Archives of Razi Institute, Vol. 76, No. 5 (2021) 1237-1244

DOI: 10.22092/ari.2021.355845.1726

Original Article

Effect of Anti-TNFα Therapy by Infliximab against Pancreatic Tissue Damage in Severe Acute Necrotizing Pancreatitis

Alekhin, S. A[1 *], Firsova, T. I[1], Nazarenko, D. P[1], Bezhina, E. N[1], Druzhikin, L. V[1]

1. Belgorod State University, Pobedy St., 85, Belgorod, 308015, Russia

Received 1 September 2021; Accepted 17 September 2021
Corresponding Author: s_alehin@mail.ru

Abstract

Nowadays, it is difficult to find a more complicated inflammatory disease of the abdominal organs in its pathogenesis than acute pancreatitis (AP). The application of antimediatory drugs and antimetabolites is the most promising direction in the correction of inflammatory pathological processes. The study of possible applications of a new group of drugs (monoclonal antibodies) that may trigger inflammation is also of great interest. The present study aimed to study the effect of infliximab on the lethality, volume, and nature of pancreatic lesions in severe necrotizing ductal pancreatic necrosis. The study was conducted on female Wistar rats (n=30) of similar age in the weight range of 200-250g. All manipulations were performed under general anesthesia by intraperitoneal injection of zoletil at a dose of 60 mg/kg, as well as chloral hydrate at a dose of 125 mg/kg. Model of severe acute necrotizing pancreatitis was performed through the injection of 0.5 ml of a buffer solution containing a bile acid salt-sodium taurocholate introductory. The animals were divided into the following groups: Group A (n=6): normal values; Group B (n=6): the mortality study was conducted in acute destructive pancreatitis in a period of 24 h; Group C (n=6): the simulation of acute severe necrotic pancreatitis was performed in this group along with the study of the volume of pancreatic lesions for a period of 6 h from the moment of modeling; Group D (n=6): in this group, the effect of infliximab (at a dose of 60 mkg/kg) was studied on mortality in severe destructive pancreatitis for a period of 24 h from the moment of modeling; Group E (n=6): in this group, the effect of infliximab (at a dose of 120 mkg/kg) was studied on the volume of pancreatic lesions in severe destructive pancreatitis for a period of 6 h from the moment of modeling. During the assessment of pancreatic damage, the mean±SD volume of pancreatic lesions was determined to be 34.8%±1.2% in a period of 6 h after modeling. Assessment of pancreatic damage in group E and the protective effect of infliximab at a dose of 60 mg/kg showed that the total volume of the necrotic pancreatic lesion was determined to be 21.3%±1.4% after a period of 6 h from the moment of AP modeling. In the course of this study, it was revealed that the application of infliximab at a dose of 60 mcg/kg led to a pronounced positive effect on the pancreatic lesion, manifested by up to 50% decrease in mortality for one day in group D. Infliximab had a definite protective effect in AP, decreasing the volume of the injury, as well as the mortality rate by half for 24 h. Therapy with anti-tumor necrosis factor with infliximab could significantly reduce the volume of pancreatic lesions in severe forms of pancreatic necrosis, which contributed to a pronounced decrease in mortality for 1 day from the moment of pathology reproduction.

Keywords: Infliximab, Severe acute necrotizing pancreatitis, pancreatic damage

1. Introduction

Nowadays, it is difficult to find a more complicated inflammatory disease of the abdominal organs in its pathogenesis than acute pancreatitis (AP). This pathology is included in the group of diseases united by the features of medical care, called “acute abdomen”,

