Коррекция РТПХ-индуцированных сочетанных расстройств иммуно- и гемопоэза

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Показана возможность моделирования различных по патогенезу анемических синдромов, возникающих на фоне вторичного иммунодефицита, индуцированного РТПХ. В полуаллогенной системе DBA/2 → B6D2F$_1$ у мышей B6D2F$_1$ с иммунодефицитом развиваются разные варианты сочетанных нарушений эритро- и иммунопоэза, когда иммунодефицит сочетается либо с гемолитической анемией, либо с гемолитической анемией и иммунокомплексным гломерулонефритом. Развитие аутоиммунной патологии в полуаллогенной системе DBA/2 → B6D2F$_1$ сопровождается изменением пролиферативной активности стволовых кроветворных клеток и функциональной активности гемопоэтических предшественников эритроидного и гранулоцитарного направлений дифференцировки. В аллогенной системе у мышей BALB/c с иммунодефицитом развивается гипопластическая анемия с подавлением костномозгового эритропоэза. Различия в патогенезе анемических синдромов связаны с функциональными свойствами макрофагов и продукции ими цитокинов. Полученные нами данные о сочетанных нарушениях иммуно- и эритропоэза при РТПХ-индуцированных расстройствах иммунитета, а также факты, свидетельствующие об иммуносупрессивной роли ядросодержащих эритроидных предшественников, позволяют подойти с новых позиций к коррекции иммунопатологии, а именно через воздействие на эритропоэз. С этой целью проводили коррекцию РТПХ-индуцированных нарушений иммуно- и эритропоэза с помощью эритротропного воздействия - хронической гипоксии и новых производных алканкарбоновых кислот (соединение BM-2-84 и трекрезан). Хроническая гипоксия у больных мышей B6D2F1 обладала положительным эффектом: повышала гуморальный иммунный ответ, купировала анемию и нормализовала эритропоэз на уровне ранних и поздних предшественников. Соединение BM-2-84 обладало выраженным эффектом на эритропоэз у мышей с иммунодефицитом, начиная с ранних этапов дифференцировки эритрона: снижалось число ранних эритроидных предшественников и возрастало количество предшественников гранулоидно-макрофагального ряда. Уменьшением фагоцитоза и продукции ИЛ-1 под влиянием препарата предположительно можно объяснить повышение массы тела, снижение СОЭ и протеинурии у больных мышей. Повышение спонтанной и ЛПС-индуцированной продукции IgG под действием BM-2-84 у мышей с гломерулонефритом согласуется с известными данными о восстановлении иммунокомпетентности мышей NZB/WF1 с гломерулонефитом после применения циклоспорина А. Соединение BM-2-84, устраняя анемический синдром у мышей B6D2F1 с иммунокомплексным гломерулонефритом, стойко (до двух месяцев после окончания введения) и достоверно снижало протеинурию, и по данным морфологического исследования тормозило пролиферацию мезангиоцитов и хронического воспаления с иммунологическим компонентом. Трекрезан также стойко и длительно достоверно сокращал протеинурию. Трекрезан, устраняя анемию, снижал гиперплазию эритрона у мышей с иммуносупрессией, начиная с уровня БОЕ-э. Такое действие трекрезана на эритропоэз могло быть связано как с прямым влиянием препарата на клеточные элементы эритроидного ростка, так и с опосредованным - через монокины. Полученные в работе факты об эффективности соединений, обладающих сочетанными эритро- и иммунопоэз-модулирующими свойствами, открывают новые пути целенаправленной регуляции расстройств иммунитета.

Ключевые слова: РТПХ, гемопоэз, анемия, иммунолефицит, препараты

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The Correction of Combined Immuno- and Hemopoiesis Disorders Induced by Graft-Versus-Host Reaction

