratory Disease, Pt. J. N. M. Medical College,
Raipur, Chhattisgarh.
E-mail: rkpandaatinu@gmail.com

Date of Submission: 07/10/2015.
Date of Peer Review: 08/10/2015.
Date of Acceptance: 10/10/2015.
Date of Publishing: 12/10/2015.