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The antibacterial effect of mesenchymal stem cells on graft infections: An experimental study

Mezenkimal kök hücrelerin greft enfeksiyonlarında antibakteriyel etkisi: Deneysel bir çalışma

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ABSTRACT

Background: In this study, we aimed to investigate the antibacterial effects of mesenchymal stem cells, compared to tigecycline, on graft infection related with methicillin-resistant *Staphylococcus epidermidis* in a rat model.

Methods: A total of 42 male adult Wistar rats (age >6 months; weight 300 to 350 g) were divided into six groups including seven rats in each. Group 0 did not undergo any procedure; Group 1 was infected, but untreated; Group 2 was infected and treated with tigecycline without graft placement; Group 3 was infected and received mesenchymal stem cells without graft placement; Group 4 was infected and treated with tigecycline after graft placement; Group 5 was infected and treated with mesenchymal stem cells after graft placement. The pockets created were either left empty or implanted with Dacron grafts. Treatment was commenced at 48 h. Specimens were collected on Day 13. Perigraft tissues were evaluated histopathologically and bacterial colony numbers were counted.

Results: No bacterial colonization was observed in Group 0, whereas there was a significant colonization in Group 1. Complete eradication was achieved in Group 2 and Group 3 (graft-free groups), and near-complete eradication was achieved in Group 4 and Group 5 (graft-implanted groups). The histopathological findings significantly differed between Group 1-Group 2 and between Group 1-Group 3 (graft-free groups). The histopathological findings were similar between Group 2-Group 3 and between Group 4-Group 5.

Conclusion: Our study results suggest that mesenchymal stem cells may be a novel, contemporary alternative to antibiotherapy and may decrease the bio-burden of Staphylococcus at the infected graft areas, and mesenchymal stem cell treatment may be as effective as tigecycline.

Keywords: Infection; mesenchymal stem cell; Staphylococcus epidermidis; tigecycline; wound.

ÖZ

Amaç: Bu çalışmada, sıçan modelinde, tigesikline kıyasla, mezenkimal kök hücrelerin metisiline dirençli *Staphylococcus epidermidis* ile ilişkili greft enfeksiyonu üzerindeki antibakteriyel etkileri araştırıldı.

Çalışma planı: Toplam 42 erkek erişkin Wistar cinsi sıçan (yaş >6 ay; ağırlık 300-350 g) her grupta yedi sıçan olacak şekilde altı gruba ayrıldı. Grup 0 herhangi bir prosedürden geçmedi; Grup 1 enfekte edildi, ancak tedavi edilmedi; Grup 2 enfekte edildi ve greft yerleştirilmeden tigesiklin ile tedavi edildi; Grup 3 enfekte edildi ve greft yerleştirilmeden mezenkimal kök hücre ile tedavi edildi; Grup 4 greft yerleştirildikten sonra enfekte edildi ve tigesiklin ile tedavi edildi; Grup 5 greft yerleştirildikten sonra enfekte edildi ve mezenkimal kök hücre ile tedavi edildi. Oluşturulan cepler boş bırakıldı veya Dacron greftle implante edildi. Tedaviye 48 saat sonra başlandı. Numuneler 13. günde toplandı. Perigreft dokular histopatolojik olarak değerlendirildi ve bakteri koloni sayıları tespit edildi.

Bulgular: Grup 0'da bakteri kolonizasyonu gözlenmez iken, Grup 1'de belirgin kolonizasyon görüldü. Grup 2 ve Grup 3'te (greftsiz gruplar) tam eradikasyon sağlandı ve Grup 4 ve Grup 5'te (greft yerleştirilen gruplar) tama yakın eradikasyon elde edildi. Histopatolojik bulgular açısından Grup 1-Grup 2 ve Grup 1-Grup 3 arasında (greftsiz gruplar) anlamlı bir fark vardı. Histopatolojik bulgular Grup 2-Grup 3 ve Grup 4-Grup 5 arasında benzerdi.

Sonuç: Çalışma sonuçlarımız, mezenkimal kök hücrelerin antibiyotik tedavisine yeni ve modern bir alternatif olabileceğini ve enfekte greft alanlarında Staphylococcus'un biyoyükünü azaltabileceğini ve mezenkimal kök hücre tedavisinin tigesiklin kadar etkili olabileceğini göstermektedir.