consistently occupying 2-3 places in this group along with acute cholecystitis. According to the World Health Organization, AP affects between 200 and 800 people per one million of the world's population. According to the State Statistics Committee, the incidence of AP in the Russian Federation ranges from 36 to 40 cases per 100,000 population. The prevalence of destructive forms is currently 15-20% of all cases, from 75 to 80% of the diseases that are called abortive or edematous. The development of pancreatic tissue destruction is a life-threatening complication with a mortality rate of over 80% Goodchild, Chouhan (1). The extension of the necrotizing process in the pancreas causes ischemic damage, which leads to activation of acute inflammation (2-4). One of the most important factors in the treatment of patients with AP is the early diagnosis of the disease. Mild pancreatitis is easy to treat; however, treatment for AP includes intensive care. Access to and observation of the pancreas is not possible without surgery, and imaging observations may not provide sufficient information to the physician (5). There are also inherited and chronic forms of the disease that can have irreversible effects throughout one's life. Patients often suffer from pain and malnutrition and are more likely to have a higher risk of pancreatic cancer (6).

Conservative treatment is an approach to treat some ailments, such as low back pain, neck pain, and spinal diseases using non-surgical treatment options, such as physiotherapy, medication, and injections (7). The development of conservative therapy methods requires research and the creation of methodological complex approaches to understanding the place and role of certain pharmacological targets (8-13).

One of the treatment methods is the application of synthetic antibodies that have an inhibitory effect on pancreatic enzymes. Therefore, anti-protein drugs are expected to prevent necrotic changes in the pancreas and reduce mortality (7). The application of antimediator and antimetabolites treatment is one of the most promising directions in the correction of inflammatory pathological processes (11, 14-17).

The tumor necrosis factor-alpha (TNF-alpha) is one of the initial mediators of inflammation which has recently been proven to be involved with systemic inflammation in pancreatic necrosis. Norman, Fink (18) showed that tumor necrosis factor gene expression occurred locally during AP and that large amounts of TNF were produced within the pancreas with continuous levels higher than those in serum. The overall increase in TNF concentration in tissue and serum was directly related to the severity of pancreatic damage and inflammation, and they stated that intrusive macrophages played the largest role in this process (18). It was found that the concentration of TNF-alpha in the blood increased notably after the induction of AP (19).

Today, the study of the possible effects of a new group of drugs (e.g., monoclonal antibodies) that can trigger inflammation is of great interest. Some studies have suggested the effectiveness of monoclonal antibodies (TNF-alpha) in AP. However, in the analysis of these research works, it was revealed that the effects of this drug were investigated on "non-severe" models of AP with low mortality, which is most often represented in the foreign literature as mild necrotizing pancreatitis (20). Therefore, the question of extrapolating the results of these studies to clinical conditions is debatable.

The effect of infliximab on the lethality, volume, and nature of pancreatic lesions was studied in severe necrotizing ductal pancreatic necrosis.

2. Materials and Methods

The experiment was performed on females white Wistar rats (n=30) in a similar weight range (200-250g). All studies were performed in compliance with the rules of humane treatment of animals. Rats without external signs of the disease have been selected for this study. These rats have passed the quarantine regime and were kept in standard conditions.

The animals were divided into the following groups:

• Group (n=6): Control value
• Group B (n=6): A 24h mortality study was conducted on acute destructive pancreatitis in this group.
• Group C (n=6): The simulation of acute severe necrotic pancreatitis was performed along with the study of the volume of the pancreatic lesion for a period of 6 h from the moment of modeling.
• Group D (n=6): In this group, the effect of infliximab at a dose of 60 mkg/kg was studied on mortality in severe destructive pancreatitis for a period of 24 h from the moment of modeling.
• Group E (n=6): In this group, the effect of infliximab (at a dose of 120 mkg/kg) on the volume of pancreatic lesions in severe destructive pancreatitis was studied for a period of 6 h from the moment of modeling.

All manipulations were performed under general anaesthesia by intraperitoneal injection of Zoletil at a dose of 60 mg/kg, as well as chloral hydrate at a dose of 125 mg/kg.

The model was performed under general anesthesia. Intraperitoneal injection of Zoletil at a dose of 50 mg/kg, together with chloral hydrate at a dose of 125 mg/kg was carried out after the surgical field was treated with antibiotic solutions. Subsequently, the abdominal cavity was opened layer by layer. A loop of the duodenum was pulled into the wound. The main papilla of the duodenum was found during transillumination.

