ISSN 2220-3230 (online)

World Journal of *Transplantation*

World J Transplant 2021 August 18; 11(8): 320-355

Published by Baishideng Publishing Group Inc

WJT World Journal of Transplantation

Contents

Monthly Volume 11 Number 8 August 18, 2021

World Journal of Transplantation

Monthly Volume 11 Number 8 August 18, 2021

Contents

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INDEXING/ABSTRACTING

The *WJT* is now abstracted and indexed in PubMed, PubMed Central, Scopus, China National Knowledge Infrastructure (CNKI), and Superstar Journals Database.

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Production Editor: *Yu-Jie Ma*; **Production Department Director:** *Yu-Jie Ma*; **Editorial Office Director:** *Jia-Ping Yan*.

NAME OF JOURNAL
World Journal of Transplantation

ISSN
ISSN 2220-3230 (online)

LAUNCH DATE
December 24, 2011

FREQUENCY
Monthly

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PUBLICATION DATE
August 18, 2021

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World J Transplant 2021 August 18; 11(8): 320-334

DOI: 10.5500/wjt.v11.i8.320

ISSN 2220-3230 (online)

REVIEW

Factors affecting complications development and mortality after single lung transplant

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Conflict-of-interest statement: The authors declare no conflict of interests.

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Abstract

Lung transplantation (LT) is a life-saving therapeutic procedure that prolongs survival in patients with end-stage lung disease. Furthermore, as a therapeutic option for high-risk candidates, single LT (SLT) can be feasible because the immediate morbidity and mortality after transplantation are lower compared to sequential single (double) LT (SSLTx). Still, the long-term overall survival is, in general, better for SSLTx. Despite the great success over the years, the early post-SLT period remains a perilous time for these patients. Patients who undergo SLT are predisposed to evolving early or late postoperative complications. This review emphasizes factors leading to post-SLT complications in the early and late periods including primary graft dysfunction and chronic lung allograft dysfunction, native lung complications, anastomosis complications, infections, cardiovascular, gastrointestinal, renal, and metabolite complications, and their association with morbidity and mortality in these patients. Furthermore, we discuss the incidence of malignancy after SLT and their correlation with immunosuppression therapy.

Manuscript source: Invited manuscript

Specialty type: Transplantation

Country/Territory of origin: Bulgaria

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

Received: March 5, 2021
Peer-review started: March 5, 2021
First decision: March 31, 2021
Revised: April 15, 2021
Accepted: June 28, 2021
Article in press: June 28, 2021
Published online: August 18, 2021

P-Reviewer: Bos S, Meng FZ
S-Editor: Zhang L
L-Editor: Filipodia
P-Editor: Yuan YY

Key Words: Lung transplantation; Single lung transplant; Primary graft dysfunction; Native lung complications; Technical transplant complications; Vascular transplant complications; Graft rejection; *De novo* malignancy

Core Tip: Improvement in surgical techniques and adequate intra-and post-operative management significantly increased patients' short- and long-term survival after a single lung transplant. Conditions such as volume overload, cardiovascular complications, antibody-mediated rejection, aspiration, and/or pneumonia could mimic the lung allograft's acute dysfunction. However, events related to improved surgical techniques and post-operative control of pulmonary immunogenicity through immunosuppressive therapy are among the reasons leading to the reduction of early mortality and prolonged survival of these patients. Thus, the post-operative management after single lung transplantation has to be multidisciplinary and complex.

Citation: Sekulovski M, Simonska B, Peruhova M, Krastev B, Peshevska-Sekulovska M, Spassov L, Velikova T. Factors affecting complications development and mortality after single lung transplant. *World J Transplant* 2021; 11(8): 320-334
URL: https://www.wjgnet.com/2220-3230/full/v11/i8/320.htm
DOI: https://dx.doi.org/10.5500/wjt.v11.i8.320

INTRODUCTION

Lung transplantation (LT) is a life-saving therapeutic procedure that prolongs survival in patients with end-stage lung diseases such as chronic obstructive pulmonary disease (COPD), cystic fibrosis, idiopathic pulmonary fibrosis (IPF), pulmonary arterial hypertension (PAH), and alpha-1 antitrypsin deficiency[1]. Since the first successful LT in 1981, there have been many improvements in surgical and anesthetic procedures[2]. These events lead to a significant increase in post-LT survival in these patients[3]. As a therapeutic option for high-risk candidates, single LT (SLT) could be a feasible option because the immediate morbidity and mortality after transplantation are lower compared to sequential single (double) LT (SSLTx). Still, the long-term overall survival is, in general, better for SSLTx. Patients with IPF, PAH, and COPD could be appropriate candidates for SLT because of more negligible operative trauma, shorter ischemic time, and ethical considerations-one donor helps 2 patients[4,5]. It is estimated that more than 4000 lung transplants are currently performed annually worldwide, with significantly lower morbidity and mortality rate compared to data from 20 years ago[5,6]. Despite the great success over the years, the early post-SLT period remains a perilous time for these patients. Approximately 7% of SLT recipients have a short-life expectancy (30 d), while a larger percent are expected to develop complications[6]. Patients who underwent SLT are predisposed to evolve early or late post-operative complications. Primary or chronic lung allograft dysfunction (CLAD), anastomosis complications, infections, cardiovascular disease, renal, metabolic, and gastrointestinal (GI) disorders, as well as *de novo* malignancy (DNM) are the most common[7,8]. Events related to improved surgical techniques and post-operative control of pulmonary immunogenicity through immunosuppressive therapy are among the reasons leading to the reduction of early mortality and the prolonged survival of these patients[9]. Thus, the post-operative management after SLT has to be multidisciplinary and complex.

