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EFFECT OF INTRAMYOCARDIAL ALLOGENIC BIOMATERIAL INJECTION ON ANGIOGENESIS AND POSTISCHEMIC SCAR REMODELING IN RATS

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Scar smoothing out, angiogenesis stimulation and cardiomyogenesis in myocardial infarction still remain pressing issues despite the variety of existing methods. One of the ways to correct them is intramyocardial implantation of an alloplant biomaterial (ABM) suspension. ABM serves as an inhibitor of fibroneogenesis in various tissues with chronic inflammatory processes. No studies have been carried out with regards to acute myocardial infarction. **Objective:** to assess the dynamics of the number of bFGF-1$^+$ cells and CD68 macrophages, the degree of angiogenesis amidst the use of ABM in the formation of postinfarction scar in the experiment. **Materials and methods.** Experimental studies were performed on 100 male Wistar rats weighing 0.18–0.25 kg. Coronary artery ligation was performed on all animals. In the experimental group, the ABM suspension (12 mg) was injected intramyocardially. We used histological, electron microscopic, immunohistochemical (CD68, bFGF-1), morphometric and statistical research methods. Hearts were procured at day 3, 7, 14, 30, and 45. **Results.** The use of an allogeneic biomaterial immediately after coronary artery stenosis could reduce the area of cicatricial myocardial degeneration by two fold by accelerating inflammatory response and the onset of early proliferative phase. In the reactive zone after ABM implantation, macrophage myocardial infiltration significantly decreased in comparison to the control group. The use of ABM ensures significant predominance of bFGF-1$^+$ cells in the initial period of inflammation (3–14 days). Subsequently (14–45 days), inflammatory cytokine expression became several times less, which corresponded to biodegradation and resorption of the biomaterial. In the control group, during the acute phase of inflammation (3–14 days), bFGF-1$^+$ cells were low in number. Subsequently (14–45 days), cytokine expression increased significantly, causing rapid accumulation of collagen fibers and scarring. In myocardial regeneration after a heart attack in the experiment, ABM stimulated angiogenesis, whose level was three times higher than in the control group. It was noted that ABM serves as a regulator of the neofibrillogenesis-fibroclasia balance in tissue. **Conclusion.** Macrophage migration inhibition and suppression of pro-inflammatory orientation of macrophages should be indicated as one of the directions of therapeutic correction strategy for ischemic myocardial injuries. Alloplant biomaterial used in the acute phase of myocardial inflammation can serve as such alternative.

Keywords: myocardium, allogeneic biomaterial, regeneration, bFGF, macrophages.

INTRODUCTION

The problem of scar smoothing out, stimulation of angiogenesis and cardiomyogenesis in myocardial infarction remains relevant to this day. Such methods of regenerative medicine as gene and cell technologies, along with their undeniable advantages, have certain disadvantages. The introduction of gene constructs into the myocardium leads to angiogenesis and scar limitation. However, the introduction of the plasmid vector does not achieve an adequate degree of cardiomyocyte transfection (no more than 10%). The frequent development of immune responses to viral proteins, fragility in tissues limit their widespread use [1].

The use of cellular products also does not have a sufficiently high efficiency, they are difficult to manufacture, carry the risk of infection, teratogenicity, etc. Even if all biological safety requirements are met, cellular products do not integrate into the recipient's tissues, but have only a paracrine effect [2]. Also, great attention is paid to the use of various kinds of biomaterials for the regeneration of damaged tissues and organs. All the methods under consideration face one problem. Currently, there are no available and effective methods to combat excessive fibrosis during postischemic myocardial remodeling. It is known that biomaterials of the Alloplant® series serve as an inhibitor of fibroneogenesis [3]. They are developed at the Federal State Budgetary Institution "All-Russian Center for Eye and Plastic Surgery" of the Ministry of Health of the Russian Federation in Ufa and are manufactured in accordance with TU 42-2-537-87. Biodegra-

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dation products of the biomaterial are chemoattractants of M1 macrophages in the implantation zone. Thus, macrophages become direct participants in the phagocytosis of biomaterial, wound detritus, immune complexes, and excess collagen. In addition, macrophages exert a paracrine effect by releasing proinflammatory factors: TNFa, IL1, etc. Monokines, in turn, inhibit the expression of profibrogenic factors (bFGF-1, TGF-b1) and regulate the activation of fibroblastic cells [4]. These results of the study were obtained during the application of defects in the skeletal muscle, the wall of the uterus, in the correction of such chronic degenerative-inflammatory diseases as cirrhosis of the liver, periodontitis, stomach ulcers, skin burns, degeneration of the retina and optic nerve. It was found that allogeneic biomaterials in the process of replacement contribute to the neoangiogenesis of the forming regenerate [5, 6]. However, no studies have been conducted for acute myocardial infarction.

It is known that the main angiogenic factors are VEGF, TGFb, bFGF, etc. [7]. Moreover, according to some data, bFGF stimulates neovascularization to a greater extent than VEGF [8].

