Homeopathy In Multi Drug Resistance Pulmonary Tuberculosis - A Double Blind Placebo Control Trial

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ABSTRACT

Multi Drug Resistance Pulmonary Tuberculosis (MDR-TB) [resistance to anti tubercular drugs (ATT) Isoniazid and Rifampicin] is a major, worldwide public health problem with conventional intensive multi-drug regimens focused on bacilli. The pathogenesis of TB indicates that endogenous factors are equally important in the development of active disease.[4] Homeopathy has potential of immune-modulation[5].

In India, MDR-TB cases are on rise in spite of a well run DOTS program. Reserve line ATT drugs are expensive, given for longer duration and have multiple side effects, hence patients often consult homeopaths. Inspired by encouraging results with homeopathy, an explorative prospective study was conducted at New Delhi, India.

Methodology: *During explorative phase, indicated homeopathic remedies were added to ATT regimen of 142 cases of MDR-TB. A group of most effective remedies and their indications were identified; Ars.30, Bry.30,200, Calc.30, Ip.30, Lyc.30, Nat-m.30, Nux-v.30, Phos.30,200, Puls. 30, Sep.30,200, Sulph.30, Tub.200.*

In the second phase, above remedies were added according to the indications, in coded form, to the reserve line ATT, using randomized, parallel, and double blind placebo control design. 120 cases were studied during 53 months (2003-07). 99 cases completed the study, on un-blinding, 50 cases were in verum and 49 in placebo group.

Results: *Cases were assessed by sputum smear/ culture, x-ray chest, weight gain, hemoglobin and ESR. Verum group showed better improvement in all parameters, being statistically highly significant in x-ray ($p<0.0001$). The new soft tissue lesions healed faster with less fibrosis. The relapse rate was high in placebo group.*

Conclusion: *This is a preliminary study, significant improvement in radiological status in chronic cases of MDR-TB indicates that there is a scope for further research. If Homeopathy is incorporated as complimentary to the conventional therapy, there may be a possibility of reduction in incidence of chronic pulmonary disease and relapse rate.*

Introduction

Tuberculosis (TB) has been known since antiquity. There are references to TB in India around 2000 BC[1]. Around 460 BC, Hippocrates identified phthisis as the most widespread disease of the times which was always fatal. During the middle ages in England and France, the touch of the sovereign was thought to be curative.[2] The era of adopting general hygienic measures and sanatorium for treatment of TB started with first sanatorium opened in Poland in 1859, another in the United States in 1885[1].

Homeopathy was used in the treatment of TB during 19th century. In 1827 Baron Boenninghausen was treated for purulent T.B.[3]. Dr.Hempel in 1859 stated that Arsenic excites respiratory organs in the same manner that TB does and advocated its use[4]. Richard Hughes in 1878 stated that Homeopathy would enable you to keep down pulmonary inflammation without lowering the system[5]. Burnett reported 54 cases of various types of TB successfully treated with a nosode *Tuberculinum(Tub)/Bacillinum(Bac)*[6]. The discovery of streptomycin[7] and other antibiotics marked the end of general measures and reduced the usage of Homeopathy[8].

During last five decades, World health organization (WHO) launched various global public health initiatives to control TB[9]. Today, TB is still a major, concern, resulting in over 8.8 million new cases and nearly two million deaths per year. In India, National Tuberculosis Control Programme was started in 1962 and revised (RNTCP) in 1993[10]. The Anti Tubercular treatment (ATT) constitutes regimens of multiple antibiotics. Category I (CAT I) [Thrice weekly doses of: *Isoniazid (INH), Rifampicin(R), Ethambutol(ETH), Pyrazinamide(PYZ)* for 2 months and *INH, R* for 4 months] is given to new smear positive and seriously ill smear negative and seriously ill extra pulmonary cases. Category II (CAT II) [Thrice weekly doses of : *INH, R, ETH, PYZ, Streptomycin(STR)* for 2 months and INH*, R, ETH, PYZ* for one month and *INH, R, ETH* for 5 months] is given to smear positive, relapse, failure and default cases. Category III (CAT III) [Thrice weekly doses of: *INH,R, PYZ* for 2 months and *INH, R* for 4 months] is given to not seriously ill smear negative and extra pulmonary cases. Directly Observed Treatment-Short course (DOTS) strategy has been adopted to reduce default rate and increase the compliance of patient, wherein ATT is administered in front of physician or health worker. The success rate of this strategy is more than 90% against the first time infection but it has not been able to prevent the emergence