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We have shown the possibility to modulate various anemic syndromes during acquired immunodeficiency differed in pathogenesis and induced by graft versus host reaction (GVHR). There are different variants of combined erythro- and immunopoiesis disorders in the semiallogeneic system DBA/2→B6D2F1: immunodeficiency plus hemolytic anemia and immunodeficiency plus hemolytic anemia plus immunocomplex glomerulonephritis. In the allogeneic system C57BL/6→BALB/c there is immunodeficiency plus hypoplastic anemia with reduced bone marrow erythropoiesis. Differences in pathogenesis of anemic syndrome are connected with the functional properties of macrophages and cytokine production by macrophages. There is some positive effect of chronic hypoxia on GVHR-induced immunopathology in B6D2F1 mice: it increases humoral immune response, has favorable effect on anemia and corrects early and late committed precursor number. The absence of any influence of chronic hypoxia on the secreted activity of macrophages gives an evidence to the direct influence of erythron on the humoral immune response. VM-2-84 has favorable effect on anemia (suppresses IL-1 production, reduces the number of early erythroid precursors and stimulates the amount of the granulocyte and macrophage precursors) in B6D2F1 mice with glomerulonephritis. The compound from alkancarboxylic acids - VM-2-84, up to two months decreases proteinuria and reduces proliferation of mezangiocytes and chronic inflammation with the restoration of immune system. Trecrezan, while having beneficial effect on anemia, reduces a hyperplasia of erythron in mice with immunodeficiency; it influences the production of monokines. The obtained facts about effectiveness of preparation possessing combined erythro- and immunopoiesis-modulating properties, open new ways of a target regulation of disorders of immunity.

INTRODUCTION

Intersystem approaches for solution of the key problems of immunology and hematology are based on the existence of a single progenitor - stem cell and close interaction between immune and hemopoietic systems [1, 2].

It has been shown that dysfunction of erythropoiesis is one of the pathogenetic links in the formation of the immune pathology with various experimental models: autoimmunity (NZB mice), lymphoproliferative diseases (AKR mice), senile (aged) immunodeficiency (mice with age 24-28 months) [3-6]. It has been determined that a decrease in hemopoietic stem cell proliferative activity by natural hemopoietic inhibitors causes normalization of the immune system with autoimmune, immunodeficiency and other disturbances [7].

We have shown the possibility to modulate various anemic syndromes during acquired immunod-

Key words: graft-versus-host reaction, hemopoiesis, anemia, immunodeficiency, correction

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eficiency differed in pathogenesis and induced by graft-versus-host reaction (**GVHR**). There are different variants of combined erythro- and immunopoiesis disorders in the semiallogeneic system DBA/2→B6D2F1: immunodeficiency plus hemolytic anemia and immunodeficiency plus hemolytic anemia plus immunocomplex glomerulonephritis. The formation of immunocomplex glomerulonephritis in this semiallogeneic model is accompanied by alteration of hemopoietic stem cell proliferative capacity and modification of functional activity of erythroid and granuloid hemopoietic progenitors. In the allogeneic system C57BL/6→BALB/c there is immunodeficiency plus hypoplastic anemia with reduced bone marrow erythropoiesis. Differences in pathogenesis of anemic syndrome are related to the functional properties of macrophages and cytokine production by macrophages [8, 9].

Our results concerning combined immuno- and erythropoiesis disorders in GVHR-induced immunopathology as well as the data on the immunosuppressive role of nuclear erythroid progenitors propose some new approaches to the correction of immunopathological states based on erythropoiesis modulating influences.

In the present study we have evaluated the possibility of the correction of immunopathology by erythromodulating influences.

MATERIALS AND METHODS

Animals

Mice (C57Bl/6xDBA/2)F1 (B6D2)F1, DBA/2, 8-12 weeks aged, female, were obtained from Breeding Unit Stolbovaya of RAMS and Experimental-Biological Animal Clinic of SB RAMS.

Induction of Chronic GVHR

Cell suspensions were prepared in Hanks' balanced salt solution from DBA/2 lymphoid organs (cells from spleen, thymus and lymph nodes in ratio 6:3:1). The suspensions were filtered through nylon mesh, adjusted to $100x10^6$ cells/ml and $50x10^6$ cells were injected into tail vein of B6D2F1 mice. Five days later mice received the same repeated injection.

The formation of glomerulonephritis was tested by urine protein (more than 3 mg/ml) [10]. The protein level was determined by calorimetric method with Kumassi brilliant blue (Loba Feinchemie) at λ=570 nm. The induction of GVHR was taken as the onset of a disease. The controls were B6D2F1 mice matched for age and sex.

Drugs

Compounds from alkancarboxylic acids (**CAA**) have been produced at Irkutsk Institute of Organic Chemistry, SB RAS and kindly given by professor A.N. Mirskova. The chemical structure of compounds is an object of the Copyrights. They are named as VM-2-84, VM-38-80, VM-38-81. All substances are non-toxic and hypotoxic as shown previously. LD_{50} of these compounds is 1340-6000 mg/kg. Cyclosporin A (**CsA**, Sandimmune, Sandoz Pharmaceutical) and indomethacin (Sigma) were also used.

