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# The Use of Mesenchymal Stem Cells in the Treatment of Acute Pancreatitis and Pancreatic Necrosis: Clinical and Experimental Studies

**Sh. K. Atadjanov, M. D. Urazmetova, G. K. Saparbayeva**

Republican Research Centre of Emergency Medicine, Tashkent, Uzbekistan

The morbidity of acute pancreatitis (AP) has increased worldwide and varies depending on the region from 4.9 to 73.4 (on average 34) cases per 100 thousand worldwide for recent years [1]. Pancreatic necrosis is the presence of focal or diffuse non-viable pancreatic parenchyma or peripancreatic fat [2-3]. Pancreatic necrosis (pancreonecrosis) is a complication of severe acute pancreatitis (SAP) and occurs in 15-25% of patients with acute pancreatitis [4]. It represents one of the most serious complications of SAP with a mortality rate from 20 to 30% [5].

Pancreatitis is an inflammatory disease of the exocrine part of the pancreas. In most cases, it is caused by reflux of bile acids from gallstones or fatty acid/ethanol metabolites as a result of excessive consumption of alcohol and fats, in which pancreatic enzymes injure pancreatic tissue, which leads to the death of acinar cells, as well as to local and systemic inflammation [6]. Thus, gallstones migrating from the gallbladder and causing transient obstruction of the pancreatic duct and the effect of components of the bile ducts on the pancreas are still the most common cause of acute pancreatitis. The second most common cause of acute pancreatitis is alcohol abuse [7].

Thanks to timely and accurate diagnosis and treatment, the mortality and morbidity of AP have decreased over the past decade, however, the consequences of AP remain serious [10-11]. More importantly, from a clinical point of view, prediabetes or diabetes mellitus is developed in about 37% of patients after the initial episode of AP; in general, patients are at twice the risk of developing diabetes in the following 5 years after an episode of AP than the general population [12].

The exact pathogenesis of acute pancreatitis is unknown, and studies at the molecular level are going on. Clinical studies using stem cell products in regenerative medicine are aimed at treating a wide range of conditions using various types of stem cells. To date, there have been few reports of safety issues associated with autologous or allogeneic transplantation. Many injected cells show a temporary presence for several days with a trophic effect on immune or inflammatory responses [13].

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Mesenchymal stem cells (MSCs) have attracted the attention of researchers as a source of cells for regenerative medicine. MSCs are also known as multipotent stem cells or adult stem cells [14]. They can regenerate and differentiate into several cell lines, including mesoderm (osteocytes, chondrocytes and adipocytes), as well as endoderm and ectoderm [15]. MSCs are adult stem cells isolated primarily from the bone marrow. In a study conducted by Smukleretal, the number of stem cells derived from the pancreas was very limited (1 in 5,000 pancreatic cells), although they were capable of producing various cells such as endocrine cells and neurons [16]. In contrast, a study conducted by Gongetal with nestin (a stem cell marker) revealed evidence that the pancreas did not contain stem cells, and any identified stem cells may originate from bone marrow (BM) [17]. It means that stem cells originating from the bone marrow will contribute to the restoration and regeneration of injured pancreatic tissues. There is also a study that shows that the bile ducts are a source of stem cells for the pancreas, as it was shown by Wangetal [18]. Their study showed that the pancreas and bile systems were closely related to each other and that there were always stem cells that could give rise to certain types of pancreatic cells, such as ducts and pancreatic glands [19].

MSCs can self-renew and undergo multilinear differentiation [20]. MSCs express specific surface markers such as CD105, CD90 and CD73 but do not express CD45, CD34, CD14, CD11b, CD79 alpha, CD19 or HLA-DR. MSCs-like cells have been isolated from other tissues, including human placenta [21], peripheral blood [22], umbilical cord [23], adipose tissue [24], endometrium [25], and pancreas [26].