Anahtar sözcükler: Enfeksiyon; mezenkimal kök hücre; Staphylococcus epidermidis; tigesiklin; yara.

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Non-hematopoietic cells of the bone marrow can differentiate into osteoblasts, adipocytes, and chondrocytes and are, thus, termed mesenchymal stem cells (MSCs).[1] Several subsequent studies have demonstrated that such cells may give rise to both mesoderm- and non-mesoderm-derived cells.[2]

The features of MSCs vary by origin in terms of numbers, genetic structures, and phenotypic characteristics. The MSCs release cytokines and chemokines as well as antimicrobial peptides.[3,4] Previous studies have found that MSC-derived antimicrobial peptides enhance the innate immune response to bacterial infection, although these unique characteristics of MSCs have not been, yet, evaluated in controlled studies of methicillin-resistant *Staphylococcus epidermidis* (MRSE) infection featuring the placement of vascular Dacron grafts.[5,6] When exposed to pathogenic agents, macrophages and endothelial cells induce the aggregation and migration to the infected region.[7]

Dacron is the most widely used vascular graft. The incidence of graft infection is 0.5 to 1% and mortality rates (10 to 25% with infected vascular grafts) remain high, despite the use of many precautions and antibiotics.[8] Methicillin-resistant *Staphylococcus epidermidis* is one of the most common agent of such infections and is resistant to many antibiotics.[9] Indeed, methicillin-resistant Staphylococcus strains which are resistant even to glycopeptides have been reported.[10] However, graft infections often do not respond to antibiotherapy, and graft excision may be required, which is associated with high morbidity and mortality.[11]

Broad-spectrum new-generation tetracyclines, such as tigecycline, are one of the most potent treatment options for vascular graft-related excessive resistant *Staphylococcus* infections.[12] However, graft infection-related morbidity and mortality and antibiotic use may be reduced by prophylactic MSC administration.

In this study, we aimed to investigate the well-known local chemotactic effects of MSCs on infection and to evaluate whether these can provide a novel therapeutic alternative to antibiotherapy.

MATERIALS AND METHODS

This study was performed with the approval of our local Animal Research Ethics Committee (No. 17/06, Date: 01/03/2017).

Organisms and susceptibility testing

Agents were isolated in 2016 from a 72-year-old male with MRSE osteomyelitis. A colony purified from a single graft infection was identified by Gram-staining, catalase reaction, tube coagulation test, and API-Staph test (BioMérieux, Lyon, France). Methicillin resistance was analyzed using the Kirby-Bauer disc diffusion method.[13]

Drugs

Tigecycline (Pfizer®, Istanbul, Turkey) was administered at a dose of 10 mg/kg, which has been shown to be effective in rats.[14] The tigecycline susceptibility of the strains was confirmed.

Isolation of MSCs from adipose tissue

The rat adipose tissues were excised from the inguinal region and transferred into the culture dishes containing penicillin/streptomycin/amphotericin B (GIBCO, Grand Island, NY, USA) and Dulbecco's modified Eagle's medium (DMEM). Then, the cells were inoculated into T25 plates. Cell development was monitored (Leica, Wetzlar, Germany).

Flow cytometric identification of MSCs

The cells were suspended after their second passage and placed in three tubes, at 150,000/tube, in a flow cytometry device. The cell suspensions were centrifuged in phosphate-buffered-saline (PBS). Anti-CD45R, -CD11b/c, -CD90, and -CD44 antibodies were incubated with the cells. Data were collected

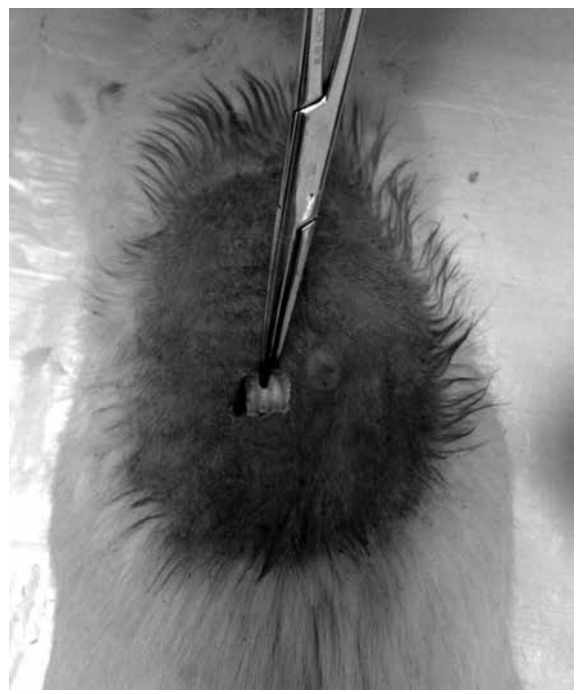

Figure 1. 1 cm^2 Dacron graft was implanted into the pockets of the rats in Groups 4 and 5.

using the FACS-ARIAIII (BD, Foster City, CA, USA) device.