Hematocrit and Hemoglobin Measurement

Hematocrit was determined by microcentrifuge MCH-8. The hemoglobin level was determined by 8-channel spectrophotometer Multiscan at 405 nm.

Reticulocyte Count and Myelogram

Two hundred microliters of the peripheral blood was mixed with equal volume of azur II, containing sodium citrate, then it was incubated at 37°C for 60 min. The reticulocyte number was counted per 1000 erythrocytes. Mice bone marrow smears were stained with azur II:eosin by Papengeim-Kryukov and percentage of nuclear erythroid progenitors was determined.

IgM- and IgG-PFC in vivo

The conventional hemolytic plaque assay was used for testing the number of IgM- and IgG-PFC in spleen after i.v. immunization with $2x10^8$ SRBC. The primary and the secondary humoral immune response was tested [11]. Mice were treated i.v. or i.p. with various doses of drugs in the inductive phase of humoral immune response.

Phagocytosis Testing

The determination of macrophage Fc-mediated phagocytosis of SRBC was made by spectrophotometric method [12].

Estimation of the Number Bone Marrow Progenitors of Erythropoiesis and Granulocyte-Macrophage Bone Marrow Precursors in vitro

The determination of bone marrow progenitors of erythropoiesis (**BFU**) and granulocyte-macrophage bone marrow precursors (**CFU-GM**) was made by the conventional method with 0.9% methylcellulose culture [13]. Drugs were added to cultural medium.

Estimation of the Spontaneous and LPS-Induced IgG Production in vitro

IgG production by spleen cell culture *in vitro* was made by conventional method with LPS (*E. coli* 055:B5). IgG concentration was determined by ELISA. The results were presented in absolute values (μg/ml) and as an index of stimulation (**IS**):

IS = LPS-induced IgG/spontaneous IgG

IL-1 and TNFα Production

IL-1 activity was tested by a biological method: the proliferation of thymocytes to suboptimal dose of Con A [14]. TNFα activity in supernatants of macrophage cultures was tested using TNFα-sensitive cell line L-929 [15].

Radiation

Animals received sublethal and lethal doses of radiation by RUM-150/30-101 at dose 0.5 Gr/min, U 130 kV, I 10 Ma, filter A1-3.2.12.

Induction of Hypoxic State

Chronic hypoxia was induced by «climb» of the height of 3000 m in pressure chamber. The «climb» was carried out for 18 h, 6 times at 30 h intervals.

Statistical Analysis

Statistical analyses were performed using the non-parametric test U.

RESULTS

The Influence of O,S-Containing CAA and Hypoxia on IgM Response in vivo

Both screening results and study of the immunopharmacological activity of some new CAA permits to choose O,S-containing compounds - trecrezan and VM-2-84 - to study erythro- and immunotropic properties on experimental models.

B6D2F1 mice with immunodeficiency demonstrate a dramatically reduced IgM response, treatment with trecrezan causes a significant IgM-PFC increase in spleen (2.4 times). Chronic hypoxia greatly increases the number of IgM-PFC (2.1 times) in spleen of immunodeficient animals. No significant influence of VM-2-84 on IgM response was revealed.

The Influence of O,S-Containing CAA - VM-2-84 on IgG Production in vitro

VM-2-84 significantly increases the reduced spontaneous and LPS-induced IgG production but its level remains significantly lower than in controls.

The Influence of O,S-Containing CAA and Hypoxia on Hemoglobin Level, Hematocrit, Reticulocyte and Late BFU Number

