Efficacy and Safety of Phytoconcentrate Dzherelo (Immunoxel) in Treatment of Patients with Multi-Drug Resistant TB (MDR-TB) in Comparison to Standard Chemotherapy

[1]S.I. Zaitzeva, [1]S.L. Matveeva, [1]T.G. Gerasimova, [1]Y.N. Pashkov, [1]D.A. Butov,
[2]V.S. Pylypchuk, [3]V.M. Frolov and [3]G.A. Kutsyna
[1]Department of Phtysiatry and Pulmonology, Kharkov National Medical University, Kharkov, Ukraine
[2]Ekomed LLC, Kiev Ukraine
[3]Luhansk AIDS Center and Luhansk State Medical University, Luhansk, Ukraine

Abstract: Safety and efficacy of phytoconcentrate Dzherelo (Immunoxel) as an adjunct immunotherapy for treatment of TB was compared to a standard anti-mycobacterial chemotherapy by enrolling 66 patients with active pulmonary tuberculosis. Among them 48 individuals presented with Multi-Drug Resistant (MDR) form of TB who were divided into 2 matching groups to receive either individualized Anti-TB Therapy (ATT) or ATT with 50 drops of Dzherelo twice-per-day. Patients were followed for 3 months and then assessed for sputum smear clearance rate, radiological findings and liver damage markers such as bilirubin, ALT, cholinesterase, gamma-glutamyl transpeptidase and thymol turbidity test. At the end of the 3rd month of follow-up 81.8% (27/33) of patients on Dzherelo had negative sputum smear, whereas, only 7 out 33 patients (21.2%) on ATT had converted (p = 0.0002). Administration of Dzherelo resulted in complete healing of pulmonary infiltrations and cavities in 12 (36.4%) patients in Dzherelo group, while only one patient (3%) treated with TB drugs had improved (p = 0.0008). Our results indicate that when Dzherelo is added to ATT it can produce significant clinical, microbiological and radiological improvements. Based on liver function tests Dzherelo was found to be safe and improved or reversed liver damage caused by ATT. Our findings support clinical studies by other investigators showing that immune intervention with Dzherelo accelerates and enhances the outcome of tuberculosis therapy.

Key words: MDR-TB, *Mycobacterium tuberculosis*, immunotherapy, immunomodulator, herbal, phytomedicine, medicinal plants

INTRODUCTION

Nearly 9 million people develop Tuberculosis (TB) each year and 2 million die from the disease. Tuberculosis has become an emerging global public health priority. The incidence of TB continues to increase in Ukraine as well (Dye *et al.*, 2005). In 1962, the incidence of TB in Ukraine was 178 cases/100,000 individuals, which then gradually declined to 73, 42 and 41.6 cases/100,000 in 1972, 1982 and 1992, respectively. However this trend reversed and by 2002, TB incidence and prevalence became 80.4 and 330 per 100,000, respectively. TB mortality almost doubled from 10.2/100,000-21.6/100,000 between 1990 and 2001 (Drobniewski *et al.*, 2005).

Similarly to situation in Africa the success rates of therapy in Eastern Europe, including Ukraine, are substantially below average when compared with other regions of the world (Atun and Olynik, 2008). In addition the Ukraine has worsening epidemics of drug resistant TB that is increasingly converging with HIV (Dubrovina *et al.*, 2008). Despite availability of TB drugs the situation is far from ideal and better therapeutic interventions are clearly needed to reverse the current trend.

Oral immunomodulator Dzherelo (Immunoxel) is used in Ukraine for the management of both TB and HIV infections, including patients co-infected with TB and HIV. Dzherelo was approved in 1997 by the Ministry of Health of Ukraine as an immunomodulating supplement, which so far has been used by hundreds of thousands individuals for various indications including chronic bacterial and viral infections, autoimmune diseases and malignancy. In 1999 Dzherelo was recommended by the health authorities of Ukraine as an immune adjunct for

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Corresponding Author: Svetlana Zaitzeva, Department of Phtysiatry and Pulmonology, Kharkov National Medical University, Kharkov, Ukraine

treatment of tuberculosis (Melnik *et al.*, 1999). Clinical studies have indicated that Dzherelo helps to achieve better clinical response when combined with standard Anti-Retroviral (ART) or Anti-Tuberculosis Therapy (ATT) (Chechitiany *et al.*, 2007; Prihoda *et al.*, 2007, 2008; Nikolaeva *et al.*, 2008a, b; Zaitzeva *et al.*, 2008). Dzherelo has been found to reduce the incidence of opportunistic infections and reverse TB-associated wasting. Dzherelo has also been found to alleviate the hepatotoxicity associated with ATT as evidenced by improvement of liver function tests. However, these studies have not dealt with the effect of Dzherelo on other clinical parameters associated with TB. Our study was, thus, aimed at defining the adjunct effect of Dzherelo on sputum conversion and radiological symptoms as well as select biochemical and liver function among patients with active pulmonary TB. The advantage of adjunct Dzherelo immunotherapy was compared to a treatment regimen consisting of ATT alone.

