کارکاه های آموزشی مرکز اطلاعات علمی جهاد دانشگاهی

کارکاه آنلاین
کاربرد نرم افزار SPSS در پژوهش
کارکاه آنلاین
اصول تنظیم قراردادها
کارکاه آنلاین
پروپوزال نویسی
Phase 1 Trial of Autologous Bone Marrow Mesenchymal Stem Cell Transplantation in Patients with Decompensated Liver Cirrhosis


Background: The standard treatment for decompensated liver cirrhosis is liver transplantation. However, it has several limitations. Recent animal studies suggest that bone marrow stem cell transplantation can lead to regression of liver fibrosis. The objective of this study was to determine the safety and feasibility of autologous bone marrow-mesenchymal stem cell transplantation in patients with decompensated liver cirrhosis.

Methods: In this phase 1 trial, four patients with decompensated liver cirrhosis were included. Their bone marrow was aspirated, mesenchymal stem cells were cultured, and a mean 31.73×10^6 mesenchymal stem cells were infused through a peripheral vein. Primary outcomes were evaluating the safety and feasibility of the work. Secondary outcomes were evaluating changes in the model for end-stage liver disease score, and the quality of life of the patients.

Results: There were no side-effects in the patients during follow-up. The model for end-stage liver disease scores of patients 1, and 4 improved by four and three points, respectively by the end of follow-up. Furthermore, the quality of life of all four patients improved by the end of follow-up. Using SF-36 questionnaire, the mean physical component scale increased from 31.44 to 65.19, and the mean mental component scale increased from 36.32 to 65.55.

Conclusion: Mesenchymal stem cell transplantation seems to be feasible and safe in the treatment of decompensated liver cirrhosis.

Keywords: Bone marrow • cirrhosis, liver • MELD score • mesenchymal stem cells • quality of life

Introduction

S

 Cirrhosis represents a late stage of progressive hepatic fibrosis characterized by distortion of the hepatic architecture and formation of regenerative nodules. Liver transplantation is considered as the standard treatment for advanced decompensated liver cirrhosis. However, it has several limitations such as long waiting list, high cost, and several complications. Stem cell therapy may be a potential alternative to liver transplantation.

We and other groups have shown that human embryonic stem cells could trans-differentiate into hepatocytes in two- as well as three-dimensional culture systems in vitro. Also, recent studies have shown that circulating adult stem cells can differentiate into mature hepatocytes or cholangiocytes in human body. Bone marrow is a reservoir of various stem cells, including hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs). While MSCs have been shown to be capable of mesodermal and

Original Article

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neuro-ectodermal differentiation, they have the potential of endodermal differentiation; their differentiation into functional hepatocyte-like cells has also been demonstrated. Recent animal studies have shown that infusion of MSCs through the tail vein can protect against experimental rat liver fibrosis. Moreover, infusion of nonhematopoietic bone marrow stem cells can lead to regression of liver fibrosis in mice. While, both HSCs and MSCs have the ability to trans-differentiate to hepatocytes in vivo, MSCs are the most potent component of bone marrow cells in hepatic differentiation. Thus, bone marrow stem cell transplantation, particularly MSC transplantation can be a potential treatment for liver cirrhosis.

Previous human studies have shown that transplantation of MSCs as well as HSCs is safe and may be effective in patients with acute myocardial infarction. Furthermore, in a recent study, infusion of HSCs through the hepatic artery or portal vein has led to improvement in liver function tests in some patients with liver cirrhosis. However, to the best of our knowledge, yet there has been no human study on MSC transplantation for liver cirrhosis. We conducted a phase 1 trial to determine the safety and feasibility of MSC transplantation in patients with decompensated liver cirrhosis.

