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The effect of different Paricalcitol doses on the spleen zones in BALB/c mice infected with the H1N1 subtype influenza virus

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Abstract: Recent studies have revealed that vitamin D and its synthetic analogues possess protective antioxidant and anti-inflammatory effects on experimental models of ischemia and autoimmune conditions across various organs. However, limited information is available regarding their impact on the spleen during severe viral infections. The primary aim of this research was to investigate the effects of different doses of Paricalcitol on spleen zones in BALB/c mice infected with the influenza virus subtype A/WSN/1/33 (H1N1). The study involved male BALB/c mice, weighing between 16 and 18 grams and aged 4 to 6 weeks, which showed no external pathological signs. The experiments were conducted in two stages: first, to assess the impact of various doses of intraperitoneally administered Paricalcitol on histological changes in the murine spleen; second, to evaluate the effect of a 50 ng/mouse dose of Paricalcitol during influenza infection on spleen histology. The findings demonstrated that infection with the highly pathogenic influenza virus A/WSN/1/33 (H1N1) initiated the destruction of lymphatic nodules within the spleen. Notably, the average area of lymph nodes in animals receiving a high dose of 100 ng/mouse was reduced by 1.7 times compared to the control group. Based on these results, a dose of 50 ng/mouse of Paricalcitol was selected for further experiments involving viral infection. The intraperitoneal administration of 50 ng/mouse of Paricalcitol on the 10th day of infection significantly increased the average area of the marginal zone of B-lymphocyte maturation compared to the group that did not receive the drug, indicating a potential protective effect on spleen histology during influenza infection.

Keywords: *Influenza virus, Lymphatic nodules, Paricalcitol, Spleen, Mice.*

1. Introduction

Influenza is one of the most important socially significant infections, ranking first among infectious diseases in terms of morbidity, which to date has not shown a downward trend. Every year, up to 500 million people in the world become ill with influenza, and in 3-5 million cases the infection is severe [1-3]. The World Health Organization cites data on 250-500 thousand deaths from influenza in the world annually. Influenza is also the cause of so-called "additional mortality" during periods of increased epidemic morbidity associated with pneumonia, strokes, and heart attacks [4].

Influenza pandemics occur much less frequently, have the most severe medical and social consequences, accompanied by increased morbidity (3-4 times higher than current epidemics), an increased frequency of severe and complicated forms of infection and a 5-10-fold increase in mortality. There is a risk of the formation of reassortants of human, avian, and swine influenza viruses, which are highly pathogenic to humans [5]. In recent years, the epidemic situation regarding influenza has been complicated by the epidemic spread of diseases caused by the influenza A(H1N1)pdm09 virus, which has been assigned the sixth (maximum) level of danger to humans [6].

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The influenza virus has a number of pathogenetic effects on the human body. The main ones are cytopathic, vasopathic, immunosuppressive [7].

1. Cytopathic (cytolytic) effect of the virus on the epithelium, first of all, of the bronchi, trachea and alveoli, vascular endothelium, as well as neuroepithelium, trophoblast cells causes their alteration, necrosis, desquamation.

2. Vasopathic (vasoparalytic) effect causes plethora,stasis, plasma- and hemorrhage.

3. Immunosuppressive effect of the virus is manifested in the inhibition of the activity of neutrophils (suppression of phagocytosis), monocytic phagocytes (suppression of chemotaxis and phagocytosis), in dysfunction of the immune system (development of allergies, appearance of pathogenic immune complexes).

The development of influenza vaccines effective against a new circulating pathogen requires a relatively long period of time. Therefore, during this period, etiotropic preventive drugs may be the only means of preventing the spread of viral infection. In this regard, the search for and the possibility of using new or existing antiviral drugs that are active against virus variants is of great practical importance. To date, more than 80,000 scientific studies have been conducted on this vitamin. Studies have shown that vitamin D has a protective effect against acute respiratory infections, which include coronavirus [8].

