Treatment of cavitary and infiltrating pulmonary tuberculosis with and without the immunomodulator Dzherelo

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Abstract

An open-label, 60-day trial was conducted in 75 newly diagnosed tuberculosis (TB) patients to assess the adjunctive effect of the oral immunomodulator Dzherelo with standard anti-TB chemotherapy (ATT) consisting of isoniazid, rifampicin, pyrazinamide and streptomycin (HRZS) administered as directly observed therapy (DOT). Group 1 (n = 28) with cavitary TB and group 2 (n = 17) with infiltrating pulmonary TB received 50 drops of Dzherelo twice daily in addition to HRZS. Group 3 (n = 30), which served as a control, received ATT only. Liver damage indicators, bilirubin, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) decreased to normal levels in groups 1 and 2, but increased significantly in group 3. Kidney failure markers, urea and creatinine, normalized in Dzherelo recipients, but were unchanged or worsened in the ATT-only group. The changes in serum lactate dehydrogenase, catalase, malondialdehyde and diene conjugates suggested that Dzherelo downregulates TB-associated inflammation. The anti-inflammatory property of Dzherelo was further supported by a favourable haematology profile, reduced erythrocyte sedimentation rate and faster defervescence. Radiological recovery was significant in both Dzherelo groups, but not in the control group (p = 0.0085, p = 0.025 and p = 0.23, respectively). These findings correlated positively with sputum smear conversion and clinical findings (r = 0.94; p < 0.05). Mycobacterial clearance at day 30 was observed in 77%, 72% and 40% of patients in groups 1, 2 and 3, respectively. After 2 months sputum conversion rates in groups 1, 2 and 3 were 93%, 89% and 70%, respectively. Sixty-day treatment outcomes in groups 1, 2 and 3 were assessed by improvement in clinical features and respiratory function attained respective p-values of 0.008, 0.25 and 0.72, and 0.013, 0.48 and 0.0015. Dzherelo is thus useful as an immunotherapeutic adjunct in the management of TB.

Keywords: Botanical, cavitary, DOT, hepatotoxicity, herbal, immunotherapy, Mycobacterium, phytoconcentrate, phytomedicine, phytotherapy, X-ray

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Introduction

Tuberculosis (TB) is a re-emerging global public health problem, the incidence of which has increased in the Ukraine, as it has in other countries [1]. The incidence of TB in the Odessa region was 178 cases per 100,000 individuals in 1962. It gradually declined to 73.0, 42.0 and 41.6 cases per 100,000 in 1972, 1982 and 1992, respectively. This trend, however, then reversed, and by 2002 the incidence and prevalence of TB had risen to 80.4 and 330 cases per 100,000, respectively. Mortality caused by TB more than doubled from 10.2 per 100,000 to 21.6 per 100,000 between 1990 and 2001 [2]. The success rates of therapy in Eastern Europe, including the Ukraine, as in Africa, are substantially below those in other regions of the world [1]. In addition, the Ukraine has worsening epidemics of drug-resistant TB, which is increasingly converging with HIV. Despite the availability of anti-TB drugs the situation is far from ideal and better therapeutic interventions are clearly needed to reverse the current trend.

The oral immunomodulator Dzherelo, which contains extracts of many plants (see below), is used in the Ukraine for the management of both TB and HIV infections, including...
simultaneous infections by both. Dzherelo was approved in 1997 by the Ukrainian Ministry of Health as an immunomodulating supplement and has been used extensively for various indications, including chronic bacterial and viral infections, autoimmune diseases and malignancy. In 1999 Dzherelo was recommended by the Ukrainian health authorities as an immune adjunct in the treatment of tuberculosis [3]. Previous clinical studies have indicated that Dzherelo can increase CD4 T-lymphocytes and decrease viral load, and that it improves the clinical response when combined with standard anti-retroviral (ART) or anti-tuberculosis therapy (ATT). 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 in liver function tests [4–10]. 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 clinical and radiological symptoms as well as on select biochemical and blood parameters among patients with cavitary and infiltrating pulmonary TB. The addition of Dzherelo to standard ATT was compared with a treatment regimen consisting of ATT alone.