After finding the ampoule and the outlet of the main papilla of the duodenum, 0.5-0.6 cm was dissected from it and a needle with a diameter of 32G was used to perforate the anterior wall of the duodenum. Cannulation of the common bile duct was performed using a 36 G catheter (Figure 1).

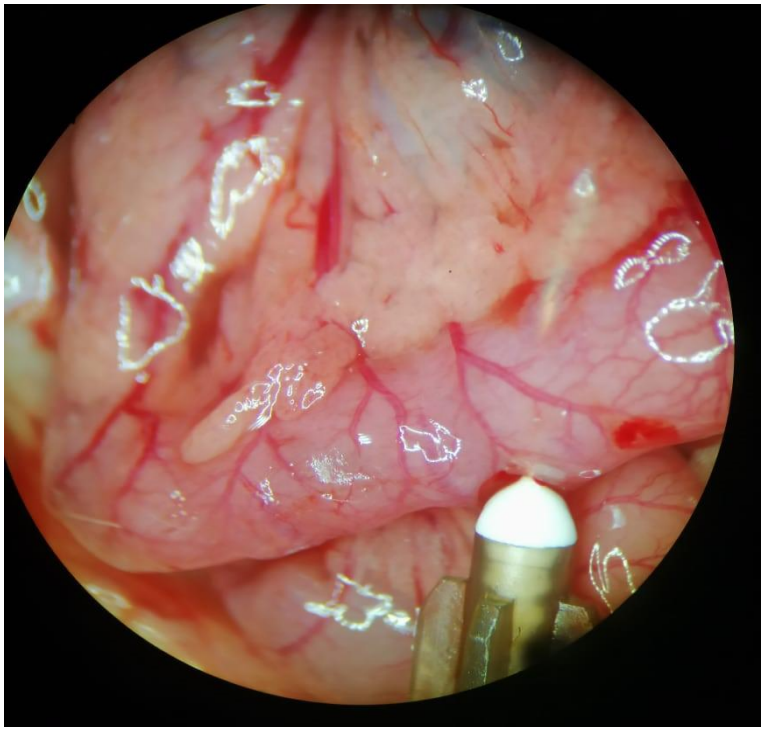

Figure 1. Cannulated common bile duct

Insulating clips were applied to the cannula to reproduce severe destructive pancreatitis, distal to the place of duodenal duct junction, and the common bile duct so that the injected solution completely entered the pancreatic ducts.

Failure to comply with this condition may lead to the discharge of the solution into the duodenum. Subsequently, an excessive amount of the solution will enter the common bile duct which performs the function of the gallbladder in a rat, damps the excessive pressure, and accumulates a significant amount of bile. After isolation, 0.5 ml of a buffer solution containing a bile acid salt-sodium taurocholate was injected into the pancreatic ducts. The isolation clips were removed 1 min after administration which allowed the solution to penetrate deeper into the pancreatic parenchyma. At the next stage, the clips and cannula were removed from the ducts, and the abdominal cavity was sutured layer by layer completely. The ignorance about the pancreatic ducts system in rats can lead to a sharp decrease in the volume of its lesion, which is reflected in a lower mortality rate.

After the macroscopic evaluation, the pancreas, liver, kidneys, and lungs were collected for histological examination. The organs were collected, weighed, and fixated in a 10% neutral formalin solution. After fixation, the tissue areas were washed in running water, dehydrated, and poured into paraffin according to the standard procedure. Paraffin sections of the pancreas with a thickness of 5-7 mkm were prepared at standard intervals of all parts of the organ. The sections were stained with hematoxylin and eosin.

Histological processing was performed using the equipment of the company "Leica" (Germany). During the microscopic examination, the finished micro-preparations were scanned using archiving and image analysis system "MIRAX Desk". Image analysis and morphometry were performed using the program "Pannoramic Viewer"1.15.4. Quantitative data were recorded in MS Excel software.