The aim of this review is to emphasize factors leading to post-SLT complications in the early and late periods and their association with morbidity and mortality in these patients. Furthermore, we discuss the incidence of malignancy after SLT and its correlation with immunosuppression therapy.

POST SLT COMPLICATIONS RELATED TO GRAFT FUNCTION

Improvement in surgical techniques and adequate intra- and post-operative management significantly increased short- (up to 30 post-operative days) and long-term (> 1 year) survival[6]. Due to acute worsening of pulmonary function status with a rapid increase in shortness of breath, graft failure is the leading early post-operative complication. Conditions such as volume overload, cardiovascular complications, antibody-mediated rejection (AMR), aspiration, and/or pneumonia can mimic acute lung allograft dysfunction (ALAD)[10]. Therefore, the primary focus should be on circulatory and ventilatory support in the intensive care unit (ICU). In patients without early post-operative complications, early ventilator weaning during the first 12 h is recommended. Nevertheless, the mortality rate in this period is still high[11].

Primary graft dysfunction

Primary graft dysfunction (PGD) is one of the leading causes of mortality (42%) after SLT in the early post-operative period[12]. A study by Liu *et al*[13] reported that mortality rates in patients after SLT with PGD are eight times higher than recipients without this kind of complication. The Consensus Statement of the International Society for Heart and LT (ISHLT) defines PGD as an acute lung injury (in the first 3 post-operative days) after LT, most often caused by mechanical ventilation, immunological and inflammatory processes, and "possibly" infectious agents. In general, this injury clinically manifests as pulmonary edema, leading to reduced lung vascular compliance and ineffective graft oxygenation. In clinical practice, PGD is most often mistaken for acute respiratory distress syndrome as a consequence of increased permeability and alveolar damage to the pulmonary capillaries[14,15]. PGD is characterized by diffuse alveolar infiltrates on chest radiographs, which correlates with the degree of hypoxemia[16]. PGD severity is rated (from 0 to 3) based on the presence of radiographic lung infiltrates and the ratio of alveolar oxygenation to the fraction of inspired oxygen. The classification of PGD presented by ISHLT is presented in Table 1 [15]. An interesting study by Whitson *et al*[17] showed that patients who developed PGD1 and PGD2 had better long-term survival compared to those with PGD3. A prospective study by Diamond *et al*[18] between 2002 and 2010 registered PGD3-30.8% in the first 72 h after LT. Furthermore, Mulligan *et al*[1] reported that PGD3 correlated with a mortality rate of 23% in 3 post-operative months and 34% in 1 year, compared to 5% and 11% for those without PGD, respectively.

A large number of studies have been conducted to obtain an appropriate classification of risk factors associated with PGD. We summarized the most common possible risk factors in Table 2[18-21]. Mechanisms related to PGD3, especially in SLT, include: Diluting effect of inadequate oxygenation related to the shunting in the remaining native lung, higher cardiac output through the graft vascularization, and higher capillary tension in cases of size mismatch (*i.e.* lobar or undersized LTx)[15]. All of these complications can prolong the duration of mechanical ventilation and ICU stay. Therefore, an inappropriate treatment strategy may affect long-term survival since PGD is a risk factor for CLAD development[22-26]. Events such as ischemia-reperfusion injury, innate immunity mechanisms, oxidative and nitrosative stress, inflammatory response, and vascular dysfunction with loss of alveolar architecture are thought to be the basic pathophysiological mechanism for the development of PGD. Intensive care strategy includes careful use of sedation and muscle relaxants, lung-protective mechanical ventilation, inhaled nitric oxide or/and prostaglandin, restrictive fluid balance, and prevention of nosocomial infection and extracorporeal membrane oxygenation[23,27,28]. Proper donor selection, pre-operative optimizing matching, and improved therapies and techniques for lung preservation after explanation could prevent the development of PGD[29].