MATERIALS AND METHODS

Patients: The study involved 66 patients most of whom had with first-diagnosed pulmonary TB. Only 9% of patients had been treated previously with anti-TB drugs. The ratio of males/females was 54/12. All study patients presented with active form of pulmonary TB. Most common symptoms were prolonged heavy cough, pain in the chest, high fever, profuse night sweats, fatigue, dyspnea, hemoptysis and loss of weight and appetite. Active pulmonary tuberculosis was certified by a medical history and clinical findings compatible with tuberculosis, a chest X-ray showing lung involvement and positive sputum smear for Acid-Fast Bacilli (AFB) and the culture of *M. tuberculosis*. The prevailing majority of these patients 48/66 (72.2%) had Multi-Drug Resistant TB (MDR-TB). The categories of observed pulmonary involvement on chest X-ray were infiltrating (72%), milliary (18%) and cavitary (10%) forms of TB. Every patient was positive for *Mycobacterium tuberculosis* by sputum smear and culture. Patients' age ranged between 19-60 years. Patients were divided into 2 groups matched by gender, age and disease severity. The conduct of the trial was approved by the internal review board of the University. The participation in this study was voluntary and patients were eligible to enroll only after signing the written consent.

Treatment regimen: All patients received standard individualized TB therapy. The anti-TB drugs were procured through the centralized national supply system of Ukraine. Patients in adjunct immunotherapy group in addition to the same regimen of TB drugs received 50 drops of Dzherelo, given in a glass of water twice daily; usually 2 h after breakfast and 30 min before supper. The treatment was administered for 3 months as Directly Observed Therapy (DOT) to patients hospitalized in our TB dispensary. The over-the-counter phytoconcentrate, Dzherelo (Immunoxel) was generously supplied by Ekomed company. It contains concentrated aqueous-alcohol extract from medicinal plants such as aloe (*Aloe arborescens*), common knotgrass (*Polygonum aviculare*), yarrow (*Achillea millefolium*), 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*), 3-lobe beggarticks (*Bidens tripartite*), sage (*Salvia officinalis*), dog rose (*Rosa canina*) and juniper berries (*Juniperus communis*). Dzherelo approved in 1997 by the Ministry of Health of Ukraine as dietary supplements. In 2006, it received status of a functional food-a superior category of herbal supplements which can carry medical claims as substantiated by clinical evidence.

Clinical endpoints and exclusion/inclusion criteria: Every patient who presented with active pulmonary TB was eligible for this study. No restrictive exclusion criteria for study enrollment were set up except disallowing patients who tolerated poorly chemotherapy. Primary endpoints of interest in this study were the effect of prescribed therapy on microbiology and radiological findings. Secondary endpoints were changes in liver biochemistry.

Laboratory evaluation: In addition to clinical and radiological evaluation a standard microbiology examination of sputum smear staining by Ziehl Neelsen method was conducted prior to study entry and at 2nd and 3rd months post-treatment. Liver function was assessed by measuring ALT transaminase, total bilirubin, cholinesterase, Gamma-Glutamyl Transpeptidase (GGT) and thymol turbidity test.

Statistical analysis: The obtained results were analyzed with statistical software GraphPad (GraphPad Software, Inc., La Jolla, CA 92037). The baseline quantitative values relative to the end of study values were evaluated by paired or unpaired Student t-test. Other statistical

calculations such as determination of standard deviation, mean and median, were performed with the same software. The non-parametric or categorical values of treatment outcomes were compared by Fisher's exact 2×2 test. All statistical analyses were done on intent-to-treat basis, involving the total number of patients without subgrouping them into responders and non-responders. The resulting probability values were considered as significant at $p \leq 0.05$.

RESULTS AND DISCUSSION

Clinical improvements: The improvement of baseline clinical symptoms such as night sweats, dyspnea, nausea, fatigue and general malaise was observed within 2-3 weeks. By 8-10 weeks increase in body weight, disappearance of fever and weakness were clearly established. The improvement in quality of life signs among patients on ATT was less common and usually correlated with other endpoints. Due to subjective nature of clinical symptoms and difficulty of measuring them in an objective manner these effects are not presented in this study.

