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Results of Surgical Treatment in Patients with Acute Pancreatitis

Ganiyev Andyor Adizovich, Bakhtiyor Zarifovich Khamdamov, Khaydarov Farrukh Nuriddinovich, Khamdamov Ilxom Bakhtiyorvich

Bukhara State Medical Institute, Uzbekistan

Abstract Despite significant advances in the field of modern surgery, the problems associated with the treatment of AP continue to cause active discussions in domestic and foreign literature. Particularly lively discussions arise around the issues of surgical intervention in AP, including the optimal timing and indications for surgical procedures [1,3,5,7]. When it comes to acute non-destructive pancreatitis, most authors tend to believe that conservative treatment is preferable. However, issues related to surgical treatment remain open, especially in the context of early surgical interventions [2,4,6,8].

Keywords Despite significant advances in the field

1. Introduction

In light of the unsatisfactory results of AP treatment, expressed by a high level of complications and mortality, there has recently been a tendency to revise strategies in the surgical approach to this disease [9,11,13,15]. The introduction of minimally invasive diagnostic procedures is becoming especially relevant, especially in cases of biliary etiology. Active discussions are also underway regarding AP caused by other factors [10,12,14,26,27,28,29,30]. Some researchers suggest the most conservative treatment within 3-4 weeks from the onset of the disease, reserving surgical interventions only for cases of purulent complications that have developed. Others suggest the early use of laparoscopy, although this method is most often used for diagnostic purposes. In the first case, the mortality rate reaches 20-25%, in the second - 35-50% [17,19,21,31,32,33,34,35,36,37,38, 39,40,41,42].

In the presence of fluid accumulations in the abdominal cavity, such as enzymatic peritonitis, various treatment methods are offered: laparoscopic sanitation and drainage, drainage under the control of computed tomography, peritoneal lavage, puncture emptying of liquid accumulations. However, there is no unity in the methods of interventions, their timing and criteria for deciding on an operation [16,18,20,22].

Treatment of AP may vary depending on the etiology of the disease, as well as on whether the course is abortive or progressive. Currently, general principles of treatment are applied, taking into account various scenarios of the disease [23,24,25].

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2. The Purpose of the Study

To evaluate the results of treatment of patients with acute pancreatitis with immunomodulatory therapy.

3. Material and Methods

A prospective controlled study of 120 patients with acute pancreatitis (AP) aged 25 to 65 years was conducted. Of these, 61.7% (n=74) had an abortive course, and 38.3% (n=46) had a progressive course. The analysis of the anamnesis of the clinical course of patients established in the 1st and 2nd groups of patients with abortive course of AP of non-alcoholic and alcoholic origin, the following degrees of severity, given below in Table 1.

Table 1. The number of patients in groups with abortive course of AP according to the severity of the disease

1st group (n=41)		2nd group (n=33)	
Light degree	**Moderate severity**	**Light degree**	**Moderate severity**
23 (56,1%)	18(43,9%)	17 (51,6%)	16 (48,4%)

According to the protocol of management of patients with AP, hospitalization of patients with abortive course with mild AP was performed in the surgical department. The treatment was based on a basic treatment complex, which included: Hunger; probing and aspiration of gastric contents; analgesics (nonsteroidal anti-inflammatory drugs) 3 times a day; antispasmodics; infusion therapy in a volume of up to 40 ml per 1 kg of body weight of the patient with increased diuresis for 24-48 hours; antibacterial therapy.

It is important to note that basic therapy was enhanced with pancreatic secretion inhibitors. In the absence of the effect of the therapy for 6 hours and the presence of at least

one of the signs of severe pancreatitis (assessment of the severity of patients on integral scales), severe / moderate pancreatitis was detected and the patient was transferred to the intensive care unit and treated according to severe /moderate AP. To assess the effectiveness of the applied therapy, immunological parameters were determined after 7 days in 40 patients of the 1st group of non-alcoholic genesis (23 patients) and the 2nd group of alcoholic genesis (17 patients) AP with an abortive course. The results are shown in the table 2. below.

Table 2. Immunological parameters in groups 1 and 2 of patients with mild abortive course

Indicator	Cont. group, n=27	Group 1 (b/w 7 days after treatment+Ronkoleikin)	
		Before treatment	Basic treatment.
C3	8,33±0,36	7,02±0,29	7,89±0,21*
C5	12,31±0,54	10,53±0,25	11,65±0,19***
IL-1β	17,10±0,91	61,99±1,87	42,51±1,53***
IL-2	12,27±0,44	10,74±0,36	11,21±0,47**
IL-6	8,11±0,42	41,51±1,29	24,81±1,23***
TGF-β	55,93±2,78	178,68±5,10	112,70±4,57***
Group 2 (b/w 7 days after treatment without immunocorrection)			
C3	8,33±0,36	7,12±0,42	7,67±0,21^
C5	12,31±0,54	9,69±0,55	10,53±0,35^
IL-1β	17,10±0,91	66,17±2,44	62,38±1,56^
IL-2	12,27±0,44	9,16±0,39	10,04±0,22*
IL-6	8,11±0,42	39,45±1,36	33,47±0,98***
TGF-β	55,93±2,78	206,40±4,39	184,28±2,87***