Mesenchymal stem cell differentiation

After the second passage, the MSCs were induced to differentiate into adipocytes, osteocytes, and chondrocytes. The cells were, then, examined under a microscope.

Cell defrosting

We used a fast defrost technique. The cells were removed into a 37°C water bath and centrifuged. The supernatant was removed, and the pellet was re-suspended. The cell counts and viabilities were measured (Countess®, Invitrogen, San Diego, CA, USA). In total, $1x10^6$ cells per injection was prepared for each rat.[15]

In vivo rat model

The graft infection model used was based on that of Yasim et al.[11] Forty-two male adult Wistar rats (age >6 months; weight 300 to 350 g) were divided into six groups of seven rats in each. Group 0 was graft-free, infection-free, antibiotic-free; Group 1 was graft-free, infected, and not treated; Group 2 was graft-free, infected, and treated with tigecycline; Group 3 was graft-free, infected, and treated with MSCs; Group 4 were Dacron graft implanted, infected, and treated with tigecycline; Group 5 was Dacron graft implanted, infected, and treated with MSCs.

Surgical technique

All rats were anesthetized with ketamine hydrochloride (Pfizer, Luleburgaz, Turkey) and xylazine hydrochloride (Bayer AG, Leverkusen, Germany). The rats were shaved and cleaned with povidone-iodine. Subcutaneous pockets were created on the backs. Under sterile conditions, a Dacron graft (Gelwave, Sulzer Vascutek Ltd., Inchinnan, UK) was implanted. (Figure 1). Then, MRSE (2×10^7 colony-forming-units [CFUs]) were inoculated into the grafts using a tuberculin syringe.[16] At 48-h, MSCs (2×10^6 cell)[15] were injected into the pockets of Group 3 and Group 5. Tigecycline was applied twice-daily intraperitoneally for 10 days.

All grafts were explanted after lethal anesthesia 13 days after the implantation.

Histopathological examination

Perigraft and subcutaneous tissue samples were collected, fixed in formalin for two days, soaked