There is a significant decrease of hemoglobin concentration in peripheral blood of B6D2F1 mice with immunodeficiency (**Figure 1A**). There is also a significant decrease of hematocrit that serves as a sign of the development of anemia. These mice have the increased number of reticulocytes (**Figure 1B**), the number of bone marrow nuclear erythroid progenitors is also increased. Treatment of B6D2F1 mice with immunodeficiency plus anemia with trecrezan has favorable effect on anemia and increases hematocrit and hemoglobin level significantly (Fig. 1A). Treatment with VM-2-84 also causes the normalization of hematocrit and hemoglobin parameters of B6D2F1 mice with immunodeficiency and B6D2F1 mice with immunocomplex glomerulonephritis (Fig. 1A and 2A). Hypoxia has the same effect (Fig. 1A). Trecrezan and VM-2-84 greatly reduce the increased number of reticulocytes of B6D2F1 mice with immunodeficiency (Fig. 1B). VM-2-84 normalizes reticulocytosis of B6D2F1 mice with immunocomplex glomerulonephritis (**Figure 2A**). The normalization of reticulocyte number of peripheral blood after hypoxia was shown in both groups. Hypoxia decreases the reticulocyte number in B6D2F1 mice with immunodeficiency up to 51.4% (Fig. 1B) and B6D2F1 mice with immunocomplex glomerulonephritis up to 37.5%.