The volume of pancreas lesion was measured through the calculation of the ratio of the area of necrosis to the unaffected area of the pancreas, on digitized computer images that were obtained using a digital microscope in the "total scan" mode, as well as Mirax Desk and Pannoramic Viewer software (Version1.15.4). The ratio was expressed in percentage.

Infliximab (MSD Remicade) was administered 1 h before the AP modeling at a dose of 60 mkg/kg.

Statistical analysis of the obtained data was carried out using Microsoft Excel (Version 2007), and through calculating the mean of indicators, the error of the average m, and the confidence criterion (p). A p-value ≤ 0.05 was considered statistically significant.

3. Results

The mortality rate at the study period was one of the most accurate integral indicators to evaluate the effectiveness of a particular treatment method. It should be noted that 24 h after modeling severe pancreatic necrosis developed by researchers in the present study, the mortality rate was 100%.

In group C, a large amount of hemorrhagic effusion was localized in all parts of the abdominal cavity 6 h from the modeling of AP. The liver had marks of venous hyperemia with a smooth surface and sharpened edges of the lobes. Moreover, there was hyperemia of the spleen.

The greatest changes affected the pancreas, which was sharply edematous, with areas of hemorrhagic pancreatic necrosis. The retroperitoneal tissue was edematous. There was a hemorrhagic effusion with hyperemia of the parietal and visceral pleura in the chest. The areas of diapedesis hemorrhage were noted in the basal parts of the lungs.

Acute destructive pancreatitis was characterized by typical large-focal hemorrhagic pancreatic necrosis changes after a period of 6 h from the moment of modeling. The zone of the necrotic lesion in the duodenal part of the pancreas affected 50% of this part and was localized closer to the wall of the duodenum spreading along the duct.

The greatest destruction was noted in the gastro-splenic part of the gland in form of coagulation necrosis

of acinar cells, fibrinoid necrosis of vascular walls and stromal elements, partial necrosis of acini, and severe neutrophil infiltration centrilobular with a primary lesion (Figure 1 and Figure 2).

The volume of pancreatic damage was found to be 34.8%±1.2 during 6 h after the modeling.

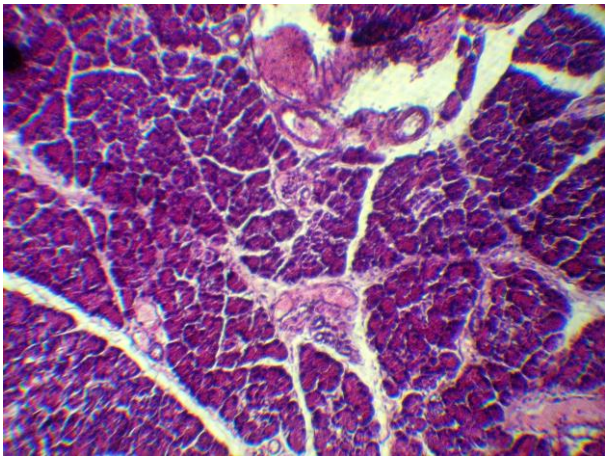

Figure 2. Intact rat pancreas. G+E, magnification X 90

Assessment of pancreatic damage in group D, as well as the protective effect of infliximab at a dose of 60 mkg/kg revealed that the total volume of the necrotic pancreatic lesion was estimated at 21.3%±1.4% for a period of 6 h from the moment of modeling AP. An increase in infliximab dose up to 120 mkg/kg did not lead to a significant reduction in the volume of pancreatic destruction and mortality rate which was 50% in this group (Table 1).

