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PORCINE BIFERON-C APPLIED TOGETHER WITH MEDICINAL PROPHYLAXIS IN COMMERCIAL PIG BREEDING PROVIDES IMMUNOSTIMULATION OF SOWS AND AN INCREASED VIABILITY OF THEIR PIGLETS

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Abstract

Immunodeficiency of pigs resulting from the effect of various infectious and invasive pathogens, mycotoxins, heavy metals, wide usage of chemotherapeutic agents and other xenobiotics, nutritional deficiencies, deficiency of some vitamins and microelements, stresses of various etiology is one of the main causes of high morbidity in breeder herds and the offspring. In this paper, the immune status of sows and safety of suckling piglets under the effect of recombinant alpha- and gamma-interferons, the main active substances of Biferon-C preparation (the Republic of Belarus), applied in combination with conventional measures for prophylaxis with antibiotics and chemoprophylaxis are studied for the first time. It is found that the treatment of sows improves their immune status with a 2-fold increase in safety of their piglets while the offspring of untreated sows shows only a 4 % increase in viability after injections of Biferon-C. For the experiment, two groups of 10 farrow sows each were formed (Zolotaya Niva, Znamenskii Region, Tambov Province, 2017). The animals of basic variant (group I) were treated after farrowing according to the scheme accepted in the farm: during the first 24 hours after farrowing and on day 3 and day 5, one time a day, sows were intramascularly injected with Metramag and treated intrauterinely with Iodopen. Sows of test group II were additionally injected intramuscularly with Biferon-C (10 ml per sow) 24 hours before farrowing and 2 days post farrowing. Newborn piglets of group I born from mother sows not treated with Biferon-C (basic variant, $n = 332$) were treated according to the scheme accepted in the farm, and the animals of test group II ($n = 333$) additionally received two intramascular injections of Biferon-C (0.1 ml/kg of body weight) at 24-hour intervals. Experimental sows and piglets were clinically observed till weaning (24-26 day), considering the percent of morbidity, mortality and growth dynamics of piglets. Blood samples were tested for morphological and immunological indices before the application of the preparations and at the end of the experiment. The basic level of immune indices showed that immune status of sows of all the groups practically did not differ and corresponded to their physiological state. Receiving recombinant proteins by sows led to a significant increase in relevant and absolute blood levels of monocytes, lymphocytes, T- and B-lymphocytes, complementary and lysozyme blood serum activity, phagocytosis. Higher immune status of sows promoted the prophylaxis of their postpartum pathologies and a 2-fold increase in viability of their litters. The injectionы of Biferon-C to piglets led to the decrease in intestinal infection frequency, increasing the safety of the herd.

Keywords: Biferon-C, recombinant proteins, immune status, sows, piglets, postpartum pathology, intestinal infections

One of the main reasons for the high incidence of pig breeding stock and their offspring is immunodeficiency caused by exposure to the various infectious and invasive pathogens [1, 2], mycotoxins [3, 4], heavy metals [5], widespread use of chemotherapeutic agents and other xenobiotics, deficiencies of certain

vitamins, nutrients and microelements [6, 7], stresses of various etiologies (8). Industrial pig farms often face postnatal pathology (acute postnatal purulent catarrhal endometritis, mastitis-metritis-agalactia, MMA) in breeding stock and diarrhoeal and respiratory disease in pigs caused by a variety of infectious agents on the background of reduced immune reactivity [9-13]. Different measures and methods have been offered for their prevention and therapy [14, 15].

In view of the etiology and pathogenesis of postpartum diseases in sows, a complex of prevention measures is promising with the immunostimulatory substances including recombinant interferon with a complex action resulting from the activation of the immune system. Interferons act against the reproduction of many viruses, express tissue specificity, and are insensitive to antiviral antibodies [16, 17]. Interferons possess antibacterial features. The bacteriostatic effect is due to the significant violation of bioenergetic processes in microorganisms by depleting tryptophan and a secondary bactericidal effect is due to the generation of nitric oxide and reactive oxygen species in macrophages [18-21]. The protective role of interferons in the body during bacterial infections is also associated with the activation of T-lymphocytes, macrophages, and natural killer cells, performing a protective function [22]. In the light of detected and investigated properties of interferons indicating their participation in maintaining homeostasis, the preparations are developed with antiviral and immunomodulatory properties [23-26].