Patients and Methods

Harvesting and culture of MSCs
Bone marrow aspirates (80 – 100 mL) were obtained from the posterior iliac crest of the patients after local anesthesia. MSCs were cultured and harvested by the method of Wexler et al. The aspirates were diluted 1:2 with 2 mM EDTA/PBS. The mononuclear fraction was isolated by density gradient centrifugation at 435 g for 30 min at room temperature using Ficoll-Hypaque solution (Innora, Germany) and seeded at a density of 1×10^6 cells/cm^2 into T75 cell culture flasks (Nunc, Austria). The cells were plated in Dulbecco’s modified Eagle’s medium-low glucose (DMEM-LG, GIBCO, UK), supplemented with 10% fetal calf serum (Sigma, Germany) and 1% penicillin-streptomycin (Gibco, UK), and cultured at 37°C in a 5% CO₂ atmosphere. After three days, non-adherent cells were removed and the adherent cells were cultured for another seven days with media changes every three days. Cells were grown to confluence, then harvested by incubation with 0.25% trypsin/1 mM EDTA (GIBCO, UK), centrifuged at 1200 rpm for five min, and subcultured at a 1:3 split ratio in new culture flasks. After reaching confluence for the second time (after eight days), the harvested cells were defined as passage one, and the replated cells were cultured and serially subcultured until passage two to four. Cell viability was evaluated by Trypan blue exclusion dye method.

To determine their immune phenotype, the surface expression of typical marker proteins was analyzed using fluorescence-assisted cell sorting (FACS) flowcytometry. For this, cells were labeled with the following antihuman antibodies: CD166 (Serotec, UK), CD105 (Serotec, UK), CD31 (Dako, Denmark), CD90 (Dako, Denmark), CD44 (Dako, Denmark), CD13 (Dako, Denmark) (MSC surface markers), CD34 (Dako, Denmark), and CD45 (Dako, Denmark) (HSC surface markers). Mouse isotype antibodies served as respective controls (Dako, Denmark). Ten thousand labeled cells were then acquired and analyzed using a FACSCalibur flowcytometer running the CellQuest software (Bekton-Dikenson). Finally, the cells’ multipotent MSC characteristics were thoroughly evaluated using osteogenic, adipogenic, and chondrogenic differentiation assays as described earlier.

By the end of the last passage, the cells were washed with tyrode salt (Sigma, Germany) and incubated with M199 medium (Sigma, Germany) for an hour. Cells were detached with trypsinization and washed with normal saline supplemented with 1% human serum albumin (Blood Research and Fractionation Co., Iran) and heparin three times and resuspended at a concentration of 1 – 1.5×10^6/mL in M199. This washing process eliminates trace amounts of fetal bovine serum as well. Moreover, bacteriological tests were performed on the samples for every passage and at the time of injection.

RNA extraction and reverse transcriptase polymerase chain reaction
Total RNA was extracted from cultured cells using the NucleoSpin ® RNA II kit (Macherey-Nagel, Düren, Germany). Prior to reverse transcription (RT), RNA samples were digested with DNase I (EN0521; Fermentas) to remove contaminating genomic DNA. Extracted RNA was treated by DNase I to avoid cross contamination of RNA by genomic DNA. Standard RT was performed using 2 µg total RNA, oligo (dT) 18 and the RevertAid H Minus First strand cDNA
Synthesis kit (K1622; Fermentas) according to the manufacturer’s instruction. The cDNA samples were subjected to polymerase chain reaction (PCR) amplification using human-specific primers of endodermal- and hepatocyte-specific genes including hepatocyte nuclear factor 3β (HNF3β), α-fetoprotein (AFP), albumin (ALB), α-antitrypsin (AAT), cytokeratin-18 (CK-18), tyrosine aminotransferase (TAT), glucose-6-phosphatase (G6P), cytochrome P450 subunits 7A1 (CYP7A1), and CCAAT/enhancer binding protein (C/EBP) beta (CEBPB).