The purpose of the present study was to evaluate the role of macrophages and bFGF on postinfarction myocardial remodeling and vascularization in the experiment.

MATERIALS AND METHODS

For the regeneration of cardiac muscle tissue, a decellularized biomaterial (DCBM) was used, made of fibrous connective tissue formations and processed using the TU 42-2-537-87 technology. A prerequisite for its use is allogenicity; therefore, for this study, the biomaterial was made from rat tendons.

Experimental studies were carried out on 100 male Wistar rats weighing 0.18–0.25 kg. All animals were divided into 2 groups. In the control group (n = 50), myocardial infarction was modeled as follows: left-sided thoracotomy was performed under intramuscular anesthesia (zoletil solution) followed by ligation on *r. interventricularis paraconalis a. coronarii sin.* of the left ventricle. After the intervention, the wound was sutured in layers.

In the experimental group (n = 50), ligation of the artery was accompanied by the introduction of a DCBM suspension into the pool of the stenotic artery in a total amount of 12 mg. The dose was chosen at random. Before use under sterile conditions, a suspension of the biomaterial in physiological solution was prepared (100 mg of the biomaterial was suspended in 5 ml of physiological solution). Along the perimeter of the left ventricle, 5–6 intramyocardial injections of the suspension were made, 100 μl each. The total volume of the injected suspension was 600 μL. The particle size of the biomaterial was 50–80 μm for free passage through the injection needle. In the control group, 5 days later, 0.9% saline was administered in an adequate volume. The animals were kept under standard vivarium conditions.

The animals were removed from the experiment by insufflation of a lethal dose of ether vapor after 3, 7, 14, 30, 45 days. The studies were carried out in accordance with the rules of laboratory practice in the Russian Federation, in accordance with the rules adopted by the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (Strasburg, 1986), and in accordance with an approved written protocol in accordance with the investigator's standard operating procedures and guidelines on laboratory animals and alternative models in biomedical research [9]. For histological examination, the hearts were fixed in a 10% solution of neutral formalin, dehydrated in a series of alcohols of increasing concentration, and embedded in paraffin according to the standard method. Sections were prepared on a LEICA RM 2145 microtome (Germany), stained with hematoxylin and eosin, according to Van Gieson, according to Mallory. To determine the size of the postinfarction myocardial scar, each heart was cut across into 5 sectors. Scar area index (SAI) was measured on cross-sectional preparations of rat hearts stained according to Mallory, using the "ITEM" software as follows: the ratio of the scar area to the left ventricular wall area was multiplied by 100%.

For immunohistochemical studies, paraffin sections with a thickness of 4 μm were stained using a Leica Microsystems Bond™ immunohistostiner (Germany). The first antibodies used were CD 68, bFGF-1 at a dilution of 1:300 (Santa Cruz Biotechnology, USA). For unmasking, an indirect streptavidin-biotin detection system Leica BOND (Novocastra™, Germany) was used. The specificity of the reaction was evaluated by staining sections without the first antibodies. Positively stained cells were counted in 20 fields of view of each sample (n = 6) at ×400 magnification. The study and visualization of preparations were carried out using a light microscope Leica DMD 108 (Germany) with specialized software for managing settings and image capture.

For electron microscopic examination, 1–2 mm^3 pieces of the myocardium were used, fixed in a 2.5% glutaraldehyde solution prepared in a cacodylate buffer (pH 7.2–7.4) with additional fixation in a 1% OsO_4 solution in the same buffer. The material was dehydrated in alcohols of increasing concentration and poured into epon-812 according to the generally accepted method. On an EM UC 7 ultratome (Leica, Germany), semi-thin sections were prepared and stained with a solution of toluidine blue in a 2.5% solution of anhydrous soda. On these sections, we selected areas for electron microscopic examination. Ultrathin sections were contrasted with a 2% aqueous solution of uranyl acetate, lead citrate according to Reynolds and studied under a JEM-1011 transmission microscope (Jeol, Japan).

Analysis of SAI and the total area of capillary lumens (CLTA) data was carried out using nonparametric methods – one-way analysis of variance according to Kruskal–Wallis and comparison of uncorrelated data by the Mann–Whitney method [10]. The diagram was built using the Statistica 6.0 software.

RESULTS

As a result of the experiment (after 45 days), it was revealed that SAI in the control group was 26.65 ± 16.10%, and in the experimental group after DCBM 9.72 ± 1.08%. The multiplicity of intergroup differences was 2.74 times (Fig. 1).

The course of the inflammatory reaction after ischemia of cardiac muscle fibers in the experimental groups occurred in different ways. In the experimental group, at the initial stage of inflammation (3 days), signs of an early onset of the proliferative phase of inflammation and the formation of granulation tissue were revealed at the site of ischemically damaged cardiomyocytes. Thin collagen fibers, macrophage-fibroblastic infiltration, and mesenchymal cells were detected in the regenerate. Along with hemorrhagic impregnation, thin-walled hemocapillaries with a multi-vector orientation were determined. Particles of biomaterial infiltrated by poorly differentiated cells and macrophages were determined (Fig. 2).