**Materials and Methods**

**Patients and ethical approval**

The study involved 75 patients with newly diagnosed pulmonary TB. All patients were males aged between 19 and 68 years. All patients who presented with newly diagnosed pulmonary TB were enrolled in this study. No restrictive exclusion criteria for study enrolment were set up except that we disallowed patients who tolerated chemotherapy poorly or had resistant strains of *Mycobacterium tuberculosis*. Patients were allocated to the Dzherelo and ATT-only groups without formal randomization. All patients received standard ATT, consisting of orally administered isoniazid (H; 300 mg), rifampicin (R; 600 mg) and pyrazinamide (Z; 2000 mg), and intramuscular injection of streptomycin (S; 1000 mg). The anti-TB drugs were procured through the Ukraine’s centralized national supply system. Patients in groups 1 and 2 also 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 60 days as directly observed therapy (DOT) to patients hospitalized in our TB dispensary at Kharkov National Medical University, between March and May 2006.

The over-the-counter phytoconcentrate Dzherelo (Immunoxel) was generously supplied by Ekomed LLC (Kiev, Ukraine). It contains a concentrated aqueous alcohol extract from medicinal plants, including: aloes (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 (*Origanum majorana*); marigold (*Calendula officinalis*); sea buckthorn 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*); fenel (*Foeniculum vulgare*); chaga (*Inonotus obliquus*); thyme (*Thymus vulgaris*); three-lobe beggar ticks (*Bidens tripartita*); sage (*Salvia officinalis*); rose (*Rosa canina*), and juniper berries (*Juniperus communis*). Dzherelo was approved in 1997 by the Ukrainian Ministry of Health as a dietary supplement. In 2006 it received the status of a ‘functional food’, placing it in a superior category of herbal supplements which can carry medical claims substantiated by clinical evidence.

**Clinical endpoints**

Primary endpoints of interest in this study were the effect of prescribed therapy on clinical manifestations and radiological and microbiological findings. The clinical manifestations of TB that were evaluated comprised a complex of so-called ‘intoxi-
cation’s symptoms and signs, including fever, night sweats, loss of appetite, weight loss, weakness, depression, cough, and lung crepitations, etc. [11,12]. The second aspect of clinical evaluation concerned respiratory function and included symptoms such as dyspnoea and lung function tests, including total lung capacity (TLC), forced vital capacity (FVC), forced expiratory volume (FEV), residual volume (RV), carbon monoxide transfer factor, oxygen ubiquitin and calcium dioxide according to the Dembo and Liberman classification [11,12]. In both cases, the features or tests were given a score ranging from 0 (severely affected) to 3 (absent or normal) and the mean of these scores was used to define the overall result as indicative of no, mild or severe abnormality. In addition, information on the potential adverse effects of Dzherelo administered in combination with chemotherapy was sought via questionnaires completed by the patients.

**Laboratory evaluation**

A standard microbiological examination of a sputum smear stained by the Ziehl–Neelsen method was conducted prior to study entry and at days 30 and 60 from the start of treatment. Isolates of *M. tuberculosis* were tested for sensitivity to first- and second-line anti-TB drugs with a commercially available kit (Tulip Diagnostics Pvt Ltd, Goa, India) [7].

These tests were supplemented by regular examination of haematological and biochemical parameters. Plasma levels of catalase, malondialdehyde (MDA), lactate dehydrogenase (LDH) and diene conjugates (DC) were measured as markers of oxidative stress, as described earlier [7].

**Statistical analysis**

The results were analysed with the statistical software GraphPad (GraphPad Software, Inc., La Jolla, CA, USA). Baseline quantitative values were compared with end-of-study values by paired or unpaired Student’s t-test. Non-parametric or categorical values of treatment outcomes were compared by McNemar or chi-square contingency tables. All statistical analyses were performed on an intent-to-treat basis, involving the total number of patients without subgrouping them into responders and non-responders. The resulting probability values were considered significant at \( p \leq 0.05 \).

**Results**

**Lack of adverse reactions**

During the entire follow-up no adverse reactions attributable to Dzherelo were identified. In particular, no dyspepsia, malaise, intolerance or allergic reactions were evident at any time (data not shown).

**Effect on body temperature**

The dynamics of body temperature among treated patients are shown in Fig. 1. All three groups showed a decline in mean body temperature during the investigation. Group 1, however, showed a clear tendency towards more rapid normalization: the mean axillary temperature on day 30 reached a ‘normal’ level, at 36.65 ± 1.24 °C, compared with 37.17 ± 2.02 °C in group 3 (\( p < 0.005 \)). Group 2 had a similar rate of decline to group 1, whereas group 3 showed a slower rate of decrease.