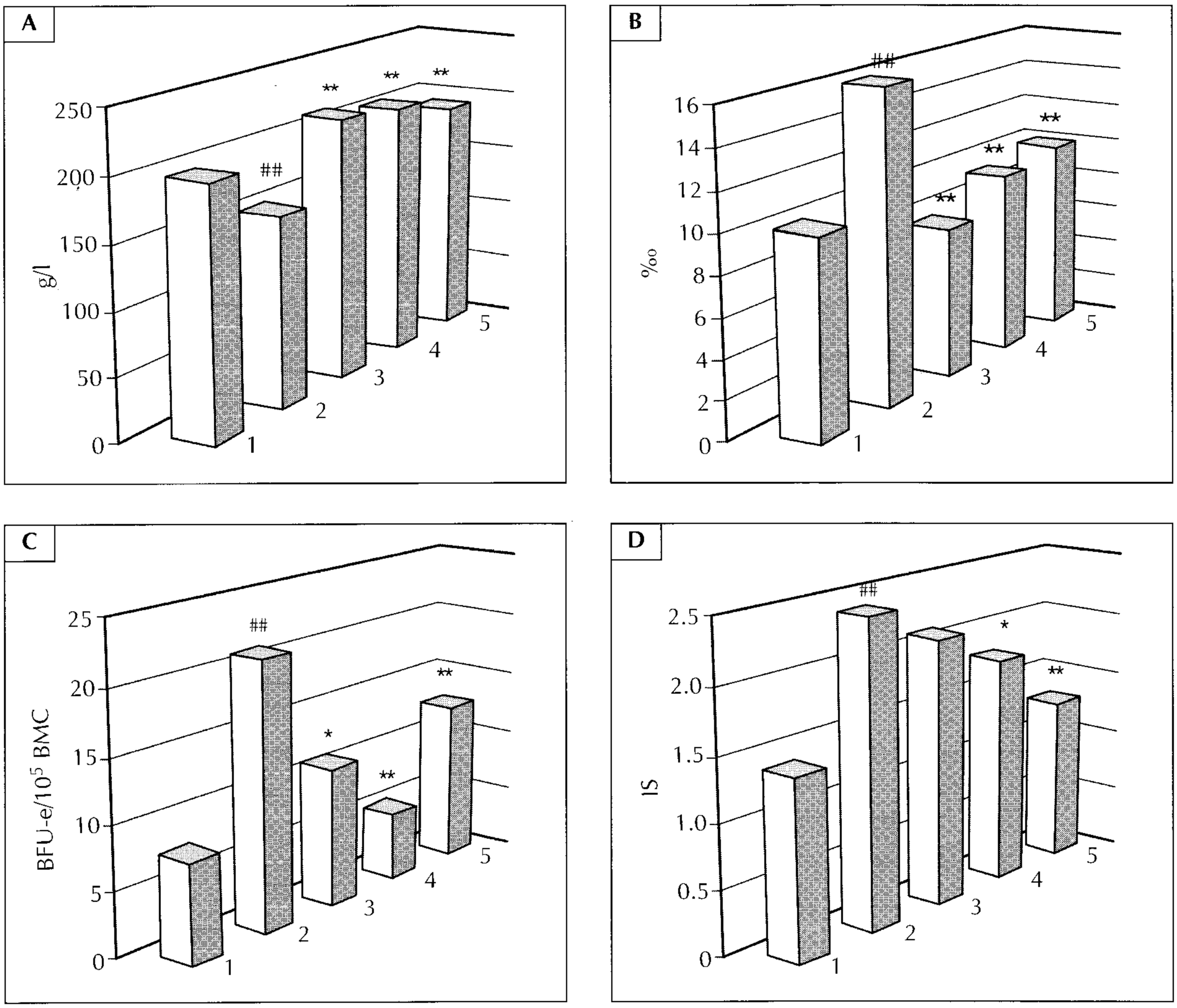

Figure 1. The influence of hypoxia and CCA on the immuno- and hemopoiesis in B6D2F2 mice with immunodeficiency. [A] - the level of hemoglobin; [B] - the number of reticulocytes; [C] - the number of BFU-e; [D] - spontaneous IL-1 production. (1) - control; (2) - immunodeficiency; (3) - immunodeficiency + hypoxia; (4) - immunodeficiency + VM-2-84; (5) - immunodeficiency + trecrezan. (#) - significant differences compared with control groups (#$p<0.05$; ##$p<0.01$); (*) - significant differences compared with immunodeficiency groups (*$p<0.05$; **$p<0.01$).

Hypoxia decreases the number of bone marrow erythrokaryocytes from 36.3±1.5% to 27.7±2.8% ($p<0.05$), trecrezan also significantly decreases the bone marrow nuclear erythroid progenitors from 34.4±1.5% to 27.8±2.3% ($p<0.05$).

The Influence of O,S-Containing CAA and Hypoxia on the Early BFU

Anemic syndrome of B6D2F1 mice with immunodeficiency and immunocomplex glomerulonephritis is accompanied by reticulocytosis in peripheral blood and significant increase of late and early BFU **(Figure 1C)** that is the evidence of the erythropoiesis stimulation. In this case the changes of bone marrow hemopoietic progenitor colony forming activity of B6D2F1 mice with immunodeficiency and immunocomplex glomerulonephritis are in accordance with significant increase of early erythroid progenitors and significant decrease of GM progenitors. Anemia of B6D2F1 mice with immunodeficiency and immunocomplex glomerulonephritis is accompanied by reticulocytosis and hyperplastic bone marrow erythropoiesis and is characterized by Coombs positive reaction. B6D2F1 mice with im-