Table 1. Effect of different doses of infliximab on the volume of pancreatic destruction in severe acute necrotizing pancreatitis

Group	Volume of pancreatic tissue damage (%)
Group C (6h model of acute necrotizing pancreatitis, n=6)	34.8±1,2
Group D (Infliximab 60 mkg/kg, n=6)	21.3±1.4 *
Group E (Infliximab 120 mkg/kg, n=6)	19.3±1.2 **

Note: * P<0.05: A significant difference, compared to the control group
** P≥0.05: No significant difference, compared to group D

In the course of the work, it was revealed that the use of MAB infliximab at a dose of 60 mcg/kg led to a pronounced positive effect on the pancreatic lesion, manifested by a decrease in mortality rate up to 50% by 1 day in group D.

Positive protective effect of monoclonal antibodies to tumor necrosis factor in a dose of 60 mkg/kg 1h before modeling of acute destructive pancreatitis is manifested in the reduction of interstitial edema, a decrease in centrilobular areas of necrosis, and reduction in zones and degree of leukocyte infiltration (Figure 3 and 4).

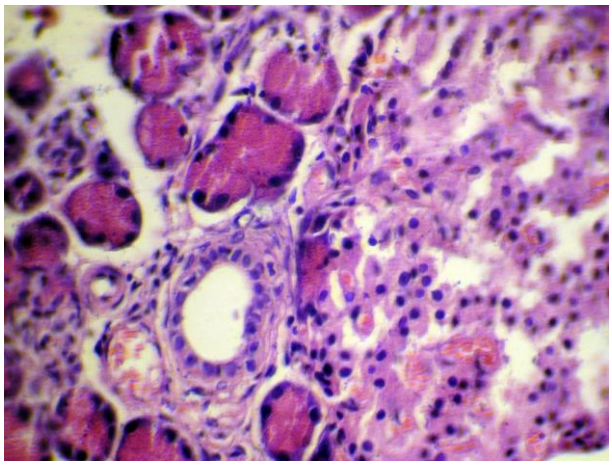

Figure 3. Severe centrilobular lesion of the pancreas with neutrophil infiltration of the necrotic zone during 6 hours from the moment of modeling AP. G+E, magnification X 400

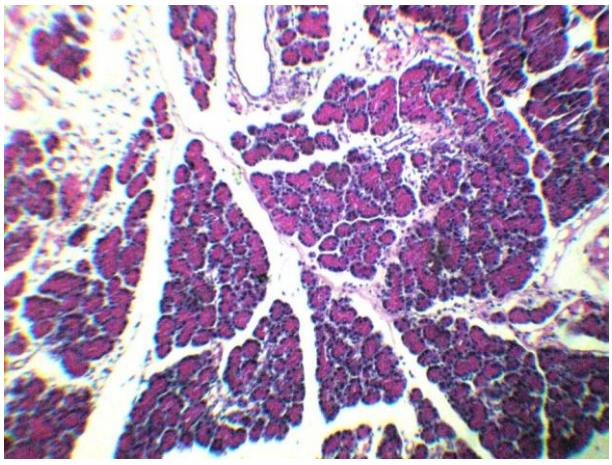

Figure 4. Centrilobular necrosis with a moderate lesion volume when corrected with infliximab at a dose of 60 mkg/kg in the simulation of AP for a period of 6 h from the moment of the simulation. G+E, magnification X 200

4. Discussion

Biologic drugs act on a TNF molecule and are called TNF blockers or anti-TNF drugs, which are used to treat rheumatoid arthritis, pediatric arthritis, psoriatic arthritis, and ankylosing spondylitis (21). Remicade or infliximab is used to reduce the pain and swelling of certain inflammatory diseases (e.g. rheumatoid arthritis, and psoriasis) and certain intestinal diseases, such as Crohn's disease (22). Infliximab reduces inflammation by blocking interleukin-12 and interleukin-23 (a substance made by the body that causes inflammation) (23). Although infliximab does not cure the disease, it helps reduce the symptoms of the disease. This drug can help reduce the number of plaques in plaque psoriasis, pain and swelling in arthritis, and heartburn and cramps in Crohn's disease (24).

