Comparative effect of an immunomodulator Immunoxel (Dzherelo^{TM}) when used alone or in combination with antiretroviral therapy in drug-naïve HIV-infected individuals.

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Abstract: Immunomodulating agent Immunoxel (Dzherelo) has been evaluated in 70 HIV-positive individuals divided into three arms: first, control arm, received standard antiretroviral therapy zidovudine/lamivudine/efavirenz (AZT/3TC/EFV); second-AZT/3TC/EFV+Immunoxel and third, Immunoxel alone, given orally, twice daily. At 32 weeks of follow-up CD4 cell counts increased in all arms, reaching + 102, +190 and +175 cells/mm^3, respectively. The proportion of patients who experienced adverse events attributable to study medication was 65%, 24% and 5%. Immunoxel attenuated hepatic toxicity in patients receiving ART as determined by liver function test. Baseline values for ALT aminotransferase were 36, 62 and 72 U/L, which at study conclusion have risen to 78 U/L in arm A, but declined to 38 and 31 U/L in arms B and C. Immunoxel also reversed AIDS-associated wasting. The average weight gain was 1.4, 6.9 and 5.1kg. The results indicate that Immunoxel is safe and exerts beneficial effect in AIDS patients.

Keywords: cachexia; hepatotoxicity; immune tolerance; immunotherapy; phytotherapy; transaminase.

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1 Introduction

The antiretroviral drug resistance, drug toxicity and adherence are major concerns in clinical management of HIV infection. On the other hand, the immune activation caused by immune reaction to HIV, is now recognised as a major cause of depletion of CD4 T-cells and resulting immunodeficiency (Appay et al., 2005). In fact, African monkeys, the natural hosts of simian immunodeficiency virus have adapted to this retrovirus by blocking immune activation and thus remaining healthy. These problems are driving force for research on new therapies that can provide an answer. Most optimal therapeutic solution is an effective and safe immunotherapy that could regulate the immune response in a manner favourable to a host.

Immunoxel is an oral immunomodulating agent produced in Ukraine by Ekomed company. It contains concentrated extracts from medicinal plants. In vitro studies on cultured thymocytes and epithelial thymic cells have shown that Immunoxel can induce synthesis of serum thymic factor and other substances with thymus like activity (Grinevich, 2001). Experiments on laboratory animals demonstrated the restoration of endocrine function and increase of thymus weight after partial thymectomia (Grinevich, 2001). It has been successfully used in the past for the therapy of various infectious diseases of viral origin such as herpes and Epstein-Barr viruses. The choice of the given immunomodulator for our study was made on the basis of the analysis of prior evidence indicating the tendency to restore suppressed immunity characteristic to chronic bacterial infections and malignant diseases (Barabai et al., 2004; Chechitiany, 2003, 2004; Grinevich, 2001; Shapovalovi, 2004; Zeleniy, 2003). Furthermore, Immunoxel has shown the efficacy in treatment of autoimmune diseases (Bodnar et al., 2002).

Preliminary data from pilot trials conducted by us in HIV-infected individuals have been very encouraging (Kutsyna et al., 2003, 2004, 2005). The results have shown that Immunoxel is safe, can increase the total and CD4 lymphocyte counts and reduce the incidence of Opportunistic Infections (OI). In addition it appeared to have favourable effect in diminishing the hepatoxicity of antiretroviral drugs. In order to further evaluate the clinical benefit of Immunoxel in comparison to standard ART we initiated the multicentre trial conducted at four regional hospitals in Ukraine. Here we present data from 32-week, open label, three-arm trial in 70 HIV-infected individuals who were treated either with zidovudine (AZT), lamivudine (3TC) and efavirenz (EFV), (AZT/3TC/EFV) in combination with Immunoxel or Immunoxel alone, assigned to arms A, B and C, respectively.

2 Materials and methods

2.1 Patients' population

In this trial 70 male or female adults with HIV/AIDS were enrolled. Most of them were hepatitis virus C (HCV) coinfected, with significant proportion of them suffering from alcohol abuse or/and drug addiction. Significant metabolic disorders and underlying hepatic injury caused by chronic alcohol, drug addiction and hepatitis coinfection were common for study cohort. At study initiation 21% had active OI and 71% had grade three or more laboratory or clinical abnormalities. Patients were divided into three arms, their baseline characteristics were comparable. All participants were antiretroviral drug naïve. Each participant provided an informed consent and was free to withdraw from the study at any time. All patients were given symptomatic therapy for OI if required. The trial is designed to continue until the last enrolled patient reaches 48 weeks on therapy.