Biferon-C is a marketed product with anti-viral and immune stimulatory activity, which is a mixture of porcine species-specific recombinant α and γ - interferons with the total antiviral activity not less than 1.0×10^4 TCD_{50}/cm^3. According to the pharmacological properties of the preparation, it affects the natural resistance (as an inductor bactericidal and lysozyme activity) and immune status (induction of cellular and humoral immunity of a system of endogenous cytokines) of sows and piglets. It should be noted that the literature contain limited data on the impact of Biferon-C. We know one work with the data on a study of the influence of recombinant bovine α- and γ-interferons of a biological product Biferon-B on pregnancy completion and the status of cows and calves after birth [27].

The accumulation of information on the use and effectiveness evaluation of recombinant proteins with species specificity is of obvious scientific interest and of practical importance. We were first to examine the change in the immune status of sows and the safety of suckling piglets influenced by recombinant α- and γ-interferons, the principal active ingredients of Biferon-C (Republic of Belarus) used with the accepted antibiotics and chemoprophylaxis. It was found that the treatment of pregnant sows twice increases the safety of pigs whereas the safety of pigs from non-treated sows is increased by Biferon-C by only 4%.

Objective was to evaluate the effect of Biferon-C using as an additive to the standard scheme of medical prophylaxis of postnatal pathologies of sows and to improve the immune status of suckling piglets in an industrial complex.

Techniques. For the study (Zolotaya Niva LLC, Znamensky district, Tambov Prvince, 2017), two groups were formed (n = 10 each) of crossbred sows (large white + landrace + Duroc breeds) at later stages of pregnancy. On day 107 of gestation after sanitizing the pigs were placed in individual pens in disinfected isolated box of the farrowing area. Microclimatic indices were optimal for the physiological condition of the animals (average temperature in box was 20-23 °C, relative humidity 65-71%). During the experiment, sows were fed with SC-2 feed (Russia), balanced for all the declared nutrients, according to the manufacturer.

Animals from group I (control) after the farrowing were treated according to the guidelines adopted at the farm: in day 1 after farrowing and next at

day 3 and day 5, Metramag (Mosagrogen, Russia), containing 4 IU/ml of oxytocin and 100 mg/ml of ciprofloxacin, was injected intramuscularly once a day and Iodopen (NITA-FARM, Russia), suppositories, each containing 1.5 g of Povidone-Iodine, were used. For sows from group II (experimental) the adopted basic scheme of veterinary processing was supplemented by 10 ml of Biferon-C intramuscularly (Scientific and production center ProBioTeh, LLC, Republic of Belarus; the preparation is a mixture of porcine species-specific recombinant α- and γ-interferons with the total antiviral activity not less than 1.0×10^4 TCD_{50}/cm^3) 24 h before and 2 days after the farrowing. Clinical observation (percentage of incidence, thermometry in the first 4 days after farrowing) of the sows was conducted prior to weaning piglets (days 24-26). Prior to the use of the preparations and at the end of the observation period (days 24-26), the blood was sampled from the animals in blanching Green Vac-Tube tubes (Green Cross, South Korea) to study the morphological and immunological parameters (whole blood and blood serum clinical study).

Newborn piglets from untreated sows also formed the two groups: group I (control; $n = 332$), and group II (experimental; $n = 333$). The control piglets day 1 after birth were docked with tusks removed, and on day 3 got Ursoferran-200 (VIC-Animal Health, Republic of Belarus) containing 200 mg of iron per 1 ml in the form of iron (III)-dextran-heptonic acid, and boar pigs were castrated. The experimental group was injected with Biferon-C intramuscularly at a dose of 0.1 ml/kg Bw on days 1 and 2. Clinical observation of the pigs performed for the weaning from sows (days 24-26) included a selective body temperature measurement, accounting percent of ill and dead animals, and the growth indices (by group weighing).