The development of acute destructive pancreatitis is accompanied by the disruption of the pancreatic stroma. The parietal and visceral peritoneum is edematous and hyperemic in almost all parts. There is pronounced edema of the intestinal mesentery. The application of TNF-α is one of the most effective treatments for AP. Based on the obtained results in this study, TNF-α was significantly increased in pancreatic tissue in AP, and anti-TNF-α treatment significantly improved pathological and biochemical findings (25). The disorder of pancreatic exocrine secretion is one of the important features. A significant amount of amylase is secreted during pancreatitis, indicating the release of the enzyme from damaged cells (26). The disruption of pancreatic tissue leads to an increase in lipase and cytokine levels and oxidative tissue stress (27). Therefore, infliximab has a pronounced protective effect in AP, reducing the volume of the lesion as well as the mortality rate up to 50% for a period of 24 h. It can be concluded that further research on the application of monoclonal antibodies against tumor necrosis factor-alpha will form the basis for its application in clinical conditions in severe forms of necrotizing pancreatitis (28).

The TNF drugs, such as infliximab, may be an alternative treatment for patients who do not respond to treatment with corticosteroids or immunosuppressants (29). Based on the results of some studies, the blocking of TNF leads to minimization of inflammation and limitation of pancreatic damage (30, 31). TNF-α is responsible for the local and systemic effects in pancreatitis, and it is thought that inhibition of TNF-α can reduce local and systemic complications (32). TNF blockade in AP could reduce the complications associated with pancreatitis. Some researchers have reported that the inhibition of TNF-α solution can reduce the severity of experimental pancreatitis and mortality; however, it does not affect pancreatic vacuolation, necrosis, and inflammatory cell infiltration. Oruc, Ozutemiz (33) pointed that infliximab has anti-inflammatory effects in the model of edematous and necrotic pancreatitis which can be explained by the differences in the performance between different molecules used in the studies. Other researchers reported that a TNF-receptor fusion protein etanercept could improve the histological scores and biochemical parameters in the necrotizing Na-taurocholate pancreatitis model (34, 35).

5. Conclusion

Based on the obtained results, it can be concluded that anti-TNF therapy with infliximab can significantly reduce the volume of pancreatic lesions in severe forms of pancreatic necrosis, which contributes to a pronounced decrease in mortality for one day from the moment of pathology reproduction.

The main findings of the current study can be summarized in the following three statements:

1. Administration of infliximab (at a dose of 60 mkg/kg) in a model of severe acute necrotizing pancreatitis helped to reduce the death rate by 50% at a period of 24 h.

2. The application of infliximab at 60 mkg/kg dose at a period of 6 h after modeling of severe acute necrotizing pancreatitis led to the reduction of pancreatic damage volume from 34.8%±1.2% in group

C to 21.3%±1.4% in group D.

An increase of infliximab dose up to 120 mkg/kg in group E did not lead to a significant reduction in the volume of pancreatic destruction, compared to group D.

Authors' Contribution

Study concept and design: S. A. A. and T. I. F.
Acquisition of data: S. A. A., T. I. F. and L. V. D
Analysis and interpretation of data: D. P. N.
Drafting of the manuscript: E. N. B.
Critical revision of the manuscript for important intellectual content: S. A. A. and T. I. F.
Statistical analysis: L. V. D.
Administrative, technical, and material support: S. A. A.