In the control group, in place of the collapsing cardiomyocytes, a wide cell wall was formed, consisting of macrophages, lymphocytes, neutrophils, signs of rupture of blood vessels and diapedesis of erythrocytes in the interstitium of the myocardium were noted (Fig. 3).

In the control group in the ischemically altered cardiac muscle tissue in the reactive zone, the number of CD 68 macrophages also exceeded the values of the experimental group practically throughout the entire experiment. In the control and experimental groups, the tendency to rise and subsequent decline was generally highly significant (Chi-Square = 76.3, $p << 0.0001$ and Chi-Square = 45.2, $p << 0.0001$, respectively). The number of CD 68+ cells in the control group statistically significantly exceeded their number in the experimental group during the observation period of 3–14 days ($p < 0.003$ and less). In the period of 30–45 days in the control group, attenuation of myocardial remodeling and scar formation occurred, which caused a decrease in the number of macrophages in both groups ($p > 0.12$) and initiation of the healing stage (Fig. 4).

At studying bFGF-1^+ cells in the experimental and control groups, the number of these cells significantly depended on the beginning of the experiment ($\chi^2 = 49.8$, $p << 0.0001$ and $\chi^2 = 60.0$, $p << 0.0001$, respectively) and had certain differences. After 3 days, the range of variation in bFGF-1^+ cells in the experimental group equaled 38–55 (median 44). After 7 days, their number increased to 54–68 (median 61) ($p < 0.0001$). However, on the 14th day, the interindividual variation in the number of bFGF-1^+ cells increased sharply (22–72, median 60) and turned out to be statistically insignificant ($p >$

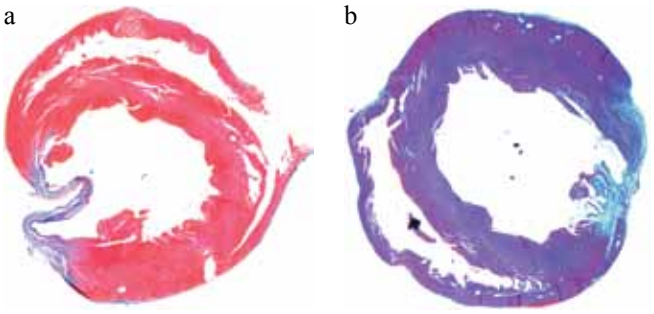

Fig. 1. Myocardial cross-section in 45 days: a – control group; b – experimental group. Mallory stain. ×40

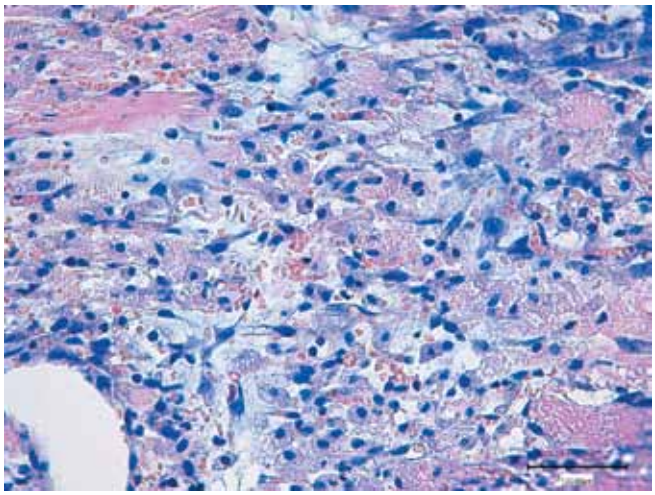

Fig. 2. Granulation tissue formation and infiltration by macrophages, mesenchymal cells, fibroblasts in rat myocardium 3 days after coronary occlusion and biomaterial insertion (experimental group). Stained with hematoxilin and eosin. ×400

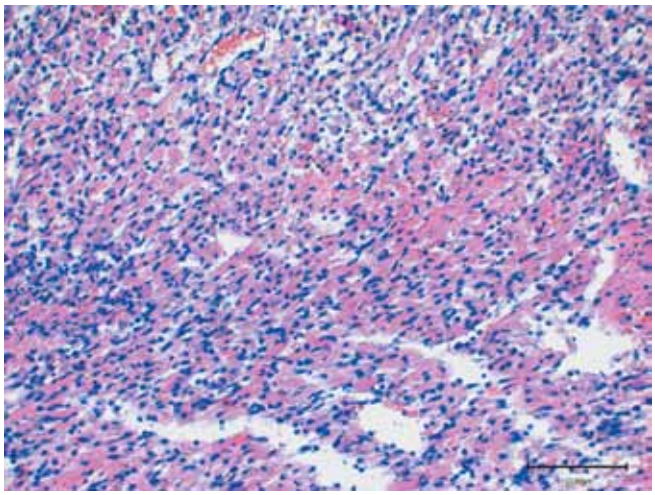

Fig. 3. Macrophage-lymphocytic cell wall in the zone of necrotically altered cardiomyocytes 3 days after coronary occlusion (control group). Stained with hematoxilin and eosin. ×200