Blood morphology was studied on a hematologic analyzer AVH Micros 60 (ABX Diagnostics, France) with the determination of leukocyte formula according to recommendations (M.I. Reckij, A.G. Shakhov, V.I. Shushlebin, etc. Methodical Instructions. Voronezh, 2005).

Immune parameters, including complement (SCA) and lysozyme (SLA) activity, total immunoglobulins (Ig), circulating immune complexes (CIC) in blood serum (humoral serum factors of natural nonspecific resistance), phagocytic activity of leukocytes (PAL), phagocytic number (PN), phagocytic index (PI), T- and B-cells count (cell-mediated immunity), were determined using standardized and harmonized methods in accordance with the recommendations (A.G. Shakhov, Yu.V. Masjanov, M.I. Reckij, etc. Methodical recommendations on the evaluation and correction of the immune status of animals. Voronezh, 2005). Reserve function of oxygen-dependent bactericidal system of phagocytes (spontaneous and stimulating nitroblue tetrazolium test, spNBT and stNBT), reserve index (RI) and neutrophil activation index (NAI) were assessed by cytochemical reaction with the calculation of intracellular diformazane, an insoluble form of reduced nitroblue tetrazolium, deposits in accordance with the recommendations (Technique of human neutrophils functional activity assessment by nitroblue tetrazolium recovery test. Kazan, 1979) and description [28].

The data obtained were statistically processed using the Statistica 6.1 software (StatSoft, Inc., USA). The study results are presented as the arithmetic mean (M) and the arithmetic mean error (±SEM). The significance of the differences between the test and control groups was assessed by Student's t-test. Differences were considered statistically significant at $p < 0.05$.

Results. The background blood immunological research of sows in both groups showed that the majority of indices tested was consistent with the optimal values for the end of gestation, without no significant differences between

the groups.

Sows treated with Biferon-C showed at the end of the experiment (days 24-26) the increase of relative and absolute number of monocytes, causing an intensification of phagocytosis compared to the base case by 54.8% ($p < 0.001$) and 51.9% ($p < 0.01$), respectively. Such changes under the influence of interferons have occurred also in the lymphocytes content although to a lesser degree. The animals in the group II showed a tendency to increased relative and absolute lymphocyte count compared to the similar values in group I by 6.9% and 6.7%, respectively, while increasing of T-and B-lymphocytes numbers was significant: 57.5% ($p < 0.0001$) and 34.6% ($p < 0.01$), and 100% ($p < 0.001$) and 58.1% ($p < 0.01$), respectively, indicating the positive effect of Biferon-C on cells responsible for all the specific immune response (see Table 1).

1. Morphological blood indices and lymphocyte profile in crossbred sows influenced by Biferon-C on days 24-26 (*M*±SEM, Zolotaya Niva LLC, Tambov Province, 2017)

Indices		Group I (control, $n = 10$)	Group II (test, $n = 10$)
Erythrocytes, $\times 10^{12}$/L		4.82±0.30	5.17±0.08
Leucocytes, $\times 10^{9}$/L		12.70±0.66	12.70±0.56
Hemoglobin, g/L		122.20±2.17	125.20±3.54
Hematocrit, %		31.70±1.61	32.80±0.48
White blood cell differential count:			
bands	% of	4.10±0.16	2.20±0.31***
	overall	0.53±0.05	0.28±0.05***
segmented neutrophils	% of	45.3±1.63	47.50±2.79
	overall	5.97±0.49	6.00±0.42
eosinophils	% of	4.70±0.52	3.07±0.31*
	overall	0.60±0.07	0.39±0.06*
monocytes	% of	2.10±0.17	3.25±0.09**
	overall	0.27±0.04	0.41±0.03*
lymphocytes	% of	42.0±2.13	44.90±1.77
	overall	5.34±0.36	5.70±0.10
T lymphocytes, 92	% of	29.2±1.86	46.00±2.71***
	overall	1.82±0.17	2.45±0.19*
B-cells	% of	12.0±1.34	24.00±2.70**
	overall	0.74±0.09	1.17±0.11*

N o t e. Description of the groups is given in the Techniques section.
*, **, *** Differences with control are statistically significant at $p < 0.01$, $p < 0.001$, and $p < 0.0001$, respectively.