Vitamin D shows diverse effects on the immune system, beyond its important role in calcium and phosphorus metabolism [9]. Vitamin D, and particularly its active form, 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$), has been reported to be protective in several experimental models of inflammatory responses, such as shock and sepsis [10, 11]. Recent studies have revealed that vitamin D and its synthetic analogues have a protective antioxidant and antinflammatory effect on experimental ischemic and autoimmune models in several organs, but little is known about its effect on the spleen during severe viral infection [12].

Paricalcitol was synthesized in 1985 and actively used since 1998, it belongs to the third generation of synthetic analogues of vitamin D, which are compounds based on 1-, 25-hydroxyvitamin D with structural modifications. The presence of a bond with a hydroxyl group in the 1st and 25th positions in the paricalcitol molecule ensures its high-affinity binding to the vitamin D receptors (VDR) what shows less side effects than high doses of natural vitamin D. Paricalcitol (19-nor-1α, 25-dihydroxyvitamin D_2) was developed by removing the methylene group from the 19th position of the hydrocarbon chain and has a side chain similar to ergocalciferol. Such changes in the chemical structure are associated with selective activation and varying degrees of influence on VDR, which is maximal in the parathyroid glands and significantly less in the intestine and bones [13-17].

The aim of the research was to study the effect of different Paricalcitol doses on the spleen zones in BALB/c mice infected with the influenza virus subtype A/WSN/1/33(H1N1).

2. Material and Methods

2.1. Material

The experiment involved male BALB/c mice without external pathological signs, weighing 16–18 g and aged 4–6 weeks.

The experiments were conducted in two stages:

1 – studying the effect of various doses of intraperitoneal administration of Paricalcitol on the histological changes in the murine spleen.

2 – detecting the effect of intraperitoneal administration of a dose of 50 ng/mouse of Paricalcitol during influenza infection on histological changes in the mouse spleen.

The animals were infected intranasally with influenza A/WSN/1/33(H1N1) virus under ether anesthesia by injecting 50 µl of allantoic fluid containing 10 LD 50 of the virus [18]. The initial version of the influenza virus (IV) was obtained from the Institute of Virology named after. D. I. Ivanovsky (Moscow, Russia).

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The animals were housed in standard animal house conditions in accordance with the norms and rules for the treatment of laboratory animals in accordance with the "Rules for carrying out work using experimental animals".

In the *first experiment* the animals were divided into the following groups and subgroups:

1. Healthy animals that received intraperitoneal Paricalcitol at a dose of 25 ng/mouse in 100 μl of saline solution (SS) on days 1, 2, 4, and 7 (P 25), withdrawn from the experiment on days 10 (Var 1) and 21 (Var 2) after the start of the experiment (n = 12).

2. Healthy animals that received Paricalcitol intraperitoneally at a dose of 50 ng/mouse in 100 μl of SS on days 1, 2, 4, and 7 (P 50), and were withdrawn from the experiment on days 10 (Var 3) and 21 (Var 4) after the start of the experiment (n = 12).

3. Healthy animals that received Paricalcitol intraperitoneally at a dose of 100 ng/mouse in 100 μl of SS on days 1, 2, 4, and 7 (P 100), and were withdrawn from the experiment on days 10 (Var 5) and 21 (Var 6) after the start of the experiment (n = 12).

4. Healthy animals of the control group C (Var 7), intraperitoneally administered 100 μl of SS on days 1, 2, 4, and 7, and sacrificed on day 21 after the experiment began (n = 6).

In the *second experiment* mice were infected intranasally with the influenza virus A/WSN/1/33(H1N1) (IV) under light ether anesthesia by administering 50 μl of allantoic fluid containing 5 LD50 of the virus. Frozen allantoic fluid stored at –20°C, obtained from one pool, was used in the experiment. As the viral infection developed, characteristic clinical symptoms appeared: weight loss, respiratory failure (increased respiratory rate over 200 respiratory movements per minute with the involvement of accessory muscles, cyanosis of the tail, ears, and extremities). The therapeutic scheme of Paricalcitol administration was used, introducing 50 ng in 100 μl of SS on days 1, 2, 4 and 7.