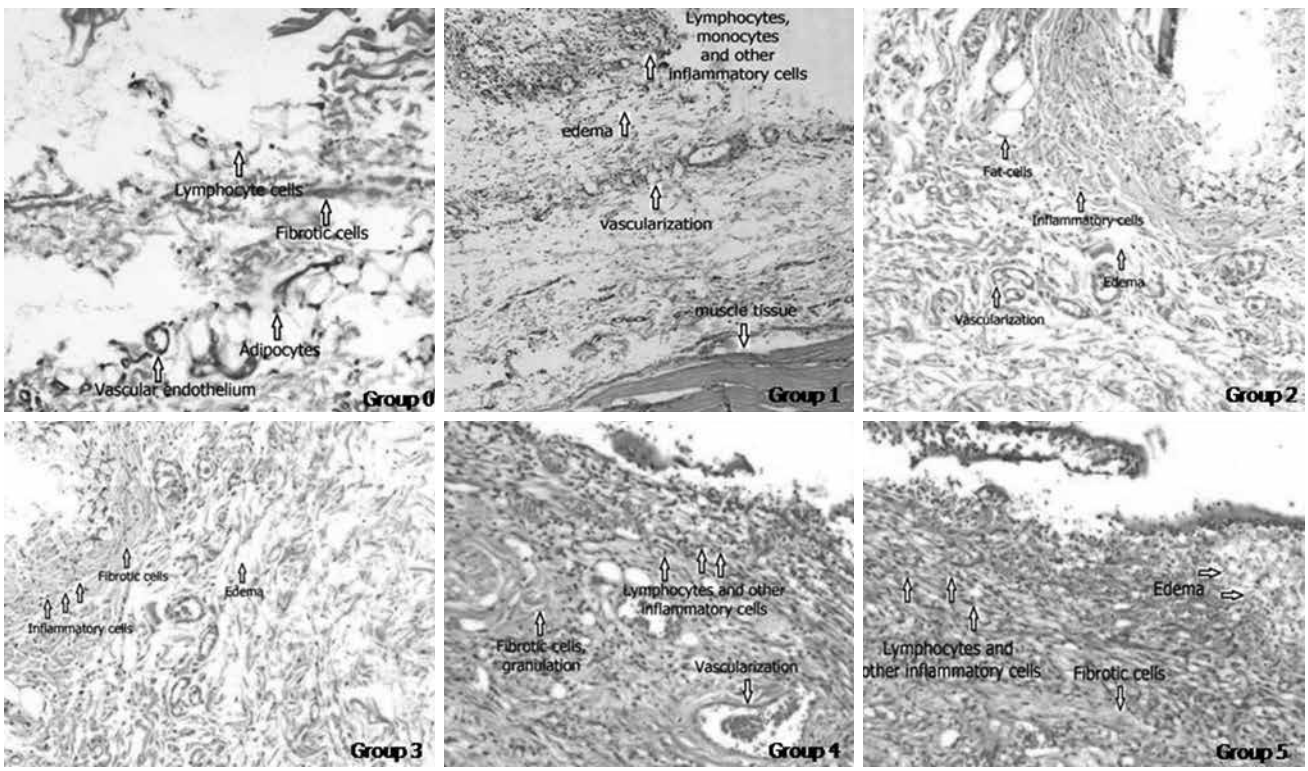

Figure 2. Histopathological results of specimens (H-E×40).

Table 1. Implanted graft material, inoculated agent, treating agents, and quantitative microbiological results

	Graft	MRSE	Tigecycline	MSC	Quantitative microbiological results
Group 0	-	-	-	-	0
Group 1	-	2×10^7	-	-	$9.6\times10^7\pm0.4\times10^7$
Group 2	-	2×10^7	$2\times1^{(10\ days)}$		0
Group 3	-	2×10^7		Single dose of MSC	0
Group 4	Dacron	2×10^7	$2\times1^{(10\ days)}$		80±10
Group 5	Dacron	2×10^7		Single dose of MSC	110±30

MRSE: Methicillin-resistant *Staphylococcus epidermidis*; MSC: Mesenchymal stem cell.

in ethanol and xylene baths, embedded in paraffin, sectioned, and stained with hematoxylin/eosin. The samples were graded semi-quantitatively for inflammation and infection as follows: Grade 0; no neutrophils, Grade 1; a few neutrophils, Grade 2; moderate number of neutrophils, and Grade 3; many neutrophils.[17]

Infection assessment

The samples were sonicated to remove bacteria adherent to the grafts and cultured on blood agar plates and counted.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). Continuous data were presented in mean ± standard deviation (SD) and non-normally categorical data in median with an interquartile range of 25-75%. The chi-square test was used to compare categorical variables among the groups. The Mann-Whitney U test and Kruskal-Wallis test (with pairwise comparisons of the groups) were carried out to compare continuous data with non-normal distributions. A *p* value of <0.05 was considered statistically significant.

RESULTS

Minimal inflammation and edema were evident in infection-free rats. Severe inflammation was observed in rats infected and not treated. Minor inflammation and moderate edema were observed in rats infected and treated with MSCs or tigecycline. Significant fibroblastic and vascularization responses with mixed infiltrations of inflammatory cells were also observed around the graft areas treated with MSCs or tigecycline. (Figure 2).

The group data, graft materials used, numbers of MRSE inoculated, treatments, and results are shown in Table 1. No bacterial colonization was observed in Group 0. However, colonization was observed in all rats of Group 1 (7/7; 9.6(5.3-8.2) x 107CFU/mL) ($p<0.05$). No treatment was administered to either of these groups (Table 2).

Methicillin-resistant *Staphylococcus epidermidis* was eradicated in all graft-free rats treated with tigecycline or MSCs. Colony numbers were compared with the Kruskal-Wallis test and pairwise comparisons of the groups (Group 1-Group 2-Group 3, $p<0.05$; Group 1-Group 2, $p<0.05$; Group 1-Group 3, $p<0.05$ were significantly different, while Group 2-Group 3, $p>0.05$ were similar). Bio-burden of MRSE decreased

Table 2. Graft use for treatment

	No treatment	Tigecycline		Mesenchymal stem cell		*p*
		Median	Interquartile range	Median	Interquartile range	
No Dacron graft implanted	$9.6\ (5.3\text{-}8.2)\times10^7$	0	0-0	0	0-0	<0.001*
Dacron graft implanted	-	81	73-86	109	93-121	0.004**

The Kruskal-Wallis test median (25-75%); * Difference between treatments in the no graft implantation groups; ** Difference between treatments in the Dacron graft implantation groups.

