Japanese Educational and Scientific Review

No.1. (9), January-June, 2015

"Tokyo University Press"
2015

ELSEVIER

東京大学
THE UNIVERSITY OF TOKYO

Japanese Educational and Scientific Review

No.1. (9), January-June, 2015

VOLUME XII

"Tokyo University Press"

2015

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PROTEFLAZID: Specific activity in Epstein-Barr virus infection in a preclinical study; efficacy and safety in the clinic (systematic review)

Abstract: We analyze the specific anti-EBV (Epstein-Barr virus)-activity of the active ingredient Proteflazid extract and preparations based on it: Proteflazid® (drops), Flavozid® (syrup). Preclinical studies have shown that the active ingredient blocks DNA polymerase and thymidine kinase in EBV infected cells, induces the synthesis of endogenous α- and γ-interferons, has antioxidant activity and also apoptosis-modulating action. Efficacy of drugs for diseases caused by the Epstein-Barr virus has been clinically proven. The safety and efficacy of Proteflazid® (drops) and Flavozid® (syrup) in children (755 patients) and adult (592 patients) in the clinic has been confirmed. The unidirectional positive therapeutic effect in 16 clinical observations in the period from 2002 to 2014 was noted.

Key words: Proteflazid®, Flavozid®, antiviral preparations, Epstein-Barr virus infection, infectious mononucleosis, treatment.

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PROTEFLAZID: Specific activity in Epstein-Barr virus infection in a preclinical study; efficacy and safety in the clinic (systematic review)

Abstract: We analyze the specific anti-EBV activity of the active ingredient of Proteflazid extract and drugs based on it: Proteflazid® (drops), Flavozid® (syrup). Preclinical studies have shown that the active ingredient has poly pharmacological effect: it blocks DNA polymerase and thymidine kinase in EBV infected cells, induces the synthesis of endogenous α- and γ- interferons, has antioxidant activity and also produce apoptosis-modulating effect. The ethiopathogenetic efficacy of antiviral drugs of plant origin that contain flavonoids (Proteflazid® and Flavozid®) in Epstein-Barr virus has been clinically proven. The safety and therapeutic efficacy of drugs in children (755 patients) and adults (592 patients) in the clinic had been confirmed and proven; the unidirectional positive therapeutic effect in 16 clinical studies in the period from 2002 to 2014 was noted.

Keywords: Proteflazid®, Flavozid®, antiviral drugs, Epstein-Barr virus infection, infectious mononucleosis, treatment.

Rationale. One of the most common form of herpes virus infection is an infection caused by Epstein-Barr virus (EBV, herpes virus 4), belonging to the Gammaherpesvirinae subfamily [1, 2]. The rate of EBV infection in adults is almost 90-100%, and in children these indicators vary from 50% to 80%, according to different authors [3]. The time of the first contact with the virus depends on the social conditions: in developing countries or in unfavorable families most children get infected before reaching the age of three years, and all the population - before adulthood; in developed countries EBV infection can occur later. In most cases, the initial EBV infection stays undistinguished, symptom-free or leading to moderate increase of liver enzymes [4, 5]. Only 1/6 of patients has such clinical manifestations as infectious mononucleosis (acute form of Epstein-Barr virus infection (EBVI) [6, 7]. A special feature of EBV infection is a tendency to relapsing course, which is observed in 1/3 of patients and the development of chronic forms of the disease [8].

The specialists pay a special attention to an acute form of EBVI, which mainly proceeds favorably, but does not end with full elimination of the causative agent. The further course of the disease becomes latent, which may show no signs throughout a person's life, but the presence of immune deficiency or other adverse factors can cause the reactivation of infection with serious damage to organs and systems. Clinically, it manifests as meningitis, encephalitis, polyradiculitis, hepatitis, etc. [8,9]. In 10-25% of cases EBVI can have adverse consequences with further formation of lymphoproliferative, oncohematological diseases, chronic fatigue syndrome, EBV-associated hemophagocytic syndrome, autoimmune pathology, etc. [10, 11, 12]

EBV infection is an immunological paradox: virus infects B-lymphocytes and persists in these cells-representatives of immune system [13, 14]. Clinical manifestations and pathogenesis of infection are the result of the immune fight between the infected B-lymphocytes and cytotoxic lymphocytes. EBV has a powerful immunosuppressive effect, causing disorders of the immune response [1, 2, 3, 15]. The formation of immunity in EBV is a complex multi-component process, which includes both compensatory (response to persistent antigen) and inadequate regulation of specific immune response to virus [15, 16]. In the context of a weakened immunological control, the complete elimination of the intracellular virus is not just impossible, but there are also favorable conditions for the spread of the virus from cell to cell by intercellular bridges or extra cellular [16, 17]. The virus can infect and persist in immunocompetent cells, which results in absence of the possibility of causative agent elimination and full organism sanitation, and in development of immunopathological reactions with various organs and systems damages and clinical manifestation of immunodeficiency [9, 10, 11, 16, 17].