Note: * - reliable compared to the initial data of this group (* - P<0.05, ** - P<0.01,*** - P<0.001), ^ - unreliable compared to the initial data of this group *(^ - P>0,05)*

It should be noted that such serum levels of CRP and Lac in all groups of patients, although they decreased, however, these values were unreliable and were not close to the control ones, therefore these indicators were not included in the tables.

According to the results of immunological studies, a positive trend has been established in all the studied indicators. Thus, a significantly significant increase in complement proteins was revealed in the 1st group of patients with AP C3 (P<0.05) and C5 (P<0.001), however, in the 2nd group these indicators were unreliably increased (P>0.05). It is important to note that after the relief of the inflammatory process, with the help of immunomodulation with Roncoleukin® , a significantly increasing synthesis of IL-2 in the blood serum was established in the 1st group of patients with abortive course of AP (IL-2 - P<0.01), but it should be noted that the basic treatment also contributed to the insignificant synthesis of this mediator of the immune response (IL-2 - P<0.05). It was also found that the serum concentrations of such indicators as IL-1β, IL-6, and TGF-β were significantly reduced in both groups (P<0.01 - P<0.001) (Table 2.), which means that compliance with the protocol of treatment of patients with mild severity of AP in the abortive course of alcoholic and non-alcoholic genesis can positively affect the course of the disease. As mentioned above, in addition to patients with mild AP severity, in the 1st and 2nd groups of AP with abortive course, according to the analysis of anamnestic data, patients with moderate severity were identified.

Table 3. Methods of treatment of patients with moderate severity of AP in groups with abortive course

	Conservative treatment	Cholecystectomy	Laparoscopy (diagnostic)	Total
1st group	8 (19,5%)	7 (17,1%)	3 (7,3%)	18 (43,9%)
2nd group	4 (12,1%)	8 (24,2%)	4 (12,1%)	16 (48,4%)
Total	12	15	7	34

According to the protocol for the management of patients with AP, the main type of treatment is conservative therapy. The applied basic treatment complex for patients with mild to moderate AP was supplemented by specialized therapeutic therapy. It should be noted that the effectiveness of the specialized treatment complex was maximized at the early start of treatment (the first 2 hours from the onset of the disease). Upon admission of patients with moderate AP, after excluding diagnostic errors, they were hospitalized in the intensive care unit. In the absence of organ failure and disease progression during the day, patients with moderate AP were transferred to the surgical department. If patients with moderate AP in the surgical department showed signs of organ dysfunction or insufficiency, which indicates the progression of the disease, they were transferred back to the intensive care unit. Specialized treatment: Inhibition of pancreatic secretion. The optimal period is the first three days of the disease. A) antisecretory therapy: Sandostatin 100 mcg 3 times a day subcutaneously (the daily dose can reach up to 1200mcg, depending on the severity and prognosis of the disease); Omeprazole 40 mg 2 times a day intravenously; Reserve drugs – 5-fluorouracil (5% - 5ml intravenously) and kvamatel 40 mg 2 times a day intravenous day. B) anti-enzyme therapy: A counter-dose of at least 50,000 units / day. intravenously; or Gordox of at least 500,000 units/ day. intravenously. C) active rheological therapy. Infusion therapy in total of at least 40 ml of appropriate infusion agents per 1 kg of body weight with increased diuresis in the presence of organ dysfunction. The ratio of colloidal and crystalloid solutions was calculated as 1:4. D) antioxidant and antihypoxant therapy. The evacuation of toxic exudates was carried out according to indications. In case of enzymatic peritonitis, sanation laparoscopy was performed. In the presence of exudate, percutaneous drainage of the abdominal cavity under ultrasound guidance or laparocentesis was performed. E) conducting antibacterial therapy. Pefloxacin 400 mg 2 times a day intravenously in combination with metronidazole 500 mg 3 times a day

intravenously; With signs of secondary infection: cefaperazone / sulbactam, cefepim, imiperem, meropenem.

Immunomodulatory therapy. It is known that during surgical interventions, changes occur in all components of the immune system: cellular, humoral links of immunity and the phagocytic process, which contributes to the development of postoperative complications. In this regard, the problem of immunocorrection is relevant in surgical practice and can be used both for the prevention and treatment of postoperative complications.