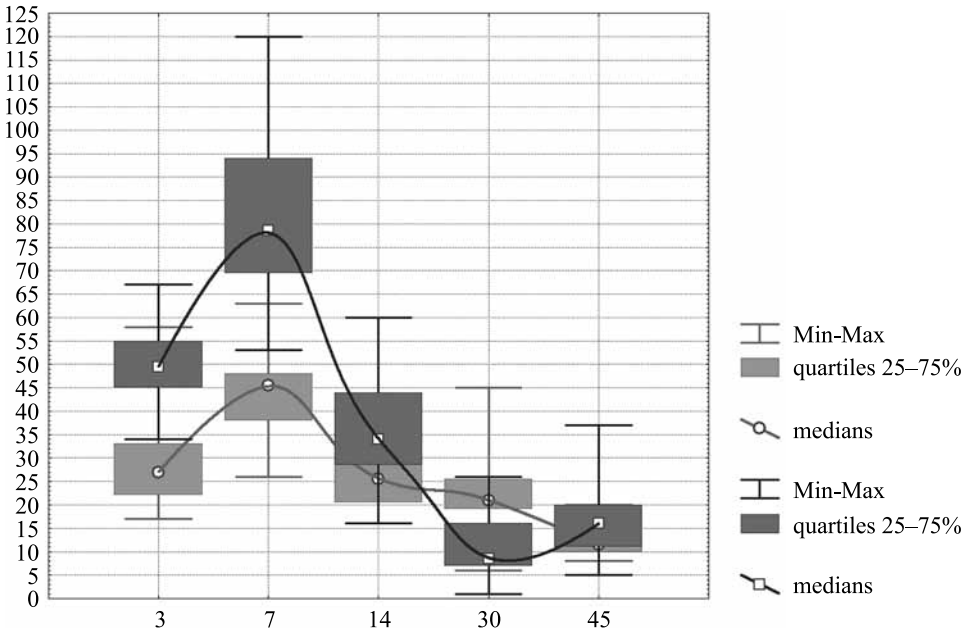

Fig. 4. The number of CD 68^+ in the myocardium of rats in the control group (blue graph) and after the insertion of the biomaterial (red graph). GDI – limits of confidence intervals for the average area values, ±CO – standard error of the average value

0.46). After 30 days, the number of bFGF-1^+ cells in the main group sharply decreased (9–16, median 11), and on the 45th day it slightly, statistically significantly ($p < 0.03$) decreased to the range of 4–16 cells (median 9).

In the control group, the expression with bFGF-1^+ cells was completely different. The number of bFGF-1^+ cells was minimal in the first week from the beginning of the experiment (5–15, median 10), on day 3, 10–19 cells (median 14). After 14–30 days, the number of bFGF-1^+ cells in the control group increased sharply – up to 80–109 cells (median 84) and 67–104 cells (median 101), respectively, but the difference was not significant ($p > 0.66$)… A statistically significant ($p < 0.0001$) decrease in the number of bFGF-1^+ cells to 54–96 (median 64) in this group occurred only by the 45th day. In the control group, after 14, 30, and 45 days, the intragroup random spread in the number of such cells sharply increased to 29, 37, and 41 cells, respectively. In the experimental group, in the period of 30–45 days relative to 14 days, the variation in the number of such cells, on the contrary, sharply decreased (Fig. 5).

The results of the analysis showed that the effect on CLTA of the reactive zone of the regenerate both the factor of group belonging of objects ("control", "experience") and the factor of time (days) ($\eta^2 = 15\%$, $F = 31$, $p << 0.0001$ and $\eta^2 = 14\%$, $F = 9$, $p << 0.0001$, respectively).

In the experimental group, CLTA decreased from 1432.2 ± 1179 μm^2 on the 3rd day to 577 ± 348 μm^2 on the 7th day ($p < 0.0003$). Thereafter, CLTA remained stable (611 ± 445.8 and 632.3 ± 406.6 μm^2 on the 14th and 30th days, respectively). In the control group, on the 3rd day after coronary occlusion, CLTA was significantly 3 times lower than in the experimental group (510.6 ± 537 μm^2). In the subsequent periods of observation, CLTA decreased, but this decrease was statistically significant ($p < 0.003$) only after 14 days (146 ± 97 μm^2), i. e., almost 3 times lower than on the third day. During all periods of observation, the CLTA of the reactive zone of the regenerate in the control group was significantly and statistically significantly lower than in the experimental group. The greatest difference was noted in the period of 3 days (Fig. 6).