On the 4th, 10th and 21st day after infection, the animals were withdrawn from the experiment by decapitation under ether anesthesia and the spleen was removed for further study. The animals were divided into 4 groups:

1. Healthy animals, which were the control group (C), which received 100 μl of SS intraperitoneally, withdrawn from the experiment on the 21st day

2. Animals infected intranasally with IV without correction: subgroup CV 1, withdrawn from the experiment on the 4th day and CV 2, withdrawn from the experiment on the 10th day.

3. Animals infected intranasally with IV and given intraperitoneal Paricalcitol at a dose of 50 ng/mouse: subgroup VP 1, withdrawn from the experiment on the 10th day, and subgroup VP 2, given Paricalcitol according to a similar scheme and withdrawn from the experiment on the 21st day of the experiment.

4. Healthy intact animals of the control group: subgroup P 1, which received Paricalcitol intraperitoneally at a dose of 50 ng/mouse, were withdrawn from the experiment on the 10th day, and subgroup P 2, which received Paricalcitol according to a similar scheme and were sacrificed on the 21st day of the experiment

2.2. Histological Methods

Spleen tissue was prefixed in a 10% formalin solution, then dehydrated in a series of alcohols of increasing concentration (70°, 80°, 90°, 96°, absolute alcohol), butanol, xylene and were enclosed in a paraffin filling mixture HISTAMIX (Russia). Sections with a thickness of 2-5 microns were prepared on a rotary microtome HM 34036E (Carl Zeiss, Germany). Paraffin sections were stained with hematoxylin and eosin to perform a descriptive analysis of morphological transformations followed by morphometric assessment using the Aperio Image Scope program (Leica Biosystems, USA). Measurements were made at magnification x 200 in 20 fields of view on an image area of 1 mm^2. The sections were used to determine the total area of the spleen and lymphoid nodules (LN) (S, mm^2), as well

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as the percentage (relative LN area), and the areas of the marginal and mantle zones of the lymphoid nodules (S, mm^2).

2.3. Statistical Methods

Statistical processing of the obtained quantitative results was performed using Microsoft Excel and specialized software Statistica 10 (StatSoft Inc., USA). The statistical analysis included the construction of variation series of quantitative data, the determination of the normality of their distribution using the Kolmogorov-Smirnov criterion and the degree of uniformity of the variances of the compared samples, as well as the calculation of descriptive statistical parameters, including the mean (M) and the error of the mean (m). Due to the relatively small sample sizes, the reliability of the differences in the compared values was determined using the nonparametric Mann-Whitney U-test. The results were presented in the form of M±m. The differences between the compared quantitative indicators were considered significant at a significance level of $\alpha = 5\%$ ($p < 0.05$).

3. Results and Discussion

In the control groups no visible pathohistological changes were detected in the spleen. In case of influenza infection without administration of Paricalcitol (group II) the spleen showed a decrease in the density and swelling of the lymphoid tissue in the white pulp, dystrophic changes in the endothelium of the arteries, and hemorrhages. Foci of necrobiosis in the red pulp: necrosis of capillaries and macrophages (the capillary network is destroyed along with the macrophages), discomplexation of the tissue, and edema in the red pulp of the spleen (*Fig. 1*). In other words, there is an increased breakdown of the cellular elements of the lymphoid tissue in the spleen.

In the 3rd group diffuse lymphoid hyperplasia in the follicles, white pulp and red pulp was observed in the spleen in the case of influenza infection with administration of Paricalcitol. The formation of a large number of macrophages, pericapillary edema and diffuse erythrocyte hyperplasia in the red pulp were detected.