2. Immune status in crossbred sows on days 24-26 influenced by Biferon-C (*M*±SEM, Zolotaya Niva LLC, Tambov Province, 2017)

Parameter	Group I (control, $n = 10$)	Group II (test, $n = 10$)
SCA, hemolysis in %	30.70±0.65	33.20±1.83
SLA, rg/mL	3.53±0.08	3.83±0.10*
PAL, %	83.80±1.91	85.40±1.29
PN	3.58±0.21	4.61±0.36*
PI	7.34±0.54	7.51±0.48
IG, g/L	25.10±0.83	25.20±1.08
CIC, g/l	0.26±0.01	0.17±0.01***
spNBT, %	33.20±2.08	43.20±1.93**
stNBT, %	47.60±3.04	67.80±2.96**
RI, units.	1.43±0.03	1.57±0.05*
IAN, units	0.30±0.01	0.36±0.01**

N o t e. Description of the groups is given in the Techniques section. SCA — serum complement activity; SLA — serum lysozyme activity; PAL — phagocytic activity of leukocytes; PN — phagocytic number; PI — phagocytic index; CIC — circulating immune complexes; spNBT — spontaneous NBT test; stNBT — stimulated NBT test; RI — reserve index; and NAI — neutrophils activation index.
*, **, *** Differences with control are significant at $p < 0.05$, $p < 0.01$, and $p < 0.0005$, respectively.

Use of Biferon-C enhanced the natural non-specific resistance against any infectious and non-infectious agents. So, the animals in the experimental group showed a steady tendency to increased activity (8.1% compared to control; Table 2) of complement system, the components of which bind bacteria, playing an important role in inflammation and in the development of resistance to infectious agents [29]. The serum content of lysozyme, antimicrobial protection factor (see Table 2), in sows of group II compared to those in group I increased by 8.5% ($p < 0.05$), indicating a higher lysozyme-synthesizing granulocytes, monocytes, and macrophages proliferative activity influenced by Bif-

eron-C comprising interferons.

Animals in the experimental group showed the neutrophils absorbency more significantly compared to the control, with the 18.8% higher phagocytic index ($p < 0.05$) (Table 2). The positive effect of interferon on phagocytosis system is shown by indices characterizing the cells digestive function. The spNBT test assessing the oxygen-dependent bactericidal properties of blood phagocytes in vitro [30] in group II was 30.1% ($p < 0.01$) higher than in the control, indicating the strengthening of phagocytes cytotoxicity under the influence of interferons injected (see Table 2). Under the influence of Biferon-C, stNBT test characterizing the phagocytic cells activity in the presence of an antigen and indicating their ability to the completed phagocytosis [30] was in the sows 42.4% higher ($p < 0.01$). Functional reserve of the cells (the difference between the number of activated and spontaneous diformazane-positive phagocytes) in animals from the experimental group increased by 9.8%, and NAI by 20.0% ($p < 0.01$). The results obtained allow us to postulate an increase of phagocytes metabolic reserve and digestive function under the influence of interferons from Biferon-C.

CIC (antigen-antibody reaction products involved in the homeostasis) in sows from both groups corresponded to the physiological value (less than 0.5 g/l). However, animals in the experimental group showed the CIC number 34.6% ($p < 0.0005$) less than in group I, apparently in association with declining impact of technological immunosuppressive factors and antigenic burden on the body influenced by interferons (see Table 2).