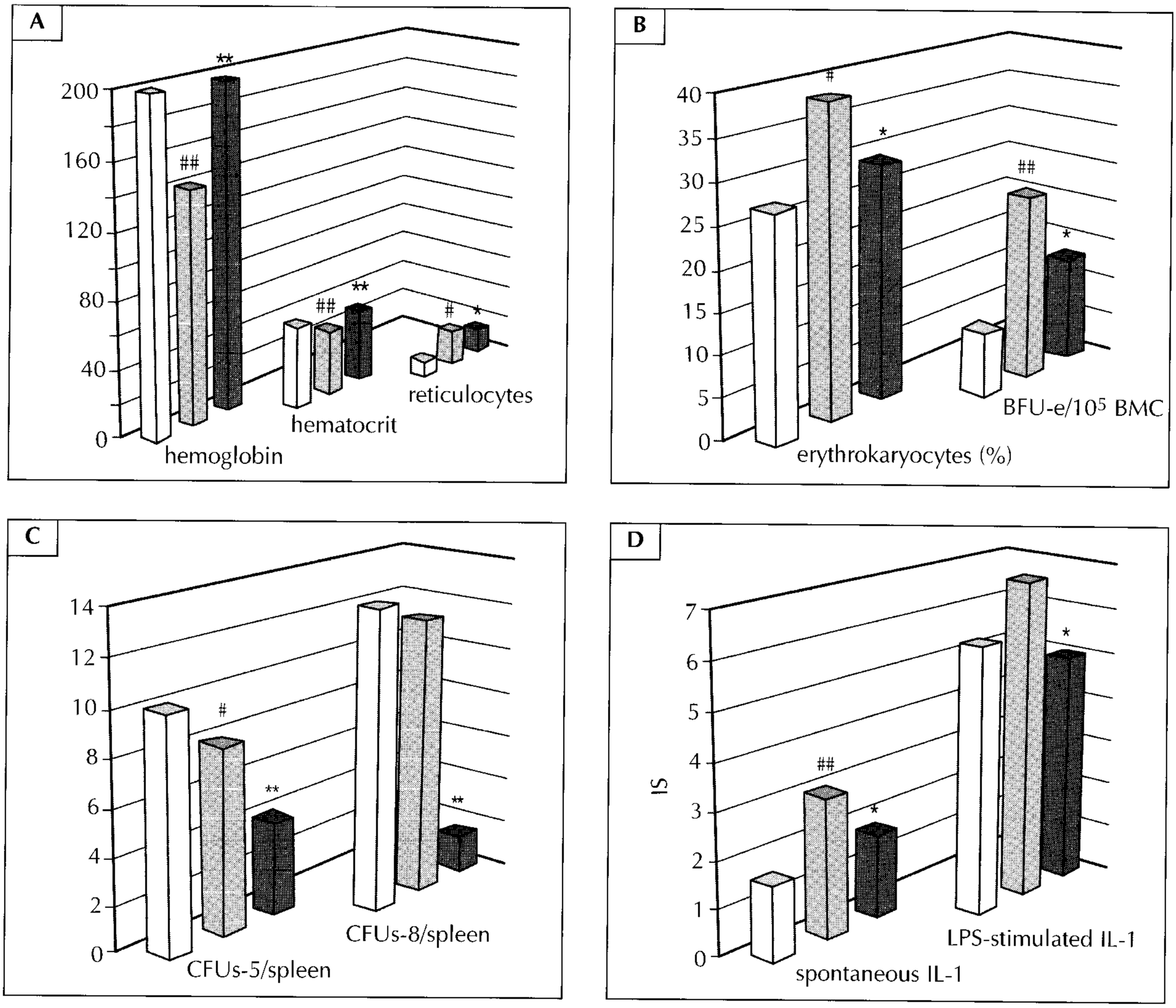

Figure 2. The influence of VM-2-84 on the immuno- and hemopoiesis in B6D2F2 mice with glomerulonephritis. [A] - the level of hemoglobin, hematocrit and reticulocyte number; [B] - the number of erythrokaryocytes and BFU-e; [C] - the number of CFUs; [D] - spontaneous and LPS-stimulated IL-1 production. (▭) - control; (▭) - glomerulonephritis; (▬) - glomerulonephritis + VM-2-84. (#) - significant differences compared with control groups (#p<0.05; ##p<0.01); (*) - significant differences compared with glomerulonephritis groups (*p<0.05; **p<0.01).

munodeficiency plus anemia and B6D2F1 mice with immunodeficiency plus anemia plus immunocomplex glomerulonephritis are Coombs positive.

Chronic hypoxia, trecrezan and VM-2-84 treatment significantly decreases the early BFU number in B6D2F1 mice with immunodeficiency (Fig. 1C). B6D2F1 mice with immunocomplex glomerulonephritis have decreased number of early and late erythropoietic progenitors after VM-2-84 treatment (**Figure 2B**). VM-2-84 has influence on bone marrow hemopoietic progenitor colony forming activity of intact mice in culture *in vitro*: the number of CFU-GM significantly increases and the number of BFU decreases.

The influence of O,S-Containing CAA and Hypoxia on the CFUs-5 and CFUs-8 Numbers

B6D2F1 mice with immunodeficiency have significant increase of CFUs-5 number which reflect the intensity of erythropoiesis potential and in this case chronic hypoxia and trecrezan have no effect on CFUs-5 number, but VM-2-84 significantly decreases CFUs. B6D2F1 mice with immunocomplex glomerulonephritis have reduced CFUs-5 number in com-

Table 1. The influence of VM-2-84, trecrezan, GR-1, cobasol treatment on urine protein concentration of B6D2F1 mice with immunocomplex glomerulonephritis

Drugs	Urine protein concentration (mg/ml)		
	Before treatment	After treatment	2 months after treatment
VM-2-84 (5mg/kg)	7.3±0.9 n=14	5.6±0.9 n=14	2.5±0.4** n=12
Trecrezan (5mg/kg)	9.8±1.7 n=10	5.9±1.4 n=10	4.7±1.4* n=10
Gr-1 (5mg/kg)	7.8±1.8 n=11	4.2±0.9 n=11	6.3±1.8 n=10
Cobasol (15 mg/kg)	10.8±1.5 n=9	7.9±1.5 n=9	5.6±1.2* n=9

Significant differences compared with groups before treatment (*p<0.05, **p<0.01).

parison with intact animals and VM-2-84 influences the CFUs-5 number by the same manner (**Figure 2C**). In this case the increased CFUs-8 number of B6D2F1 mice with immunodeficiency and the normal CFUs-8 number of B6D2F1 mice with immunocomplex glomerulonephritis were in 2.6 and 7.7 times reduced after VM-2-84 treatment (Fig. 2C).