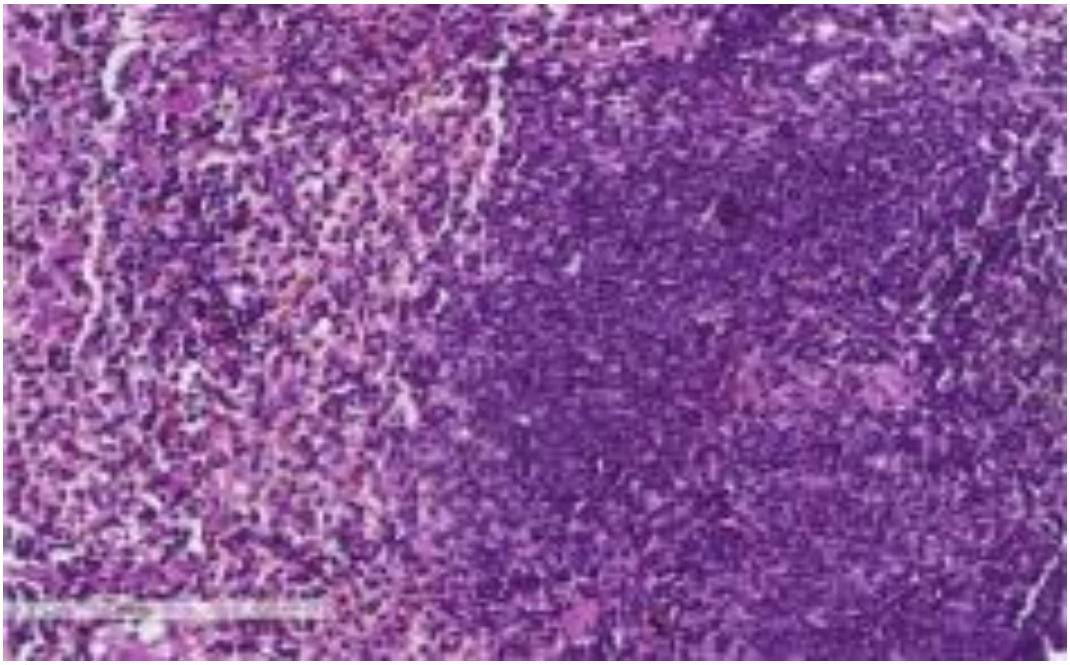

Figure 1.
Section of the spleen of the BALB/c mouse inoculated with the A/WSN/1/33(H1N1) virus. Hematoxylin and eosin staining, ×200.