Numerous studies confirmed that EBV leads to malignant transformation of infected cells. It is proved that such types of cancer as nasopharyngeal cancer, laryngeal cancer, cancer of blood-vascular system, renal cell carcinoma, genital cancer, and cancer of the nervous system are often associated with this virus [9, 10].The mechanism of EBV action is that the LMP-1 protein of Epstein-Barr virus not only blocks the apoptosis, but helps the pathogenic cells to grow, multiply and even migrate [18, 19]. There are no affected cells that undergo apoptosis at the molecular level, and thereby the tumor process is developed [20]. One of the targets, which activates viral protein, is the epidermal growth factor receptor (EGFR). This receptor affects the cell in the same way as viral LMP-1 protein. That is, the virus provokes and supports the carcinogenesis in the body of an infected person bilaterally - through its LMP-1 protein and the cellular EGFR protein [10, 11, 12, 13, 20]. If EGFR, due to its function, triggers oncogenesis, LMP-1 (along with the abovementioned functions) blocks the cells of the immune system and supports angiogenesis (formation and growth of new vessels), creating favorable conditions for the growth and development of tumor [18, 19, 20].

The approaches to EBV treatment are based primarily on clinical data. The priority is given to nucleoside drugs (acyclovir, ganciclovir, valaciclovir, valganciclovir) based on the reasonability of these drugs administration, despite the fact that they have a significant number of contraindications. At the same time, in the treatment process, practicing physicians have noted insufficient efficacy of monotherapy by mentioned drugs and try to potentiate it with specific immunoglobulins and interferons that, in return, leads to greater damage to homeostatic capacities of the organism, and to the development of sustainable autoimmune processes.

Due to the different approaches to the EBV treatment, lack of highly effective and safe treatment algorithms, development of resistance to several drugs, the creation of new effective and quite safe EBV treatment regimens has become relevant [21, 22, 23].

Antiviral drugs with such active ingredient as flavonoids Proteflazid extracts (Proteflazid® (drops) and Flavozid® (syrup) by LLC @Scientific and Production “Ecopharm” (UKRAINE) meet the highest therapeutic requirements [24, 25].

Proteflazid extract is obtained by alcohol extraction (96% of ethanol) of herbal substances (wild grasses – *Calamagrosis epigeios* L. and *Deschampsia caespitosa* L.). The drug contains flavonoids extracted from grasses (flavone and flavonol glycosides), presented in the form of stable molecular complexes: tricin, apigenin, luteolin and quercetin [25].

The purpose of the work: to confirm the efficacy and safety of pharmaceutical products based on Proteflazid extract (Proteflazid®, drops, Flavozid®, syrup) in treatment of diseases, which were caused by Epstein-Barr virus, basing on systematic analyses of preclinical and clinical studies in children and adults.

Materials and methods: Scientific publications on the preclinical (4 works) and clinical (16 works) studies; systematic analyses.

Results of studies and discussion.

Preclinical studies. Rybalko C.L. (2003), Zagorodnyaya et al. (2009) have shown the efficacy of active ingredient of Proteflazid extract in vitro in *Raji* lymphoblastoid cells culture (human B-lymphocytes) in relation to Epstein-Barr virus in studies to determine the cytotoxicity and specific anti-EBV activity. Antiviral activity was estimated by PCR method for percent reduction of genome equivalents of EBV DNA per cell. The findings show dose response between the concentration of the Proteflazid extract and EBV reproduction. Adding a drug concentration of 0,1 μg/ml results in a 50% reduction in the amount of genomic EBV DNA equivalents per cell [24, 27].

It is confirmed that Proteflazid extract has a fairly high selective index (SI). The SI is from 250 to 1500 under different solvents and schemes of Proteflazid extract using [24, 26, 27]. In accordance with the methodological recommendations on preclinical studies, the substance, the SI values of which are equal to or above 16, can be considered highly active and promising for further studies [29].

