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*Full Length Research Paper*

# Open label trial of adjuvant immunotherapy with Dzherelo, Svitanok and Lizorm, in MDR-TB, XDR-TB and TB/HIV co-infected patients receiving anti-tuberculosis therapy under DOT

**Nathalia D. Prihoda[1], Olga V. Arjanova[1], Lyudmila V. Yurchenko[1], Nina I. Sokolenko[1], Lyudmila A. Vihrova[2], Volodymyr S. Pylypchuk[3], Galyna A. Kutsyna[4]***

[1]Lisichansk Tuberculosis Dispensary, Lisichansk, Ukraine.
[2]Lisichansk Regional Hospital, Lisichansk, Ukraine.
[3]Ekomed LLC, Kiev, Ukraine.
[4]Luhansk Regional AIDS Center and Luhansk State Medical University, Luhansk, Ukraine.

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**Open label trial of anti-tuberculosis therapy (ATT) combined with oral immunomodulators derived from medicinal plants, Dzherelo, Svitanok, and Lizorm, was conducted in a representative group of 14 Ukrainian patients, half of whom (7) were dually infected with HIV. Among them 9 individuals had multidrug-resistant form of TB (MDR-TB) including 2 (22%) patients who presented with extensively drug-resistant TB (XDR -TB). Patients hospitalized in our TB dispensary were treated under directly observed therapy (DOT) until they became culture negative and their radiological and clinical symptoms improved. All patients, except one, gained weight, ranging between 3-17 kg with median gain of 9 kg (P=0.0002) . The liver function tests revealed that the level of total bilirubin had decreased from 15.5 to 12 mol/L – an improvement that was statistically significant (P=0.03). Alanine transaminase (ALT), another marker of hepatic damage, declined from abnormally high 55.4 IU/L to a normal 38.2 IU/L level (P=0.03) . The median time to bacterial clearance was 32 days. The mean duration of therapy was 3.9 months - shorter than average 12 months time needed to treat drug- resistant TB. These findings indicate that the combination of Ekomed's phytopreparations with ATT enhances the efficacy of TB therapy and is safe and beneficial even to patients with poor prognosis due to drug resistance and/or co-infection with HIV.**

**Keywords:** MDR-TB, XDR-TB, Mycobacterium tuberculosis, HIV, herbal, phytotherapy.

## INTRODUCTION

The TB epidemic is on the rise in most countries, include-ing Ukraine. This problem is further compounded by HIV co-infection, since one-third of HIV/AIDS-related deaths results from TB. Ukraine has the highest preva- lence of TB/HIV co-infection in Eastern Europe (van der Werf et al., 2006). The effectiveness of TB therapy is significantly lower among patients with HIV/AIDS. The World Health Organization (WHO) estimates that a per-son with both HIV and TB infection is thirty times more likely to become ill with TB than a person with *Mycobacterium tuberculosis* infection alone (Reid et al., 2006).

The rate of relapse and mortality are consistently higher even when TB/HIV patients are treated with anti-tuberculosis therapy (ATT) under directly observed treatment regimen (DOT) (Khauadamova et al., 2001). Drug resistance accompanied by HIV-associated immunodeficiency is the main cause of treatment failure. The recently published survey of Nikolayevskyy et al., (2007) indicates that in Ukraine the multi-drug resistant form of TB (MDR-TB) was found in 27.3% of TB patients and was twice higher (54.8%) among incarcerated individuals.

The first line of TB drugs includes isoniazid (H), rifampicin (R), ethambutol (E), pyrazinamide (Z), and streptomycin (S). There are six classes of second-line TB drugs including aminoglycosides: amikacin, kanamycin; polypeptides: capreomycin, viomycin, enviomycin; fluoroqui-

*Corresponding author. E-mail: kutsyna@list.ru.

nolones: ciprofloxacin, moxifloxacin; thioamides: ethionamide, prothionamide; cycloserine; and para-aminosalicylic acid. Other TB drugs, which are not on the WHO list, include: rifabutin; clarithromycin; linezolid; thioacetazone; thioridazine; arginine; vitamin D; and R207910. MDR-TB is diagnosed when *M. tuberculosis* is resistant to at least isoniazid (H) and rifampicin (R), the two most powerful, first line drugs. The extensively resistant form of TB (XDR-TB), in addition to lack of sensitivity to H and R, is also resistant to any of fluoroquinolones, and at least one of second-line injectable drugs, e.g., kanamycin and amikacin (Migliori et al., 2007). These emerging strains of drug-resistant TB became of particular concern after recent publication of outbreak in South Africa where 52 of 53 patients with XDR tuberculosis died within 16 days from the time of diagnosis (Gandhi et al., 2006).