The Influence of O,S-Containing CAA and Hypoxia on the IL-1 Level

B6D2F1 mice with immunodeficiency and immunocomplex glomerulonephritis have significant increase of both spontaneously and LPS-induced IL-1 production (**Figure 1D** and **2D**). Trecrezan treatment reduces significantly both spontaneous (to 38.1%) and LPS-induced (to 54.2%) IL-1 production in B6D2F1 mice with immunodeficiency (Fig. 1D). Both spontaneous and LPS-induced IL-1 production by peritoneal macrophages is decreased after VM-2-84 treatment of B6D2F1 mice with immunodeficiency and immunocomplex glomerulonephritis (Fig. 1D and 2D). Chronic hypoxia practically doesn't influence both spontaneous and LPS-induced IL-1 production in intact animals. Hypoxia does not reduce significantly the spontaneous and LPS-induced IL-1 production by macrophages of B6D2F1 mice with immunodeficiency (Fig. 1D).

The Influence of O,S-Containing CAA on Proteinuria and Kidney Pathology of Mice with Immunocomplex Glomerulonephritis

B6D2F1 mice with immunocomplex glomerulonephritis at the 5-6th month of a disease have been treated with drug dose 5 mg/kg for 40 days at daily intervals (15 injections). The dynamics of the change of urine protein concentration was observed (**Table 1**).

All B6D2F1 mice with immunocomplex glomerulonephritis have urine protein with average concentration is 7.3±0.9 mg/ml before VM-2-84 treatment (mice with more than 3 mg/ml urine protein were used). Immediately after the treatment urine protein concentration in 78% of mice was reduced and its average level becomes 5.6±0.9 mg/ml, at 2 month interval after treatment urine protein concentration in 86% of mice is significantly reduced in comparison with the initial level and its average content is 2.5±0.4 mg/ml ($p<0.01$). Immediately after trecrezan a reduced urine protein concentration is observed and it remains during 2 months after the treatment. After comparison of the effects of CAA (VM-2-84 and trecrezan) with new immunoactive organic compounds of germanium (**GR-1**), as well as with new erythrotropic substance (cobasol), VM-2-84 pretends to be the most effective substance because VM-2-84 treatment maximally reduces urine protein concentration. Morphological study shows suppression of mesangial proliferation, immune complex fixation in kidney and formation of lymphoid infiltrates in marrow and cortical tissue which are the morphological characteristics of chronic inflammation with immune component after VM-2-84 treatment of mice with experimental mesangial glomerulonephritis. Thus, VM-2-84 has a favorable therapeutic effect on inflammatory course in kidney.

DISCUSSION

The development of an acquired immunodeficiency - GVHR-induced suppression of humoral immunity is known, but the mechanism is not exactly clear. Recently it has been shown that disbalance of the Th and their cytokines may cause decrease of IgM response [16]. Apparently, hemopoiesis plays a crucial role in pathogenesis of the wide range of disturbances in the immune system: immunodeficiency, autoimmune and lymphoproliferative disorders. The modification of proliferation activity of stem cell and early hemopoietic committed precursors has been found to play a crucial role in immunopathological disturbances including immunodeficiency [6, 7]. Now it is evident that early erythroid precursors - erythrokaryocytes possess immunosuppressive property and produce soluble low molecular weight factor (1-10 kD) [17]. The increased number of erythrokaryocytes, that possess immunosuppressive property, may be not only the universal reaction in limiting of B cell clone ability to antibody production but also one of the mechanism abilities to shape GVHP-induced immunosuppression. From our investigation in B6D2F1 mice with GVHR-induced immunopathology it is clear that anemia occurs in peripheral blood with an increased number of erythrokaryocytes and BFU in the bone marrow. Anemia is accompanied by reticulocytosis which has a direct relation to the expression of anemic syndrome and gives an evidence in favor of bone marrow regeneration. While comparing our results with literature data, it can be concluded that anemia develops as a result of increased hemolysis and has autoimmune mechanism. This is confirmed by presence of auto-Ab to erythrocytes (Coombs+) and an increased number of IgG in blood in B6D2F1 mice with GVHR-induced immunopathology by our and literature data [9, 10, 18]. In the development of anemic syndrome in mice, a dysfunction of macrophages and their increased IL-1 and TNFα production play a certain role. These cytokines while regulating erythropoiesis, participate in pathogenesis of autoimmune hemolytic anemia [19].