of MDR-TB [resistance to minimum two ATT drugs *Isoniazid* and *Rifampicin*][11,12,13]. Such cases are treated with reserve line drugs comprising of *Amikacin, Kanamycin, Enviomycin, Levofloxacin, Moxifloxacin, Ethionamide, Prothionamide, Cycloserine, P-aminosalicylic acid*. These are very expensive, often toxic and have to be taken for 18 to 24 months. The success rate is also not more than 40-50%.

Medical pluralism is unique in Indian health care delivery and homeopathy is the second most popular system in India. Homeopathic infrastructure in India includes 234 hospitals, 5910 dispensaries, 182 colleges[14]. Chronic cases of TB often visit Homoeopathic physicians in search of safe and affordable treatment. There are certain experiences with Homoeopathy but no control trials have ever been undertaken.[15,16]

During 2000-03, an exploratory prospective study of 142 MDR-TB was undertaken, of these few cases were presented in LIGA congress at Berlin in 2005.[17] These experiences lead to the short listing of 12 Homoeopathic remedies, indication, and efficacious potencies (Box-1), which were frequently used.[18] These remedies have been subjected to randomized double blind placebo control trial during 2003-2007.

Methodology

The aim of this clinical trial was to explore the effectiveness of identified Homoeopathic remedies in the treatment of MDR TB. The informed consent of patients was obtained. The Scientific and ethical clearance was obtained before starting the trial. It was a double blind placebo control trial undertaken at Gulabi Bagh Chest Clinic, New Delhi.

Preparation of quota: Each quota had 15 identical vials of selected remedies (Box -1), either the entire set was placebo or medicinal. These were prepared and coded by the project director who was not involved in the day to day prescribing. Of these, 50% were kept as placebo/controls using simple randomized table. Every patient was treated from the same quota assigned at the time of induction. The homeopathic remedy/ placebo were prescribed in the same style to all the patients.

Box 1: Remedies, Potencies & indications

Arsenic Album 30 Anxiety about own health <at midnight with much wheezing . > Warm drinks. Drinks little and frequently.		**Bryonia 30,200** Cough dry as if coming from stomach with stitches in side of chest. <talking,laughing ,eating ,hot weather, getting into warm room from cold. Pain chest <night, motion, right side, inspiration. >rest, lying on painful side, pressure. Thirst for large quantities of water at long intervals. Constipation, dry, hard stool Irritable temperament, does not want to be disturbed
Calcarea carb 30 Leuco-phlegmatic Constitution, takes cold easily Fat or very thin Sweaty head on sleeping which soaks the pillow Desire eggs. Affinity for Right middle lobe of lung complaints. Dyspnoea < ascending stairs,exertion, cold Early, profuse menses. Ice-cold feet, wants to wear socks yet want to uncover them when warm		**Ipecacuanha 30** No appetite, constant nausea with haemoptysis Haemoptysis bright red,< least exertion Incessant, rattling cough, suffocation
Lycopodium 30 Right sided Irritable,peevish esp. after sleep. Easy satiety or no appetite Flatulence. (esp.lower abdomen) Desire sweets/hot drinks. Nose block,breathing from mouth. Aggravation evening Associated urinary complaints		**Natrum Muriaticum 30** H/O grief, emaciated neck Desire to be alone & consolation aggravates. Associated hair-fall, headache Great craving for salt, meat & spices Constipation,irregular timing of stool.
Nux Vomica 30 Chilly, wants to be covered Frequent, in-effectual, urge for stool Dyspepsia < eating, drinking, exertion Nausea/Vomiting. Desires stimulants-tea /coffee / alcohol.		**Phosphorus 30,200** Young tall, weak, narrow chest, anxious look with pale face. Bleeding tendency, sensitive to odours Great anxiety about future & his own health, Fear of darkness & being alone. Catches cold easily with desire for open air Desires - cold drinks, salt, spices. Pain chest < lying on left side, inspiration & cough.