Ethics

All studies were performed in compliance with the rules of humane treatment of Belgorod State University, Russia.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Goodchild G, Chouhan M, Johnson GJ. Practical guide to the management of acute pancreatitis. Frontline Gastroenterol. 2019;10(3):292-9.
2. Anderson MC, Bergan JJ. Significance of vascular injury as a factor in the pathogenesis of pancreatitis. Ann Surg. 1961;154:58-67.
3. Firsova TI AS, Bezhina EN, Lukyanchikov GF, Reznikov RM, Stepchenko AA, Lazareva GA. The degree of pancreatic edema in ischemic damage during acute pancreatitis in the conditions of pharmacological correction with infliximab. Int J Pharm Sci Res. 2020;12(1):1092-6.
4. Hoffmann TF, Leiderer R, Waldner H, Arbogast S, Messmer K. Ischemia reperfusion of the pancreas: a new in vivo model for acute pancreatitis in rats. Res Exp Med (Berl). 1995;195(3):125-44.
5. Goulden MR. The pain of chronic pancreatitis: a persistent clinical challenge. Br J Pain. 2013;7(1):8-22.
6. Zerem E. Treatment of severe acute pancreatitis and its complications. World J Gastroenterol. 2014;20(38):13879-92.
7. Takeda K. Antiproteases in the treatment of acute necrotizing pancreatitis: continuous regional arterial infusion. J Pancreas. 2007;8(4):526-32.
8. Danilenko LM. Doxorubicin-associated Cardiomyopathy: New Approaches to Pharmacological Correction Using 3-(2,2,2-trimethylhydrazinium) Propionate Derivatives. Res. Results Pharmacol. 2018;4(1):81-6.
9. Kalmykov VA, Kusov PA, Yablonskaia MI, Korshunov EN, Korshunova DS, Kubekina MV, et al. New personalized genetic mouse model of Lesch-Nyhan syndrome for pharmacology and gene therapy. Res Results Pharmacol. 2018;4(4):115-22.
10. Kazbekovna BS FK, Vitalevich VD, Phillipovich SK. Pleyotropic antiaggregant effects of an innovative antiarrhythmic of class III SS-68, an indole derivative. Res Results Pharmacol. 2017;3(2).
11. Kurganov NA, Blinova EV, Semeleva EV, Gromova IA, Blinov DS, Novikov AV, et al. 2-aminoaethanesulfonic acid compounds possess protective property in reperfusion-induced heart jnjury. Res Results Pharmacol. 2018; 4(2):19-26.
12. Shulginova AA, Konoplya AI, Bystrova NA. Disorders of the immune status in patients with chronic cerebral ischemia; differentiated pharmacological correction. Res Results Pharmacol. 2018;4(2):95-112.
13. Voronkov AV, Pozdnyakov DI. Endothelotropic activity of 4-hydroxy-3,5-di-tret-butylcinnamic acid in the conditions of experimental cerebral ischemia. Res Results Pharmacol. 2018;4(2):1-10.
14. Avdeeva NV, Sidorova SA, Gudyrev OS, Osipova OgA, Golubev IV. Mechanism of neuroprotective effect of mGluR4 agonists. Res Results Pharmacol. 2019;5(2):43-7.
15. Korokin M, Gureev V, Gudyrev O, Golubev I, Korokina L, Peresypkina A, et al. Erythropoietin Mimetic Peptide (pHBSP) Corrects Endothelial Dysfunction in a Rat Model of Preeclampsia. Int J Mol Sci. 2020;21(18).
16. Palikov VA, Palikova YA, Borozdina NA, Nesmeyanova EN, Rudenko PA, Kazakov VA, et al. A novel view of the problem of Osteoarthritis in experimental rat model. Res Results Pharmacol. 2020;6(2):19-25.
17. Stupakova EG, Lazareva GA, Gureev VV. Correction of morphofunctional disturbances arising when modelling Preeclampsia with resveratrol and nicorandil. Res Results Pharmacol. 2018;4(1):59-71.