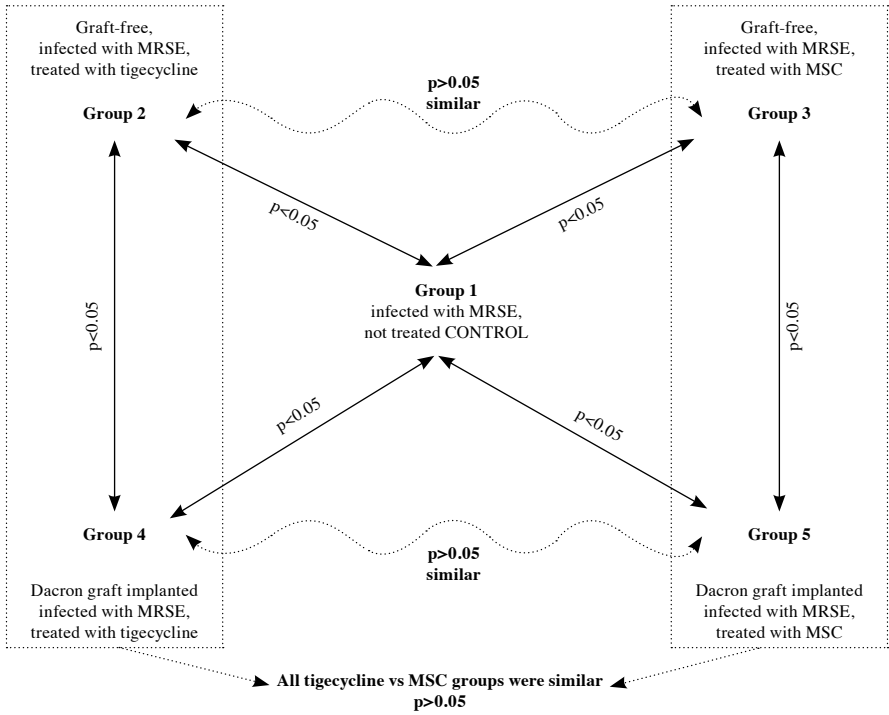

Figure 3. Colony numbers compared with Kruskal-Wallis test and pairwise comparisons of groups or Pearson's chi-square test.
MRSE: Methicillin-resistant *Staphylococcus epidermidis*; MSC: Mesenchymal stem cell.

in the graft-implanted rats and reductions in colony numbers were significantly evident (Group 1-Group 4-Group 5, $p<0.05$; Group 1-Group 4, $p<0.05$; Group 1-Group 5, $p<0.05$ were significantly different, while Group 4-Group 5, $p>0.05$ were similar). Colony numbers were compared in pairs, treated with tigecycline using the Mann-Whitney U test. It was found significantly lower in Group 2 (graft-free) than Group 4 (Dacron-graft) ($p<0.05$) and in Group 3 (graft-free) than Group 5 (Dacron-graft) ($p<0.05$) (Figure 3).

Table 3. Histopathological findings of inflammation

	Grade 0	Grade 1	Grade 2	Grade 3
Group 0	3	4	-	-
Group 1	-	1	1	5
Group 2	1	3	2	1
Group 3	-	3	3	1
Group 4	1	-	3	3
Group 5		1	2	4

* Figures show rat numbers in related groups.

Irrespective of the graft use, all treated rats were compared in terms of the numbers of culture-positive rats to assess the overall therapeutic success using the Pearson's chi-square test (Group 1 vs. tigecycline [Group 2+Group 4]; $p<0.05$; Group 1 vs. MSCs [Group 3+Group 5]; $p<0.05$). Tigecycline and MSC-treated groups were similar ($p>0.05$). The numbers of culture-positive rats were significantly lower at no graft-implanted rats than the Dacron graft-implanted rats ($p<0.05$) (Figure 3).