Pulsatilla n 30 Acute complaints like cold, fever (hot at 2 PM, followed by chill at 4 PM and sweating at night) Cough dry at night & loose in morning. Aversion to fat, warm food . Dry mouth yet thirstless. Weepy, consolation <.		**Sepia 30,200** Indifference towards husband, children. Sallow complexion, Butterfly dispigmentation on face. Pelvic inflammatory disease with all gone/bearing down sensation
Sulphur 30 Alternatively cold and hot burning feet, which must be put out of bed to cool them. lean, debitilated & stoop shouldered . Red dry lips Constipation with difficult & hard stool Morning diarrhea, drives out of bed. Drinks much & eats less. Accompanied skin complaints		**Tuberculinum Bovinum 200** Family History of TB, inter-current remedy. Tendency to take cold easily yet desires cold, open air

Sample size: 120 cases were registered against the target of 100 cases.
Inclusion criteria: All the cases (male/female) of MDR-TB, taking Reserve line ATT, some were sputum positive and others were sputum negative but were symptomatic, were included in the study. These cases were required to continue their respective reserve line drugs.

Exclusion criteria: The pregnant women & cases with concomitant diseases such as AIDS, malignancy, diabetes etc. were excluded from the study.

Investigations: All the cases were subjected to following investigations at the time of induction.
X-Ray chest
Sputum smear & culture sensitivity for AFB
Haemogram – Hb, TLC, DLC, ESR
Blood Biochemistry – Sugar Fasting & PP
Liver Function Test
Elisa for HIV

Treatment: Homoeopathic remedy was selected after proper assessment of the case. The selection was limited to the identified remedies. Patient was treated from the same quota throughout the study. In acute episodes, the remedy was given more frequently. When no improvement was seen, case was re-assessed and another remedy was prescribed from

the same quota. *Tub.*200 was given inter-currently from the same quota when the selected remedy failed to act.

Follow up: The cases were followed up for subjective and objective improvement fortnightly. As per protocol, sputum smear and culture was reviewed after every 3 months. Haemogram, blood biochemistry and X-Ray chest were also reviewed every six months.

Analysis : The experiment was un-blinded in March 2008. All those patients who had adequate follow up with at least two X-rays, and at least two culture reports, one at the beginning of the study and other subsequent one, were analyzed and rest were dropped.

Results

On un-blinding, it was found that 60 were treated with reserve line ATT and homeopathic remedies verum (v) group, 60 were treated with only reserve line ATT drugs placebo (p) group. 21 cases (10 from v and 11 from p group) were dropped. The data of the cases in respect of all the variables have been given in table 1-7

Table 1: Sputum smear conversion

Smear	v group		p group	
		In %		In %
Pos—Neg	21	42	22	45
Neg—Pos	3	6	7	14
Pos—Pos	8	16	6	12
Neg—Neg	18	36	14	29
TOTAL	**50**		**49**	

Table No 2 : Sputum conversion (culture)

Culture	v group		p group	
		In %		In %
Pos—Neg	21	42	16	33
Neg—Pos	2	4	6	12
Pos—Pos	10	20	9	18
Neg—Neg	17	34	18	37
TOTAL	**50**		**49**	

Sputum culture conversion from positive to negative was more in the verum group though not statistically significant, but relapse rate (negative to positive) during the course of treatment was significantly less in verum.

Radiological status: The radiological analysis was carried out in consultation with a TB specialist and a clinical radiologist. The changes in the chest X-ray were noted in the lungs, mediastinum and pleura and compared in subsequent X-rays. It was found that new parenchymal changes in the lungs tissue healed without much fibrosis and calcification in patients in the verum group.