During the study of the immune status in all groups of patients with different genesis of AP, a deficiency in the synthesis of IL-2, which is one of the key regulatory cytokines of the immune response, was revealed, and an informed decision was made to use Roncoleukin® (Roncoleukin).

Since a single protocol for the management of patients with a certain degree of severity of AP was used for treatment, including surgical measures for all patients, immunocorrection in complex therapy was applied to patients of group 1, and patients of group 2 received traditional treatment according to standards.

Recombinant interleukin-2 (rIL-2), a structural and functional analog of endogenous interleukin-2 (IL-2). IL-2 is produced by a subpopulation of T lymphocytes (T helper cells I) in response to antigenic stimulation. Synthesized IL-2 affects T-lymphocytes, enhancing their proliferation and subsequent synthesis of IL-2.

The biological effects of IL-2 are mediated by its binding to specific receptors present on various cellular targets. IL-2 has a direct effect on the growth, differentiation and activation of T and B lymphocytes, monocytes, macrophages, oligodendroglial cells, Langerhans cells. The development of cytolytic activity of natural killers and cytotoxic T-lymphocytes depends on its presence. IL-2 causes the formation of lymphokine-activated killers and activates tumor-infiltrating cells. The expansion of the spectrum of the lysing action of effector cells causes the elimination of a variety of pathogenic microorganisms, infected and malignized cells, which provides immune protection against tumor cells, as well as pathogens of viral, bacterial and fungal infections.

Immunomodulation consisted in the use of Roncoleukin® as part of complex therapy (two subcutaneous or intravenous injections) at 250 00 IU (with a body weight of less than 70 kg) - 500 000 IU (with a body weight of more than 70 kg) with an interval of 2-3 days. Immunotherapy with Roncoleukin® was performed after completion of surgical interventions aimed at eliminating the life-threatening consequences of the underlying disease, sanitation and adequate drainage of the infectious focus.

In this study, we performed diagnostic laparoscopy on all patients with moderate severity. The use of this method is explained by the fact that the importance of timely diagnostic laparoscopy in AP can be justified by the following factors: Accurate diagnosis - the ability to examine the abdominal cavity and pancreas directly, which allows you to clarify the diagnosis and determine the degree of lesion. Determining the cause - helps to identify the cause of acute pancreatitis, such as gallstones, trauma or other abnormalities, which is important for proper treatment planning. Assessment of the degree of tissue damage - provides information about the degree of inflammation, the presence of gangrene or infected areas, which is important for determining the severity of the disease. Making decisions about surgical intervention - detected complications such as purulent processes, pseudocysts or necrotic areas of the pancreas, laparoscopy can be a decisive moment for deciding on an emergency surgical intervention. Treatment and drainage - used for surgical treatment of complications of acute pancreatitis, including drainage of pseudocysts, removal of necrotic tissues and other surgical procedures. Minimal invasiveness is associated with less trauma and a faster recovery postoperative period, which may be important in the case of acute pathology.

According to the measures carried out and the tasks set, we conducted a comparative analysis of the immunological parameters of patients in the 1st group with immunocorrective complex therapy and the 2nd group of patients with moderate severity with abortive course of non-alcoholic and alcoholic origin. The results are shown below in the table 4.

It is important to note that the clinical condition after diagnostic laparoscopy, and in some patients and cholecystectomy, according to ultrasound data, pancreatic edema abruptly decreased in patients with AP of both groups, as well as fluid accumulations that were detected in some began to resolve, and most of the patients did not need repeated drainage.

A comparative analysis of immunological data in the 1st group of patients with AP who received conservative treatment + Roncoleukin found significant changes in serum concentrations of the studied parameters. Thus, a significant increase in the studied complement proteins C3 ($P<0.05$), C5 ($P<0.05$), IL-2 ($P<0.001$), as well as a decrease in IL-1β ($P<0.001$), IL-6 ($P<0.001$), TGF-β ($P<0.001$) was revealed (Table 4.).

When comparing the immunological parameters of the 2nd group of patients with AP who received conservative treatment without the use of immunocorrection, I found significantly significant changes in serum concentrations of the studied parameters, such as IL-6 ($P<0.01$), TGF-β ($P<0.01$). However, in such indicators as C3 and C5 complement components, IL-2, IL-1β, no significant changes were found ($P>0.05$) (Table 4.).

Comparative analysis of immunological parameters in the 1st group of patients with AP, after diagnostic laparoscopy, significant changes in the serum content of the studied parameters were found in patients receiving complex therapy + Roncoleukin. Thus, a significant increase in complement components C3 and C5 ($P<0.05$), IL-2 ($P<0.01$), as well as a significant decrease in IL-1β ($P<0.001$), IL-6 ($P<0.01$), TGF-β ($P<0.001$) was revealed (Table 4.).