Jung K.N. et al. were the first who reported AP therapy with MSCs [44]. It was found that MSCs can reduce the expression of inflammatory markers such as TNF-a, IL-1beta and IL-6 in the pancreas, on the one hand, and increase the number of positive regulatory Fox-p3 T-cells in the lymph nodes and pancreas, on the other side [45]. Subsequent studies have also confirmed that MSCs have

anti-inflammatory properties by downregulating serum and pancreatic tissue levels of pro-inflammatory cytokines, increasing the expression of anti-inflammatory factors, and regulating the balance between pro-inflammatory and anti-inflammatory factors [46]. In other experimental models, acute pancreatitis has been induced by injection of molecules such as cerulein, L-arginine, and lipopolysaccharides (LPS) as described elsewhere, with comparable results [47]. The trigger for AP is intraacinar activation of digestive enzymes, which leads to the production of inflammatory molecules, vacuolization and death of acinar cells with the following organ failure. All of these models demonstrated the ability of MSCs to reduce the symptoms of pancreatitis, as well as parenchymal injury and necrosis [48]. The main protective mechanism manifested by MSCs is their anti-inflammatory effect both due to the direct release of anti-inflammatory cytokines and due to the modulation of pro-inflammatory cytokines (TGF-β, INF-γ and TNF-α), which led to a decrease after the introduction of MSCs. In particular, Zhao H. et al. observed the migration of intravenously injected MSCs into the pancreas, followed by a decrease in IL 1-1β and TNF-α [49]. Although the role of MSCs migration in the treatment of acute pancreatitis is still controversial, as it is not always observed [50], a decrease in serum levels of inflammatory cytokines after injection of MSCs is now guaranteed, and it has been proposed as a regulatory mechanism for Foxp3-positive regulatory T-cells and abolishing the proliferation of CD3 positive T-cells. This innate immunomodulatory ability of MSCs can be enhanced by genetic manipulation. Hua J. et al. demonstrated that transfection with the angiopontin-1 gene further reduced inflammation, serum amylase and lipase levels, and pancreatic damage, thereby enhancing the effect of human cord-derived MSCs. This synergistic effect was probably associated with angiogenesis-driven stimulation of the angiopontin-1 gene, which led to vascular stabilization and an increase in endothelial cell survival [51].

MSCs transplanted immediately after AP induction had a better anti-inflammatory effect than MSCs transplanted a few hours after AP induction. It was confirmed that the anti-inflammatory properties of MSCs cell therapy positively correlated with the time and dose of exposure. Another mechanism of MSCs inhibition of inflammation in AP is an anti-apoptotic effect [52]. By blocking the JNK pathway, MSCs regulate transcription of downstream apoptosis-related target genes and expression of apoptotic proteins in a transcription-dependent manner. MSCs mediate apoptosis of acinar cells by protruding the death receptor and the mitochondrial pathway. Besides, MSCs can promote injured tissue repair and angiogenesis through the SDF-1a/C-X-C axis of the type 4 chemokine receptor (CXCR4) [53]. Some bioactive molecules secreted by MSCs play an important role in the regulation of inflammatory immunity, although the exact mechanism of the anti-inflammatory action of MSCs is still controversial. It was previously reported that microcapsules from MSCs can alleviate injury caused by AP [54,47]. The results showed that MSCs could specifically migrate to the injured pancreatic tissue. Confocal results also suppose that MSCs migration may be connected with the degree of inflammation. In the pancreatic necrosis group, after MSCs intervention, the levels of biochemical parameters, such as amylase and lipase in pancreatitis, also decreased significantly. Pathological results also showed that pancreatic tissue hyperemia and edema, inflammatory cell infiltration, parenchymal hemorrhage, acinar cell necrosis and apoptosis were significantly reduced. Similarly, in the mild pancreatitis group, namely the edematous pancreatitis group, MSCs also effectively reduced the degree of pancreatic edema. Besides, MSCs significantly suppressed the activity of myeloperoxidase (MPO) and effectively reduced the effect of oxidative stress caused by peroxidase [44]. It was found in additional studies that MSCs intervention at the beginning of pancreatic necrosis can more effectively alleviate pancreatic injury, reduce SIRS levels, reduce the incidence of external organ damage and reduce mortality compared to MSCs intervention earlier and a few hours after the onset of pancreatic necrosis. The results showed that MSCs had a certain time and dose dependence on SAP treatment [55].