The established fact of the efficacy of active ingredient of Proteflazid extract against Epstein-Barr virus in *Raji* cells culture allows including drug to active and perspective drugs for therapy of diseases caused by this virus [24, 27]. As shown in subsequent studies by C.L. Rybalko (2010), D.B. Starosyly (2011), flavonoids included in Proteflazid extract, are capable of inhibiting the synthesis of virus specific enzymes DNA polymerase and thymidine kinase in the virus-infected cells [25, 26].

It should be noted that in series of preclinical studies, the potential of the substance of Proteflazid extract to exert an antiviral effect on other herpesviruses such as HSV-1, HSV-2, has been confirmed 24, 25, 26, 27].

In addition to antiviral effect, the active ingredient of the Proteflazid extract shows antioxidant effect: it increases cell resistance to free radical stress in infections, reduces the negative effects of drug chemotherapy, helps the organism to adapt to adverse environmental conditions. It is proved that the drug suppresses in more than 2 times the intensity of free radical processes induced by hydrogen peroxide. At the cellular level it is shown that Proteflazid inhibits superoxide anion radical generation almost to zero in 24 hours from the time of the drug administration, in other words, supports antioxidant status of cells [24].

C.A. Kramareva et al. proved that in the pathogenesis of chronic EBV, the violation of apoptosis mechanisms is very important [28]. Proteflazid also manifests apoptosis-modulating effect, promotes primary prevention of oncological diseases with chronic (latent) virus infections. The active ingredient of Proteflazid extract restores the ability of virus-infected cells apoptosis through caspase 9 activation, reducing the activity of proliferative processes in the mutated cells [25].

In terms of acute toxicity, the antiviral herbal drugs containing flavonoids (Proteflazid®, Flavozid®) are classified as relatively safe agents. In the context of preclinical studies we have not revealed any teratogenic, mutagenic and embryotoxic effect. [24, 25, 26].

Clinical studies. The Proteflazid® is used for EBV treatment in clinical practice since 2002.

V.I. Matyash et al. (2002) developed relevant schemes of ethiopathogenetic therapy of severe form of herpes infection. The study findings allow us to establish the relevance of the complex causal treatment including Proteflazid in therapy of severe form of herpes infection including EBV, that helps to achieve a sustainable effect on restoration of affected organs and systems function [30].

T.O. Nikiforova et al. (2004) have carried out the study of clinical immune efficacy of Proteflazid® in patients with confirmed EBV. As the results of observations, the drug administration contributed to the rapid disappearance of intoxication and lymph proliferative symptoms, reactivation of liver function, significantly reduced the level of IgG in the blood [31].

A.I. Gley (2005, 2008) have demonstrated the efficacy of Proteflazid® as antiviral and immune-modulating drug for the treatment of infectious mononucleosis caused by EBV. It is shown that the administration of the drug for 2 months on the specified instructions for use of the drug scheme reduces the time of viremia, duration of disease, prevents the formation of a chronic form of the disease [32, 33].

E.V. Usacheva et al. (2005) have proved the efficacy of Proteflazid® in complex therapy, that shown positive dynamics on the part of the clinical symptoms of the disease, and indicators of hemogram in the study of clinical efficacy and acceptability of Proteflazid® in children with infectious mononucleosis. In the setting of Proteflazid® administration, a more rapid termination of cytolysis of hepatocytes syndrome, which characterizes the manifestation of disease severity, was noted [34].

E.L. Panasyuk (2006), as the results of a comprehensive study, it was found the predominance of association of herpes virus infections, which include viruses that have different antiviral susceptibility. Under these conditions, they studied the influence of the Proteflazid® on clinical course of the disease, the dynamics of the immune reactivity of interferon induction in patients with different associations of herpes viruses, including EBV. It proved that Proteflazid® reduces toxicity and increases the efficiency of antiviral therapy; the

interrelation of the dynamics of interferon conversion with the terms of positive clinical dynamics was established. According to the study the indications and dosage regimens of Proteflazid® administration with the anti-relapse aim were developed. It is proved that chronic administration of Proteflazid in convalescence period (decubation) is safe and reduces in 1,9 times the virus-positive and virus-negative relapse rate. Also, a comparative assessment of the effectiveness of complex treatment regimens based on different Proteflazid® (drops) combinations and other drugs was made [35].