Table 4. Immunological parameters in groups 1 and 2 of patients with moderate severity and abortive course

Indicator	Cont. group	Group 1 (7 days after the start of treatment + Roncoleukin)			
		Before treatment	Conservative treatment	Cholecystectomy	Laparoscopy (diagnosis.)
C3	8,33±0,36	7,02±0,29	7,81±0,27*	7,69±0,12*	7,69±0,15*
C5	12,31±0,54	10,53±0,25	11,54±0,42*	11,27±0,15*	11,37±0,32*
IL-1β	17,10±0,91	61,99±1,87	49,87±1,01***	54,34±0,88***	52,44±0,47***
IL-2	12,27±0,44	10,74±0,36	11,84±0,27***	10,91±0,23***	11,64±0,32**
IL-6	8,11±0,42	41,51±1,29	35,21±0,87***	38,01±0,39**	37,52±0,51**
TGF-β	55,93±2,78	178,68±5,10	135,02±2,03***	152,41±2,17***	143,61±1,91***
Group 2 (7 days after the start of treatment + without immunotherapy)					
C3	8,33±0,36	7,12±0,42	7,52±0,29^	7,48±0,22^	7,53±0,32^
C5	12,31±0,54	9,69±0,55	11,51±0,19^	10,79±0,31^	10,69±0,33^
IL-1β	17,10±0,91	66,17±2,44	62,31±1,02^	61,20±0,97^	62,04±0,44^
IL-2	12,27±0,44	9,16±0,39	9,87±0,19^	9,62±0,23^	9,81±0,16^
IL-6	8,11±0,42	39,45±1,36	35,84±0,33**	34,51±0,76**	33,04±0,26***
TGF-β	55,93±2,78	206,40±4,39	172,05±1,23**	184,30±1,95***	191,12±1,08**

Note: * - reliable compared to the initial data of this group (* - P<0.05, ** - P<0.01,*** - P<0.001), ^ - unreliable compared to the initial data of this group (^ -*P>0,05)*

Table 5. Methods of treatment of patients with moderate severity of AP in groups with progressive course

	Cholecystectomy (cholecystolithiasis /choledocholithiasis)	Laparoscopy (diagnosis-and I am) (acute gid.accumulated)	Laparotomy	Total
3rd group	11 (44%)	8 (32%)	2 (8%)	21 (84%)
The 4th group	7 (33,4%)	9 (42,8%)	2 (9,5%)	18 (85,7%)
Total	18	17	4	38

A comparative analysis of immunological parameters in the 2nd group of patients with AP, after diagnostic laparoscopy, in patients receiving postoperative standard treatment found that the serum content of the studied parameters was significant only IL-6 (P<0.01), TGF-β (P<0.01). Also, an unreliable increase in serum levels of C3 and C5 complement components, IL-2, IL-1β (P>0.05) was revealed (Table 4.).

A comparative study of immune parameters in the 1st group of patients with AP, after cholecystectomy, who received complex therapy + Roncoleukin revealed that the studied parameters of nonspecific immunity were unreliably elevated, and the cytokine status had significant dynamic changes. Thus, the indices of complement components C3 (P>0.05), C5 (P>0.05), as well as IL-1β (P<0.001), IL-6 (P<0.001), TGF-β (P<0.001), IL-2 (P<0.001) had significant changes (Table 4.).

An analysis of the studied immune parameters in the 2nd group of patients with AP, after cholecystectomy, who received standard therapy revealed that only IL-6 (P<0.01), TGF-β (P<0.01) had significant significance. However, in such indicators as C3 and C5 complement components, IL-2, IL-1β, no significant changes were found (P>0.05) (Table 4.).

We assume that the positive dynamics of immunological parameters when using immunomodulators in groups of patients with moderate severity of AP with an abortive course of non-alcoholic origin, in the context of AP, is explained by the fact that, firstly, the selected immunomodulator has an anti-inflammatory effect, which can help reduce the inflammatory process characteristic of AP and activate the Th response, secondly, the immunomodulator affects various components of the immune system, improving its functionality, and thirdly, probably, the selected immunomodulator can promote tissue regeneration, which may be especially important in the context of AP, where damage to the pancreas is a key aspect, fourth, an immunomodulator can help reduce the risk of complications associated with AP, such as infections, which can also have a positive effect on overall immunity.

The immune status of patients with progressive course of AP after therapy. Severe acute pancreatitis is associated with high morbidity and mortality due to the development of pancreatic and extrapancreonecrosis, their subsequent infection and multisystem organ failure (MPON).

According to the protocol for the management of patients with severe AP, the main type of treatment is intensive care. The applied basic treatment complex for severe AP is insufficiently effective and must be supplemented with a specialized treatment complex. The effectiveness of a specialized treatment complex is maximal at the early beginning of treatment (the first 12 hours from the onset of the disease).