The sequences of the primers were published previously, except CEBPB (forward: 5’GTCCACAAACCGCACAT3’ and reverse: 5’CAACAGCCCGTAGGAACAT3’). Glyceraldehyde-3-phosphate dehydrogenase (GADPH) used as internal control. Amplification conditions were as follows: initial denaturation at 94°C for 30 sec, annealing at 59 – 70°C for 45 sec, extension for 45 sec at 72°C and a final polymerization at 72°C for 10 min. The PCRs were performed in triplicate. The PCR products were analyzed by gel electrophoresis on 1.5% agarose, stained with ethidium bromide (10 µg/mL), visualized and photographed on a UV transluminator (Uvidoc, UK). As a positive control, human hepatoma cell line, PLC/PRF/5 (Alexander) (Pasteur Institute, Tehran, Iran) was used.

Transplantation of MSCs

One gram of vancomycin was intravenously administered one hour before the stem cell infusion. The cells were diluted in normal saline to a final volume of 20 mL. Subsequently, the stem cells were slowly infused by a heparinized syringe through the cubital vein of the arm over 30 min. The patients were discharged after six hours of observation.

Patients

After approval of the project by the Ethics Committee and the Research Council of Digestive Disease Research Center, Tehran University of Medical Sciences, four patients were recruited. All patients signed a written informed consent. Inclusion criteria were age 18 – 60 years, chronic hepatic failure, ultrasonographic evidences of cirrhosis and portal hypertension, abnormal serum albumin and/or bilirubin and/or prothrombin time, and a “model for end-stage liver disease” (MELD) score of 16 or higher which has not been decreased over one month. Exclusion criteria were history of moderate to severe hepatic encephalopathy or variceal bleeding during the last two months before enrolment; serum creatinine ≥2 mg/dL, or GFR< 40 mL/min; serum sodium<129 mEq/L; serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) more than three times the upper limit of normal; lines of evidence of active autoimmune liver disease (serum gammaglobulin > twice normal; serum transaminases > three times the upper limit of normal); human immunodeficiency virus or hepatitis C virus seropositivity; serum hepatitis B virus DNA of more than 10,000 copies/mL in patients with positive hepatitis B surface antigen; lines of evidence of extrahepatic biliary diseases (e.g., presence of primary sclerosing cholangitis, or dilated common bile duct on ultrasonography; presence of active untreated infectious disease; presence of hepatic, portal, or splenic vein thromboses on Doppler ultrasonography; presence of severe comorbid diseases (e.g., severe renal, respiratory, or cardiac disease), or presence of any types of malignancy; history of alcohol use, or use of hepatotoxic drugs within the last six months before enrolment; active substance abuse; lack of a supportive family; and unwilling to sign the informed consent. All patients were on the waiting list of liver transplantation.

Follow-up visits and outcome measures

Initially, the study was designed to follow the patients for six months after the procedure. However, we were concerned about the occurrence of any side-effects after the six months, and we decided to extend the duration of follow-up for up to 12 months posttransplantation.

The following tests were performed on days 0, 1, 4, and 7, weeks 2, 3, and 4, months 2, 3, 6, 9, and 12 posttransplantation: complete blood counts, PT and international normalized ratio (INR), serum albumin, urea, creatinine, AST, ALT, serum alkaline phosphatase, serum total and direct bilirubin, and AFP. Also, 10 mL of the patients’ serum samples were collected and stored frozen at -70°C at each visit.

History taking and physical examinations were also performed at each visit. Peripheral edema was graded as 0 for “no edema,” trace if we had indention caused by pressure over the dorsum of the foot, 1+ if there was indention at shin, 2+ if we had indention at knee, 3+ if indention existed above the knee, and 4+ if there was generalized edema with indention over hip and lower back.

www.SID.ir
Liver volume of the patients was measured at baseline and after six months by multislice spiral CT scan without administration of intravenous contrast. Measurement of the liver volumes was done by a radiologist blinded to patients treatment and timing of intervention. The SF-36 questionnaire which has been previously validated in Persian language was completed by the patients one day before the stem cell infusion, and was repeated at the end of follow-up.