Acute and chronic lung allograft dysfunction

Multiple lung graft rejection forms are hyperacute, acute cellular and AMR, and chronic lung allograft dysfunction[30]. Hyperacute rejection is rare due to enhanced methods for detecting pre-formed donor-specific antibodies to human leukocyte antigen (HLA) or non-HLA antigens. It is thought that these antibodies lead to endothelial cell necrosis, coagulation cascade activation, and hemorrhagic infarction due to binding to HLA molecules on endothelial cells and activate the complement cascade[31]. In contrast, acute cellular rejection is a common complication after SLT and SSLTx. Moreover, 30% of transplanted patients (SLT and SSLTx) experience at least one episode in the first year, mostly in the first 6 mo. Still, the incidence may be as high as 40%-50%[32]. The diagnosis of acute cellular rejection is still made by trans-

Table 1 Primary graft dysfunction classification

PGD grade	Chest radiography		PaO_2/FiO_2 ratio in mmHg	SaO_2/FiO_2 ratio
	Diffuse allograft infiltration	Pulmonary edema		
0	No	No	Any	Any
1	Yes	Yes	> 300	> 315
2	Yes	Yes	200-300	235-315
3	Yes	Yes	< 200	< 235

FiO_2: Fraction of inspired oxygen; PaO_2: Partial oxygen pressure; PGD: Primary graft dysfunction; SaO_2: Oxygen saturation.

Table 2 Possible risk factor associated with the development of primary graft dysfunction

Risk factor for PGD		
Factors correlated with the recipient	Factors correlated with the donor	Other (Intra- and post-operative)
BMI ≥ 25	Heavy smoker	Intracellular type preservation solutions
Sarcoidosis	DCD	Prolonged warm or/and cold ischemia
IPF	Traumatic brain injury/DBD	SLT
PPH	Female gender	Poly-transfusion of blood product
Elevated mean PAP	African American ethnicity	Use of cardiopulmonary bypass
LVDD	Younger than 21 yr, older than 45	High fractional inspired oxygen upon reperfusion
	Alcoholism	Prolonged mechanical ventilation
	Aspiration	Peri-operative insults

BMI: Body mass index; DBD: Donation after brain death; DCD: Donation after circulatory death; IPF: Idiopathic pulmonary fibrosis; LVDD: Left ventricular diastolic dysfunction; PGD: Primary graft dysfunction; PPH: Primary pulmonary hypertension; SLT: Single lung transplant.

bronchial lung biopsy, where minimal (grade A1), mild (grade A2), moderate (grade A3), and severe (grade A4) forms exist. They have characteristic histologic findings in common: A mononuclear cell infiltrate circumferentially surrounding small vessels [31].

Clinical AMR is defined as the presence of all the following criteria: Allograft dysfunction, clinically proven; lung injury, histologically proven; capillary complement fragment 4d (C4d) deposition (optional); circulating donor-specific antibodies; and other causes for allograft dysfunction excluded[33]. However, to improve the SLT outcomes, AMR should be better diagnosed. However, factors such as C4d staining limitations, inter-observer variability, and the influence of non-DSA HLA genes may impact AMR diagnosis. Finally, although this form of rejection leads to reversible allograph failure, CLAD has a high incidence among survivors[34].

Patients can develop acute worsening of the condition of deteriorated pulmonary function in the years after SLT, with a sudden rise in shortness of breath–ALAD. This entity is another early complication. It is thought that capillary leak syndrome, anastomotic complications (*e.g.*, dehiscence of bronchial anastomoses), pulmonary embolism, and infection and allograft rejection are one of the main culprits for its development[35]. The mortality rate of ALAD is estimated at 3.6% for SLT recipients within the first 30 d. Therefore these data should be kept in mind by clinicians. There is a strong correlation between the number of episodes of ALAD in SLT recipients and developing CLAD. Therefore, this complication should not be underestimated[36]. However, if the reduction in pulmonary function is not returned to > 90% of the baseline 3 wk after ALAD, despite the treatment of the secondary causes such as infection, acute allograft rejection, or airway stenosis, CLAD diagnosis can be assumed [37,38]. CLAD is characterized by a reduction (≥ 20%) in measured forced expiratory volume in one second value compared to the baseline value. It could present with either an obstructive ventilatory pattern, a restrictive pattern, or a mixed pattern[38-40]. Furthermore, CLAD could be subdivided into clinical phenotypes: Bronchiolitis obliterans syndrome (BOS), restrictive allograft syndrome (RAS), mixed or undefined

subphenotype[38]. BOS is a condition of intraluminal airway fibrosis, defined by progressive airflow obstruction, unexplained by acute rejection, infection, or other coexistent conditions[41].