Immunomodulators Dzherelo, Svitanok and Lizorm are made from a combination of medicinal plants and are commonly used in Ukraine for the management of TB and HIV infections, including patients with dual infection (Arjanova et al., 2006; Chkhetiany et al., 2007; Prihoda et al., 2006; Zaitzeva, 2006). They have been approved in 1997 by the Ministry of Health of Ukraine as functional supplements with therapeutic indications. In 1999 Dzherelo and Svitanok were specifically recommended as immune adjuncts for the therapy of pulmonary tuberculosis (Melnik et al., 1999). So far they have been used by several hundred thousand individuals for various indications including chronic bacterial and viral infections such as TB and HIV, autoimmune diseases, and malignancy (Chkhetiany et al., 2007). Published studies have demonstrated that Dzherelo can significantly shorten the duration of treatment and helps to achieve higher response rate even in those who are HIV co-infected or have MDR forms of TB (Arjanova et al., 2006; Chkhetiany et al., 2007; Prihoda et al., 2006). Dzherelo has also been found to decrease the hepatotoxicity associated with ATT (Zaitzeva, 2006). Svitanok is commonly used for counteracting the toxic effect of drugs and in hepatitis therapy. Lizorm is commonly used for alleviating symptoms of autoimmune disorders. Our study was aimed at evaluating the combined effect of Dzherelo, Svitanok, and Lizorm in a representative sample of hospitalized patients who received the anti-TB therapy under DOT. Patients who had particularly poor prognosis due to drug resistance and/or HIV co-infection were selected to be given ATT in combination with three herbal immunomodulators.

## MATERIALS AND METHODS

### Patients

Fourteen patients with active TB and poor prognosis due to resistant TB and/or HIV co-infection were selected to be given in addition to ATT the over-the-counter phytopreparations manufactured by Ekomed company. The age of patients ranged between 24 and 58 years with mean/median age of 39 years. The female/male ratio was 3/11. The diagnosis of HIV infection was established by standard ELISA test further confirmed by Western blot. Seven patients presented with first- diagnosed or primary TB and the other half had previously treated, relapsed, or chronic TB. Nine patients had drug-resistant TB and five patients in TB/HIV subgroup were drug-sensitive. All patients with HIV were in advanced stage III of HIV infection. Neither patient has received the anti-retroviral therapy prior to and during follow-up. Active pulmonary tuberculosis was certified by a medical history and clinical findings compatible with pulmonary tuberculosis, a chest X-ray showing lung involvement, and positive sputum smear for acid- fast bacilli or the culture of M. tuberculosis. All patients received anti-tuberculosis therapy administered under DOT schedule. In addition to ATT, patients received a daily dose of Dzherelo which was given as 30 drops diluted in a half-glass of water at least 30 minutes before breakfast. Some patients received Dzherelo-PI – a modified form Dzherelo. The same 30 drops dose of Lizorm and Svitanok were given before lunch and supper respectively. The conduct of the trial was approved by the Ethical Board of Lisichansk TB dispensary. The participation in this study was voluntary and patients were eligible to enroll only after signing the written consent. Patients were treated until they were discharged from the dispensary. The decision to discharge was based on negative culture findings and satisfactory clinical and radiological findings.