2.2 Treatment regimen

After initial screening, qualifying patients were randomly divided in three arms: arm A was prescribed: zidovudine (AZT) in 300 mg doses twice-daily; lamividine (3TC) 150 mg tablets twice-daily and efavirenz (EFV) 600mg once daily. The arm B received the same ART plus Immunoxel given as 50 drops added to a glass of water, twice–daily. The arm C received immunomodulator Immunoxel monotherapy in same 50 drops twice–daily dose. Immunoxel (Dzherelo) was provided by Ekomed company, Kiev, Ukraine. It contains aqueous alcohol extract of elecampane rhizome (*Inula helenium*); fennel fruit (*Foeniculum vulgare*); juniper berry (*Juniperus communis*); licorice root

(*Glycyrrhiza glabra*); oregano herb (*Oreganum majorana*); marigold flowers (*Calendula officinalis*); rose hips (*Rosa canina*) and thyme (*Thymus serpyllum*). These herbs are considered by the FDA as Generally Regarded As Safe (GRAS) substances. Immunoxel (Dzherelo) has been approved in 1997 by the Ministry of Health of Ukraine as a dietary, immunomodulating supplement.

2.3 Evaluation

Parameters such as CD4 cell counts, AIDS defining events, relapse and new events of Opportunistic Infection (OI), adverse events and laboratory parameters were assessed at baseline and at weeks 12, 20, 32. For patients with clinical signs of adverse events laboratory tests were performed every two weeks. Baseline values for CD4 cells counts were defined as the average of the last screening and last baseline values. Adherence to treatment was assessed at each visit. Adverse events were graded by intensity and their relationship to the study medications. AIDS defining adverse events (as per 1993 Center for Disease Control definitions of AIDS) were recoded in the same way as all other adverse events.

2.4 Statistical analysis

The primary outcome measure was CD4 cells count. The secondary endpoints were levels of adherence, incidence of HIV related events, adverse events, laboratory abnormalities, liver function test, incidence of opportunistic infections or coinfections, clinical improvement and changes in body weight. The trial was designed to compare arm A with arm B and C at weeks 12, 20, 32 and 48, using the proportion of patients. All statistical tests were performed as on the Intent-To-Treat (ITT) population, which included all patients who took at least one dose of study medications; patients who discontinued for any reason were considered as treatment failures. Tests were performed on the On-Treatment (OT) population, which included only those patients with available evaluation at that time point. The safety evaluation included all patients who had at least one post-baseline safety assessment.

3 Results

3.1 Change in CD4 cell counts

Significant increases from baseline were seen in all three arms at every assessed time point. By the end of first 12 weeks of treatment, CD4 cell counts changed as follows: in arm A reaching +122 cells/mm^3; in arm B decreasing but not significantly –10 cells/mm^3 and in arm C increasing +36 cells/mm^3 but not in a significant manner. On the follow-up CD4 counts increased progressively in all arms, reaching +108, +85 and +103 cells/mm^3 by 20 weeks and +102, +190 and +175 cells/mm^3 by 32 weeks, for arms A, B and C, respectively (OT analysis).

There was a significant difference between arm A compared with arms B and C in terms of change in CD4 counts from baseline to week 12. In arm A CD4 cell counts increased significantly compared with arm B, in which cell counts decreased

(A versus B; $p < 0.04$) and with arm C, where increasing CD4 count was not significant from baseline level (A versus C; $p < 0.05$).

The first statistically significant increase in CD4 counts from baseline was observed in groups B and C at week 20. By week 32 progressive increase in CD4 cells in these two groups was higher than in arm A (B versus A; $p < 0.05$ and C versus A; $p < 0.05$).

The arm C had three patients in terminal stage of AIDS and who had very low levels of CD4 cells count at baseline 65, 64 and 128 cells/mm^3. After treatment initiation CD4 cells have risen to 80, 111 and 194 cells mm^3 by 12 weeks and165, 109 and 1171 cells mm^3 by 20 weeks. In parallel with rising CD4 cell counts these patients experienced progressive clinical improvement (Table 1).