**Effect on haematological parameters**

The effects of ATT and Dzherelo on blood cell counts, erythrocyte sedimentation rate (ESR) and haemoglobin are shown in Table 1. Patients in groups 1 and 2 reacted in a similar manner and displayed changes which appeared to be specific to Dzherelo intervention as opposed to the effect of ATT alone in group 3 patients. In particular, the relative content of lymphocytes almost tripled among Dzherelo-treated patients, reaching normal levels, whereas patients in the control group failed to attain normal values. Elevated counts of cells, such as neutrophils, eosinophils and total leukocytes, commonly associated with inflammation, were reduced to a greater extent in Dzherelo-treated patients, although the decrease was also statistically significant in group 3 patients. By contrast, monocyte levels were almost unchanged among patients who received Dzherelo, whereas patients in the comparison group had a greater reduction in these cells. Other cells such as erythrocytes behaved in a similar manner in all three groups. Erythrocyte sedimentation rate declined faster in the Dzherelo groups. Haemoglobin concentrations decreased at the same rate in all patients. In general, Dzherelo appeared to have greater effect in normalizing the haematology profile than ATT treatment alone.

**Effect on liver and kidney function**

Serum biochemistry markers of liver and kidney function improved markedly among Dzherelo recipients, whereas

![FIG. 1. Mean axillary temperature (°C) followed for 60 days.](image-url)
TABLE 3. Changes in oxidative stress markers

<table>
<thead>
<tr>
<th>Patients</th>
<th>Lactate dehydrogenase, IU</th>
<th>Catalase, IU</th>
<th>Diene conjugates, μM/L</th>
<th>Malondialdehyde, nM/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0</td>
<td>Day 60</td>
<td>Day 0</td>
<td>Day 60</td>
</tr>
<tr>
<td>Groups 1 and 2 (n = 45)</td>
<td>1.84 ± 0.2</td>
<td>2.5 ± 0.3</td>
<td>4.9 ± 0.36</td>
<td>3.8 ± 0.2</td>
</tr>
<tr>
<td>Groups 3 (n = 30)</td>
<td>1.79 ± 0.41</td>
<td>4.38 ± 0.54</td>
<td>5.49 ± 0.26</td>
<td>2.65 ± 0.3</td>
</tr>
</tbody>
</table>

Effect on oxidative stress markers

The effect of therapy on plasma levels of catalase, MDA, LDH and DC as markers of oxidative stress and lipid peroxidation are presented in Table 3. There is a clear impression that Dzherelo helps to slow down the pathological processes associated with TB and its treatment. For example, concentrations of LDH, a marker indicative of cell injury and inflammation, in patients receiving Dzherelo remained within the normal range (0.8–2.5 IU), but almost tripled in patients on ATT alone. Increases in levels of DC and MDA were lower in Dzherelo recipients than in ATT-alone recipients. The decrease in antioxidant catalase levels was smaller in the Dzherelo groups, whereas, among those on ATT alone, these were more than halved.

Effect on mycobacterial clearance

Bacterial clearance, evaluated by repeated sputum Ziehl-Neelsen staining at monthly intervals, is shown in Fig. 2. At day 30, 77% and 72% of patients in groups 1 and 2, respectively, had negative findings, whereas only 40% of patients in group 3 showed sputum clearance of bacteria. After 60 days the corresponding figures were 93%, 89% and 70%, respec-

patients in group 3 showed a decline in liver function (Table 2). All three evaluated hepatic markers, bilirubin, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), decreased in groups 1 and 2 but increased in group 3 in a statistically significant manner. Levels of urea and creatinine normalized in Dzherelo recipients but were unchanged or worsened in ATT-alone patients.

