

Impact of Adjunct Immunotherapy with Multi-herbal Supplement Dzherelo (Immunoxel) on Treatment Outcomes in End-stage TB/HIV Patients

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Abstract

Prognosis for TB/HIV co-infection is very unfavourable. In terminally-ill patients treatment options are often limited to palliative care. In our salvage, 2-month therapy of 40 late-stage TB/HIV patients we administered to half of the patients TB drugs along with over-the-counter botanical immunomodulator Dzherelo (Immunoxel). Despite best possible care 6 patients had died. Remaining 14 patients experienced marked clinical improvements and one patient was discharged due to full recovery. Among 20 matched subjects on conventional TB regimen, 12 died and only one was slightly better-off. These results indicate that Dzherelo might reduce mortality ($P=0.055$) and improve significantly the quality of life ($P=0.00002$). Improvement in quality of life is also supported by substantial weight gain (mean/median 3.3/4 kg) in much higher proportion of patients than among those who received TB drugs only, i.e., 16 vs. 1 ($P=0.000001$). At the end of two months 13 (65%) patients became sputum smear negative versus only one individual (5%) in ATT group ($P=0.00007$). These results suggest that adjuvant immunotherapy improves significantly therapy outcome and reduces mortality. Larger study is warranted to confirm the benefit of Dzherelo.

Keywords: AIDS; End-stage; Herbal; Mycobacterium; Mortality; Quality of life; Salvage therapy; Survival; Terminal disease

Introduction

HIV-positive individuals with tuberculosis are particularly vulnerable since standard anti-TB (ATT) and anti-HIV drugs (ART) are not very effective in this category of patients and prognosis is worse than for two infections separately (Kang'ombe et al., 2004). In the terminal stage of TB/HIV treatment options are severely restricted and it is usually too late to seek any meaningful therapy. Patients with TB/HIV are often from the low social strata and cannot afford expensive antiretroviral therapy, which could potentially prolong their life. Ukrainian health authorities do provide free TB drugs, but supplies of ART are limited and terminal TB/HIV patients are not on the priority list and thus seldom have a chance to receive them. Due to these unfortunate circumstances most patients are left without ART option. These patients are often ostracized, denied medical care at specialized AIDS clinics due to fear of airborne spread of tuberculosis, and usually end up in TB dispensaries where their only treatment

option is antibiotics. At this stage the quality of life is very poor and mortality is high.

Dzherelo is a multi-herbal oral immunomodulator, recommended but not approved by the health authorities of Ukraine as an adjunct therapy for TB (Chechitany et al., 2007). We and others have conducted several clinical trials involving TB/HIV-positive volunteers, which have shown that when Dzherelo and ATT are combined the quality of life and TB cure rates are drastically improved (Chechitany et al., 2007; Prihoda et al., 2007a; Nikolaeva et al., 2008a; Nikolaeva et al., 2008b; Prihoda et al., 2008). Adjunct immunotherapy has been shown to achieve faster and higher score of mycobacterial clearance, reduce HIV burden, accelerate healing of pulmonary lesions, decrease inflammation and liver damage, improve hematology picture, e.g., higher hemoglobin levels and CD4 counts, and enhance significantly quality of life (QOL) such as weight gain, fever, respiratory function, physical fitness, emotional well-being and better mood. In end-stage stage disease, however, the death is a critical endpoint, which defines unequivocally the merit of therapeutic intervention. In this study we investigated whether in addition to previously demonstrated positive clinical and QOL outcomes Dzherelo can reduce mortality rate.

Materials and Methods

Patient population and intervention

This project started as a salvage therapy for patients with extremely poor prognosis (Prihoda et al., 2008). At any given time our TB dispensary has 80-100 end-stage hospitalized TB patients of which about 2/3 are HIV infected. The turnover is quite fast - an average upper life expectancy is about 5-6 months. Since dramatic differences were observed when we used Dzherelo in non-terminal TB and HIV cases, we thought that terminally-ill

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Received September 12, 2009; **Accepted** December 30, 2009; **Published** December 30, 2009

Citation: Arjanova OV, Prihoda ND, Yurchenko LV, Sokolenko NI, Vihrova LA, et al. (2009) Impact of Adjunct Immunotherapy with Multi-herbal Supplement Dzherelo (Immunoxel) on Treatment Outcomes in End-stage TB/HIV Patients. *J Antivir Antiretrovir* 1: 086-088. doi:10.4172/jaa.1000013

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patients may also benefit from this intervention. We thus gave Dzherelo to those without any reasonable prospect of survival, but surprisingly the outcome was startling and much better than we initially anticipated. Such results were clearly unprecedented but a control was needed to advance our findings beyond anecdotal level. After long deliberation our Ethics board had decided that our salvage therapy can evolve into a clinical trial with matching arms provided that patients in ATT alone arm gave their informed consent. For us, it was and still is a difficult ethical issue as to which patient will receive potentially life-saving intervention and which one will not. In May 2008 the MAPI Trust graciously gave us a small contribution, which we used to start this project. Twenty end-stage TB/HIV patients received individualized TB drugs regimen while matching control group of patients had same TB drugs supplemented with 50 drops of Dzherelo given in a half-a-glass of water twice-a-day.