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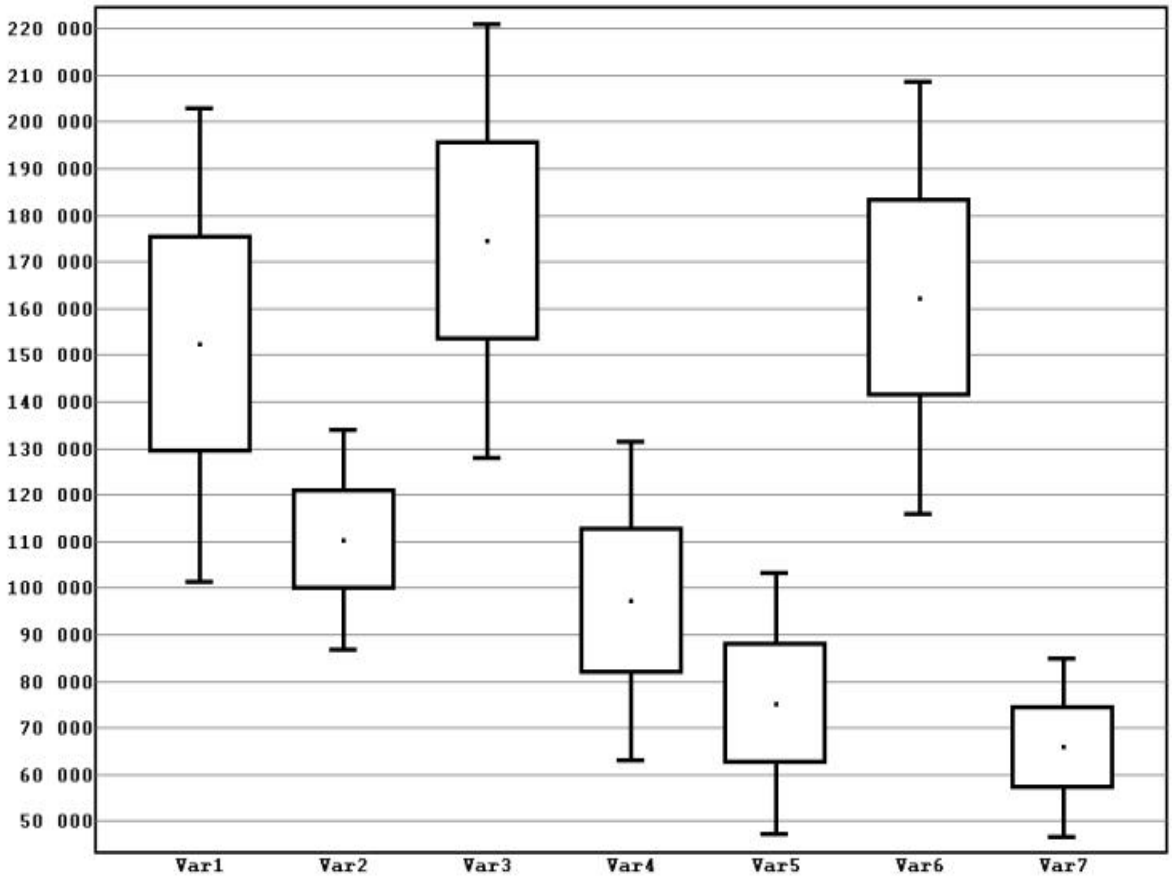
As can be seen from Figure 2, according to the morphometric analysis data on the 10th day after the start of paricalcitol administration, a statistically significant increase in the average area of lymphoid nodules is observed between the groups of animals receiving P at doses of 25 and 50 ng / mouse (Var 1 and Var 3) and the control group. The increase in the average LN area was 2.2 and 2.4 times, respectively, compared to the control (Var 7). At the same time, a statistically significant difference in the area of lymphoid nodules was established between the groups of animals receiving P at doses of 50 and 100 ng / mouse (Var 3 and Var 5). The decrease in the average area of lymph nodes in animals receiving a high dose of P was 1.7 times.