On the other hand, RAS is characterized as pleuroparenchymal fibroelastosis, most often triggered by a variety of microorganisms isolated in sputum or bronchoalveolar lavage, which lead to an excessive fibrotic reaction[42]. However, RAS was also associated with AR development (and especially AMR) and chronic rejection, where inflammation plays a significant role. Literature data showed that within the first 5 years following SLT, approximately 50% of recipients are diagnosed with either BOS- or RAS-related CLAD. BOS-related CLAD has been more common after SLT and represents 70%, of all CLAD complications, in contrast to RAS-related CLAD, which develops in one-third of all SLT recipients[6,43]. The main three mechanisms for complications after SLT are presented in Figure 1.

As there is typically a higher chance of rejection after lung transplant, SLT recipients need life-long and intense immunosuppressive treatment to prevent graft rejection. Immunosuppressive regimen after LT most often involves a triple combination of corticosteroid, cyclosporine/tacrolimus, and azathioprine/mycophenolate mofetil[44,45].

Despite the unclear treatment algorithm, several authors reported azithromycin's role in delaying CLAD progression because of its antibiotic, anti-inflammatory, and promotility effects. Another feasible option for the management of CLAD is switching classes of immunosuppressive drugs[46,47]. However, the last therapeutic option in treating end-stage CLAD is retransplantation.

TECHNICAL COMPLICATIONS RELATED TO SLT

Since the early days of LT, anastomotic complications have been recognized as one of the risk factors for post-LT mortality (2%-3%)[48]. Many authors classify anastomotic complications as obstructive (persistent airway stenosis) and necrotic (including partial or full-thickness ischemia)[49]. The most common anastomotic obstructive complications are airway stenosis as a result of excessive production of granular tissue, cicatrix fibrosis, and dynamic collapse secondary to bronchomalacia. On the other hand, bronchial dehiscence (with or without pleural fistula), anastomotic ulceration, and sloughing of the eschar mucosal tissue are necrosis-related complications [49]. Technical anastomotic complications are frequently complex, influenced by different factors such as surgical, immunosuppressive treatment, mechanical ventilation, reperfusion time (ischemic injury), and donor-related factors. For example, a size mismatch between donors' or recipients' airways and blood vessels is associated with PGD3. Simultaneously, the usage of positive pressure mechanical ventilation could lead to early graft failure[50]. Besides, from a surgical perspective, absorbable suture materials and shortened bronchial cuffs decrease the risk of anastomotic complications (10.9%)[51].

Moreover, Yserbyt *et al*[52] reported that surgical anastomotic complication has right-sided predominance with a frequency of 67%. Contrariwise, Benvenuto *et al*[53] showed that compared to left SLT for patients with COPD, right SLT has decreased mortality risk. They reported that COPD recipients with right SLT had significantly higher short-term and long-term survivals compared to left SLT recipients. Benvenuto *et al*[53] considered that reduced survival in left SLT recipients resulted from intense native lung hyperinflation. Therefore, right SLT is more successful because the left lung has a smaller size and heart-limiting excessive hyperinflation. The authors also reported that post-LT infectious airway complications are lower in patients with right SLT. Another critical factor for developing anastomotic complications is the type of immunosuppressive therapy and different regimens, especially high-dose steroids, which might affect the graft function and patient's outcome[54]. High-dose corticosteroids can increase the risk of airway complications by increasing susceptibility to infection, by delaying healing[48].

CARDIOVASCULAR COMPLICATIONS AFTER SLT

Cardiovascular complications (CVCs) are one of the major causes leading to high mortality rates after SLT. There are plenty of CVCs in the post-SLT period. Still, atrial dysrhythmias are the most common early complication with an incidence of 25%-35%. It was established that the usage of catecholamines, adverse effects of medications, and

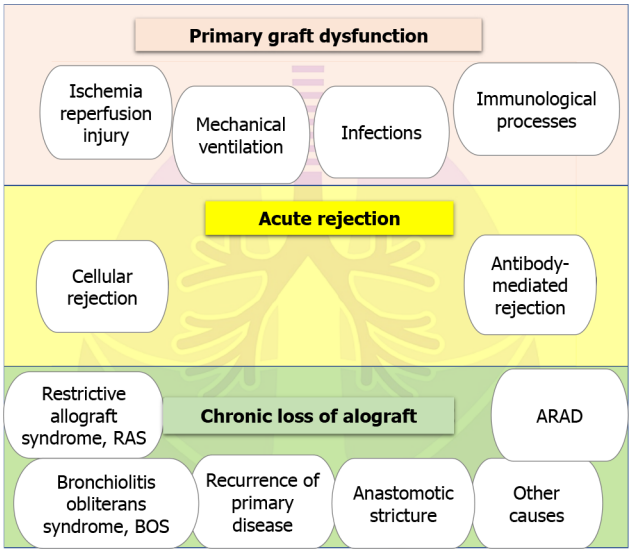

Figure 1 Complications after single lung transplantation. The major complications associated with a single lung transplant: Primary graft dysfunction, as a consequence of organ procurement, cold storage, and implantation; cell- and antibody-mediated acute and chronic rejection (CLAD). CLAD phenotypes are presented mainly as bronchiolitis obliterans syndrome (BOS), restrictive allograft syndrome (RAS), recurrence of primary disease, anastomotic stricture, and azithromycin-responsive allograft dysfunction, as well as other specific causes of decline in lung function.