### Anti-tuberculosis drugs and phytopreparations

All anti-TB drugs were supplied through the centralized national supply system of Ukraine. Phytopreparations, Dzherelo, Svitanok, and Lizorm, were generously provided by Ekomed LLC. DZHERELO contains concentrated aqueous-alcohol extract from medicinal plants such as Aloe (*Aloe arborescens*), Common knotgrass (*Polygonum aviculare*), Yarrow (*Achillea millefolium*), Purple coneflower (*Echinacea purpurea*), St. John's Wort (*Hypericum perforatum*), Centaury (*Centaurium erythraea*), Snowball tree berries (*Viburnum opulus*), Nettle (*Urtica dioica*), Dandelion (*Taraxacum officinale*), Sweet-sedge (*Acorus calamus*), Oregano (*Oreganum majorana*), Marigold (*Calendula officinalis*), Seabuckthorn berries (*Hippophae rhamnoides*), Elecampane (*Inula helenium*), Tormentil (*Potentilla erecta*), Greater plantain (*Plantago major*), Wormwood (*Artemisia sp*.), Siberian golden root (*Rhodiola rosea*), Cudweed (*Gnaphalium uliginosum*), Licorice (*Glycyrrhiza glabra*), Fennel (*Foeniculum vulgare*), Chaga (*Inonotus obliquus*), Thyme ( *Thymus vulgaris*), Three-lobe Beggarticks (*Bidens tripartite*), Sage (*Salvia officinalis*), Dog rose (*Rosa canina*), and Juniper berries (*Juniperus communis*). SVITANOK contains flowers of Immortelle (*Helichrysi arenarii*), Barberry roots (*Berberis vulgaris*), Chicory roots (*Cichorium intybus*), Coriander seeds (*Coriandrum sativum*), Marigold (*Calendula officinalis*), Wormwood (*Artemisia sp*.), and Maize cores with stigmas ( *Zea mays*). LIZORM contains concentrated aqueous-alcohol extract from Barberry roots (*Berberis vulgaris*), Aronia berries (*Aronia melanocarpa*), St. John's Wort (*Hypericum perforatum*), Centaury (*Centaurium erythraea*), Nettle (*Urtica dioica*), Common knotgrass (*Polygonum aviculare*), Wild strawberry leaves ( *Fragaria vesca*), Greater celandine (*Chelidonium majus*), and Immortelle ( *Helichrysi arenarii*). All phytoconcentrates were approved in 1997 by the Ministry of Health of Ukraine as dietary botanical supplements. In 2006 they have received so-called status of functional food – a special category of herbal supplements that can carry medical claims which were substantiated by clinical evidence.

### Test for drug resistance

The cultures of *M. tuberculosis* derived from sputum of each patient were inoculated into ready-to-use tubes each containing one of first-line and second-line TB drug that were incorporated at

predetermined concentrations into standard Löwenstein-Jensen agar slants. The drug resistance was evaluated with commercially available kit (Tulip Diagnostics, Goa, India). The cultures were incubated at $37^{o}$ C and checked periodically until appearance of colonies in control, drug-free tubes.

**Statistical analysis**

The obtained results were analyzed with the aid of statistical software STATMOST (Datamost, South Sandy, UT). The baseline cell numbers relative to the end of study were evaluated by paired Student t-test. All statistical calculations were done on total number of patients without subgrouping them into responders and non-responders. When required stratification analysis was carried out to determine the difference between distinct categories of patients. The resulting probability values were considered as significant at P 0.05.

## RESULTS

The treatment lasted until patients were discharged from the dispensary upon negative culture findings and satisfactory clinical and radiological findings. The duration of DOT ranged between 10.6-30.3 weeks with average/median 16.7/16.2 weeks (Table 1). While patients with HIV co- infection were treated on average 3 weeks longer, the difference was not statistically significant (P=0.17). The time to negative culture ranged between 10-62 days with mean/median 32/33 days. The patients with HIV became culture negative at 36 instead of 30 days as in patients with TB alone but the difference was not significant (P=0.2). Similarly, no difference was seen between chronic, previously treated TB and first-diagnosed TB cases in terms of days to discharge, i.e., 113.3 vs 120.4 (P=0.38) or days to bacterial clearance, 34.7 vs 31.4 (P=0.33). The comparison of treatment outcomes between 9 drug- resistant and 5 drug-sensitive cases also failed to reveal statistical difference. Time to negative culture was 34 vs 31.4 days and time to discharge 107 vs 135 days with probability values P=0.33 and P=0.18 respectively.

As a result of combination treatment our patients experienced better quality of life and were tolerating ATT at much higher degree than those who received ATT without phytotherapy. This is reflected and supported by intriguing observation that almost every patient had gained substantial lean body mass – an effect that was evident within one month from initiation of the therapy. Except patient #10 who lost 10 kg, all other patients gained weight, ranging between 3 and 17 kg by the end of 3.9 months of follow-up. The average accrual in lean body mass was 8.4 kg (median 9 kg) which was statistically highly significant (P=0.0002).