Clinical studies have shown that intravenous administration of cord blood reduces the degree of intoxication and anemia in patients with necrotic pancreatitis, normalizes glucose and protein profile of the blood, reduces the manifestations of cytolytic syndrome, namely, there is a dynamic decrease in the activity of aspartate aminotransferase, alanine aminotransferase and gamma-glutamyltranspeptidase, lactate dehydrogenase [56]. The mechanism of cord blood stem cells action should be considered the result of humoral stimulation of reparative processes, which is caused by the unique property of neonatal cells, cytokines and growth factors that are in the preparation. However, the most important for the issue of acute necrotic pancreatitis is that stem cells, adapting to microenvironment conditions and responding to local organ- and tissue-specific regulatory signals, can act as a producer of autocrine stem regulatory mediators. At the same time, stem precursors can realize the potential of a "plastic building" material capable of restoring the structures of injured parts of organs and tissues. In cord tissue transplantation, the effect is achieved through local action, as a result of the possible migration of endothelial stem and mesenchymal cells, which are located in large numbers on the inner surface of the umbilical cord, and also due to hemostatic action as a result of the release of fibrinogenesis factors. There is a high probability that stem cells stimulate the obliteration of pancreatic ducts, prevent the formation of post-necrotic pancreatic fistulas and cysts [57]. Kebkalo A.B. et al. [3] developed a new method for the treatment of pancreatic necrosis using cord blood stem cells and umbilical cord tissue. The treatment was tested in a randomized placebo-controlled clinical trial, the purpose of which was to evaluate the efficiency of the umbilical

cord blood stem cell drug "Pancrostem". The clinical trial was preceded by preclinical animal studies that showed the efficiency of that approach. The results of the clinical study showed that interventions with umbilical cord blood and umbilical cord tissue correlated with a statistically significant improvement in the outcomes and survival of patients with pancreatitis. The results obtained demonstrate the efficiency of cryopreserved umbilical cord blood TNAs (Pancrostem) as part of the complex treatment of patients with necrotic pancreatitis.

Moreover, several studies have shown that MSCs can manifest their effects without accumulating them at the site of inflammation or tissue injury, which indicates their action through paracrine secretions. In addition, it was shown that TNF-α-induced gene/protein 6 (TSG-6) was a key secreted mediator of the MSCs anti-inflammatory response in peritonitis, myocardial infarction, inflammatory bowel diseases, skin wound healing and lung injury [58-61]. Li Q. et al. [62] in their study assessed the therapeutic effects of iintraperitoneally administered hAT-MSCs in a mouse model of SAP co-induced by cerulein (50 mcg/kg) and lipopolysaccharide (LPS) (10 mg/kg). The inflammatory response and ER stress were measured in pancreatic tissue samples, and the inflammatory effects were evaluated using quantitative reverse transcription polymerase chain reaction (qRT-PCR), Western blotting and immunofluorescence analysis. Inflammatory response and ER stress decreased after hAT-MSCs injection, and beneficial effects were seen in the absence of significant hAT-MSCs engraftment. hAT-MSCs transfected by gene/protein 6 (TSG-6) targeting siRNA targeting tumor necrosis factor were unable to inhibit ER stress and inflammation. In addition, TSG-6 from hAT-MSCs significantly suppressed stress-induced ER apoptosis and the activity of nuclear factor kappa B (NF-kB) in SAP mice. The authors concluded that TSG-6 secreted by hAT-MSC protects PAC in SAP model mice by inhibiting ER stress as well as inflammatory responses. This study has identified a new area for ER stress therapy in SAP patients.

As it was shown by Huang Q. et al., exogenous CP-MSCs can survive and colonize injured tissues such as lungs, pancreas, intestines and liver. Blockade or impairment of autophagy promotes infiltration of the pancreas by inflammatory (M1) and fibrogenic (M2) macrophages. Meanwhile, the authors found that CP-MSCs alleviate pancreatic injury and systemic inflammation by inducing macrophage polarization from M1 to M2 in AP. Besides, data show that CP-MSCs induce M2-polarization of macrophages by secreting TSG-6, and TSG-6 plays a vital role in alleviating pancreatic injury and systemic inflammation in AP. Environment with high inflammation can stimulate CP-MSCs to secrete TSG-6. The authors concluded that exogenous CP-MSCs tended to colonize in injured tissue and reduced pancreatic injury and systemic inflammation in AP due to the induction of M2-polarization of macrophages by TSG-6 secretion. This study suggests a new strategy for the treatment of pancreatic necrosis and initially explains the potential protective mechanism of CP-MSCs in AP [63].

So, there is still more research to be done on the safety of MSCs transplantation. Regulation of the differentiation process is important and should be monitored, as it can potentially lead to tumors. Besides, it is necessary to evaluate the function of differentiated cells that arise from the stem cells themselves to make sure that they can fulfill their intended role. Ethical issues also arise when people are involved in the use of stem cells. Therefore, further research and trials are needed, although MSCs transplantation appears to have significant therapeutic potential in both acute and chronic pancreatitis.

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