Table 1 Summary of patients at study initiation

Characteristics	*Arm A (N = 20)* AZT/3TC/EFV 600/300/600mg daily N(%)	*Arm B (N = 30)* AZT/3TC/EFV + Immunoxel 600/300/600mg +100 drops daily N(%)	*Arm C (N = 20)* Immunoxel 100 drops daily N(%)
Male	8(40%)	18(59%)	16(80%)
Female	12(60%)	12(41%)	4(20%)
Body weight (Mean ± SD)	64.2 ± 8.9kg	68.9 ± 7.6kg	67.3 ± 8.4kg
CD4 cell counts (cells/mm^3)	361	421	462
Prior ART (%)	0	0	0
Patients with TB	7(35%)	7(23%)	9(45%)
Hepatitis C or B	9(45%)	11(33.3%)	12(50%)
Oral or oesophageal candidiasis	7(35%)	19(62.7%)	15(75%)
Herpes zoster	5(25%)	7(23%)	11(55%)
Laboratory abnormalities			
↓ Neutrophils	1(5%)	2(7%)	
↑Aspartate aminotransferase	6(30%)	11(33%)	7(35%)
↑Alanine aminotransferase	7(35%)	9(29%)	8(40%)
↓ Hemoglobin	2(10%)	2(7%)	1(5%)

3.2 *Adverse events*

Over 32 weeks of treatment significant differences were observed between arm A as compared with arms B and C in terms of overall incidents of adverse events. At least one adverse event, which possibly and probably was related to the study medications, was reported in 65, 24 and 5% of patients in arms A, B and C, respectively. Most clinical adverse events were mild – gastrointestinal symptoms were the most frequently reported adverse events. Over 32 weeks period, the most common adverse events considered as possibly related to study medication as well as those of moderate or severe intensity are shown in Table 2. There were clear differences between arms in a pattern or incidence of adverse events: the levels of diarrhoea and nausea were significantly higher in arm

A compared with arm B. In contrast in arm C gastrointestinal symptoms were not observed throughout the study period. Occurrences of headache and fatigue were also significantly higher in arm A when compared with arm B and these symptoms were not observed in arm C. Seven patients (35%) in arm A experienced serious adverse events, which were considered to be possibly or probably related to study medication. In this arm 1(5%) patient refused further therapy and 6(30%) patients needed replacement therapy due to progressive fatigue, vomiting and gastrointestinal disorders and/or hepatotoxicity. In arms B and C no incidents of interruption or changing therapy were observed. There were also significant differences between three arms in respect to laboratory findings (Table 2).

Table 2 Percentage of patients with clinical adverse events considered as possibly related to treatment and of moderate or severe intensity

Adverse events	*Arm A (N = 20)*	*Arm B (N = 30)*	*Arm C (N = 20)*
	AZT/3TC/EFV 600/300/600mg daily N(%)	*AZT/3TC/EFV + Immunoxel 600/300/600mg +100 drops daily N(%)*	*Immunoxel monotherapy 100 drops daily N(%)*
Gastrointestinal system			
Diarrhoea	6(30%)	2(7%)	
Nausea	7(35%)	2(7%)	
Vomiting	2(10%)		
Abdominal pain	7(35%)	3(10%)	
Neurological disorders			
Headache	3(15%)	1(3%)	1(5%)
Peripheral neuropathy			
General disorders			
Fatigue	11(55%)	3(10%)	1(5%)
Laboratory abnormalities			
↓Neutrophils*	2(10%)		
↑Aspartate aminotransferase**	5(25%)	1(3%)	
↑Alanine aminotransferase***	6(30%)	2(6%)	
↓Haemoglobin****	2(10%)		
↑Cholesterol *****	2(10%)		

*Defined as a fall from 1000–1500/mm^3 to <5000/mm^3 or from >1500/mm^3 to <749/mm^3.

**Defined as a rise from 1.25–2.5 ULN to >10 ULN or from 1.25 ULN to >5 ULN.

***Defined as a rise from 1.25–2.5 ULN to >10 ULN or from 1.25 ULN to >5 ULN.

**** Defined as a reduction from normal levels < 9.0 g/dl.

*****Defined as a rise from normal levels >6.3 mmol/l.

3.3 Opportunistic or coinfection defined events

During 32-week reporting period, OI were observed in all three arms under therapy. OI were observed in 6 (30%), 4 (13%) and 4(20%) patients for A, B and C arms, respectively (Table 3). There was a clear distinction between treatment arms in terms of frequency OI and co-infection events. These events were significantly higher in arm A compared with arms B or C.