The changes were classified into five grades to assess qualitative improvement/deterioration or no change. (Table-4) Majority of cases showed extensive lesions in both lungs with cavities, fibro-calcific changes, post tubercular cystic changes, segmental lobar atelectasis, collapse' of entire lung with pleural lesions (effusion/adhesions) of varying extent.(Figures 1-9) In was also noticed that significant compensatory hypertrophy took place during the course of treatment, such cases had been graded high (Figure 1-4). The deterioration has also been graded accordingly. (Figure 5-7) It was a subjective assessment, based on decrease in the size of the cavities, improvement in the pleural changes and expansion of the lung tissue using scale of nine.

Table no-3 Radiological assessment:

X-RAY Grading	v	P
-5	0	0
-4	0	1
-3	0	5
-2	2	2
-1	0	10
0	10	11
1	13	4
2	10	6
3	9	7
4	4	2
5	2	1
TOTAL	**50**	**49**

The addition of homeopathy to the regimen caused highly significant radiological improvement ($p<0.001$). Only two out of fifty patients in verum group showed worsening of X-ray chest, while twelve out of forty-nine had worsening of X-ray in placebo group. Fifteen out of fifty showed marked improvement in verum, ten out of forty-nine in placebo group. This was particularly with respect to new lesions which healed without much fibrosis and calcification.

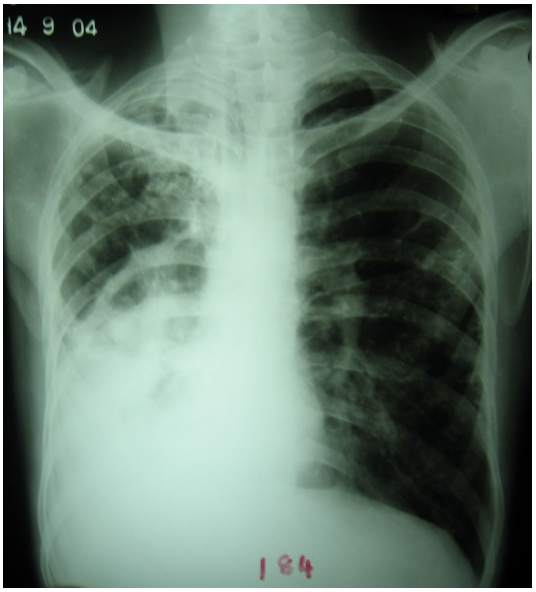

Figure 1: case no 184 (14/ 09/ 04)

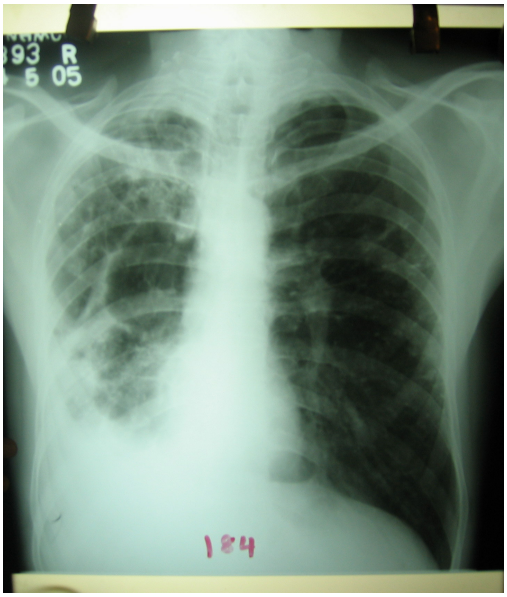

Figure 2: case no 184 (04/ 05/ 05)