After 14 days, in the perifocal zone of the experimental group, signs of resorption of collagen fibers were revealed (Fig. 7). In the myocardium in the perifocal zone, scattered short fragments of collagen fibers surrounded by rounded and large cells with an oval nucleus were detected (Fig. 7, a). Fibroclasts were found in the form of large oval cells with long outgrowths of cytolemma, forming phagocytic vacuoles. In the cytoplasm, channels of the granular endoplasmic reticulum, secondary vacuoles with fragments of striated collagen fibers, enclosed in the cytoplasm, were found. The nuclei were rounded with signs of functional activity, containing euchromatin (Fig. 7, b).

Thus, under conditions of DCBM application, signs of fibroclasia were found in the reactive zone of the myocardium, which could also affect the volume of the scar in the myocardium.

DISCUSSION

In the present study, a targeted approach was used and the pathomorphological processes of spontaneous myocardial healing were demonstrated after coronary artery ligation and under the influence of allogeneic bio-

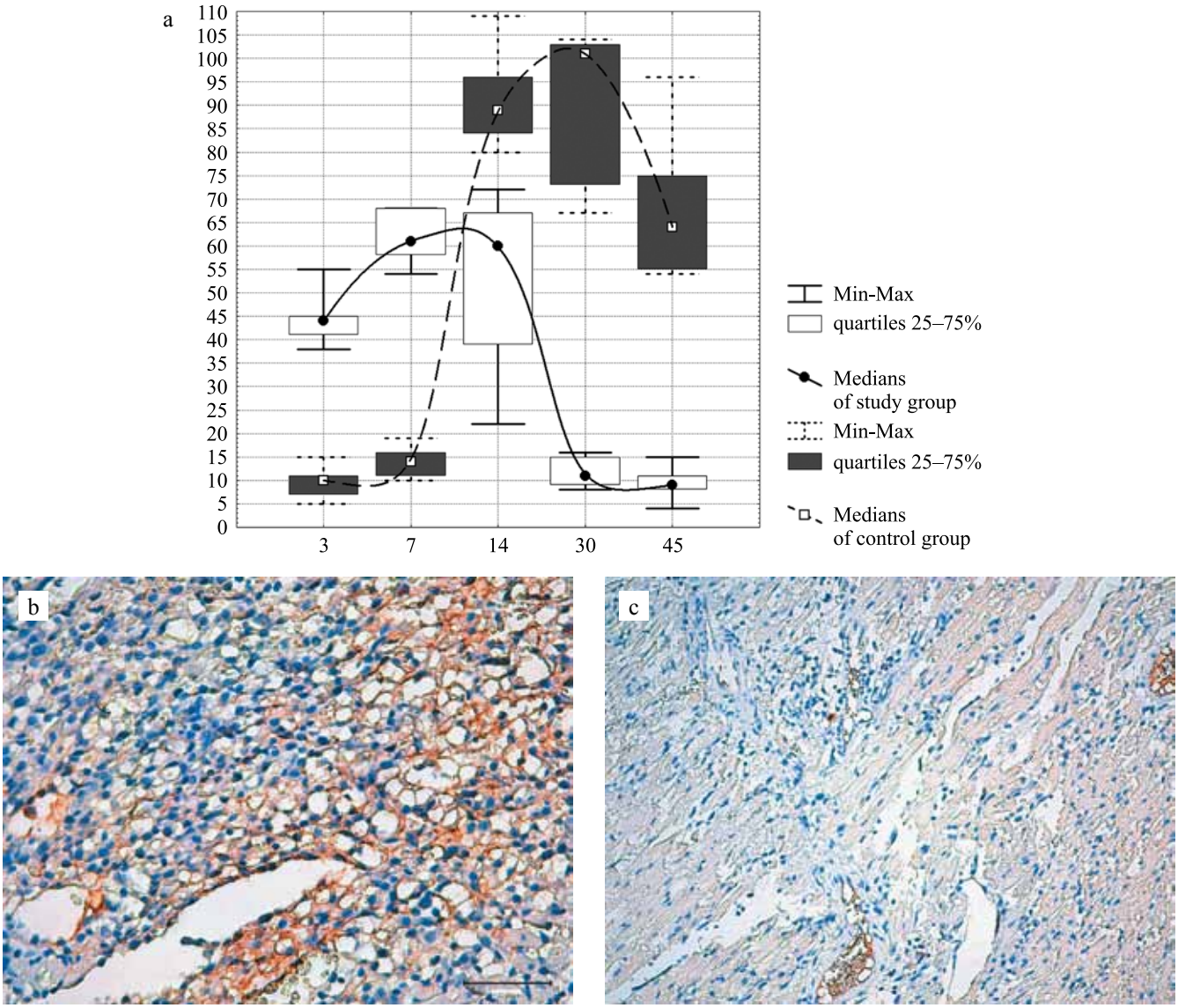

Fig. 5. The reaction of FGF-1$^+$ cells in the myocardium of rats: a – dynamics of the number of bFGF-1$^+$ cells in the experimental group (light graph) and in the control group (dark graph); b – expression of bFGF-1 in the experimental group after 7 days. ×400; c – expression of bFGF-1 in the control group after 7 days. Indirect immunoperoxidase method for detection of bFGF-1 stained by hematoxylin. ×200

material. DCBM implantation showed new strategically important mechanisms of the regenerative potential for the myocardium associated with cardioprotection: angiogenesis, inhibition of macrophages, fibroclasia. It was found that under the conditions of DCBM application at a dose of 12 mg, the scar area was reduced by more than 2 times.