mechanical stresses related to vascular anastomoses could be risk factors for atrial dysrhythmias[55]. A study by D'Angelo *et al*[56] that involved 652 lung transplant recipients, showed that the appearance of atrial arrhythmias is associated with prolonged hospital stay and significantly increased the mortality rate of these patients. Additionally, the authors determined that atrial arrhythmias could be a feasible independent predictor for determining mortality rate after SLT. Another important CVC that leads to a high mortality rate after SLT is developing coronary artery disease (CAD) and myocardial infarction (MI). Risk factors such as dyslipidemia, hypertension, chronic kidney disease (CKD), chronic usage of corticosteroids, and immunosuppressive medications are thought to be the significant causes for CAD and MI[55].

Venous thromboembolism after SLT

Venous thromboembolic (VTE) complications, especially deep venous thrombosis (DVT) and pulmonary embolism (PE) are important and common post-operative complications after LT. The announced frequency of PE and DVT is 5%-15% and 20%-45%, respectively. Factors such as SLT, hypercoagulable status, immunosuppressive therapy, high doses of corticosteroids, and prolonged ICU stay duration are strongly associated with VTE development[54]. Moreover, a study by Fan *et al*[57], including 316 lung transplant patients, showed that 19 (6%) patients developed VTE during the follow-up period. Furthermore, the part of SLT in the VTE group was higher than that in the non-VTE group (78.9% *vs* 48.5%). The thrombotic events could dramatically deteriorate the patient's outcome; thus, efforts must be directed towards the early and adequate prophylaxis after SLT.

NATIVE LUNG COMPLICATIONS

Even though SLT has several benefits over bilateral LT, it is still a double-edged sword regarding the native lung, which remains one of the major causes of post-SLT complications[58,59].

In contrast to SSLTx, SLT recipients are more likely to experience pneumothorax, hyperinflation, and opportunistic infections, especially with Mycobacterium species and Aspergillus associated with native lung. Therefore, this can potentially compromise both early and late outcomes[58,60].

Pneumothorax is often a result of post-operative mechanical ventilation in the underlying native lung disease (*e.g.*, emphysema and pulmonary fibrosis). However, it could develop later, years after the transplant, depending on the primary disease[61].

Other important complications in the native lung are opportunistic infections, which frequently had a lethal outcome in patients, despite normal preoperative sputum

examination and bronchoscopy. The persistence of bacterial colonization despite proper pharmacotherapy is one indicator that favors double LT (DLT), especially in pulmonary fibrosis patients. This assessment aims to reduce the chance of bacterial complications arising in the native lung and spread of the infection to the graft after immunosuppression onset[58]. Reduced mucociliary clearance, altered sputum characteristics, and in some cases, chronic bacterial colonization might contribute to the predisposition to infections as well as their early spreading[62].

Considering the immunosuppressive treatment, one might expect a high infection rate, especially fungal, after SLT. The prevalence of fungal infection among lung transplant recipients is estimated to be 15%–35%, with *Candida* and *Aspergillus* being the most common pathogens. In the perioperative phase, however, invasive fungal infection in lung transplant recipients was comparatively low. Antifungal prophylaxis and care should be tailored to the fungal dissemination status of each organism[63].

In the current context of native lung complications, it is well admitted that acute native lung hyperinflation (ANLH) is a post-SLT complication characterized by radiographic mediastinal shift and ipsilateral diaphragmatic flattening. This entity has an occurrence rate of 15%–30% after SLT[64]. Clinically, ANHL presents with hemodynamic instability, the necessity of catecholamine therapy, and respiratory failure due to allograft compression[65]. Body plethysmography can provide useful information about this entity, but the diagnosis is based on the aforementioned specific radiographical signs[66,67]. Several critical points prevent ANLH, such as early post-operative extubation and respiratory physiotherapy, with the patient's early mobilization[68,69].

Furthermore, Shehata *et al*[59] emphasized mechanical ventilation regimens intending to treat ANLH. They suggested that prophylactic noninvasive positive pressure ventilation was the first-choice treatment because it reduces the weaning time and risk of prolonged invasive mechanical ventilation. Also, Roca *et al*[70] have shown that high-flow nasal cannula has a significantly beneficial role in treating ANLH as well. They concluded that high-flow nasal cannula reduces the necessity of invasive ventilation in LT recipients readmitted to the ICU with acute respiratory failure. The noninvasive positive pressure ventilation or high flow nasal cannula could be a feasible option to prevent respiratory failure in ANLH.