The primary objective of this study was to assess the safety and feasibility of intervention. Secondary endpoints were to assess changes in the MELD score, liver volume, and quality of life of the patients by the end of follow-up.

Evaluation of safety and feasibility

Patients’ safeties were evaluated at each visit according to the above-mentioned schedule. Clinical, laboratory, and safety-related data were prospectively collected.

Procedural complications were defined as any hemodynamic instability during the cell infusion. Major side-effects were defined as development of any of the following complications during the follow-up: acute renal failure, worsening hepatic decompensation that requires urgent liver transplantation, progressive elevation in serum AFP, or development of liver mass on follow-up CT scans.

Results

Viability and function of MSCs

The mean number of cells achieved at the end of culture was $31.7 \times 10^6$ cells (range: 10.2 – 60×10⁶). The mean number of passages was 2.5 (range: 1 – 4). The mean duration of culture was 73 (range: 64 – 85) days. The rate of viability which was studied by Trypan blue method was over 95%. The results of flowcytometric analysis for CD13, CD31, CD44, CD 90, CD105, and CD166 were positive, and for the hematopoietic markers—CD34 and CD45—were negative. We have also previously shown that mesenchymal cells preserve their transdifferentiation potential in long-term culture.

RT-PCR results

RT-PCR showed that cultured MSCs were positive for some endodermal- and hepatocyte-specific genes such as CK-18, CEBPB, and AAT (Figure 1). However, the cells were negative for AFP, albumin, TAT, G6P, and HNF3β.

Clinical results

Four patients (three females) with the mean age of 47.3 (range: 34 – 56) years were enrolled and underwent the entire procedure (Table 1). Medications were not changed during the study period.

Vital signs of the patients remained stable during the stem cell infusion. The results of the study are shown in Tables 1 and 2. There were no procedural complications or side-effects in the patients during the follow-up. Follow-up CT showed no evidence of focal liver lesion in any of the patients.

All patients had peripheral edema at baseline. Their edema significantly improved during the follow-up (Table 2). The doses of diuretics were

![Figure 1. RT-PCR analysis of endodermal and hepatocyte-specific gene expression by MSCs of one patient without any treatment. As a positive control, human hepatoma cell line, PLC/PRF/5 was used.](www.SID.ir)
decreased in patient 1, and remained unchanged in other three patients during the study. In patients 1 and 4, liver function tests and MELD scores improved during and at the end of the follow-up (e.g., month 12). The improvement was most significant on month six posttransplantation (Table 2). Although there were some improvements in the liver function tests and MELD scores of patient 3 on month six, her MELD score came back to pre-transplantation status on month 12. The MELD score and liver function tests of patient 2 remained stable without significant change during the follow-up.

Follow-up CT showed that liver volumes of the patients 1, 2, and 4 increased on month six post-transplantation (Figure 2).

SF-36 questionnaire showed that the quality of life of all patients had significantly improved by the end of follow-up (Table 3). The mean physical component scale increased from 31.44 to 65.19 and the mean mental component scale increased from 36.32 to 65.55.

Table 1. Baseline characteristics of the patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>46</td>
<td>56</td>
<td>34</td>
<td>53</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Etiology of cirrhosis</td>
<td>Cryptogenic</td>
<td>Cryptogenic</td>
<td>AIH</td>
<td>Cryptogenic</td>
</tr>
<tr>
<td>Presence of portal vein thrombosis</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Medications</td>
<td>Spironolactone, furosemide, and propranolol</td>
<td>Spironolactone and furosemide</td>
<td>Spironolactone, furosemide, prednisolone, azathioprine (inactive AIH on medications since two years before enrolment)</td>
<td>Spironolactone and furosemide</td>
</tr>
</tbody>
</table>

AIH=autoimmune hepatitis.