All the admitted patients with severe AP were hospitalized in the intensive care unit. All therapeutic and diagnostic

measures of patients with severe AP were carried out in the conditions of the intensive care unit and intensive care unit, and after the relief of organ failure (if any) and stabilization of the condition, patients were transferred to the surgery department.

The specialized treatment carried out consisted in the fact that the treatment protocols of patients with (mild and moderate degrees) basic and conservative therapy in AP were supplemented with: Extracorporeal detoxification methods according to the indications: A) plasmapheresis (with replenishment of the volume of circulating fluid and in the absence of endotoxin shock) with plasma exchange (1-3 sessions after 24-48 hours, the average volume of plasma exfusion at least 1 liter); B) hemofiltration; C) the detoxification process in patients with severe AP was achieved by evacuation of peritoneal, and especially retroperitoneal exudate and flow-washing drainage of the abdominal cavity and retroperitoneal tissue with double-light drains. Nasogastric probing for decompression and, if possible, nasogastrointerstitial probing for early enteral support. Correction of hypovolemic disorders. It is advisable to perform an epidural blockade at the Th7-9 level (method of choice: constant infusion of 0.2% ropivacaine solution at a rate of 6-12 ml/hour). Conducting antibacterial therapy with broad-spectrum drugs. It is advisable to prescribe a disaggregated antithrombotic therapy. In patients with identified parapancreatic infiltration, therapy was carried out with conservative treatment. Laparotomy in the second week of surgery was performed only when surgical complications (destructive cholecystitis, gastrointestinal bleeding, acute intestinal obstruction, etc.) were detected, which cannot be eliminated by minimally invasive technologies.

A further step in the composition of the treatment complex included: Continuation of basic infusion-transfusion therapy aimed at replenishing water-electrolyte, energy and protein losses according to indications. Therapeutic nutrition: table 5 for moderate AP; nutritional support (oral, enteral or parenteral) for severe AP. Systemic antibiotic prophylaxis (cephalosporins of III-IV generations or fluoroquinolones of II-III generations in combination with metronidazole, reserve drugs - carbapenems). Immunotherapy (with correction of cellular and humoral immunity). Cytokine therapy (Roncoleukin) in a dose 250 000 – 1 000 000 IU until the indicator is restored (on average 2-5 injections).

As in other groups with abortive course of AP, in groups with progressive course of AP of non-alcoholic and alcoholic genesis, a comparative analysis of the studied immunological parameters of patients was carried out. The results are shown in the table below 6.

The obtained data from immunological studies allow us to draw a parallel, according to which the clinical condition of patients undergoing diagnostic laparoscopy, after identified and performed cholecystectomy, as well as drainage with detected fluid, according to ultrasound data, pain disappeared in patients with AP of both groups, swelling of the pancreas subsided and positive dynamics was observed.

A comparative study of immune parameters in the 3rd group of patients with AP, after "closed" drainage, who received complex therapy with the use of an immunomodulator revealed that the studied parameters of nonspecific immunity were unreliably elevated, and the cytokine status had significant dynamic changes. Thus, the indices of complement components C3 (P>0.01), C5 (P>0.001), as well as IL-2 (P<0.001) tended to increase, while there was a significant decrease in IL-1β (P<0.001), IL-6 (P<0.001), TGF-β (P<0.01) (Table 6.).

Table 6. Immunological parameters in groups 3 and 4 of patients with moderate severity and progressive course

Indicator	Counter. group	Group 3 (7 days after the start of treatment + Roncoleukin)			
		Before treatment	Cholecystectomy	Laparoscopy (diagnosis.)	Laparotomy
C3	8,33±0,36	5,92±0,29	7,67±0,21***	7,11±0,17**	6,24±0,05^
C5	12,31±0,54	7,46±0,51	10,23±0,32***	9,97±0,25***	7,63±0,12^
IL-1β	17,10±0,91	94,56±3,57	72,32±2,14***	79,14±1,31***	89,44±0,17^
IL-2	12,27±0,44	5,64±0,33	9,35±0,33***	8,91±0,23***	7,44±0,22***
IL-6	8,11±0,42	64,84±2,35	47,21±0,37***	53,15±0,29***	57,14±0,14**
TGF-β	55,93±2,78	233,01±9,89	173,17±3,42***	195,24±3,07**	212,17±3,93*
Group 4 (7 days after the start of treatment + without immunocorrection)					
C3	8,33±0,36	5,31±0,30	6,52±0,12*	5,97±0,16^	5,52±0,12^
C5	12,31±0,54	6,99±0,24	7,32±0,21^	7,14±0,33^	7,09±0,05^
IL-1β	17,10±0,91	85,86±2,73	80,11±1,09^	81,03±0,34^	83,21±0,32^
IL-2	12,27±0,44	5,14±0,20	5,66±0,17^	5,54±0,31^	5,69±0,26^
IL-6	8,11±0,42	65,41±2,66	58,25±0,26*	59,01±0,44*	62,33±0,17^
TGF-β	55,93±2,78	242,37±8,89	212,51±2,04**	231,03±1,65^	229,25±0,78^