Table 3 Frequency of clinical OI or co-infection defined events during 32 weeks treatment period

OI and co-infections	*Arm A (N = 20)* *AZT/3TC/EFV 600/300/600mg daily N(%)*	*Arm B (N = 30)* *AZT/3TC/EFV+Immunoxel 600/300/600mg + 100 drops daily N(%)*	*Arm C (N = 20)* *Immunoxel 100 drops daily N(%)*
Oral/oesophageal candidiasis	4(20%)	2(7%)	2(10%)
Herpes	4(20%)	4(13%)	3 (15%)
Tuberculosis lungs	2(10%)	2(7%)	
Cachexia	3(15%)		
Hepatitis C	2 (10%)	1(3%)	

Among most frequently reported relapses of OI and coinfection were oral or oesophageal candidiasis 4(20%), 2(7%) and 2(10%), herpetic infections 4(20%), 4(13%) and 3(15%) patients in the arms A, B and C, respectively. Acute tuberculosis was observed in 2(6%), 2(7%) patients in arms A and B, respectively. Similarly, the relapses of hepatitis C were observed only in arms A and B, 2(10%) and 1(3%), respectively.

3.4 Effect on liver function

Most patients enrolled in study had underlying liver pathology. Signs of progressing chronic inflammatory process in liver caused by persistent viral infection, toxicity and alcohol were registered as mean values of standard Liver Function Test (LFT). Baseline ALT or/and AST were elevated in 7/20 (30%), 13/30 (43%), 11/20 (55%) patients in arms A, B and C, respectively. Mean baseline values for ALT were 36, 62 and 72 U/L, respectively. The median cumulative change from baseline ALT values were + 22, +18 and –16U/L at 12 weeks, +30, –36 and –34U/L by week 20 and + 42, –24, –41U/L by week 32 for arms A, B and C, respectively. At week 32 ALT values have increased to a mean 78U/L in arm A and declined to 38 and 31 U/L in arms B and C, respectively. The difference between arms B and C compared with arm A in terms of ALT values (B versus A; $p < 0.05$, C versus A; $p < 0.03$). In arm C ALT values were decreasing progressively under therapy and became significant lower than baseline levels ($p < 0.01$). Similar trends were observed with AST marker. The mean baseline values of AST were 42, 49, 58U/L for arms A, B and C, respectively. At week 32 AST values increased to a mean 68U/L in arm A and decreased to 42, 26 U/L in arms B and C, respectively. The number of patients with ART related hepatotoxicity was 6(30%), 2(6%) patients in arm A and B, respectively. In arm C no cases of drug-related hepatotoxicity were noted.

3.5 Effect on body weight

Mean values for baseline body weight were 64.2 ± 8.9; 68.9 ± 7.6; 67.3 ± 8.4 kg for arms A, B and C. Among arms A, B and C 7(35%), 11(33%), 6(30%) patients had cachexia. The body mass steadily increased during therapy, gaining additional 1.4; 6.9 and 5.1 kg at week 32 for arms A, B and C, respectively. Weight gain varied for every patient ranging from 0.5–2 kg up to 6–9 kg during the therapy period. At the end of study, the mean weight values were 65.6 ± 7.3; 75.8 ± 6.9; 72.4 ± 8.6 kg for arms A, B and C respectively.

4 Discussion

AIDS is a significant threat to the mankind and the search for effective anti-HIV therapies is of paramount importance. Several chemical anti-HIV agents have been developed. However, besides the high cost, there are adverse effects and toxicity associated with use of chemotherapy. The herbal medicines have frequently been used as alternative or adjunct means of therapy by HIV positive individuals and AIDS patients. Except few instances, there is insufficient evidence to support the benefit of plant-derived medicines (Liu et al., 2005). Potential beneficial effects of medicinal plants need to be confirmed by rigorous clinical trials, preferably by comparing them to standard ART.

In this study we compared the safety and efficacy of immunomodulator Immunoxel with standard ART AZT/3TC/EFV or combination of AZT/3TC/EFV with Immunoxel using as the primary endpoint the change in CD4 lymphocyte counts. The increase from baseline in CD4 cells was seen in all three arms at every assessed time point, except for arm B at 12 weeks. However, patients on standard ART therapy gained lowest number of cells when compared to B and C arms, that is, +102, +190 and +175 cells/mm^3.