Yu. P. Kharchenko, G.A. Shapoval (2007) have made comparative clinical study where they studied the efficacy of Flavozid® (syrup) administration in complex therapy in children with infectious mononucleosis taking into account the clinical and immunological status. The results of study have shown that the drug administration allow to reduce the average time of hospital stay at the in-patient department in 1,5 times, to reduce the duration of fever, reduce the severity of intoxication syndrome, reduce the duration of lymph proliferative syndrome and hepatosplenomegaly. The authors state that Flavozid® oppresses active viral replication and has a pronounced immunomodulating and antioxidant effect [36].

C.A. Kramarev et al. (2008) have conducted clinical studies of efficacy and tolerance of Flavozid® (syrup) in children with EBV in reactivation phase. It was shown that the drug administration in the complex therapy of disease increases effectiveness, greatly reducing viremia and does not cause side effects [37, 38].

V.V. Chopiak et al. (2008) presented the results of study of Proteflazid® (drops) in patient with chronic EBV in reactivation phase in the setting of replicative virus activity (DNA +). Prolonged (up to 2 months) Proteflazid® (drops) administration lead to faster regression of clinical manifestations of disease and to improvement in general condition of patients. Specific molecular genetic studies using PCR method confirmed that the drug has pronounced anti-viral properties. On the basis of complex immunological study it can be concluded that Proteflazid® helps to increase the number of T-cytotoxic lymphocytes (CD8+), stabilize the functional activity of NK cells, reduce the activity of suppressive subpopulation of regulatory CD4+/CD25+ lymphocytes, increase the absorption capacity of phagocytes. Complex of the mentioned factors stimulate antiviral response [39].

In the studies of C.A. Kramarev, O.V. Vygovskoy (2011) the children with EBV in reactivation phase were under observation. The clinical and laboratory data show the effectiveness of Flavozid® (syrup) that was included in a comprehensive treatment of the disease [40]. In the study of the efficacy, tolerability and possible side effects of Flavozid® (syrup) in 2012 in treatment of children with EBV in activation phase, the authors confirmed the antiviral effect of Flavozid® (syrup) in the clinic (in vivo studies). The reduction of anti-EBV VCA-IgM (IgM antibodies to virus capsid antigen) and of DNA EBV in saliva and blood were registered through serological and PCR studies for the presence of EBV. The drug is found to be safe in the treatment of acute and chronic active EBV in children [41].

In extensive study, C.A. Kramarev et al. (2014) have shown the efficacy of Flavozid® (syrup) in treatment of EBV infectious mononucleosis, which resulted in pronounced positive dynamics of T-cell and B-cell immunity, the elimination of severe inflammatory reaction from the organs and body systems, clinical recovery, absence of prolonged and chronic infection. The study results suggest a high clinical efficacy of Flavozid® syrup, which manifests significant antiviral and immune correcting activity in the treatment of EBV IM in children [42].

According to clinical data, G.A. Biletskaya (2011) have shown that the Proteflazid® administration in complex therapy in children with EBV IM reduces the duration of clinical manifestations and terms of hospital stay at the in-patient department, and reduces the possibility of relapse [43].

T.P. Borisova, E.N. Tolchennikova (2013, 2014) have been estimated the efficacy of complex antiviral and immunotropic therapy of chronic EBV infection in children with hematuric form of chronic glomerulonephritis (HFCGN). Study results indicate the positive dynamics of HFCGN and related EBV and cytokine status after conducting a comprehensive and immunotropic antiviral therapy with Proteflazid®. The decrease of respiratory disease

incidence, subfebrility, asthenic syndrome, systemic lymphadenopathy, hepatomegaly, bowel syndrome, lymphocytosis and elimination of splenomegaly were noted [44, 45].

The results of preclinical studies are consistent with those obtained in the practice medicine.

The table below shows the main results of 16 clinical studies in chronological order.

In clinical studies, described in the table, in EBV complex and monotherapy, Proteflazid® (drops) and Flavozid® (syrup) have antiviral activity, as evidenced by the disappearance of active viral replication markers from the blood and saliva of patients: anti-EBV VCA-IgM, EBV DNA in blood after treatment. The established fact is confirmed by preclinical data on a specific antiviral activity of the active ingredient of the Proteflazid extract against EBV.