TABLE 2. Changes in biochemical markers of liver and kidney function

<table>
<thead>
<tr>
<th>Patients</th>
<th>Bilirubin, μM/L</th>
<th>ALT, μM/L</th>
<th>AST, μM/L</th>
<th>Urea, μM/L</th>
<th>Creatinine, μM/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0</td>
<td>Day 30</td>
<td>Day 0</td>
<td>Day 30</td>
<td>Day 0</td>
</tr>
<tr>
<td>Group 1 at baseline</td>
<td>29.22 ± 1.45</td>
<td>110 ± 9</td>
<td>76 ± 6</td>
<td>9.21 ± 0.22</td>
<td>76.50 ± 5.23</td>
</tr>
<tr>
<td>Day 60</td>
<td>11.23 ± 0.75</td>
<td>47.8 ± 39</td>
<td>39 ± 3</td>
<td>6.97 ± 0.23</td>
<td>68.57 ± 2.43</td>
</tr>
<tr>
<td>Group 2 at baseline</td>
<td>32.06 ± 4.32</td>
<td>135 ± 24</td>
<td>134 ± 10</td>
<td>8.66 ± 0.53</td>
<td>83.32 ± 5.67</td>
</tr>
<tr>
<td>Day 60</td>
<td>18.19 ± 1.65</td>
<td>59 ± 11</td>
<td>67 ± 7</td>
<td>6.82 ± 0.26</td>
<td>76.22 ± 5.24</td>
</tr>
<tr>
<td>Group 3 at baseline</td>
<td>22.54 ± 2.52</td>
<td>79 ± 11</td>
<td>79 ± 7</td>
<td>7.99 ± 0.54</td>
<td>83.40 ± 6.40</td>
</tr>
<tr>
<td>Day 60</td>
<td>26.22 ± 4.12</td>
<td>118 ± 21</td>
<td>68 ± 19</td>
<td>7.88 ± 0.32</td>
<td>89.36 ± 6.26</td>
</tr>
</tbody>
</table>

AST, aspartate aminotransferase; ALT, alanine aminotransferase.
tively. The difference between the two groups receiving Dzherelo was not significant at either test-point (p = 0.42, p = 0.32, respectively, as tested by non-parametric chi-square analysis). When groups 1 and 2 were compared with group 3, the statistical difference was highly significant at 30 days (p < 0.0000001, p < 0.000005, respectively) and 60 days (p = 0.000028, p = 0.00088, respectively).

**Effect on clinical and respiratory symptoms**

The response rates of patients receiving chemotherapy with or without immunotherapy are shown in Figs 3 and 4. Changes in two categories of clinical manifestations were evaluated: the first was a complex of so-called ‘intoxication’ symptoms and the second represented ‘respiratory function’. At study entry the degree of severity of both categories of clinical manifestations was similar in all three groups. Contingency table analysis comparing baseline results between groups 1 vs. 2, 1 vs. 3, and 2 vs. 3 reveals p-values of 0.40, 0.28 and 0.002, respectively, for the intoxication and 0.22, 0.21, and 0.0008, respectively, for the respiratory function categories of clinical features. The inter-group differences between Dzherelo recipients and ATT-alone recipients became greater by the end of the first month. After 60 days of treatment, the p-values for comparisons between groups 1 vs. 2, 1 vs. 3 and 2 vs. 3 reached 0.13, 0.004 and 0.22, and 0.13, 0.00002 and 0.13, respectively, for the intoxication and respiratory function categories of clinical features, respectively. The intra-group differences between Dzherelo and ATT-alone recipients became greater by the end of the first month. After 60 days of treatment, the p-values for comparisons between groups 1 vs. 2, 1 vs. 3 and 2 vs. 3 reached 0.13, 0.004 and 0.22, and 0.13, 0.00002 and 0.13, respectively, for the intoxication and respiratory function categories of clinical features, respectively. The intra-group differences between baseline and 30 days were not significant by McNemar test. The p-values for groups 1, 2 and 3 were 0.07, 0.61 and 0.7, respectively, for intoxication, and 0.11, 1.0 and 0.5, respectively, for respiratory function categories. However, intra-group changes between baseline status and 60-day treatment outcomes for groups 1, 2 and 3 for intoxication and respiratory function attained p-values of 0.008, 0.25 and 0.72, respectively, and 0.013, 0.48 and 0.0015, respectively. These findings indicate that the addition of Dzherelo to ATT enhances the efficacy of ATT and achieves statistically significant favourable clinical responses at 2 months after treatment initiation.

**FIG. 2.** Presence of acid-fast bacilli in sputum smears (percentage of patients) at baseline and at 30 and 60 days.

**FIG. 3.** Effect of therapy on clinical features (percentage of patients) at 30 and 60 days.

**FIG. 4.** Effect of therapy on respiratory functions (percentage of patients) at 30 and 60 days.
Effect on radiological manifestations

Results of chest X-ray evaluation of lung segments affected by cavitary and non-cavitary infiltrating TB are presented in Fig. 5. Chi-square contingency table analysis comparing baseline differences between groups 1 vs. 2, 1 vs. 3 and 2 vs. 3 showed that p-values were 0.39, 0.82 and 0.18, respectively, indicating that at study entry patients in different treatment groups had similar levels of pulmonary invasion. After 60 days the differences in response to treatment became highly significant for Dzherelo recipients, but not for ATT-treated patients. Observed radiological improvement as determined by the McNemar categorical test for groups 1, 2 and 3 attained p-values of 0.0085, 0.025 and 0.23, respectively. Thus, the healing rate was greater among patients on Dzherelo than among those who received ATT only. These observations correlated positively with microscopy and clinical findings ($r = 0.94; p < 0.05$).