So, GVHR-induced models of immunopathology in B6D2F1 mice present different variants of combined disturbances of erythro- and immunopoiesis: immunodeficiency combined with hemolytic anemia and immunodeficiency combined with hemolytic anemia and immunocomplex glomerulonephritis.

It is known, that hypoxia as erythrotropic factor stimulates the production of erythropoietin by kidney and it is used for treatment anemia with a decrease of erythropoiesis [20]. But in literature there are no available data on the use of chronic hypoxia for treatment of moderate hemolytic anemia with an increase of bone marrow erythropoiesis combined with immunodeficiency. There is some positive effect of chronic hypoxia on GVHR-induced immunopathology in B6D2F1 mice: it increases humoral immune response, abolishes anemia and corrects early and late committed precursor number. Probably, the initial increase of synthesis of the erythropoietin leads to the growth of hemoglobin level in blood. Simultaneously, a secretion of IgG with fraction that contains the autoantibodies to erythrocytes is reduced, providing the beneficial effect on anemia. When a level of hemoglobin in blood was restored, the hyperplasia of erythron was stopped at the level of bone marrow cells, i.e. the decreased production of Er-suppressor factor resulted in an increase of IgM response. The absence of any influence of chronic hypoxia on the macrophage secretory activity coincides with data of the literature [21] and evidences the direct influence of erythron on the humoral immune response.

The compound VM-2-84 has a profound effect on erythropoiesis in ill animals from the early stages of erythron differentiation. A drop in IL-1 production probably results in a decrease of synthesis of Th2 cytokines (IL-4, -5 and -6) that stimulate synthesis of autoantibodies to erythrocytes by B cells. As a result, hemolysis of erythrocytes is reduced and the parameters of erythropoiesis are normalized. It is possible, that the effect of a preparation on the number of PFU in spleen is mediated through the action of IL-1. It is known that IL-1 stimulates activity of Th2 [22], and VM-2-84 administration reduces cytokine secretion. The reduction of IL-1 production results in the suppression of the number of Th2 and their functions, that is probably one of the reasons of a failure of a preparation the effect on the amount of PFC in sick mice. The increase of spontaneous and LPS-

induced IgG production under VM-2-84 action in mice with glomerulonephritis is in accordance with data of Bowles et al. [23] about restoration of immunocompetence in NZB/WF1 mice with glomerulonephritis after application of CsA.

VM-2-84 compound has curative effect on anemia (suppresses IL-1 production, reduces the number of early erythroid precursors and stimulates the amount of the granulocyte and macrophage precursors) in B6D2F1 mice with immunocomplex glomerulonephritis. The VM-2-84 up to two months decreases proteinuria and reduces proliferation of mezangiocytes and chronic inflammation with the restoration of immune system. Trecrezan also reduces a proteinuria for a long time. It is interesting to compare the effect of a VM-2-84 with the effect of a known immunodepressant CsA. It is shown, that if CsA was injected to NZB/W mice before the beginning of a proteinuria (antinuclear antibodies occur in female mice at the age of 2-3 months, and at the age of 5-6 months systemic immunocomplex disease develops with nephritis and proteinuria). Proteinuria was only prevented until the drug was applied [24].

Trecrezan, while being beneficial in anemia, reduces a hyperplasia of erythron in mice with immunodeficiency. Such an effect of trecrezan on erythropoiesis may be related to direct influence of the drug on erythropoiesis through monokines. The correction of immunodeficiency in B6D2F1 mice by trecrezan maybe due to both normalization of functions of Th1 and Th2, and correction of suppressive influence of erythroid cells mediated *via* erythron hyperplasia.

Thus, the GVHR-induced disorders of immunity - immunodeficiency and autoimmune disturbance are accompanied by changes not only in the immune, but also in the hemopoietic system, which appeared to modify proliferation of hematopoietic stem cells, activity of CFUs, colony-forming activity of the erythroid and granulocyte-macrophage hemopoietic precursors. The immunodeficiencies may be combined with different variants of disturbance of erythropoiesis that requires the differentiated approaches to correction. The obtained facts about effectiveness of preparation possessing combined erythro- and immunopoiesis-modulating properties, open new ways of a target regulation of immunity disorders.

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