Additional parameters under consideration were the incidence of adverse events, frequency of opportunistic infections and coinfections, liver function test and effect on body weight. The incidence of adverse events which possibly and probably were related to the study medications was lowest in Immunoxel arm (5%) when compared to standard AZT/3TC/EFV tri-therapy (65%). Interestingly, patients in arm B who were treated with AZT/3TC/EFV and Immunoxel had significantly lower incidence (24%) of adverse events and hepatotoxicity despite exposure to the same ART dose as in arm A.

Immunoxel seems to normalise elevated liver enzyme levels. At treatment initiation baseline values for ALT were 36, 62 and 72 U/L but at week 32 AST values have increased to a mean 78 U/L in arm A but declined to 38 and 31 U/L in B and C arms. These properties of Immunoxel are of major consequence to management of ART toxicity. In addition to iatrogenic hepatotoxicity that ranges from mild hepatitis to liver failure there is a significant threat in form of chronic viral hepatitis, that is, HCV and HBV with higher risk of morbidity and mortality. Almost half of patients participating in this trial had confirmed HCV infection. However, despite the lack of hepatitis-specific treatment, patients who were given Immunoxel, experienced normalisation of initially high ALT and AST levels without a single incident of relapse. In contrast patients on AZT/3TC/EFV had higher incidence of hepatitis relapses. The patients on the same ART regimen supplemented with Immunoxel had lower number of outbreaks and normalised liver function test. These observations suggest that Immunoxel possesses anti-inflammatory activity.

AIDS-associated wasting is the major factor that contributes to morbidity and mortality. Currently, there is no standard treatment for this condition, which remains poorly treatable even in countries with advanced medical care. Some of nutritional regimens did yield positive results, however their success was unpredictable. Weight gain observed with Immunoxel was significantly higher when compared to such supplements or ART therapy. This weight-correcting property alone represents a significant achievement that greatly augments the choice of available treatment options.

Obtained findings support our earlier open-label trials conducted on more than 200 patients. In prior studies we have observed significant increase in body weight, reduced anemia and leucopenia processes and the increase of total lymphocytes and their CD4+ subpopulation (Kutsyna et al., 2003, 2004, 2005). These data taken together with present findings indicate that Immunoxel is safe and effective for clinical management of HIV infection.

At this stage we are not certain as to what is the precise mechanism of Immunoxel action. It is possible that Immunoxel may affect directly viral replication. However, this has not been verified by in vitro studies. The broad-spectrum antiviral, antimicrobial and anti-tumor activities shown in the clinical setting also preclude such a conclusion. Preliminary results suggest that Immunoxel can correct autoimmune disorders in a variety of diseases (Barabai et al., 2004; Bodnar et al., 2002; Chechitiany, 2003, 2004; Grinevich, 2001; Shapovalovi, 2004; Zeleniy, 2003). If we consider that the immunopathogenesis of HIV-infection is inherently an autoimmune process, then the role of Immunoxel as a modulator of HIV-caused self-destructive immunity makes a sense (Appay et al., 2005; Bourinbaiar et al., 2006).

Currently, several immunotherapeutic approaches are available, which operate on the premise that AIDS is an autoimmune disease. So far most of these therapies are in the domain of so-called therapeutic vaccines and related immunotherapies (Bourinbaiar et al., 2006). Very few validated, immune-based interventions are available when it comes to products of plant origin. Most studies in this area concern Oriental medicinal plants some of which were used for treatment of autoimmune disorders such as habitual abortion (Chen et al., 2003). However, we are not aware of any examples of application of autoimmunity-regulating herbs in infectious diseases, especially HIV infection. Not every herbal preparation can possess the right property suitable for such an indication. Indeed, some herbal supplements were shown to exacerbate autoimmunity – a property contrary to the intended action of Immunoxel (Lee and Werth, 2004). On the other hand it will be a mistake to classify Immunoxel as an immunosuppressant. The decrease in the frequency of opportunistic infections and absence of new episodes of OI as demonstrated in this trial support our prior observations, indicating that Immunoxel does not compromise the native immunity. These considerations are intriguing not only from the immunological point-of-view but are also important in finding effective therapeutic solutions for diseases which so far have been refractory to existing choices of treatment.