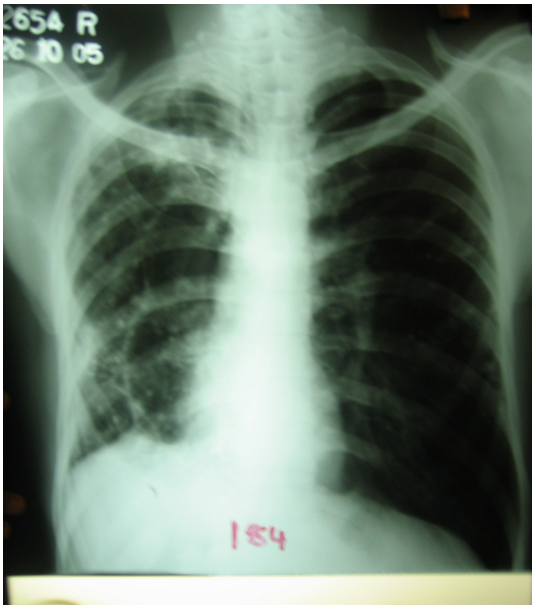

Figure 3: case no 184 (26/ 10/ 05)

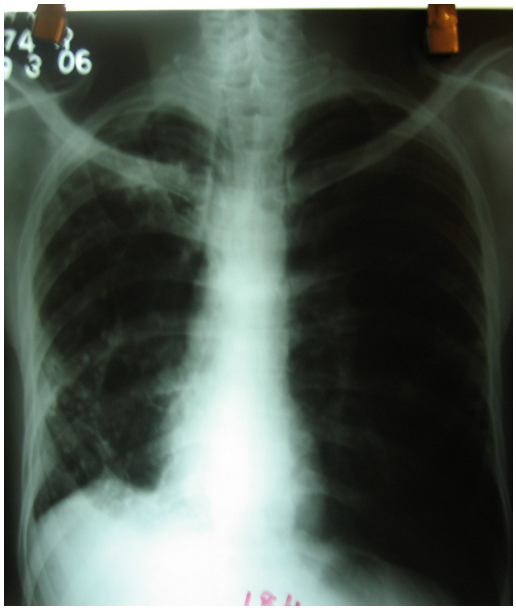

Figure 4: case no 184 (29/ 03/ 06)

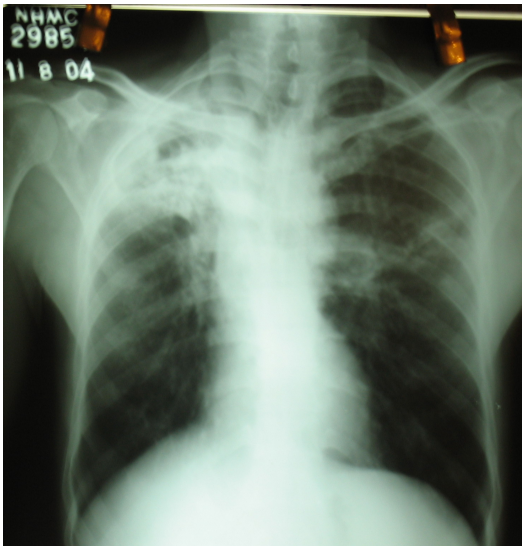

Figure 5: Case no 172 (11/ 08/ 04)

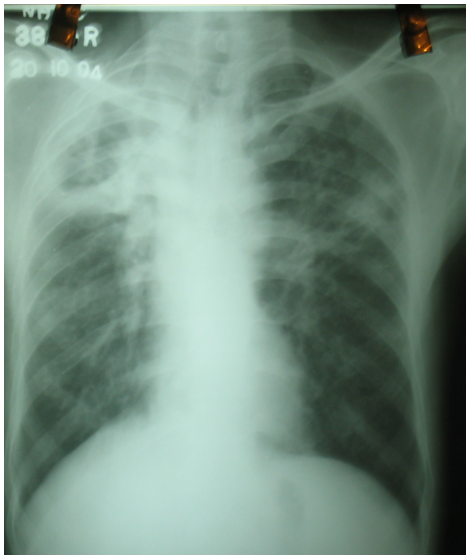

Figure 6: Case no 172 (20/ 10/ 04)