Histopathological findings were evaluated with the chi-square test. As expected, severe inflammation was observed in untreated rats (Group 1), and minor inflammation was evident in non-infected rats (Group 0) ($p<0.05$) (Group 1-Group 2-Group 3, $p<0.05$; Group 1-Group 2, $p<0.05$; Group 1-Group 3, $p<0.05$ were different, while Group 2-Group 3, $p>0.05$ were similar) (Group 1-Group 4-Group 5, $p<0.05$; Group 1-Group 4, $p<0.05$; Group 1-Group 5, $p<0.05$ were different, while Group 4-Group 5, $p>0.05$ were similar) (Tables 3 and Figure 4).

None of the rats in any group died or exhibited clinical symptoms of drug-related side effects.

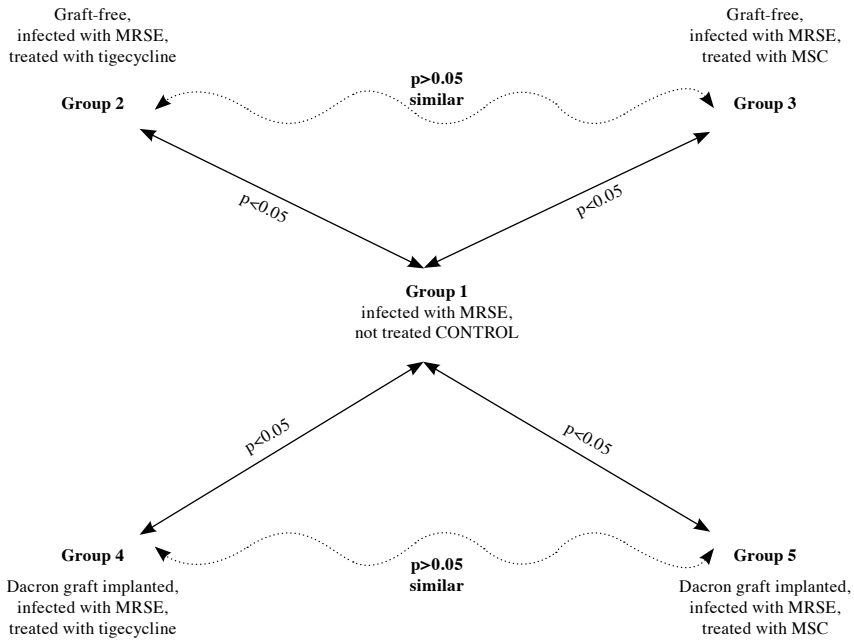

Figure 4. Histopathological findings as assessed by chi-square test.

MRSE: Methicillin-resistant *Staphylococcus epidermidis*; MSC: Mesenchymal stem cell.

DISCUSSION

Stem cell and antibiotherapy are the important preclinical topics in medical science. Recent *in vivo* studies have shown that MSCs help control bacterial sepsis and enhance bacterial clearance.[3,5] In the present study, we compared MSCs with classical antibiotherapy in rats with MRSE-infected grafts. In MRSE-infected, graft-free surgical wounds, both MSCs and tigecycline afforded complete eradication. In the rats with MRSE-infected vascular grafts, complete eradication was not achieved; however, MSC treatment was as effective as tigecycline.

Vascular surgery infections are associated with significantly increased morbidity and mortality.[8] Even if aseptic conditions are excellent, contamination cannot be entirely prevented.[18] *Staphylococcus epidermidis* adheres to and colonizes prostheses, forming biofilms, and it is commonly encountered agent.[9] Although current treatment options are systemic and local antibiotics,[19] novel options are required. Although the effects of MSCs and cell secretions on cell repair and their antibacterial actions have been investigated extensively, no report is available on the MSC-mediated effects on graft infection, compared to that of tigecycline.