On the other hand, in cases with ANHL indicated for endotracheal intubation, several authors recommend endoscopic suction and the application of bronchial blockers[71]. If this strategy fails, differential lung ventilation is another option for the management of ANHL. However, the last step of management is lung volume reduction surgery.

Last, but not least, recipients with pulmonary fibrosis and smoking-induced emphysema have a greater risk of developing bronchial carcinoma in the native lung after SLT. Pneumonectomy of the residual lung may then be used as a therapeutic option to help these patients live longer[58].

GI COMPLICATIONS AFTER SLT

Many published studies have shown that in patients who have undergone LT, GI complications are common and represent a significant cause of post-operative morbidity and mortality[72]. Gastropareses, microaspiration, diminished cough reflex, abnormal mucociliary clearance are conditions that have occurred with high frequency after LT. These entities might be associated with complications such as laryngitis, pneumonia, lung abscess, acute and chronic bronchitis after LT[73]. A correlation was established between GI complications and impaired malabsorption of medications and malnutrition after the early post-operative period, and recurrent lung allograft dysfunction[35,74,75]. GI complications may occur during the first 30 d after SLT (early complications) or if prolonged > 30 d, they are classified as late complications[71].

We found that high mortality rates after SLT are associated with early-onset (< 30 d) and severe GI complications[76]. Few studies are conducted on possible risk factors involved in the development of severe GI complications. For example, age and bilateral LT are associated with severe GI complications. Hypoxia can explain this correlation because bilateral LT is associated with longer ischemic time, more extended procedure, and reduced oxygenation, with an increased risk of primary graft failure [75]. Severe GI complications have been identified as any GI or biliary tract-related diagnosis leading to a significant repercussion for the patient that could endanger their life or involve an invasive therapeutic procedure[72].

The immunosuppressive regimen of patients after SLT plays a significant role in the development of GI complications. In patients with severe immunosuppression,

cholecystitis and diverticulosis are more common compared to the general population [77,78].

Grass *et al*[75] published a fascinating study analyzing various risk factors related to GI complications in patients after LT for a period of 17 years. They estimate a 61.5% frequency of GI complications after LT, which is higher than other studies. The authors included 205 patients; of these, 180 underwent DLT, 40 underwent SLT, and 7 underwent multiorgan transplantations. GI complications such as gastroesophageal reflux disease (GERD) (22.9%), infectious colitis (20.5%), and gastroparesis (10%) were observed with high frequency. Another important conclusion from the study was that severe GI complications were observed in 83 patients (40.5%). As risk factors, they defined DLT and early transplantation period[75]. Many authors consider GERD as one of the most common GI complications after SLT. For example, Davis *et al*[77] estimated that the prevalence of GERD is about 51%-69% in patients after LT. They showed that distal and proximal reflux depends on LT type. They demonstrated that bilateral LT or re-transplantation are associated with a higher incidence of distal and proximal reflux.

On the other hand, unilateral LT correlates with a lower percentage of GERD, regardless of the course of lung disease. Multiple factors have been involved, including intraoperative vagal nerve damage, cough reflex deficiency, impaired mucociliary clearance, and gastroparesis development. They also noted an association between calcineurin inhibitors (CNIs) and other post-transplant immunosuppression therapies in GERD development[77]. Kayawake *et al*[78] published a report about GI complications following LT among the Japanese population. They included 160 LT patients (77 Living-donor lobar lung transplant and 83 deceased donor lung transplant), 59 SLT, 101 bilateral LT. GI complications were registered in 58 of these patients. Thus, gastroparesis, followed by GERD, clostridium difficile colitis, and GI bleeding, was the most common complication. An important implication from their study is that gastroparesis and clostridium difficile colitis appeared early after LT. At the same time, cytomegalovirus gastroenteritis and pneumatosis intestinalis emerged in the late LT period[78].

Overall, the authors postulated some significant findings related to GI complications after LT. First, they established a positive correlation between gastroparesis and bilateral LT incidence with extracorporeal circulation. They also found no major disparity between higher mortality in Japanese patients with GI complications after LT than in Western countries[78].

In conclusion, GI complications after LT are more common in patients who underwent bilateral LT compared to those with SLT[79]. This correlation could be explained by longer ischemic time, more prolonged procedure, and reduced oxygenation. Careful post-operative surveillance, comprehensive monitoring, and evaluation of GI complications by a multidisciplinary team are mandatory for better outcomes after LT [80].

KIDNEY COMPLICATIONS AFTER SLT

Nowadays, SLT patients have more prolonged survival; thus, they are more prone to clinical complications. One of the common and increasingly known is renal failure [77]. Renal failure increases the difficulty of patient care in both acute and chronic settings. It leads substantially to morbidity and mortality after transplantation. It was estimated that the mortality risk is 4-to 5-fold higher in patients with CKD after LT[81].