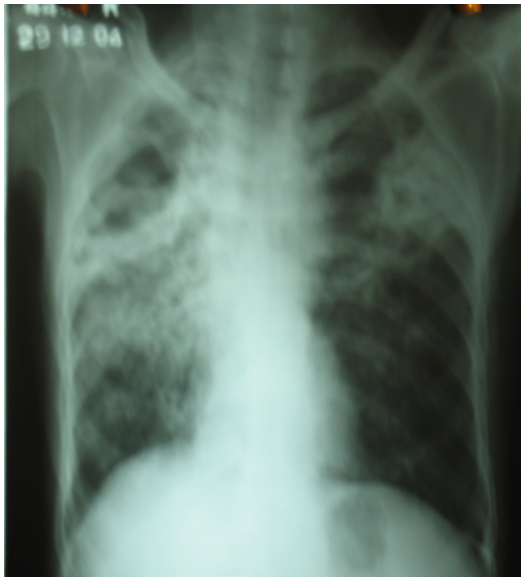

Figure 7: Case no 172 (29/ 12/ 04)

Figure 8 : Extensive Lt Lung lesions with cavities in upper lobe. Lt lower lobe collapse.

Figure 9: Collapse of Left lung with plural effusion, compensatory hypertrophy of right lung

Symptomatic assessment

Any change in general condition like fever and pain, expectoration and cough, appetite, lassitude was monitored on every visit. The change in condition was documented in four grades according to the improvement in number of modalities.

Table 4: Symptomatic assessment

GC Grading	v	p
1	4	11
2	9	13
3	23	12
4	14	13
TOTAL	**50**	**49**

Thirty-seven patients in verum group as compared to twenty-five in placebo group showed grade three & four improvement.

Weight gain:

The change in weight from the initial and final reading has been recorded and compared.(Table 7)

Table no 5: weight gain/loss

Weight (kg.)	verum	placebo
More than - 9	0	1
-3 to - 9	1	4
Upto - 3	8	10
No change	7	10
0- 3	14	5
3- 9	18	18
More than 9	2	1
TOTAL	**50**	**49**

ESR STATUS

ESR was done every six months. A difference of + / -10mm within the Normal range was considered Static.

Table no 6: Changes in ESR

ESR	v	P
Increase	5	7
Decrease	19	15
Static	26	27
TOTAL	**50**	**49**

HAEMOGLOBIN STATUS

Hemoglobin was done every six months. The difference between the initial and final reading is tabulated.

Table no 7: Changes in haemoglobin

HB.	v	P
< -4	**0**	**0**
-2 to -4	**5**	**5**
-0.1 to -2	**12**	**8**
0	**10**	**16**
0.1 to 2	**14**	**14**
2 to 4	**6**	**6**
>4	**3**	**0**

Discussion

Cases were assessed by sputum smear/ culture, x-ray chest, weight gain, hemoglobin and ESR. The above stated revealed that verum (H) group showed better improvement in all parameters, being statistically highly significant in x-ray ($p<0.0001$). The new soft tissue lesions healed faster with less fibrosis. The relapse rate was high in placebo group. The study comprises of analysis of 120 patients in serial order. Individual quota of homeopathic (v) and placebo (p) medicine has avoided any bias in patient selection. All the patients have been subjected to same questioning (attention). Hence any effect of homeopathy highlights the effectiveness of homeopathic remedy and not of homeopath.

Key observations:

The symptoms of the patients in the present study were a combination of the symptoms of the disease and the iatrogenic effect of prolonged use of ATT drugs. Since examples of such a combination are not available in the homeopathic literature, it was decided to study the effect of homeopathic remedies initially, and make a list of effective remedies in such cases. The study began with the use of single homeopathic remedy along with all the ATT drugs, repeated only when the effect of the remedy was deemed to be over.