Sputum smear conversion: At the end of 2nd month of follow-up 21 out of 33 patients (63.6%) on Dzherelo had negative sputum smear conversion, whereas only 6 patients (18.2%) on ATT had converted (Fig. 1). The difference by Fisher's exact two-way test was highly significant (p = 0.0002). Further discrepancy was observed at the end of 3rd month. Negative smear test has been found in additional 6 patients on Dzherelo whereas only one individual converted in ATT arm, bringing total to 81.8 and 21.2% (p = 0.000001).

Radiological findings: Administration of Dzherelo was characterized by remarkable clinical response as judged by treating physicians. In ATT group these improvements were seldom observed. Chest X-ray analysis confirmed these subjective impressions (Fig. 1). The healing of pulmonary lesions and cavities was seen in 12 (36.4%) patients in Dzherelo group while only one patient (3%) treated with TB drugs had shown resolution by third month (p = 0.0008).

Liver function test: Since TB chemotherapy causes hepatotoxicity we compared liver function markers in 2 groups of patients. The results are presented in Table 1. The levels of ALT appeared slightly to increase above normal in Dzherelo group (p = 0.09) while they had almost doubled in ATT group (p<0.0001). The levels of total bilirubin descended to normal in Dzherelo recipients but increased in patients treated with chemotherapy alone. The activity of cholinesterase deteriorated in ATT group but improved in immune intervention group. Levels of gamma-glutamyl transpeptidase were not much affected by either of treatment modalities. Thymol turbidity test appeared to show twice-higher inflammation process in ATT but no differences were seen in Dzherelo recipients.

Our results indicate that when Dzherelo is combined with ATT significant clinical, microbiological and radiological improvements are produced. Dzherelo was found to be safe and has improved or even reversed liver damage produced by ATT. These findings support earlier clinical investigations of Dzherelo by other investigators (Melnik *et al.*, 1999; Chechitiany *et al.*, 2007; Prihoda *et al.*, 2007, 2008; Nikolaeva *et al.*, 2008a, b; Zaitzeva *et al.*, 2008).

MDR-TB is diagnosed when Mycobacterium tuberculosis are resistant to at least izoniazid (H) and Rifampicin (R)-two most common first-line drugs. Nikolayevskyy *et al.* (2007) indicated that in the southern Ukraine the Multi-Drug Resistant form of TB (MDR-TB) was found in 27.3% of TB patients and was twice higher among formerly incarcerated individuals. According to
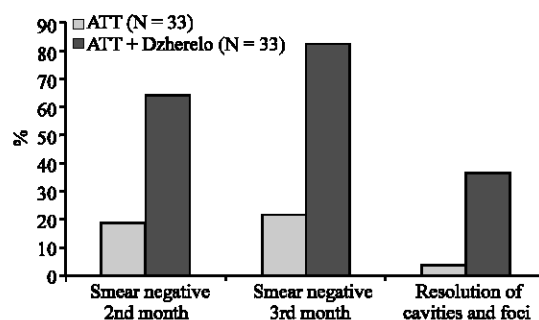

Fig. 1: Effect of ATT and ATT+Dzherelo on sputum smear conversion and resolution of pulmonary lesions on chest X-ray

Table 1: Pre- and post-treatment plasma levels of hepatic damage markers resulting from 3 months administration of ATT or ATT + Dzherelo

Biochemical parameters	Normal range in units	ATT + Dzherelo Before	After	ATT Before	After
Total bilirubin	8.5-20.5 µM/h*L	15.3±0.58	9.4±0.27	16.3±0.34	20.9±0.84
ALT aminopeptidase	10-68 IU/L	61.0±16.0	71.0±10	58.0±6.0	126±19.0
GGT	0.25-1.77 µU/L	1.28±0.18	1.45±0.08	1.12±0.21	1.35±0.04
Cholinesterase	45-95 µM/s*L	55.0±26.3	67.8±31.9	58.0±13.7	37.5±19.1
Thymol turbidity test	0-4 OD	3.25±0.38	3.68±0.5	2.29±0.59	6.38±0.23

Dubrovina *et al.* (2008) MDR-TB rates among civilian population in Donetsk region of the eastern Ukraine were 15.5 and 41.5% in newly diagnosed and previously treated TB patients. Among prisoners, these figures were 21.8% for new cases and 52.8% in previously treated TB cases. Treating drug-resistant TB is more difficult than drug-sensitive TB (Dye *et al.*, 2005). Due to high failure and relapse rate of TB therapy in such patients the immune intervention with Dzherelo has been evaluated. In the prior studies Dzherelo has been shown to enhance the success rate of ATT and shorten significantly the duration of treatment even among those who had MDR or XDR forms of TB. However, as the number of patients with drug-resistant TB in the prior study was small, we evaluated Dzherelo in a larger population of patients. We had 48 patients with multi-drug resistant TB, which were equally divided into two treatment regimens along with 12 drug susceptible individuals.