Discussion

This open-label, comparative study in a group of newly diagnosed TB patients at our dispensary reveals that when standard, first-line anti-TB drugs are combined with Dzherelo, significant clinical and radiological improvements and clearance of $M. \text{tuberculosis}$ take place at a higher rate than in patients on ATT alone. Biochemical and haematological analyses of blood samples supported this favourable adjunctive effect of Dzherelo, which did not show any adverse effects throughout the investigation. Our findings support earlier clinical studies of Dzherelo demonstrating similar results [3–10]. The proportion of TB patients cured according to sputum culture and radiology was two- to four-fold higher among Dzherelo recipients. Furthermore, the combination therapy gave results after a much shorter period.

Earlier indications showed Dzherelo to exhibit anti-inflammatory properties [5–7]. This notion is reinforced by the findings of this study. The decline in elevated body temperature to $< 36.6 \, ^\circ\text{C}$ occurred in the Dzherelo-treated groups within 30 days, as opposed to the control group, where this happened only after 60 days. As fever is an independent indicator associated with an aggressive form of TB, the outcome of treatment is likely to be influenced positively by Dzherelo [13]. Similarly, the indices of inflammation such as leukocytosis, neutrophilia and eosinophilia tended to return to normal at an earlier date and more strikingly in Dzherelo recipients than in patients on ATT alone. Elevated numbers of these cells are known to be associated with active pulmonary TB and their normalization is considered to indicate a favourable effect on the course of disease [14,15]. The observed changes in the blood profile are paralleled by findings from previous studies; in particular, lymphocyte counts almost tripled among Dzherelo recipients, whereas in control patients they failed to reach normal levels. Restoration of lymphocyte counts is considered to have a favourable prognostic significance [15]. Although Dzherelo did not affect erythrocyte counts, it did reduce the ESR (considered to be a marker of TB-associated inflammation) much more efficiently than ATT alone [16].

Lactate dehydrogenase, another indicator of inflammation, had a three-fold slower rate of accumulation in the Dzherelo group than in the ATT-alone group, suggesting a favourable anti-inflammatory property of Dzherelo [17]. During pulmonary inflammation in patients with active TB increased amounts of reactive oxygen species are produced as a consequence of the phagocyte respiratory burst. Among the manifestations of these free radical-mediated processes are higher concentrations of DC and MDA [18,19]. Increases in DC and MDA were lower in Dzherelo recipients than in ATT-alone patients, suggesting that herbal components in this preparation can downregulate the inflammatory process. Observed changes in antioxidant catalase levels in TB patients are in line with these findings as the rate of decline of this enzyme was twice as slow in the Dzherelo groups as in the ATT-alone group. The oxidative injury is an essential component of inflammatory damage.

![FIG. 5. Radiological findings prior to and after 60 days of therapy, giving the number of pulmonary segments involved. Numbers over columns represent numbers of patients.](image-url)
and it is clear that the reversal of excessive peroxidation favorably influences the outcome of the disease by lessening the impact on pulmonary tissue damage and respiratory distress [20].

The hepatotoxicity induced by anti-TB drugs has serious adverse consequences for treated patients and imposes limitations on treatment options [21]. The addition of Dzherelo reversed ATT-associated liver damage, as evidenced by the two- to three-fold reduction of baseline bilirubin and AST and ALT levels in the Dzherelo groups compared with the ATT-alone group, in which all three liver function parameters continued to rise. These observations confirm previous clinical studies in which Dzherelo has been shown to counter the hepatotoxicity of anti-TB as well as anti-HIV drugs [5–7]. Renal failure characteristics as assessed by urea and creatinine output seemed to improve upon intake of Dzherelo, whereas in group 3 patients there was practically no improvement.