It is known that the duration of the effect of a dose of remedy varies in different people and is also dependant on the acuteness of disease. Often when the patient was asked about the state of wellness from previous visit, he often said that he was better, but when specifically asked about the effect of the homeopathic remedy, the reply was that the effect lasted from few hours to few days in different people. Therefore, it was decided to repeat the selected remedy at weekly interval.

During the prolonged treatment, there was dilemma of management of concurrent acute illnesses; whether to treat, with homeopathic or allopathic medicine. It was found that suitable acute remedy often help the patient even during acute symptoms such as haemoptysis, coryza, fever etc.

Tub was used as an inter-current remedy, in active disease. Although it was not used initially in several cases, after deliberations it is felt that it should be used irrespective of indications, at regular intervals to enhance the effect of constitutional remedy.

Verum group showed better improvement in all parameters, being statistically highly significant in x-ray ($p<0.0001$) as discussed under

results. The new soft tissue lesions healed faster with less fibrosis. The relapse rate was high in placebo group.

Immune system is subjected to a complex network of cellular and molecular interactions; it seems that the "qualitative" aspect rather than the quantitative can be important. The patho-physiology of TB shows, that only 10% of the bacteria reach pulmonary alveoli after the exposure to infection, rest 90% are thrown out by the action of healthy mucosa lining the upper respiratory tract. In the alveoli, bacteria are ingested by the non-specifically activated macrophages. The degree of bactericidal activity of macrophages is dependent on innate non-specific immune resistance to infection. Once infected (latent TB) a person can develop TB at any time. The progression of latent TB to active disease is directly related to patient's degree of immuno-suppression. Physical or emotional stresses may trigger progression of infection to disease due to weakening of immune resistance[16]. Hence, endogenous factors are equally important in the development of active disease[15,16]. Under RNTCP, the focus of treatment is on exogenous factor (bacilli) by chemotherapy and endogenous factors (immunological) are addressed by advice on nutrition and rest, this appears to be insufficient and further research is needed.

It has been reported that ultra-diluted antigens can transfer signals to immune system and modulate its response when the organism is in challenge with the related antigen[17]. The auto-reactivity of T-cells is managed by the immune system, dependent upon the concentration of the antigen they encounter; if they "see" high concentration of a self-antigen, they are killed, but when exposed to low doses, they undergo a special kind of active inhibition (called 'bystander suppression'). Biotherapy is understood to be intermediary of the mechanism of inflammation (Reckeweg), their use in the treatment and prophylaxis of infectious and parasitic diseases is called dynamised micro-immunotherapy[17,18]. Danninger *et al* also reported immuno-modulatory effects (decrease of circulating immune-complexes) of a biotherapy prepared from *Staphylococcus aureus* in 12CH dilution in HIV-positive patients[19] and there are reports of the use of specific biotherapy (nosodes) in animals[20,21,22,23]. Various experiments suggest that Homeopathic remedies have potential of immune-modulation and can influence endogenous factors[17,18,24-27]. Clinically, this study suggests that homeopathy can supplement the existing regimen of conventional chemotherapy and can improve cure rate, patient satisfaction and may help in MDR-TB cases.

Conclusion

This study has been observational and experimental in nature. It has been observed that the use of Homeopathic remedies along with Allopathic drugs has a complimentary effect. The experiment of using *Tuberculinum* as an intercurrent remedy in active disease has shown promising results. This study has shown significant qualitative improvement in general condition, X-ray chest and weight gain. With ATT only, there were 6 patients who became culture positive from culture negative, while with adding Homeopathic intervention only 2 patients became culture positive from negative. Homeopathic intervention also shortened the average sputum conversion duration of the patients on reserve line. In some patients, those who took homoeopathic treatment relatively early in their course of treatment; the outcome was better and quicker.

All the cases in this study were chronic and burnt out (figure 8-9); the lung was already irreversibly destroyed in varying degrees. It is proposed that if the homeopathic intervention is started along with conventional ATT treatment initially, the healing of the lung may be with much less fibrosis and calcification. That would lead to a fall in the incidence of subsequent chronic obstructive pulmonary disease (COPD) and MDR-TB.

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