Table 2. Clinical and laboratory parameters of the patients at baseline and at the end of follow-up.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
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<tbody>
<tr>
<td></td>
<td>B M 6 M 12  B M 6 M 12 B M 6 M 12 B M 6 M 12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema*</td>
<td>2+ None 0 0 2+ None 1+ None 1+ Mild 2+ None 0 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascites</td>
<td>None None None None None None None None None None None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>2.9 3.8 3.5 2.8 2.9 3 4.1 4.3 3.9 3.4 3.2 3.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT (seconds)</td>
<td>18.5 13 15.2 20.1 18.8 18 15.7 15.1 15.5 19.1 13.8 15.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td>2.2 1.2 1.6 2.01 2 1.7 1.4 1.3 1.4 1.9 1.1 1.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cr (mg/dL)</td>
<td>0.7 0.88 0.80 1.1 0.74 1 0.55 0.85 0.66 0.73 0.92 0.70</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>1.3 2 0.9 2.7 5.32 3.2 4.43 3.25 3.33 2.18 1.9 2.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct bilirubin (mg/dL)</td>
<td>0.4 0.5 0.5 1 0.91 1.2 1.7 1.25 1.24 0.44 0.49 0.39</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST (IU/mL)</td>
<td>66 149 77 67 59 49 63 74 49 39 43 33</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT (IU/mL)</td>
<td>53 127 52 24 34 23 28 71 57 25 30 17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFP (µg/L)</td>
<td>2.6 2 5.5 4.1 2.5 5.5 2.5 2 2 1.5 2.3 0.66</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MELD score</td>
<td>16 11 12 19 20 20 16 14 15 17 10 14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver volume (cm³)</td>
<td>495 814 555 843 1115 872 795 940 —</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PT=prothrombin time; INR=international normalized ratio; Cr=serum creatinine; AST=aspartate aminotransferase; ALT=alanine aminotransferase; AFP=alpha fetoprotein; MELD=model for end-stage liver disease; B=baseline; M=month.

*Peripheral edema was graded as follows: 0=no edema; trace=indentation caused by pressure over the dorsum of the foot; 1+=indentation at shin; 2+=indentation at knee; 3+=indentation above knee; 4+=generalized edema (indentation over hip and low back).
Discussion

While orthotopic liver transplantation is the standard treatment for decompensated liver cirrhosis, cell-based therapies are emerging as an alternative to liver transplantation. Stem cell transplantation may have a great impact on the treatment of a variety of human diseases in the near future.

In this study, we showed that infusion of in vitro expanded autologous MSCs through the peripheral vein is safe and feasible in patients with decompensated liver cirrhosis.

Previous in vitro and in vivo studies have shown that MSCs can differentiate into hepatocyte and nonhepatocyte cells and that infusion of stem cells through a peripheral vein could save animals from liver failure and lead to regression of liver fibrosis.

In this study, we used RT-PCR to evaluate the gene expression profile of MSCs. Our results showed that the cultured MSCs expressed some endodermal- and hepatocyte-specific genes such as CK-18, CEBPB, and AAT. These data demonstrated that MSCs have the potential to differentiate into endodermal lineage and hepatocytes. The cultured MSCs were negative for other hepatocyte-specific gene markers such as albumin and AFP. However, previous studies have shown that the expression levels of these markers could be significantly upregulated during trans-differentiation of MSCs into hepatocytes in vitro.

Previous works have shown that the fibrolytic effects of bone marrow stem cells may be related to over-expression of matrix metalloproteinases (MMPs), especially MMP-9. Also, the migrated bone marrow stem cells may lead to hepatic stellate cells apoptosis. Furthermore, increments in the liver volume in three of four patients in our study could be explained by the fact that bone marrow stem cells may increase hepatocyte proliferation by supplying growth factors and cytokines critical for the recovery process. In a recent study, infusion of bone marrow MSCs expressing hepatocyte growth factor (HGF) helped to increase liver weight after “small-for-size liver