Note: * - reliable compared to the initial data of this group (* - P<0.05, ** - P<0.01,*** - P<0.001), ^ - unreliable compared to the initial data of this group *(^ - P>0,05)*

The analysis of the studied immune parameters in the 4th group of patients with AP after laparoscopy who received standard therapy without immunomodulation revealed relatively significant changes only in serum levels of IL-6 (P<0.05), and indicators of nonspecific protection, in the form of C3 and C5 complement components, as well as the cytokine link - IL-1ß, Although IL-2 and TGF-β tended to increase, they were insignificant (P>0.05) (Table 6.).

A comparative analysis of immunological data in the 3rd group of patients with AP who received complex treatment with Roncoleukin after cholecystectomy established significant changes in serum concentrations of the studied parameters. Thus, there was a significant increase in the studied complement components C3, C5, IL-2 (P<0.001), as well as a decrease in IL-1β, IL-6, TGF-β (P<0.001) (Table 6.).

When comparing the immunological parameters of the 4th group of patients with AP after cholecystectomy who received standard treatment with moderate progressive course without the use of immunocorrection, it was found that significantly significant changes in serum concentrations of the studied parameters were observed only with the complement component C3 (P<0.05), IL-6 (P<0.05), TGF-β (P<0.01). It was also revealed that such indicators as C5 of the complement component, IL-1β, IL-2 were unreliable, which indicates the continuation of the activity of the inflammatory process (Table 6.).

It is important to note that in the examined groups of patients with moderate severity and progressive course of alcoholic and non-alcoholic genesis, only 4 patients (in the 3rd group - 2 (8%) and 4th group – 2 (9.5%)) underwent laparotomy, due to the detection of infected pancreatic necrosis, complicated the development of peripancreatic infiltration. After the necessary postoperative complex therapeutic measures were carried out, the immunological results of some indicators in the 3rd group of patients showed relatively positive dynamics, however, in patients of the 4th group, where immunomodulatory therapy was not used, the data were insignificant and unreliable.

Thus, a comparative analysis of immunological parameters in the 3rd group of patients with progressive AP of non-alcoholic origin, after laparotomy, who received complex therapy with Roncoleukin, established significant changes in the serum content of the studied parameters. Thus, a relatively insignificant decrease in IL-6 (P<0.01), TGF-β (P<0.01) was revealed, however, the serum levels of C3 and C5 complement components, IL-1β were unreliable (P>0.05) (Table 6.)

According to a comparative analysis of immunological parameters in the 4th group of patients with a progressive course of alcoholic genesis, after laparotomy, who received postoperative standard treatment without immunomodulation, it was found that all studied immunological parameters were unreliably reduced (C3, C5, IL-1β, IL-2, IL-6, TGF-β (P>0.05)) (Table 6.).

It should be noted that patients with severe AP in groups 3 and 4 were also identified, which is characterized by the presence of either infected pancreonecrosis (purulent necrotic parapancreatitis), or/and the development of persistent organ failure (more than 48 hours). Patients with AP were urgently operated on, as a result of which it was found that among patients with severe AP of the 3rd and 4th groups there were patients with fatty and hemorrhagic PN (Table 7.).

Table 7. The number of patients in groups with progressive course of AP with severe severity of the disease

The 3rd group (n=25)		**The 4th group (n=21)**	
Severe grade 4 (16%)		**Severe degree - 3 (14,3%)**	
Fatty PN	Hemorrhages PN	Fatty PN	Hemorrhages PN
3 (12%)	1 (4%)	2 (9,5%)	1 (4,8%)

Since the identified patients were included in the exclusion criteria, these patients received appropriate emergency medical care, however, their studied parameters were not included in the present study.

Thus, the results obtained by us of the application of immunocorrection using Roncoleukin indicate a clear immunomodulatory response to the identified imbalance not only in the cytokine link, but also in non-specific factors of body protection. It was found that the use of recombinant IL-2 has a direct effect on the activation and development of T and B lymphocytes, activates monocytes and macrophages, promotes the development of cytotoxic T lymphocytes and natural killers. These effects and mechanisms of action of IL-2 make it an important component of the immune response. In the context of AP of various origins, its use can be considered as an attempt to modulate the immune response to fight infection and maintain immune protection. The study of the relationship and prognostic effectiveness of the studied genetic marker with the development of AP showed: Studies of genetic markers, such as the polymorphic variant of the IL-6 gene rs1800795 (-174G>C), in the context of AP, allow us to assess possible genetic factors affecting the development and course of the disease. The relationship and prognostic effectiveness of such studies can provide information about the risk, severity and prognosis of AP in certain groups of patients.