The conversion of sputum smear from positive to negative is considered a critical indicator of the efficacy of anti-TB intervention [22]. We observed that Dzherelo accelerated and significantly enhanced bacillary clearance (Fig. 2). A large, prospective Canadian study evaluating 428 TB cases showed that 48% of patients had converted after 4 weeks [22], a reduction which seems to be in line with our 40% conversion rate in the ATT-alone group, but is smaller than the 77% and 72% clearance rates in groups 1 and 2, respectively. In a recently reported study from India, the 2-month sputum conversion rate in newly diagnosed TB was 58%, which is also lower than our Dzherelo-facilitated conversion rates at 60 days (i.e. 93% and 89%, respectively) [23]. The difference between ATT-alone and ATT-plus-Dzherelo recipients was highly significant at both time-points, indicating that administration of this botanical immunomodulator produces better results than standard treatment. A longer follow-up study is needed to assess the bacteriological relapse rate in our patients.

The mycobacterial clearance results agree with our clinical findings. Based on two categories of clinical evaluation, features of intoxication and respiratory function, it became apparent that the combination of Dzherelo with ATT produces a faster and more profound beneficial effect than ATT alone. As Figs 3 and 4 show, only 50.0% and 33.3%, respectively, of patients on ATT alone became free of indicators after 60 days of treatment. By contrast, in groups 1 and 2, respectively, 85.7% and 94.1% were alleviated of intoxication features, and 85.7% and 76.5% became free of respiratory function problems. The proportion of patients with mild problems also fell significantly in Dzherelo-treated patients. Although the classification of clinical features into the two categories used in this study is not employed in countries outside the former Soviet Union, these categories continue to be commonly used in the Ukraine and have been proven reliable by several generations of Ukrainian TB physicians since the 1950s [11,12,24]. These categories, especially when used in combination with bacteriological and chest X-ray evaluations, appear to facilitate the dependable assessment of the efficacy of anti-TB intervention.

Indeed, radiographic examination of lung segments affected by cavitary and non-cavitary TB lesions unequivocally supported the benefits of adding Dzherelo to the standard TB treatment regimen. As Fig. 5 shows, there was clear improvement in groups 1 and 2 after 60 days compared with group 3, in which 30% of patients still had three or more affected pulmonary segments. Our findings indicate that, although radiographic involvement in one or two segments persisted in all treated patients at 60 days, the length of follow-up was perhaps too short to see complete pulmonary recovery. For this reason a longer study is required.

Throughout the study we observed statistically significant discrepancies between groups 1 and 2 in terms of response at certain therapy endpoints, for which we do not have valid explanations. It is likely that these differences are attributable to differences in pulmonary lesions in these groups. It has been reported that a predominant Th1 immune response is observed in non-cavitary patients, whereas cavitary-involved segments exhibit the presence of Th2 lymphocyte subsets [25]. This needs to be explored further in a larger population of patients.

Several immunomodulators have been tested as adjuvants for TB therapy. These include likopid, interferon-γ (IFN-γ) and environmental Mycobacterium vaccae, all of which have shown promising results in preliminary trials. Likopid is a synthetic lipid analogue of bacterial cell wall which has been developed in Russia [26]. The combination of likopid with ATT in patients with pulmonary TB resulted in positive clinical effects, including bacterial culture conversion in 80% of cases, a lower rate of positive sputum staining, lack of intoxication, and accelerated resolution of pulmonary infiltrations. Such effects were not observed in control patients who received conventional ATT. Interferon-γ has been used as an adjunct immunotherapy for TB since 1997 [27]. Several clinical trials of inhaled or injected IFN-γ have shown positive clinical outcomes, although to lesser extent than in likopid-treated cases [27–29]. Environmental M. vaccae has shown encouraging results in some trials, but was ineffective in others [30–32]. For example, treatment of drug-susceptible pulmonary TB with M. vaccae did not improve radiological responses or resolve cavitary disease [32].
In conclusion, the phytopreparation Dzherelo, which has been used as an immunomodulating adjuvant to standard TB therapy, has been shown to be safe and capable of reversing ATT-associated hepatotoxicity. In addition, Dzherelo seems to reduce inflammation, as evidenced by several haematological and biochemical markers, and significantly accelerated and enhanced the sputum smear conversion rate. Clinical and radiological improvements resulting from the combination of Dzherelo and ATT occurred earlier and at higher rates than those from ATT alone. It is hoped that when herbal medicines such as Dzherelo are validated through rigorous scientific and clinical research, their integration into modern medical practice will be more readily accepted and treatment options for TB will be expanded as a result.

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Transparency Declaration

All authors, except VSP, declare no conflicts of interest. VSP developed Dzherelo and is director of Ekomed LLC.

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