After ligation of the coronary artery in the myocardium, pathomorphological changes associated with massive colliquation necrosis of cardiomyocytes occurred. The entire chronology of the phase change of the inflammatory response was traced. Exudative inflammation occurred within 3–14 days. In the period of 14–30 days, the proliferation phase began, and after 30–45 days, healing with scar formation began.

Three days after coronary occlusion and intramyocardial administration of DCBM, macrophage-fibroblastic and mesenchymal infiltration was detected in the perifocal zone at the border of the intact myocardium and necrotic cardiac muscle tissue. The regenerate was well vascularized. A dense multidirectional network of hemocapillaries was noted, which accompanied the formation of immature granulation tissue. These signs indicated the onset of an early proliferative inflammatory stage.

It was previously established that under the conditions of using DCBM for the healing of connective tissue with a chronic course of the inflammatory-destructive process, as well as after the application of defects, the products of biodegradation of the biomaterial became chemoattractants of monocytes and macrophages. Macrophage cells determined the efficiency of regeneration due to complete phagocytosis and regulation of the proliferative phase of inflammation. They inhibited fibroblastic activity due to M1 macrophages and prolongation of the cytotoxic

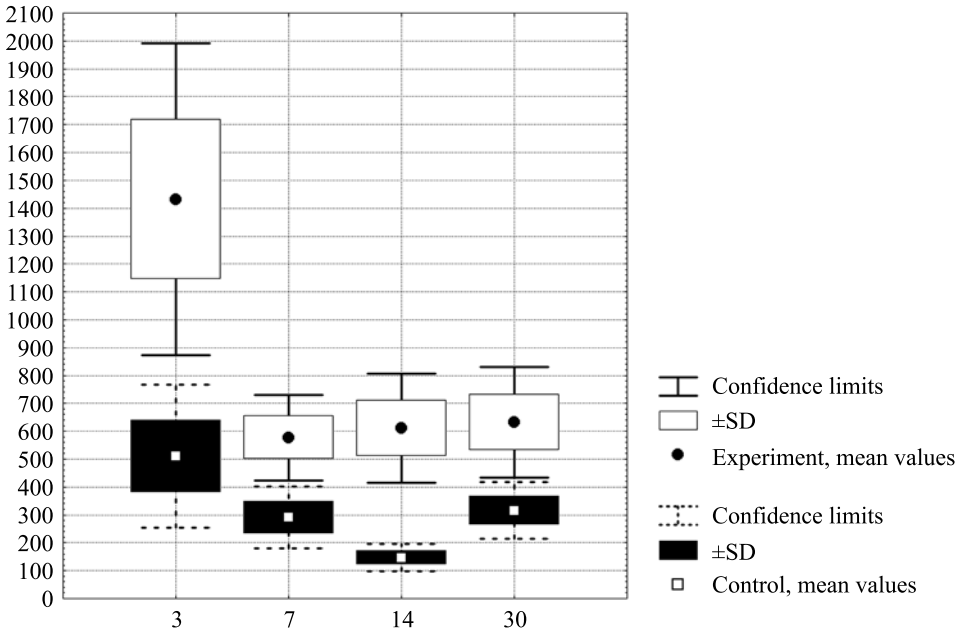

Fig. 6. Changes CSCC reactive zone of the regenerate in the "control" and "experience" in different periods of observation after coronary occlusion. GDI – limits of confidence intervals for the average area values, ±CO – standard error of the average value