18. Norman JG, Fink GW, Franz MG. Acute pancreatitis induces intrapancreatic tumor necrosis factor gene expression. Arch Surg. 1995;130(9):966-70.
19. Zhang G, Zhang Z, Liu X, Yan L, Hu W, Tian B, et al. Intrapulmonary expression of tumor necrosis factor alpha mRNA and its significance in rats with acute pancreatitis. J West China Univ Med Sci. 1999;30(4):379-83.
20. Tekin SO, Teksoz S, Terzioglu D, Arikan AE, Ozcevik H, Uslu E. Use of infliximab in treatment of acute pancreatitis. Bratisl Lek Listy. 2015;116(3):167-72.
21. Prado MS, Bendtzen K, Andrade LEC. Biological anti-TNF drugs: immunogenicity underlying treatment failure and adverse events. Expert Opin Drug Metab Toxicol. 2017;13(9):985-95.
22. Mariette X, Ravaud P, Steinfeld S, Baron G, Goetz J, Hachulla E, et al. Inefficacy of infliximab in primary Sjogren's syndrome: results of the randomized, controlled Trial of Remicade in Primary Sjogren's Syndrome (TRIPSS). Arthritis Rheum. 2004;50(4):1270-6.
23. Wong U, Cross RK. Expert opinion on interleukin-12/23 and interleukin-23 antagonists as potential therapeutic options for the treatment of inflammatory bowel disease. Expert Opin Investig Drugs. 2019;28(5):473-9.
24. Toupin-April K, Barton J, Fraenkel L, Li LC, Brooks P, De Wit M, et al. Toward the Development of a Core Set of Outcome Domains to Assess Shared Decision-making Interventions in Rheumatology: Results from an OMERACT Delphi Survey and Consensus Meeting. J Rheumatol. 2017;44(10):1544-50.
25. Wang XY, Tang QQ, Zhang JL, Fang MY, Li YX. Effect of SB203580 on pathologic change of pancreatic tissue and expression of TNF-α and IL-1β in rats with severe acute pancreatitis. Eur Rev Med Pharmacol Sci. 2014;18(3):338-43.
26. Malleo G, Mazzon E, Siriwardena AK, Cuzzocrea S. TNF-alpha as a therapeutic target in acute pancreatitis--lessons from experimental models. Sci World J. 2007;7:431-48.
27. Pandol SJ PS, Gukovsky I, Zaninovic V, Jung Y, Zong Y, Solomon TE, Gukovskaya AS, Tsukamoto H. Ethanol diet increases the sensitivity of rats to pancreatitis induced by cholecystokinin octapeptide. Gastroenterology. 1999;117(3):706-16.
28. Li R, Song J, Wu W, Wu X, Su M. Puerarin exerts the protective effect against chemical induced dysmetabolism in rats. Gene. 2016;595(2):168-74.
29. Couriel D, Saliba R, Hicks K, Ippoliti C, de Lima M, Hosing C, et al. Tumor necrosis factor-alpha blockade for the treatment of acute GVHD. Blood. 2004;104(3):649-54.
30. Malleo G, Mazzon E, Siriwardena AK, Cuzzocrea S. Role of tumor necrosis factor-alpha in acute pancreatitis: from biological basis to clinical evidence. Shock. 2007;28(2):130-40.
31. Murugesan SR, King CR, Osborn R, Fairweather WR, O'Reilly EM, Thornton MO, et al. Combination of human tumor necrosis factor-alpha (hTNF-alpha) gene delivery with gemcitabine is effective in models of pancreatic cancer. Cancer Gene Ther. 2009;16(11):841-7.
32. Hoeben D, Burvenich C, Trevisi E, Bertoni G, Hamann J, Bruckmaier RM, et al. Role of endotoxin and TNF-alpha in the pathogenesis of experimentally induced coliform mastitis in periparturient cows. J Dairy Res. 2000;67(4):503-14.
33. Oruc N, Ozutemiz AO, Yukselen V, Nart D, Celik HA, Yuce G, et al. Infliximab: a new therapeutic agent in acute pancreatitis? Pancreas. 2004;28(1):e1-8.
34. Genovese T, Mazzon E, Di Paola R, Muia C, Crisafulli C, Menegazzi M, et al. Hypericum perforatum attenuates the development of cerulein-induced acute pancreatitis in mice. Shock. 2006;25(2):161-7.
35. Sanfey H, Bulkley GB, Cameron JL. The pathogenesis of acute pancreatitis. The source and role of oxygen-derived free radicals in three different experimental models. Ann Surg. 1985;201(5):633-9.