### Table 3. Quality of life of the patients at baseline and at the end of follow-up.

<table>
<thead>
<tr>
<th>SF-36 component</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>End of follow-up</td>
<td>Baseline</td>
<td>End of follow-up</td>
</tr>
<tr>
<td>Physical component scale</td>
<td>48.5</td>
<td>90.5</td>
<td>52.5</td>
<td>75.5</td>
</tr>
<tr>
<td>Mental component scale</td>
<td>64.75</td>
<td>74</td>
<td>66.21</td>
<td>87.63</td>
</tr>
</tbody>
</table>
transplantation” in rats. Although we did not check for HGF expression in the cultured MSCs, it can be suggested that the increment in the liver volume by MSCs is a real possibility. Furthermore, we believe that increment in the liver volume of an already cirrhotic liver is a complicated issue, and it will be a valuable event if it is accompanied by regression of liver fibrosis. Obviously, this should be assessed in further controlled trials.

In the previous animal studies, cytokines and growth factors produced by nonparenchymal liver cells derived from bone marrow, regulated proliferation and maintained function of hepatocytes. However, in patient 3, the liver volume slightly decreased on month six. It may be related to the natural course of cirrhosis in this patient.

In this study, liver function tests and MELD scores in two of four patients slightly improved. Such improvement was most significant on month six postprocedure.

The above findings may suggest that the beneficial effects of MSC transplantation are transient and that infusion of higher number of MSCs may make more beneficial effects. However, we cannot claim that such improvement is definitely related to stem cell transplantation; it may be simply related to the natural course of cirrhosis in the affected patients. The implementation of a larger controlled trial with higher number of infused MSCs would clarify this issue.

In two of four patients, total bilirubin increased (Table 2), however in both of them the direct bilirubin, which is a more accurate sign of liver dysfunction, did not increased. Also, none of them showed any other signs of worsening liver dysfunction.

In a recent study, infusion of CD34+ HSCs was reported to be safe in patients with liver cirrhosis. Also, infusion of bone marrow stem cells from a peripheral vein has been reported to improve the liver function in patients with cirrhosis. However, for the first time, we showed that infusion of autologous cultured mesenchymal (e.g., nonhematopoietic) stem cells was safe and feasible in the treatment of cirrhosis.

In our study, the quality of life of all patients was improved. Such improvement may be attributed to the improved liver function, or may be due to a placebo effect. The efficacy of MSCs in improving the liver function and the quality of life of the patients should be evaluated in further controlled trials. A phase 2 sham controlled trial of MSC transplantation with the higher number of MSCs is undergoing at our center.

One of the limitations of our work was that we did not track the infused MSCs in patients’ bodies. Although tracing of infused stem cells in the body seems to be a complicated issue and the interpretation of tracing studies has recently created a lot of controversies, it is very important to understand the way stem cells act to improve liver function and liver volume. We are now planning to trace stem cells in our future works. Another limitation was that we did not document histologic improvement of cirrhosis in the studied patients. This point should also be considered in the following studies.

There are several important unresolved issues regarding the stem cell transplantation in cirrhosis. For example, the best type of the stem cells to be infused, the minimum effective number of the cells, and the best route of administration still remain obscure.

In conclusion, this study showed that autologous MSC transplantation through a peripheral vein is safe and feasible in the treatment of liver cirrhosis. Improvements in liver function tests and MELD scores of some of our patients are promising.

Acknowledgment

We kindly thank Prof. Detlef Schuppan from the Harvard Medical School for his thoughtful comments, and Dr. Ali Montazeri from the Iranian Institute for Health Sciences Research for permitting us to use the Iranian version of SF-36 questionnaire and calculating SF-36 scores. This work was financially supported by local funds from Digestive Disease Research Center and Hematology, Oncology, and Bone Marrow Transplantation Research Center, Tehran University of Medical Sciences, and Royan Institute.

References

MSC transplantation in cirrhosis


کارگاههای آموزشی مرکز اطلاعات علمی جهاد دانشگاهی

کارگاه آنلاین کاربرد نرم افزار SPSS در پژوهش
کارگاه آنلاین اصول تنظیم قراردادها
کارگاه آنلاین پروریزال نويسي

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