Proteflazid® and Flavozid® reduce the average duration of hospital stay in 1,5 times and in the same way reduce the severity of neuroautoimmune reactions [28]. It should be noted that intoxication symptoms in setting of drug administration were less apparent and were eliminated in 2,5 times faster, course of disease was easier and the fever was shorter in two times; duration of lymphoproliferative syndrome was significantly reduced, incidence of hepatosplenomegaly was decreased.

It had also been demonstrated that in clinical settings Proteflazid® and Flavozid® induce the synthesis of endogenous α- and γ- interferons (IFN), that indicates the absence of immune system refractory to interferon inducer.

Immunomodulatory activity of Proteflazid® and Flavozid® is shown in increase of body's resistance to viral infections and restoration of immunity parameters.

The efficacy and safety of repeated courses of Proteflazid® and Flavozid® therapy in EBV reactivation phase, is proved.

Table.

Clinical studies results of efficacy and safety of Proteflazid® (drops) and Flavozid® (syrup) in children and adults from 2002 to 2014.

№	Authors, year, source	Drug	Patients number		Results of Proteflazid®/Flavozid® administration in clinical practice
			Average	Drug administrated	
1	2	3	4	5	6
1	V.I. Matyash et al. 2002 [30]	Proteflazid®	25 of adults	25	There has been a steady effect on restoration of function of affected organs and systems: the lymph nodes, liver and spleen; hemogram indicators improvement. The symptoms of focal brain lesions, and disco ordination smoothed over, memory was improved in the setting of the treatment for 2-3 weeks.
2	T.O. Nikiforova et al. 2004 [31]	Proteflazid®	26 of adults	14	Temperature rise and general condition were normalized in 76.8% of patients receiving the drug, versus 50.0% of the control group. Lymphadenopathy depression was registered in 35,7% of patients versus 25,0% of control group. Indicators of bilirubin and transaminases in patients who were administrated the drug, were normalized by an average of 3,5±0,1 days faster than those of the control group. Under the influence of the drug the relative number of lymphocytes and mononuclear cells in the blood was decreased, significantly reducing IgG level in blood.1 month later, only 7.0% of the patients who were administrated the drug, have Banti's syndrome and lymphadenopathy against 25.0% in the control group.
3	A.I. Gley 2005 [32]	Proteflazid®	47 of adults	27	Clear positive dynamics in the form of rapid decrease in size of lymph nodes and spleen, hemogram markers of improvement (reduction of white blood cell numbers, disappearance or reduction of atypical mononuclear cells) and biochemical markers of improvement (normalization or reduction of transaminases) were described. 2 months later viremia was observed in 48% of patients who were administrated the drug and 98% in the control group.
4	A.I. Gley 2008 [33]	Proteflazid®	258 of adults	112	A significant reduction in the duration of viremia in the administration within 2 months in comparison with patients who did not received the antiviral therapy.
5	O.V. Usachova et al.	Proteflazid®	38 of children	17	There is almost the same average duration of hospital stay in both groups of patients (11,05±4,6 and 11,3±4,7); 35,3% of children who were administrated the drug, were

	2005 [34]				discharged with recovery, and only 19.1% of children of control group were discharged too. In 78.5% of children who have been administrated the drug, there was a gradual decrease in the severity of hepatomegaly, and ALT level was rapidly decreased in 75% of children with cytolytic syndrome. The drug was well tolerated by all patients, adverse effects were not noted.
6	O.L. Panasyuk 2006 [35]	Proteflazid®	236 of adults	159	The regression of somatic-neurological symptoms was noted on 8±2,6 days of treatment; antiviral antibody seroconversion was observed at 2,0 ± 0,8 months of treatment; increase in the number of NK cells was 17%, increase in functional activity of mononuclear cells was 20%, and increase in neutrophils was 10%; reduction of neuroautoimmune expression was in 1,5 times as compared to the control group, were observed. The depression of α- and γ- interferons is not noted. The drug administration in convalescence period allows to reduce the frequency of repeated clinical and virological (virus "+") relapses in 1.9 times and clinical relapses (virus "-") in 1,3 times, and reduce the severity of the disease and accelerate the achievement of the therapeutic effect in the re-treatment of relapse.
7	Yu.P. Kharchenko, G.A. Shapovalova 2007 [36]	Flavozid®	60 of children	30	The drug administration allows to reduce the average time of hospital stay at the in-patient department in 1,5 times, to reduce duration of the temperature rise period (fever) in two times, reduce the severity of infectious intoxication, reduce the duration of the manifestations of lesions of the lymphatic system, and reduce the incidence of hepatosplenomegaly. The drug inhibits active replication of virus and has a pronounced immunomodulating, and antioxidant effect.
8	O.E. Chernysheva et al. 2007 [46]	Flavozid®	30 of children	18	The therapy was able to stop acute infection in 67% of children, and transfer relapsing chronic EBV in latent in 64% of children.
9	C.O. Kramarev, O.V. Vygovskaya, 2008 [37]	Flavozid®	35 of children	35	In complex therapy of EBV infection, the drug has antiviral effect, which characterized by the disappearance of active viral replication markers in blood: anti-EBV VCA-IgM, EBV DNA after treatment. There was a positive involution of the clinical symptoms: intoxication syndrome, restore appetite, lymphoproliferative syndrome severity (lymph node, liver, and spleen size), and hematological disorders.
10	C.O. Kramarev et al. (2008) [38]	Flavozid®	55 of children	55	After six months from the start of treatment anti-EBV IgM VCA continue to be determined in 13.3% of children who have this marker positive on admission; EBV DNA was not detected in the blood. Side effects in drug administration are not registered.