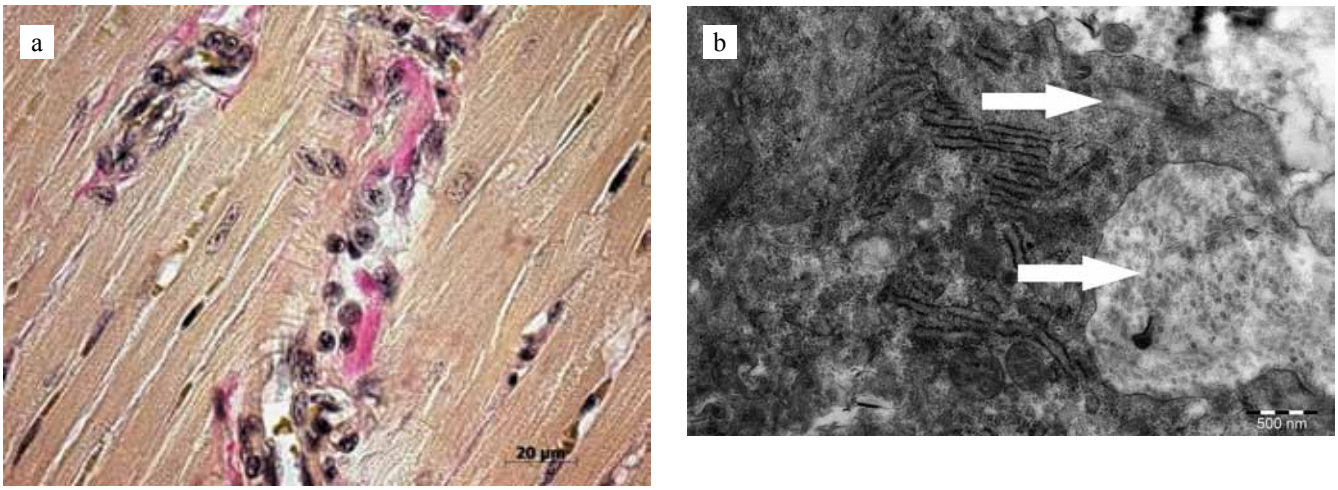

Fig. 7. Resorption of collagen 14 days after insertion of biomaterial (experimental group). a – Van-Gison stain. ×400; b – fibroclast in the myocardium with phagocytic vacuoles with fragments of collagen (↑). Electronograms. ×12 000

phase [11]. It is known that tumor necrosis factor (TNFa), in addition to initiating inflammatory reactions, can also inhibit fibrosis through the regulation of fibroblast activity, suppressing the synthesis of transforming growth factor TGFβ-induced expression of connective tissue growth factor (CTGF) protein [12].

As a result of our study, it was revealed that during the acute stage of inflammation of the ischemic myocardium, the opposite reaction occurred. The biodegradation products of DCBM stimulated the migration of macrophages to a lesser extent in the period of 3–14 days and were their inhibitors. The presence of DCBM particles was noted only in the early stages of observation; later, after 14 days, the biomaterial was resorbed and was not visualized.

In the control group, in the period of 3–14 days, pronounced infiltration of the myocardium by macrophages and the formation of a wide cell wall were determined, which corresponds to the phase of alteration and exudation. Subsequently (14–45 days) at the stage of proliferation and scarring, the number of macrophages almost proportionally decreased and leveled off in both experimental groups. Therefore, according to the data in Figure 1, macrophages contributed to the manifestation of inflammation in the myocardium, increased collagenogenesis, and, as a consequence, an increase in

the scar area. This is consistent with the data of other researchers [13].

The nature of DCBM is a decellularized allogeneic intercellular matrix – fibrous connective tissue, consisting mainly of mature type I collagen fibers and associated proteoglycans and glycosaminoglycans: hyaluronic acid, heparan-, dermatan- and keratan sulfate. During the lysis and resorption of the biomaterial, they are dosed extraction, which is initially released during the biodegradation of the graft, and subsequently begins to be secreted by the surrounding cells: macrophages, fibroblasts [11]. It can be assumed that exogenous collagen contributes to the suppression of the acute inflammatory reaction and the migration of effector cells such as macrophages. This mechanism of action probably develops according to the type of "feedback" characteristic of involution of the scar. And it was caused by excessive collagenogenesis "based on intercellular and collagen-cell interactions", as described by V.V. Serov and A.B. Schechter (1981) [14].

Excess collagen, directly in contact with fibroblasts, leads to increased fibroclasia, a decrease in the synthetic activity of fibroblasts and their destruction, which we observed after 14 days in the experimental group, which caused a sharp decline in bFGF-1$^+$ cells and the appearance of fibroclasts. Fibroclasia could also have an effect on reducing the area of the scar in the experimental group.

On the other hand, during transplantation of a decellularized extracellular matrix, cytokines such as bFGF, VEGF, HGF are released, including in the initial period after implantation (1–3 days), have bioinductive effects on myocardial fibroblasts and promote the growth of blood vessels [15]. We noted that the degree of vascularization of the reactive zone in the experimental group exceeds the values of the control one throughout the experiment, especially during the period of 3 days. It is known that bFGF has not only a pronounced angiogenic potential in conditions of ischemic myocardial damage, but also promotes the survival of endothelial cells, reduces the degree of apoptosis of cardiomyocytes [16–18]. The role of heparan sulfate (perlecan) is widely known as a "molecular glue" that plays a key role in embryonic and post-wound myocardial morphogenesis. It is a major component of the basement membrane of blood vessels, type IV collagen and laminin [19]. Consequently, endogenous heparan sulfate, as one of the biodegradation products of DCBM, can also participate in neovasculogenesis, morphogenesis, and cardioprotection.

In the control group, inflammation developed according to the classical type [20]. In the period 3–14 days, the phase of acute inflammation was accompanied by the presence of inflammatory effector cells, the formation of a wide cell shaft, which arose at the site of necrotic masses of ischemic myocardial fibers. Accordingly, the number of bFGF-1-producing cells was low. After 14 days and further, the proliferative stage of healing was characterized by the accumulation of a large number of fibroblastic cells and a more increased production of fibrokine bFGF-1 by them.