It is considered that recipient-related factors such as a low BMI and older age could be related to CKD development[82]. Aggravation of kidney function typically begins within the first 6 mo after transplantation and progressively deteriorates after that[83]. Approximately 3%-10% of patients who underwent LT ultimately develop end-stage renal disease[84]. The typical CKD presentation in LT recipients is characterized by a decrease in the GFR in the first 6 mo post-transplant, approximately 30% to 50%[85]. The main risk factors associated with arising of CKD after LT are kidney function immediately pre-transplant and in the early post-operative period, increasing recipient age at transplant time, female gender, presence of diabetes mellitus, hypertension as well as immunosuppressive treatment[81].

CNIs (*i.e.* cyclosporine, tacrolimus) are the cornerstone of immunosuppression after LT[86]. Many studies have reported the correlation between impaired kidney function and CNI administration among lung recipients. CNI-mediated nephrotoxicity can lead to both acute and chronic renal failure after LT.

A study by Solé *et al*[82] pointed out that CNI reduction is an optional strategy to improve renal function instead of total CNI withdrawal. A study by Högerle *et al*[87] demonstrated promising results using basiliximab as an induction immunosuppressant drug after LT patients to prevent kidney failure by delaying administration of CNI until the fourth post-operative day. It must be kept in mind that significant deterioration of renal function after LT confirms the need for new strategies to improve patients' outcomes after LT.

HYPERAMMONEMIA SYNDROME AFTER SINGLE LUNG TRANSPLANT

Primary hyperammonemia is a sporadic condition associated with urea cycle enzyme deficiency. Secondary hyperammonemia has been linked with various etiologies such as hepatic dysfunction as a result of different entities, obstructive uropathy with overgrowth of urea-splitting organisms, and many others[88].

In the literature, there are little data related to this rare post-SLT complication. A study by Chen *et al*[89] which included 807 LT patients, focused on hyperammonemia as a fatal complication. They diagnosed hyperammonemia in 8 patients (underwent DLT); 6 (75%) died due to this syndrome. The authors contributed a rationale treatment protocol for managing patients with hyperammonemia after LT. They recommended bowel decontamination, renal replacement therapy, amino acid supplementation, and nitrogen scavenger therapy as the main therapeutic strategies for treating hyperammonemia.

DE NOVO MALIGNANCY AFTER SLT

Considering post-transplant complications, secondary malignancies are among the most devastating ones. There are various mechanisms behind tumor initiation in transplanted patients, mainly attributed to therapeutic immunosuppression and consequent abnormalities in T-cell function, deoxyribonucleic acid repair, angiogenesis, cellular proliferation, and invasiveness[90]. Other exogenous factors such as Epstein-Barr virus (EBV), ultraviolet light, or tobacco smoking are also implicated in post-transplant tumors' etiology[91-94]. Beyond common risk factors, valid for every organ recipient, in the specific setting of SLT, one should account for an additional risk ensuing from leaving a native lung. Presumably, at the time of transplantation, the remaining organ has already suffered severe damage by preexisting chronic inflammation and fibrosis, increasing the chance for lung cancer, especially when antitumor immune surveillance is compromised by the post-transplant treatment.

The overall risk of malignancies after transplantation is several times higher than that for the general population. According to some series, nearly one-third of transplanted patients develop tumors in the first decade following transplantation[95]. The most common tumors in the post-transplant period are skin neoplasms and lymphoproliferative diseases. Still, any other kind of cancer, including those with the heaviest social burden such as colon cancer, breast carcinoma, and lung cancer, could also be encountered.

Both hematologic and solid tumors are considered among the significant reasons for death after LT, being third only to graft rejection and infections[35]. Among lung transplanted patients, cancer morbidity rises with time increasing from 3.8% in the first year to 13% in year 5[96]. Skin neoplasms account for the majority of the malignancies in the post-transplant period. A high frequency of skin cancer was demonstrated in a study by the Mayo Clinic, with an incidence of squamous cell and basal cell cancer of 28% and 12%, respectively, among lung transplant recipients, within 5 years of LT. Similar results were obtained from other LT centers (Sydney, Australia, and London, United Kingdom)[97-99].

In LT patients, their incidence is highest between years 5 and 7 after transplantation [94]. The risk of non-melanoma skin cancer is greater than that for melanoma. For specific entities like squamous cell carcinoma, it is up to 200 times higher than for the general population. These tumors tend to show more aggressive clinical behavior than those seen in non-transplant (immunocompetent) patients, with a higher tendency for local recurrence and metastatic spread. Other skin neoplasms such as basal cell carcinoma, Merkel cell carcinoma, and malignant melanoma are also found with a higher incidence among lung recipients. Of great importance for LT recipients is to receive whole-body dermatological examinations annually.