11	V.V. Chopiak et al. 2008 [39]	Proteflazid®	25 of children	25	The drug has pronounced antiviral effects, helps to increase the number of T-cytotoxic lymphocytes (CD8+), stabilize the functional activity of NK cells, reduce the activity of suppressive subpopulation of regulatory CD4+/CD25+ lymphocytes, increase the absorption capacity of mononuclear phagocytes in blood.
12	C.A. Kramarev, O.V. Vygovskaya 2011 [40]	Flavozid®	60 of children	60	After treatment the active replication markers disappear from the blood: anti-EBV IgM VCA, EBV DNA. The severity of clinical symptoms decreases significantly: disorders of the nervous system, fever, acute tonsillitis, systemic lymphadenopathy, hepatomegaly and hematological disorders.
13	G.A. Biletskaya et al. 2011 [43]	Proteflazid®	75 of children	30	The drug in complex therapy in children with IM reduces the duration of disease manifestations and time of hospital stay at the in-patient department, reduce the possibility of relapse in three times.
14	C.A. Kramarev, O.V. Vygovskaya 2012 [41]	Flavozid®	80 of children	40	The significant decrease in the detection of anti-EBV IgM VCA and reduction of EBVDNA detection in saliva and blood for the control group were registered. There were no marked side effects of the drug during the period of observation.
15	T.P. Borisova, E.N. Tolchennikova, 2013 [44]	Flavozid®	54 of children	54	The positive dynamics of HFCGN and related EBV and cytokine status, elimination of subfebrility, asthenic syndrome were noted: the incidence of systemic lymphadenopathy, hepatomegaly, bowel syndrome, and lymphocytosis was significantly reduced. Signs of chronic EBV after treatment were eliminated in 31.5% of patients compared with the control group.
16	C.A. Kramarev et al. 2014 [42]	Flavozid®	243 of children	60	The markers of T-cell and B-cell immunity have positive dynamics indicating the elimination of severe inflammatory response by the body's organs and systems and the corresponding clinical recovery, absence of lingering infection process, absence of chronic infection.

Findings. Preclinical and clinical studies in different study institutes and clinics of Ukraine have proved that the active ingredient of Proteflazid extract and the drugs on its base - Proteflazid® (drops) and Flavozid® (syrup) – have antiviral, immunotropic, apoptosis-modulating and antioxidant effect. The above-mentioned pharmacodynamic properties of the drugs cause the expediency of their appointment for the effective etiopathogenetic treatment of EBV in children and adults.

The presented studies on EBV therapy, especially in childhood, with antiviral substances of natural origin that have minimal negative impact on the compensatory processes of the body are of great importance for clinical practice.

Thus, a systematic review of clinical trials that were conducted in the period from 2002 to 2014, with 1347 of patients (592 adults and 755 children), confirm the effectiveness and the high safety profile (high margin of safety) of the use of antiviral Proteflazid® and Flavozid® for the treatment of diseases caused by the Epstein-Barr virus (in the case of mono- or mixed infections) in children and adults. The positive dynamics in the course of the disease was established in all 16 clinical studies included for the analysis.

An analysis of preclinical and clinical studies gives reason to recommend Proteflazid® and Flavozid® for widespread use in clinical practice for the treatment of diseases caused by Epstein-Barr virus in children and adults.

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