A



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B

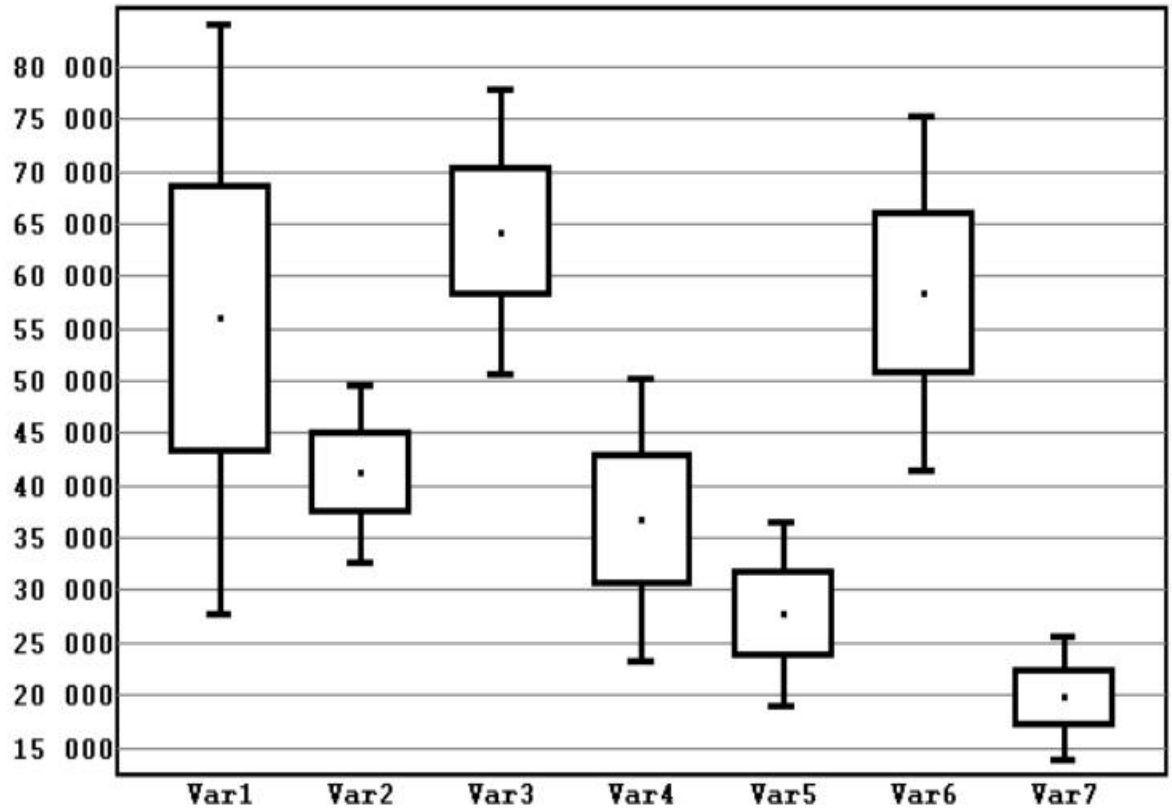

Figure 2.
Absolute values of the areas of lymphoid nodules and different zones of the spleen of mice (S, mm2) receiving Paricalcitol at different doses of intraperitoneal administration.

A - lymphoid nodules,
B - marginal zone.

On the 21st day of the experiment, a statistically significant increase in the average area of lymphoid nodules was observed in the group of animals receiving P at a dose of 100 ng/mouse (Var 6) compared to the control (Var 7), where the increase in the average area of lymph nodes was 2.2 times.

Based on the obtained data, a dose of Paricalcitol of *50 ng/mouse* was considered less toxic selected for further experiment with viral infection.

As can be seen from the *Table 1*, during the morphometric analysis of the mouse spleen, on the 4th day of viral infection (group CV 1), an increase in the relative area of the lymph nodes by 2.2 times is observed compared to the control group. Intraperitoneal administration of Paricalcitol at a dose of 50 ng / mouse on the 10th day of viral infection (group VP 1), statistically significantly increased the average area of the marginal zone compared to the group of animals that did not receive P (CV 2). Moreover, the increase in the average area of this zone was 4 times higher.

On day 21 of the experiment, the size of the average area of the marginal zone in the group receiving Paricalcitol during viral infection (VP 2) statistically significantly decreased by 8 times compared to day 10 (VP 1) but didn't show difference from control in the group CV 2.

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Table 1.
Relative and absolute values of the sizes of lymphoid nodules and spleen zones in mice infected with the influenza virus and treated with Paricalcitol at different stages of influenza infection.

Group	Total area of the site. mm²	Total area of LN mm², % of LN area from the total area	Average area of LN, mm²	Average area of the marginal zone, mm²	Average area of the mantle zone, mm²
Control	6.30	0.89 14.2%	0.07±0.01	0.02±0.00	0.05±0.01
CV 1	10.02	3.17 31.7%	0.13 ±0.01	0.04±0.00	0.08±0.01
CV 2	13.21	1.51 11.4%	0.06±0.01	0.02±0.00 p_1	0.04±0.00
VP 1	24.64	6.16 25.1%	0.18±0.01 p_K	0.08±0.017 p_K	0.10±0.01 p_K
VP 2	6.67	0.75 11.2%	0.04±0.01 p_1	0.01±0.00 p_1	0.02±0.00 p_1
P 1	11.19	4.03 36.0%	0.15±0.01	0.06±0.01	0.11±0.01
P 2	7.27	2.17 29.9%	0.10±0.01	0.04±0.01	0.06±0.01

Note: p_K – reliability of difference between the current group and control,
p_1 – reliability of difference between the current group and VP 1.