Our results indicate that 81.8% of patients on Dzherelo became negative by sputum smear as opposed to 21.2% in ATT arm as early as three months after initiation of treatment. The difference in outcome was highly significant (p = 0.000001). The proportion of sputum smear conversion appears to be not inferior of rates reported in the literature. The average successful treatment outcome of MDR-TB in Dominican Republic, Hong Kong, Italy, Russian Federation, Korea and Peru was 57% (Espinal *et al.*, 2000). The best reported 85% success rate was reported by Chan *et al.* (2004) who studied 205 MDR-TB patients in USA. However, such results were reached after prolonged therapy which lasted on average 18 months or more. Recent study by Chinese colleagues, who treated MDR-TB for 3 months, revealed 50.8% sputum conversion rate (Fu *et al.*, 2008). These findings are more relevant to our situation since we had identical treatment duration.

Sputum smear conversion is regarded as a reliable indicator of the efficacy of interventional therapy. However, this endpoint alone is not sufficient to reveal the extent of positive clinical outcome. To TB physicians the chest X ray remains the most dependable tool for gauging the outcome of treatment. The complete resolution of pulmonary infiltrations and cavities was seen in 12 (36.4%) patients in Dzherelo group, while only one patient (3%) treated with ATT had shown resolution by the 3rd month (p = 0.0008). The Chinese study has shown cavity closure and marked foci absorption in 21.3 and 50.8% of 61 patients after 3 months (Fu *et al.*, 2008). The rate of healing of local lesions was somewhat better than ours, but we had accounted only those who had shown the complete resolution. Most patients in Dzherelo had markedly improved radiological features but we did not include them due to subjective bias in evaluation of such assessments.

Adverse effects caused by TB drugs are common and can occur in up to 75% of patients (Greinert *et al.*, 2007; Shin *et al.*, 2007). We have measured the levels of liver damage markers such as total bilirubin, ALT and AST, gamma-glutamyl transpeptidase, cholinesterase and thymol turbidity. The results of liver function tests indicate that patients who received adjunct immunotherapy were better-off than those on ATT alone. The hepatoprotective effect of Dzherelo has been previously demonstrated in patients who were receiving anti-TB as well as anti-HIV therapy (Chechitiany *et al.*, 2007; Prihoda *et al.*, 2007, 2008). However, we do not know the exact mechanism of action and which specific components in the herbal preparation are responsible for this effect. Considering that on average it takes 18-24 months to treat MDR-TB the addition of Dzherelo can favorably enhance the quality of life and drug adherence of patients. The neutralization of hepatotoxic effect of TB drugs by Dzherelo represents a significant bonus in long-term management of MDR-TB patients.

The immunotherapy needs to be the indispensable part of interventional therapies against tuberculosis (Kaufmann, 2006). Several potentially effective immunomodulators were tested as adjuvant TB therapy (Wallis, 2005). These include interferon-gamma and environmental *Mycobacterium vaccae*, which have shown promising results in preliminary MDR-TB trials (Condos *et al.*, 1997; Grahmann and Braun, 2008; Stanford *et al.*, 2001; Zheng *et al.*, 2004). While often effective their mechanism is not well understood (Wallis, 2005). This drawback should be balanced against clinically confirmed benefits.

Very few medicinal plants, such as *Pelargonium sidoides*, were shown to be clinically effective against TB (Kolodziej, 2008). The prevailing majority of other herbs exerted direct or indirect antimycobacterial activity only in *in vitro* studies (Tomioka, 2004; Newton *et al.*, 2000). Unfortunately, we do not know which active ingredients in our multi-herbal preparation are responsible for the observed clinical effect. It is unlikely that Dzherelo acts as a tuberculostatic agent since *in vitro* growth of *M. tuberculosis* reference strains H32 and H37Rv was not affected directly and diverse diseases etiologically unrelated to TB were responsive to this preparation (Pylypchuk, 2003).

CONCLUSION

Our study provides additional evidence of safety and efficacy of Dzherelo (Immunoxel), which is recommended in Ukraine as an immune adjunct to TB therapy (Melnik *et al.*, 1999). Depending on specific clinical endpoint the addition of Dzherelo enhanced the therapeutic efficacy of ATT by about 3-10 fold (Fig. 1).

Further studies are needed to develop better understanding of this unique herbal preparation and to increase treatment options for TB patients, especially with drug-resistant forms of tuberculosis, such as MDR-TB and XDR-TB (Prihoda *et al.*, 2008).

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