Follow-up procedures and statistics

At study entry all patients with confirmed HIV-positive test had a physical examination, chest X-ray, and sputum analysis for the presence of *Mycobacterium tuberculosis*. Patients were given best palliative care and followed on a daily basis. Those who remained alive were analyzed again two months later. The statistical difference between two groups was measured by Fisher's exact 2x2 test with P threshold value set at =0.05.

Results

Forty terminally-ill TB/HIV volunteers entered into this comparative study. At the end of 2 months of follow-up 6 patients in Dzherelo group had died despite best possible palliative care (Table 1). In remaining 14 patients marked clinical improvement was observed and one patient was discharged due to full recovery from TB symptoms. By comparison, among 20 terminally-ill, matched group of patients receiving conventional TB drugs, 12 patients died and only one person had experienced a limited clinical improvement. These results indicate that when Dzherelo is co-administered with chemotherapy to end-stage TB/HIV patients it might reduce mortality (P=0.055) and improve significantly the quality of life (P=0.00002). Improvement in quality of life among Dzherelo recipients is also supported by substantial weight gain (mean/median 3.3/4 kg; range 1-7 kg) in much higher proportion of patients than among those who received TB drugs only, i.e., 16 vs. 1 (P=0.000001). Positive changes as evidenced by sputum smear clearance and radiological improvements were equally impressive. At the end of two months 13 (65%) patients became sputum smear negative versus only one individual (5%) in ATT group (P=0.00007). In opinion of the treating physician one patient in Dzherelo group had fully recovered and was hence discharged from the dispensary. However this was a single case and statistically not significant (P=0.5) even though none of the patients on TB drugs alone had recovered to that extent.

Discussion

In developing countries TB is the primary cause of AIDS-related deaths and it is agreed that available treatment options are not satisfactory (Kang'ombe et al., 2004; Cain et al., 2007; Ngo et al., 2007; Swaminathan et al., 2008; Saraceni et al., 2008). Our preliminary findings in 40 terminally-ill TB/HIV patients indicate that botanical immunomodulator Dzherelo can significantly improve the quality of life and reduce mortality. However, the probability value of better survival compared to conventional TB therapy was marginally significant (P=0.055) indicating that larger population is needed to verify our preliminary observation. To the best of our knowledge there is only one study, which reported positive effect of immunotherapeutic intervention on survival of terminally-ill AIDS patients (Metadilogkul et al., 2005). In that study approximately one hundred patients were enrolled to show the significance implying that we may need a similar size population.

Quality of life parameters as judged by weight gain and physician's assessed clinical improvement were highly significant, P=0.000001 and P=0.0002, respectively. We need, however, develop better methods so that patient reported outcomes (PRO) can be assessed more objectively either by adopting existing questionnaires such as SF-36 or WHOQOL-100. Ideally, we would need to measure outcomes that could assess both HIV and TB associated symptoms – instruments for these two conditions, MOS-HIV and TBscore, were developed by Wu et al., and Wejse et al., respectively (Grossman et al., 2003; Wejse et al., 2008). Such tools will help us to have better understanding of QOL parameters in dually infected patients and will certainly add more substance to our study.

We do have government-supplied free TB drugs for all patients but at terminal stage they are not very effective and many patients default treatment due to adverse effects and lack of progress. Dzherelo is not very expensive but our resources are limited to afford covering every terminally-ill patient. During other clinical trials in non-terminal categories of TB patients we had free supplies of Dzherelo from the manufacturer – Ekomed LLC (Chechitiany et al., 2007; Prihoda et al., 2007b; Nikolaeva et al., 2008a; Nikolaeva et al., 2008b; Prihoda et al., 2008). Even though Ekomed has been quite generous it is difficult to expect that a commercial company will be willing to support all end-stage patients hospitalized in the dispensary.

There is an urgent need to expand treatment options for terminally-ill TB patients with or without HIV (Cain et al., 2007; Ngo et al., 2007; Swaminathan et al., 2008; Saraceni et al., 2008; Metadilogkul et al., 2005). Our preliminary findings are encouraging but we need to carry out larger study to confirm them. This may allow us to persuade the public opinion and health authorities that an herbal supplement is worth being considered as an integral part of centralized free TB drugs supplies. As a

Terminal stage TB/HIV patients	Bacterial clearance	Clinical improvement	Recovered and discharged	Died while treated	Weight Gain
ATT alone (N=20)	1 (5%)	1 (5%)	0 (0%)	12 (60%)	1(5%)
ATT+Dzherelo (N=20)	13 (65%)	14 (70%)	1 (5%)	6 (30%)	16(75%)
Fisher's exact 2x2 test	P=0.00007	P=0.00002	P=0.5	P=0.055	P=0.000001

Table 1: Preliminary findings in 40 end-stage TB/HIV patients treated for 2 months.

result lives of many thousands TB patients may be saved in Ukraine and elsewhere. Our dream of helping terminally-ill people to improve quality of life and commute their death sentence will be then materialized.

Acknowledgements

This study was supported by compassionate financial support graciously provided by MAPI Research Trust, Lyon, France - a non-profit organization that advances the art and the use of scientific approaches to patient-reported outcome measures.

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