Vitamin D has a large number of biological effects due to its influence on the vitamin D receptor, which is present in most tissues of the body. The possible role of vitamin D in infections can be explained by its influence on the mechanisms of the innate and acquired immune response. An important effect of vitamin D is also its suppression of inflammatory processes.

Apart of its classical effects, vitamin D has the significant role in the control of metabolism, cellular growth and the immune system (so called "non-classical" actions) [19]. The VDR was recognized as a member of a superfamily of nuclear receptors. This receptor with its ligand in target cells mediates biological effects, thereby regulating the transcription of target genes (the genomic pathway in non-classical tissues). Interestingly, VDRs are present not only in tissues participating in the classic actions of vitamin D (such as bone, skin, gut, and kidneys) but also in non-classical tissues (such as brain, heart, immune cells, liver, muscle, and adipose tissue) [20].

The spectrum of 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2$ D_3) non-classical actions also greatly affect immunity cells. For many years, it has been considered that the key role of vitamin D in innate immunity was its ability to stimulate the differentiation of precursor monocytes into more mature phagocytic macrophages [20]. TLR activation in human monocytes and macrophages induces up-regulation of VDR and vitamin-D-1 hydroxylase gene expression [21]. On the other hand vitamin D3 can lead to a decrease of the mRNA and protein expression of TLR2 and TLR4 in human monocytes after lipopolysaccharide stimulation [22].

Recent studies have confirmed a direct effect of calcitriol and as we reveled in our research – Paricalcitol as well, on B-cell hematopoiesis, including increase of their differentiation into memory and plasma cells, as well as promotion of immunoglobulin-producing B-cells. Such control of B-cell activation and proliferation may be clinically important in infectious diseases, since B-cells producing antiviral antibodies [23].

4. Conclusion

The pathogenesis of infection provoked by the highly pathogenic for mice influenza virus A/WSN/1/33(H1N1) causes dystrophic and necrotic processes in the splenic lymphatic nodules of infected mice. Influenza virus exposure resulted in significant decrease of the LN area, increase in the

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megakaryocytic reaction, "blurring" of zones and erasing of nodule boundaries, as well as a decrease in the area occupied by white pulp was also observed

Emerging research suggests that vitamin D plays a crucial role in modulating immune responses, a finding that may have implications for the prevention and control of influenza. Collectively, the aforementioned evidence suggests that vitamin D may play a role in modulating the immune system.

Based on the obtained data, a dose of Paricalcitol of 50 ng/mouse was considered as less toxic and was selected for further experiment with viral infection.

We hypothesized that treatment of infected mice with a synthetic vitamin D2 analogue, paricalcitol, may attenuate influenza viral injury mainly through the stimulation of B-lymphocytes differentiation located in the marginal zones of the splenic lymphatic nodules.

Although these findings highlight the therapeutic promise of Paricalcitol for influenza management, further investigation is needed to address existing knowledge gaps before making clear recommendations for the use of vitamin D synthetic analogues in therapy of acute viral respiratory infections.

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Institutional Review Board Statement:

The study was approved by the meeting of the Ethics Committee No. 3 dated 21.03.2023 of the Crimean Federal University named after V.I. Vernadsky.

Transparency:

The authors confirm that the manuscript is an honest, accurate, and transparent account of the study; that no vital features of the study have been omitted; and that any discrepancies from the study as planned have been explained. This study followed all ethical practices during writing.

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