In conclusion, Immunoxel displays a broad-spectrum clinical activity that has far-reaching implications. It reduces drug toxicity and improves ART efficacy when used in combination with standard ART. Further studies are required to identify the mechanism of action and additional benefits associated with its use.

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References

Appay, V., Boutboul, F., Autran, B. (2005) 'The HIV infection and immune activation: "to fight and burn", Current Infectious Disease Report, Vol. 7, pp.473–479.

Bodnar, P.M., Mykhal'chyshyn, H.P., Reznichenko, V.M., Moshchych, O.P. and Pylypchuk, V.S. (2002) 'Phytoconcentrates "Dzherelo" and "lizorm" in therapy of autoimmune thyroiditis', Lik Sprava, Vol. 8, pp.127–129.

Bourinbaiar, A.S., Root-Bernstein, R.S., Abulafia-Lapid, R., Rytik, P.G., Kanev, A.N., Jirathitikal, V. and Orlovsky, V.G. (2006) 'Therapeutic AIDS vaccines', Current Pharmaceutical Design, Vol. 12, pp.2017–2030.

Lee, A.N. and Werth, V.P. (2004) 'Activation of autoimmunity following use of immunostimulatory herbal supplements', *Archives Dermatology*, Vol. 140, pp.723–727.

Liu, J.P., Manheimer, E. and Yang, M. (2005) 'Herbal medicines for treating HIV infection and AIDS', *Cochrane Database Systematic Reviews*, 20 July, Vol. 3, CD003937.

Barabai, V.A., Grinevich, Y.A. and Zhinchenko, V.A. (2004) 'Influence of immunotherapy on effectiveness of radiation treatment of tumor on immunomodulator Dzherelo example', *Problems of Ecological and Medical Genetics and Clinical Immunology*, Vol. 61, pp.67–70.

Chechitiany, R.B. (2003) 'Influence of plant derivative drug Dzherelo on cell signs of immunity among patients with chronically persistence herpetic infection with chronical fatigue syndrome', *Problems of Ecological and Medical Genetics and Clinical Immunology*, Vol. 53, pp.92–99.

Chechitiany, R.B. (2004) 'Influence of plant derivative drug Dzherelo on circulating immune complexes and their molecular content among patients with chronic persistent infection of mixed genesis (Epstein-Barr and herpetic)', *Problems of Ecological and Medical Genetics and Clinical Immunology*, Vol. 61, pp.130–134.

Chen, Z., Li, Y. and Li, Y. (2003) 'Review of study on mechanism of traditional Chinese medicine in treating autoimmunity disease', *Zhong Yao Cai*, Vol. 26, pp.218–221.

Grinevich, Y.A. (2001) 'Influence of phytoconcentrate "EcoMed" on immune system and body antitumor resistance', *Collection of Works: Modulated Medical Preventive Methods, Their Use in Medical Practice*, Vol. 1, pp.13–33.

Kutsyna, G., Chechitiany, R., Bascacov, I., Zagaynova, E. and Zaharova, I. (2005) 'Influence of a novel immunomodulator to the prevalence of new events opportunistic infections in untreated HIV– infected individuals', *Third European HIV Drug Resistance Workshop*, Athens, Greece, 4–7 April, Abstract #36.

Kutsyna, G., Zagaynova, E. and Zaharova, I. (2004) 'Effects of a novel immunomodulator in HIV infected individuals', *Seventh International Congress on Drug Therapy in HIV Infection*, Glasgow, UK, 14–18 November, Abstract #224.

Kutsyna, G.A., Chechitiany, R.B. and Zagaydanova, Y.G. (2003) 'Effects of immunomodulator Dzherelo on immune signs among HIV-infected', *Problems of Ecological and Medical Genetics and Clinical Immunology*, Vol. 53, p.56.

Shapovalovi, I.O. (2004) 'Influence of plant derivative drug Dzherelo on signs of macrophage phagocyte system among teenagers, who had acute tonsillitis of viral etiology', *Problems of Ecological and Medical Genetics and Clinical Immunology*, Vol. 61, pp.135–144.

Zeleniy, I.I. (2003) 'Effectiveness of phytoconcentrate Dzherelo on immune rehabilitation of patients with erysipiloid pustulous–necrotic complications', *Problems of Ecological and Medical Genetics and Clinical Immunology*, Vol. 53, pp.34–49.