The improvement of quality of life is further supported by quantitative liver function tests. The level of total bilirubin had decreased from mean 15.5 to 12 mol/L – a favorable change that was statistically significant (P = 0.03). Similarly the values of alanine transaminase (ALT), another marker of hepatic damage, have declined from elevated (55.4 IU/L) to normal levels (38.2 IU/L) – a change that was also statistically significant (P=0.03).

Another sign of clinical improvement is a recovery from anemia and inflammatory status. Most patients at study entry were anemic and had abnormally elevated leukocyte counts. At the end of treatment these parameters were improved in a statistically significant manner. The levels of hemoglobin had risen from 105±15.6 to 117±5.3 g/L (P=0.003), whereas leukocyte counts had returned back to normal levels from 8.7±2.9 to 6.9±1.7 $x10^{9}$ cells/L (P = 0.02).

## DISCUSSION

Results of this limited, small-scale study indicate that when ATT is combined with immunomodulating herbal preparations, Dzherelo, Svitanok, and Lizorm, the patients are cured after about 4 months and complete disappearance of *Mycobacterium tuberculosis* from spu-tum culture is observed within one month from treatment initiation. The conversion time of sputum mycobacterial culture from positive to negative is an important interim indicator of the efficacy of anti- TB intervention (Holtz et al., 2006). We observed culture conversion at median 32 days. This is twice shorter than the reported conversion time for drug-resistant TB patients in Latvia or Hong Kong (Holtz et al., 2006; Yew et al., 2003) . The mean duration of successful chemotherapy in Yew et al., study (2003) was 14.5 months with a range that appears to be anywhere between 11 to more than 24 months as reported by Japanese investigators (Yoshiyama et al., 2007) . If these studies are representative of success rates in MDR-TB therapy then our immunomodulatory intervenetion appears to produce the twofold reduction in culture conversion time and shortens treatment duration by at least three times. These results indicate that the combination of phytoconcentrates with anti-tuberculosis drugs results in significant enhancement of the efficacy of ATT. Our findings agree with earlier clinical studies of ATT that were conducted mostly with Dzherelo and occasionally with Dzherelo and Svitanok combination. They also indicated that the efficacy of ATT was enhanced and duration of treatment was considerably shortened (Arja-nova et al., 2006; Chkhetiany et al., 2007; Prihoda et al., 2006; Zaitzeva, 2006). The beneficial effects were observed in patients with MDR as well as patients with TB/HIV co-infection. Furthermore, previous studies have shown the amelioration of liver function as evidenced by normali-zation of ALT, AST, bilirubin and other markers of liver damage. This effect alone is of major significance since many of TB drugs are hepatotoxic and so far there are no effective means to counteract this negative aspect of ATT (Durand et al., 1996).

By definition, tuberculosis is a wasting disease (Edwards et al., 1971). This condition is poorly manageable and is one of the leading factors contributing to higher morbidity and mortality (Villamor et al., 2006).

**Table 1.** Baseline and end-of-study characteristics of TB patients treated with ATT in combination with Dzherelo, Svitanok, and Lizorm