Biodegradation products of DCBM are able to normalize the balance between the processes of neofibrogenesis and fibroclasia, while the synthesis of excess collagen and glycosaminoglycans slows down, which returns the process of myocardial regeneration to the physiological channel and leads to physiological scarring. In the process of pathological scarring during the transition from the phase of late inflammation to the phase of proliferation under conditions of hypoxia and impaired microcirculation, detritus accumulates in the wound and abnormal production of cytokines by an excessive number of macrophages, which leads to lengthening the stage of inflammation and prevents the activation of healing processes [21]. The products of tissue breakdown, acting as biological stimulators of fibrogenesis, cause an imbalance in the system "fibroneogenesis – fibroclasia" with the formation of a large number of fibroblastic cells characterized by high metabolism [22].

Analysis of the results of bFGF-1 expression in the experimental group confirms this assumption. The mechanism of action indicates a reverse tissue response in response to DCBM implantation than that described in previous works [23]. In the present study, it was found that in the experimental group in the peri-infarction zone during the period 3–14 days bFGF-1$^+$ cells significantly exceeded the values of the control. In the control group, during the acute phase of inflammation (3–14 days), the level of bFGF-1$^+$ cells was low compared to the experimental group, and subsequently (14–30 days), the expression of the cytokine significantly increased, which corresponded to the phase of healing and scarring – the rapid accumulation of collagen fibers.

In the experimental group, the revealed chronology of the change in cellular infiltration does not correspond to the classical understanding of the course of the inflammatory process. Apparently, the pronounced expression of bFGF-1 is an antagonist of the pro-inflammatory spectrum of cytokines and suppresses the chain of cytotoxic reactions. It is known that bFGF, by inhibiting the apoptosis of cardiomyocytes, has a protective effect on the heart after myocardial infarction, thereby reducing the size of the necrotic zone [24]. Therefore, the early proliferative phase and the formation of granulation tissue may contribute to cardioprotection.

The information has recently appeared on the use of various types of hydrogels, created on the basis of the extracellular matrix, alginate, gelatinase, collagen, hyaluronic acid, fibrin, agarose, chitosan, keratin. They cause some improvement in the remodeling of ischemically damaged myocardium, limiting the spread of fibrosis [25, 26]. Some materials can provide maintenance or improvement of functional parameters in experimental animals or be carriers of cells or growth factors [27].

Extracellular matrix biomaterials typically consist of structural proteins such as collagen, laminin, fibronectin, and vitronectin, and many glycosaminoglycans. The rate of degradation of these materials is determined by the cellular environment and factors such as concentration and degree of crosslinking. But often they have a bioresorption rate that significantly exceeds the rate of histogenesis, without significant functional and structural positive changes, including in the long-term period [28].

The biomaterial used in this study, created on the basis of a decellularized allogeneic extracellular matrix, interacts with the host tissue, changing the cytokine profile of the myocardium, promotes angiogenesis and reduces fibrosis and cell death, and serves as a chemoattractant of progenitor cardiomyogenic cells. When using DCBM, vitalization is not required, it is able to maintain a balance between degradation and reparative histogenesis, it serves as a biomimetic, biocompatible, non-immunogenic, resists long-term complications such as infection, calcification and aneurysm enlargement. The viscosity of the resulting suspension depends on its concentration and can be adjusted and depends on the type of tissue and the needs of the researcher.

This model of acute myocardial infarction does not cover the issues of chronic myocardial ischemia, which is the most common in clinical practice. Therefore, this model highlights the aspects of the influence of the biodegradation products of DCBM as bFGF-induced angiogenic growth factors on the pro-angiogenic state during the healing period after myocardial infarction. One of the directions of the strategy of therapeutic correction in ischemic myocardial damage should be indicated on the inhibition of the migration of macrophages and the suppression of their pro-inflammatory direction M1. Decellularized allogeneic biomaterial used in the acute phase of myocardial inflammation can be such an alternative.

CONCLUSION

1. The use of an allogeneic biomaterial immediately after stenosis of the coronary artery allows more than 2 times to reduce the area of cicatricial myocardial degeneration.
2. DCBM accelerates the course of the inflammatory response and the onset of the early proliferative phase of inflammation.
3. Allogeneic biomaterial reduces myocardial infiltration by CD68 macrophages compared to the control during spontaneous healing.
4. The use of DCBM provides a significant predominance of bFGF-1^+ cells in the initial period of inflammation (3–14 days). Subsequently (14–45 days), the expression of fibrokin became several times less. In the control group, during the acute phase of inflammation (3–14 days), the level of bFGF-1^+ cells was low, and subsequently (14–45 days), cytokine expression increased significantly, which caused a rapid accumulation of collagen fibers and scarring.
5. During the formation of postinfarction regenerate in the experiment, DCBM stimulated angiogenesis.
6. In the zone of myocardial regeneration, allogeneic biomaterial regulates the balance of neofibrillogenesis-fibroclasia.

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The authors declare no conflict of interest.

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