The positive effect of Biferon-C on the immune status of sows is caused by the presence of recombinant proteins [23]. α-Interferon, possessing mainly the anti-virus and antiproliferative effects, enhances the natural killer cells and T-helper cells activity, phagocytosis, B-cells differentiation, and the elimination of circulating immune complexes [31-33]. γ-Interferon synthesized by activated T-cells and NK cells is one link connecting the factors of innate and adaptive immunity [34, 35]. The stimulating effect of γ-interferon is associated with activation of phagocytic function of macrophages, the production of reactive oxygen and nitrogen species and prostaglandins. It can also activate T-helpers and T-cytotoxic lymphocytes, stimulate the differentiation of B-cells to immunoglobulin G production, and migration of lymphocytes in tissue due to adhesion to the endothelium, thus strengthening the immune cell reaction, and improve the functional activity of antigen-presenting cells [36-38].

3. Indicators of offspring preservation derived from crossbred sows treated with Biferon-C (*M* ±SEM, Zolotaya Niva LLC, Tambov Province, 2017)

Indicator	Group I (control, $n = 10$)	Group II (test, $n = 10$)
The number of sows, *n*	10	10
Piglets per sow	13.50±0.67	13.90±0.78
Piglet weight at birth, kg	1.26±0.03	1.24±0.04
Piglets weight at weaning, kg	7.68±0.56	7.95±0.49
Average daily weight gain, g/day	247.00±7.54	258.00±7.33
Death rate of piglets, %	4.20	2.15

N o t e. Description of the groups is given in the Techniques section.

The use of Biferon-C, increasing the immune status, had a positive effect on the clinical condition of sows and their piglets (Table 3), contributing to the prevention of postnatal diseases in breeding stock and improving the offspring safety. Sows from both groups showed no signs of postnatal pathology, and only some (10% less in experimental group than in control) showed a 0.1-0.3 °C increase in body temperature in the first days after farrowing. The increase of alive weight and safety of piglets obtained from sows of the experimental group also exceed those in control by 4.5% and almost 2-fold, respectively (see Table 3).

The use of Biferon-C in sicker piglets whose mothers did not receive this

preparation showed a generally positive impact on the animals' condition: their safety was 95.2% compared to 93.1% in those without using the preparation (control). Meanwhile, the incidence of gastrointestinal infections in the experimental group decreased by 4.0% and the death rate 1.4 times (Table 4).

4. Prophylactic efficacy of Biferon-C in pigs received from crossbred sows not treated with the preparation (M ±SEM, Zolotaya Niva LLC, Tambov Province, 2017)

Indicator	Group I (control, n = 10)	Group II (test, n = 10)
The number of piglets	332	333
Piglet weight at birth, kg	1.38±0.98	1.28±0.64
Piglets weight at weaning, kg	7.46±0.48	7.39±0.52
Average daily weight gain, g/day	243.30±8.19	244.50±9.32
Gastrointestinal infections, total/%	48/14.5	35/10.5
Deaths rate of pigs, total/%	23/6.9	16/4.8

N o t e. Description of the groups is given in the Techniques section.

Therefore, the study results presented in general confirm the characteristics of Biferon-C, claimed by the developers. We first studied the effect of this preparation in commercial farming conditions in combination with traditional medicamentous prevention schemes. Biferon-C use in sows 24 h prior to farrowing and 2 days after it is shown (on the background of Metramag intramuscular and of Iodopen intrauterine injection) to significantly change the quantitative ratio in several blood cells populations (bands, eosinophils, and monocytes content) and significantly increased the immune status indices: serum lysozyme activity, intensity of phagocytosis, absolute and relative content of T- and B-cells with a trend of increasing activity of the complement system. The death rate of piglets from such sows decreased twice, with practically the same other piglets' output and development indices (number of piglets per sow, weight at birth and at weaning, daily BW gain). The use of the preparation in sucking pigs from mothers not treated with Biferon-C also showed a downward trend in the incidence of gastro-intestinal infections and deaths (4%) with minor differences in the characteristics of growth and development.

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