| No | Sex | Age | Type of TB infection | TB drug resistance* | HIV status/AIDS stage | Days on therapy | Days to negative culture | Leukocyte x $10^9$L | | Hb g/L | | Weight change kg | | Total bilirubin mol/L | | ALT IU/L | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | before | after | before | after | before | after | before | after | before | after |
| 1 | M | 30 | Primary | MDR H/R/Z/O | - | 74 | 10 | 9.4 | 12 | 82 | 104 | 60 | 68 | 32.4 | 11.7 | 37 | 50 |
| 2 | M | 42 | Primary | XDR H/R/E K/O/PAS | - | 74 | 23 | 11.6 | 8.1 | 122 | 114 | 59 | 68 | 10.5 | 11.7 | 25 | 50 |
| 3 | M | 58 | Primary | MDR R/ETH CPX/PFX | - | 122 | 30 | 9.8 | 6 | 120 | 123 | 66 | 78 | 14 | 10.5 | 37 | 50 |
| 4 | M | 38 | Chronic | MDR S/H/ETH PAS | - | 131 | 30 | 14 | 6 | 108 | 120 | 52 | 68 | 16.3 | 10.5 | 62 | 12 |
| 5 | M | 44 | Primary | XDR H/R/ETH K/L/PAS | - | 143 | 34 | 4.5 | 6.8 | 120 | 118 | 63 | 69 | 18.6 | 10.5 | 12 | 50 |
| 6 | M | 32 | Primary | MDR H/E/PAS RFB | - | 122 | 55 | 5.8 | 6 | 110 | 122 | 75 | 85 | 10.5 | 10.7 | 50 | 12 |
| 7 | M | 47 | Chronic | MDR H/R/E/K | +/III | 75 | 28 | 8 | 6.8 | 106 | 122 | 66 | 78 | 14 | 19.7 | 75 | 50 |
| 8 | M | 47 | Primary | - | +/III | 212 | 34 | 6.8 | 6.9 | 128 | 118 | 77 | 80 | 11.7 | 10.5 | 50 | 50 |
| 9 | M | 39 | Chronic | - | +/III | 107 | 38 | 6.5 | 4.9 | 106 | 112 | 65 | 76 | 10.5 | 11.5 | 75 | 50 |
| 10 | M | 27 | Chronic | MDR H/K/A PAS | +/III | 125 | 62 | 11 | 6.2 | 102 | 116 | 76 | 66 | 16.4 | 10.5 | 37 | 12 |
| 11 | F | 34 | Chronic | - | +/III | 98 | 34 | 5.4 | 5.2 | 105 | 118 | 58 | 67 | 20.9 | 10.5 | 42 | 12 |
| 12 | F | 24 | Chronic | - | +/III | 74 | 24 | 6.5 | 7.3 | 95 | 118 | 63 | 70 | 10.5 | 10.5 | 75 | 50 |
| 13 | M | 45 | Chronic | - | +/III | 183 | 27 | 9 | 6.8 | 94 | 120 | 61 | 68 | 18.6 | 18.6 | 112 | 50 |
| 14 | F | 39 | Primary | MDR H/R/K Prothio | +/III | 96 | 34 | 13.3 | 7.1 | 72 | 110 | 43 | 60 | 11.7 | 10.5 | 87 | 37 |
| | 11/3 | 39 ±9 | 7/7 | 9/5 | 7/7 | 117±42 | 33±12.8 | 8.7± 2.9 | 6.9± 1.7 | 105 ±15.6 | 117 ±5.3 | 63.1 ±9.2 | 71.5 ±6.8 | 15.5 ±6 | 12± 3.1 | 55.4 ±27 | 38.2 ±17.5 |
| | | | | | | | | Mean decrease =1.8x$10^9$L P=0.02 | | Mean gain=12g/L P=0.003 | | Mean gain= 8.4 kg P=0.0002 | | Mean decrease =3.5 mol/L P=0.03 | | Mean decrease =17.2 IU/L P=0.03 | |

*Criteria for definition of XDR as per the WHO recommendations (Migliori et al., 2007). ATT drugs are abbreviated as follows: Isoniazid (H), Rimfapicin (R), Pyrazinamide (Z), Ethambutol (E), Streptomycin (S), Kanamycin (K), Amikacin (A), Ofloxacin (O), Levofloxacin (L), Pefloxacin (PFX), Ciprofloxacin (CPX), Para-aminosalicylic acid (PAS), Rifabutin (RFB), Ethionamide (ETH), Prothionamide (Prothio).

Khan et al., (2006) reported that patients with under weight problem had higher risk of TB relapse and that changes in weight were an independent predictor of treatment outcome. The remarkable aspect of our therapy is a dramatic body weight gain in 93% of our patients (P = 0.0002). TB drugs seldom enhance body weight. The only known to us report of significant weight gain has been described by Donald et al., (1997). In their placebo-controlled study the increase in body mass, that is, mean gain 8.9 kg, has been described when TB patients were administered beta-sitosterol and sitosterolin – phytosterols from a pine tree. However, this intervention had no effect on the rate of mycobacterial clearance. There are other adjunct therapies such as nutritional supple-ments and corticosteroids that can enhance weight but they also had no effect on TB (Paton et al., 2004; Smego and Ahmed, 2003). The weight loss-reversing property of Dzherelo, Svitanok and Lizorm along with substantiated therapeutic effect on TB and HIV can be particularly advantageous to those who live in resource- poor countries, where malnutrition is very common and deaths are more prevalent due to this single cause (Farmer et al., 1991) . This study includes for the first time Ukrainian patients with XDR form of TB. Despite poor prognosis we were able to achieve mycobacterial clearance and significant clinical and radiological improvement to such an extent that these patients were discharged from the dispensary within average 16 weeks. Our results contrast two available clinical studies of XDR-TB. In a study from South Africa 52 out of 53 (98%) patients had died within 2 weeks from diagnosis (Gandhi et al., 2006). However this mortality rate may be not representative of the situation when more advanced clinical care is available. The clinical survey reported by Kim et al., (2007) indicated that in South Korea the treatment failure due to XDR -TB was 44.2%, whereas 27.4% patients with MDR did not respond to the therapy.