As mentioned above, the polymorphism of the IL-6 -174G>C gene refers to one of the genetic variants of this gene. IL-6 is a cytokine that plays an important role in inflammatory processes and immune regulation. Different variants of genetic polymorphisms can affect the level and activity of IL-6 in the body.

According to the literature, a number of studies conducted to assess the relationship between polymorphisms of the IL-6 gene and AP suggest that certain genetic variants may be associated with an increased risk of AP or its severity.

However, despite the studies conducted, there are no specific genetic markers that could unambiguously predict the development of AP and its course. Work is continuing in the field of molecular genetic studies of AP, and future results may provide more accurate information about the role of genetic markers, including IL-6 -174G/C, in this disease.

As is known, relative risk, or risk ratio, is the ratio of the frequency of outcomes among those exposed and not exposed to the studied factor. The relative risk does not contain information about the magnitude of the absolute risk (morbidity). This statistical measure allows you to assess the strength of the connection and determine how significant the impact of the studied factor is on the likelihood of an outcome, and also allows you to take appropriate measures to prevent or manage risk.

To determine the relationship of the studied genetic marker, calculations of the relative risk and odds ratio for the development of AP in the studied polymorphic variant of the IL-6 rs1800795 gene were obtained, which are shown below in Table 8.

Table 8. Calculation of relative risk and relative chance with 95% CI in AP in the examined patients

Indicator	**Alleles** (G)	**Genotypes** (G/G)
Absolute risk in the main group (EER)	0.717	0.542
Absolute risk in the counter. group (CER)	0.588	0.350
RR	**1.220**	**1.548**
Standard error of relative risk (S)	0.078	0.174
95% CI	1.048-1.420	1.100-2.176
Se	0.647	0.699
Sp	0.493	0.486
The chance to find a risk factor in the main group	**2.529**	**1.182**
A chance to find a risk factor in the counter. the group	1.424	0.538
OR	**1.776**	**2.195**
The standard error of the odds ratio (S)	0.215	0.298
is 95% CI	1.165-2.708	1.225-3.932
χ^2 (p)	**6.621 (0,011)**	**6.339 (0,012)**

Note: χ2- adjusted by Yates, SE- sensitivity, Sp - specificity, RR -relative risk.

According to the calculations in Table 9., an analysis of the contribution to the development of the relative risk of the G allele of polymorphism -174G/C in the IL-6 gene revealed that the risk of developing AP was RR =1.220, with an average Se =0.647 and Sp=0.493, whereas the relative risk of developing a homozygous genotype G/G was RR =1.548 with a good Se =0.699 and Sp=0.486.

It was also found that the chance to find a risk factor in the general AP group by the G allele of polymorphism -174G/C in the IL-6 gene was 2.529, whereas the chance to find a risk factor in the control group was 1.7 times less, with OR =1.776 (χ2 =6.621, p<0.011) (Table.9.).

An assessment of the chance to find a risk factor in the general group of patients with homozygous genotype G/G polymorphism -174G/C in the IL-6 gene revealed that the risk factor among patients with carriers of the wild genotype was 1.182, while the control indicator was 0.538 at OR =2.195 (χ2 =6.339, p<0.012) (Table 9.).

The prognostic effectiveness of the studied genetic markers may vary depending on the specific conditions of the study, the characteristics of the patients and the methods used. Genetic factors usually interact with the environment, including lifestyle factors and other genetic variants. Based on the above, the prognostic efficacy (AUC) and the relationship of the studied polymorphic variant 174G/C in the IL-6 gene were studied. The calculations obtained are shown in the table below 9.

From the presented data on the evaluation of the prognostic efficacy (AUC) of the G allele of polymorphism -174G/C in the IL-6 gene, it can be concluded that the prognostic effectiveness of this locus classifier is average in order to assess the prognostic effectiveness of the trait as an independent marker of the risk of developing AP and its various clinical forms. In the general group of patients with AP, the prognostic efficacy for the G allele of this polymorphism was AUC=0.57 with a high SE=0.72 and a low SP=0.41 (OR =1.78; 95%CI: 1.17-2.71; p=0.05), which suggests the relationship and role of the G allele with the risk of AP (Table 9.).