Immunohistochemically, wounds treated with MSCs contain more dense macrophages, and MSC-macrophage crosstalk with secretions enhances wound-healing by mobilizing macrophages.[20] Also, MSCs regulate the function of macrophages. Gong et al.[21] examined the effect of bone marrow macrophages and observed significant upregulation of pro-inflammatory cytokines and growth factors in their study. The clinical benefits afforded by MSCs are based on the repair and replacement of cellular substrates, attenuation of inflammation, and enhancement of angiogenesis and therapeutic cell migration.[22] Endothelial cells and leukocytes create powerful stimuli for neutrophils and leukocytes to migrate and secrete to control the infection.[23]

In the present study, we compared the efficacy of MSCs and tigecycline, as a safe and effective antibiotic in patients with skin and soft tissue infections,[24] using a model in which therapeutic success was evaluated in terms of subcutaneous infections. There was no uncontrolled contamination (no colonization in Group 0) and bacterial inoculation was appropriate (colonization was observed in all rats of Group 1). Complete eradication was achieved in graft-free rats (Group 2-Group 3). Both treatments were similarly found to be effective in infected, graft-free rats. The treatments were less adequate in graft implanted (Group 4-Group 5) than graft-free (Group 2-Group 3) groups, although a significant bacterial decrease was evident (bordering on eradication). Although the colony

numbers differed significantly between the grafted and non-grafted groups, the fact that near-eradication was achieved might render the difference inconsequential in clinical practice. The success of the MSCs and tigecycline were assessed by counting the numbers of colonized rats (Group 2+Group 4 vs. Group 3+Group 5). Both the tigecycline and MSC-treated groups differed significantly from the untreated control group, although these two treatments did not differ. In general, all treated groups were evaluated irrespective of graft status, and colonization results were similar between the rats treated with tigecycline (Group 2+Group 4) or MSCs (Group 3+Group 5). The failure to achieve complete eradication in grafted rats can be attributed to the fact that it is difficult to control and treat graft infections. Medical treatment is usually more successful when delivered early, and the most appropriate treatment is graft removal.[25] Dacron grafts are susceptible to infection and difficult to treat, probably explaining the failure of both therapeutic options.[26]

In addition, it is possible that we might have underestimated the effects of MSCs, and it might be inappropriate to compare 10-day administration of tigecycline with a single dose of MSCs. This is the main limitation of our study. We have, therefore, planned a further study, in which MSCs would be applied for the same length of time as antibiotics, including other graft materials (such as polytetrafluoroethylene) and other infectious agents such as methicillin-resistant *Staphylococcus aureus*.

In a study, Meisel et al.[27] investigated the antibacterial effects of human MSCs and found a significant inhibition of *Staphylococcus epidermidis* proliferation by MSCs stimulated with interferon gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α). Guerra et al.[28] also observed that bone marrow-derived MSCs ($1x10^6$ cells) cannot inhibit colony-forming abilities of biofilm-associated *Staphylococcus*.

The severity of inflammation was similar between the rats treated via either method both in grafted (Group 4 vs. Group 5) and non-grafted (Group 2 vs. Group 3) animals; the two treatments decreased inflammation to similar extents. It is unsurprising that inflammation was more severe in rats with untreated infections (Group 1). The immunomodulatory effects of MSCs[29] may have contributed to this effect; however, our results were similar. We found no significant difference between the MSC- and tigecycline-treated groups, suggesting that bacterial eradication is the principal factor ameliorating inflammation.

Similarly, Qian et al.[30] revealed that MSCs with anti-bacterial and anti-inflammatory effects could treat *Staphylococcus aureus*-infected mice.[30] Alcayaga-Miranda et al.[3] used a combination of antibiotherapy and MSCs in an *in vivo* mouse model. The two treatments were strongly synergistic in terms of increasing the survival rate. In addition, inflammation was reduced in the absence of significant immunosuppression. Combined treatment is strongly recommended to treat sepsis. Although the principal treatment strategy is antibiotherapy, stimulation of the natural immune system is also important. In our opinion, combined use with various antibiotics would create new alternatives that are both more potent and less toxic. It would be vitally important to reduce organ damage during antibiotherapy for infectious patients with diabetic and elderly, mainly multiorgan failure.

According to our study results, MSCs may be as valuable as tigecycline to control MRSE infection. The side effects of potent broad-spectrum antibiotics should be considered. Side effects of MSC therapy have not been reported to date, but must be taken into account, if MSCs are confirmed to be a successful method of infection control. Although MSC application is currently more expensive than antibiotics, it may become much more economical once this method is widely employed, perhaps even by local laboratories.

Our study is a preliminary study on rats, and more comprehensive Phase 1 and 2 studies are needed to evaluate appropriate dosing and administration methods.

In conclusion, our study results suggest that mesenchymal stem cells may be a novel, contemporary alternative to antibiotherapy and may decrease the bio-burden of *Staphylococcus* at the infected graft areas, and mesenchymal stem cell treatment may be as effective as tigecycline.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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