However we had only two individuals with XDR-TB and our results need to be confirmed in larger group of patients. Judging from surveys on global prevalence of XDR-TB among MDR-TB cases we sur- mise that 2 out of 9 (22%) cases of multidrug-resistant TB in our dispensary are in the 10-20% range reported recently (CDC, 2006; Migliori et al., 2007).

The currently available chemo- therapy for the treatment of TB is not perfect (Durand et al., 1996). Multiple tuberculous drugs need to be taken in combination for long periods of time.

The extended duration of therapy, coupled with the side effects, often results in poor patient adherence, treatment failure, and the emergence of drug resistance. It is agreed that immune-based therapies are urgently needed to complement tuberculosis drug disco-very (Achkar et al., 2007; Kaufmann, 2006; Tomioka, 2004). We also believe that the immunotherapy is the indispensable part of therapeutic strategies against TB (Pylypchuk, 2003). Many effective immune interventions are available against bacteria, protozoa, fungi and vi- ruses (Ershov, 2003). While effective the mechanism of most immunomodulators is poorly understood. This draw-back should be balanced against clinically confirmed benefits.

Some medicinal herbs were shown to modulate the immune response to TB (Tomioka, 2004), while others exerted direct antimycobacterial activity (Newton et al., 2000). From the review of available to us medical literature it is apparent that very few medicinal plants have demonstrated TB-curing properties.

Recent story, describing how the Zulu's traditional herbal remedy became European phytomedicine, further highlights the difficulties of finding and introducing an effective TB drug from a botanical source (Bladt and Wagner, 2007). It is quite unlikely that herbal immunomodulators used in our study act as tuberculostatic agents since *in vitro* growth of *M. tuberculosis* laboratory strains, H32 and H37Rv, was not affected directly by Dzherelo or Svitanok (Melnik et al., 1999). The same rate of response to treatment regardless whether patients were drug resistant, re-treated, or had HIV also suggests that the combination of herbs used by us does not interfere with replication pathways of mycobacteria. Dramatic weight gain observed in our patients indicates that their mechanism of action differs from ATT since tuberculosis drugs seldom produce significant weight gain (Paton et al., 2004).

This is further supported by the fact that diseases etiologically unrelated to *M. tuberculosis* were responsive to the therapy with Dzherelo and Lizorm (Bodnar et al., 2002).

Tuberculosis remains an enormous global health problem. There are 8 million new cases and 2 million deaths from TB annually (Reid et al., 2006). Despite the overwhelming burden of disease, no new treatment regimens were developed since 1960's and current strains of TB are becoming gradually resistant to existing drugs. The emergence of XDR-TB with high mortality rate within very short period of time raises grave concerns of a future epidemic of virtually untreatable TB (Gandhi et al., 2006).

Our study provides the preliminary evidence of the efficacy of ATT in combination with Dzherelo, Svitanok and Lizorm against XDR-TB. These herbal immunomodulators were recommended in Ukraine as an immune adjunct to TB therapy (Melnik et al., 1999). The major advantage associated with our intervention is twice-reduced time to negative culture conversion and at least three-fold shortened duration of treatment. These benefits along with other significant improvements such as weight gain, lack of hepatotoxicity, reduced anemia and inflammation, impressive radiological and clinical recovery are all in favor of adjunctive immune approach to ATT.

Additional studies need to be conducted to develop better understanding of this immunomodulating combination against drug-resistant TB and to enlarge the current arsenal of TB drugs.

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