Table 9. Prognostic efficacy of the studied genetic markers (G174C polymorphism in the IL6 gene)

Factor	Groups	SE	SP	AUC	OR	95%CI	p
G	Main group // Control group	0,72	0,41	0,57	1,78	1,17 - 2,71	0,05

Factor	Groups	SE	SP	AUC	OR	95%CI	p
C	Main group // Control group	0,59	0,28	0,44	0,56	0,37 - 0,86	0,49

Factor	Groups	SE	SP	AUC	OR	95%CI	p
G/G	Main group // Control group	0,54	0,65	0,6	2,19	1,23 - 3,9	0,05

Factor	Groups	SE	SP	AUC	OR	95%CI	p
G/C	Main group // Control group	0,35	0,51	0,43	0,57	0,32 - 1,01	0,66

Factor	Groups	SE	SP	AUC	OR	95%CI	p
C/C	Main group // Control group	0,11	0,84	0,48	0,63	0,28 - 1,42	0,61

It should be noted that the prognostic efficacy of allelic polymorphism -174G/C in the IL-6 gene in the general group of patients with AP in the variant with the C allele was unsatisfactory, as well as insignificant and amounted to AUC=0.44 with an average SE=0.59 and a low SP=0.28 (OR =0.56; 95%CI: 0.37-0.86; p>0.5), which does not imply the relationship and contribution of the C allele with the risk of developing AP (Table 9.).

From the presented data on the evaluation of the prognostic efficacy (AUC) of the G allele of polymorphism -174G/C in the IL-6 gene, it can be concluded that the prognostic effectiveness of this locus classifier is average in order to assess the prognostic effectiveness of the trait as an independent marker of the risk of developing AP and its various clinical forms. In the general group of patients with AP, the prognostic efficacy for the G allele of this polymorphism was AUC=0.57 with a high SE=0.72 and a low SP=0.41 (OR =1.78; 95%CI: 1.17-2.71; p<0.05), which suggests the relationship and role of the G allele with the risk of developing AP (Table 9.).

An analysis of the AUC data of the homozygous genotype G/G of the polymorphic variant -174G/C in the IL-6 gene found that the prognostic efficacy of this genotype is average in order to assess the prognostic efficacy of the trait as an independent marker of the risk of developing AP and its various clinical forms. Thus, in the general group of patients with AP, the prognostic efficacy for the G/G genotype of this polymorphism was AUC=0.6 with an average SE=0.54 and an average SP=0.65 (OR =2.19; 95%CI: 1.23-3.9; p<0.05), which also suggests a probable relationship and role of the G/G genotype with the risk of developing AP (Table 9.).

The AUC assessment of the heterozygous genotype G/C polymorphism -174G/C in the IL-6 gene found that the prognostic effectiveness of this classifier genotype was unsatisfactory, insignificant and amounted to AUC=0.43 with a low SE=0.35 and an average SP=0.51 (OR =0.57; 95% CI: 0.32-1.01; p>0.5), which does not imply the relationship and contribution of heterozygous G/C with the risk of developing AP (Table 9.).

The study of the AUC of the homozygous C/C polymorphism genotype -174G/C in the IL-6 gene found that the prognostic effectiveness of this classifier genotype was unsatisfactory, insignificant and amounted to AUC=0.48 with a low SE=0.11 and a high SP=0.84 (OR =0.63; 95% CI: 0.28-1.42; p>0.5), which does not imply the relationship and contribution of mutant C/C with the risk of developing AP.

Thus, the obtained results of calculations of AUC and RR (OR) allow us to assume that the established relative risk is greater than 1 and the prognostic effectiveness in carrying the genotype G/G polymorphism -174G/C in the IL-6 gene indicates an increase in the probability of developing the severity of the course of AP in the group with exposure to the studied polymorphic variant compared to with the control group. It was also found that the relative risk is less than 1 and the prognostic effectiveness in the case of heterozygous G/C and homozygous mutant C/C carriers indicates a decrease in the probability of developing AP in the group with exposure to the studied polymorphism compared with the control group.

4. Conclusions

1. The use of immunocorrection using Roncoleukin indicates a clear immunomodulatory response in the presence of an imbalance not only in the cytokine link, but also in non-specific factors of body protection.
2. It has been established that the use of recombinant IL-2 has a direct effect on the activation and development of T and B lymphocytes, activates monocytes and macrophages, promotes the development of cytotoxic T lymphocytes and natural killers. These effects and mechanisms of action of IL-2 make it an important component of the immune response.
3. The obtained results of calculations of AUC and RR (OR) suggest that the established relative risk is greater than 1 and the prognostic effectiveness in carrying the genotype G/G polymorphism -174G/C in the IL-6 gene indicates an increase in the probability of developing the severity of the course of AP in the group with exposure to the studied polymorphic variant compared with the group control.

It was found that the relative risk is less than 1 and the prognostic effectiveness in the case of heterozygous G/C and homozygous mutant C/C carriers indicates a decrease in the probability of developing AP in the group with exposure to the studied polymorphism compared with the control group.

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