Another major group of transplant-related malignancies is post-transplant lymphoproliferative diseases (PTLD), which account for most of the neoplasms in the first year after LT[96]. EBV infection and immunosuppression plays significant role in their pathogenesis. In patients after LT, incidence varies widely (2.5%-20%) according to different reports[100,101].

A possible explanation for this is the difference in EBV infection prevalence and the type of immune suppression. Chronic EBV infection could already be present in the recipient at transplantation time. Still, it could also be transmitted from the donor with the graft. Secondary lymphoma risk is significantly higher when an EBV-naive recipient is transplanted with an EBV-infected graft[102]. As LT is still an evolving field, finding a suitable donor is often a challenge. This often precludes a selection based on EBV status. In these situations, when a graft from an EBV+ donor is transplanted to an EBV recipient, prevention of PTLD relies on different approaches in the post-transplant period including serial EBV monitoring, cautious lowering of the immune suppression, or implementation of antiviral prophylaxis[103]. In lung-transplant patients, secondary lung cancer is an issue that deserves special attention due to the aggressive nature and poor prognosis of this malignancy. It could occur in up to 4% of lung recipients. Apart from well-known common factors, the risk also depends on the type of transplantation: Whether it is DLT or SLT. In SLT, lung cancer sometimes originates from the transplanted lung, but 20 times more often, it develops in the native one. This means that, as already discussed, not only immunosuppression but the overall condition of the organ, affected by the preexisting disease, is a strong predisposing factor to malignancy. On the other side, the graft's rigorous assessment in this direction is also mandatory to lower the chance of any early (subclinical) malignant lesions being transplanted to the recipient. An example of the aggressive nature of secondary lung cancers after SLT is provided by Gherzi *et al*[104], who reported a 62-year-old woman with fast-progressing adenocarcinoma of the native lung only 15 mo after transplantation for pulmonary fibrosis. Due to multiple graft rejection episodes, the patient was treated with intensive immunosuppression in the post-transplant period. In this case, the clinical evolution of the carcinoma lasted for only 2 wk with no radiological evidence of any chest tumors as near as 1.5 mo before the lethal outcome.

Clinicians engaged in the surveillance of lung-transplanted patients must always stay alert of the potential occurrence of secondary malignancies, and in SLT specifically, the native lung deserves additional attention. Transplant specialists should also be aware of different prophylaxis and prevention strategies, including selecting immunosuppressive regimens with lower impact on antitumor immune response, monitoring, controlling EBV infection in the post-transplant period, and educating patients on how to reduce lifestyle risk factors.

CONCLUSION

Patients who underwent SLT are predisposed to evolving early or late post-operative complications. Primary or CLAD, anastomosis complications, infections, cardiovascular disease, renal, metabolic, GI disorder, and DNM. Events related to improved surgical techniques and post-operative control of pulmonary immunogenicity through immunosuppressive therapy are among the reasons leading to the reduction of early mortality and longer survival of these patients. Thus, the post-operative management after SLT has to be multidisciplinary and complex.

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World Journal of Transplantation

Submit a Manuscript: https://www.f6publishing.com

World J Transplant 2021 August 18; 11(8): 335-343

DOI: 10.5500/wjt.v11.i8.335

ISSN 2220-3230 (online)

MINIREVIEWS

Biomarkers of graft-*vs*-host disease: Understanding and applications for the future

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Author contributions: Nagasawa M conceptualized the idea, reviewed the literature, and wrote the main draft of the manuscript.

Supported by partly a Grant-in-Aid for Scientific Research (KAKENHI) Grant, No. 15K09639.

Conflict-of-interest statement: I have no conflict-of-interest to declare.

Manuscript source: Invited manuscript

Specialty type: Transplantation

Country/Territory of origin: Japan

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Abstract

Hematopoietic stem cell transplantation (HSCT) is widely performed as a treatment for malignant blood disorders, such as leukemia. To achieve good clinical outcomes in HSCT, it is necessary to minimize the unfavorable effects of acute graft-*vs*-host disease (GVHD) and induce the more tolerable, chronic form of the disease. For better management of GVHD, sensitive and specific biomarkers that predict the severity and prognosis of the disease have been intensively investigated using proteomics, transcriptomics, genomics, cytomics, and tandem mass spectrometry methods. Here, I will briefly review the current understanding of GVHD biomarkers and future prospects.

Key Words: Graft-*vs*-host disease; Hematopoietic stem cell transplantation; Biomarker; Cytokine; Graft-*vs*-host reaction; Organ damage

Core Tip: Graft-*vs*-host disease (GVHD) is the most unfavorable complication of hematopoietic stem cell transplantation (HSCT). Minimizing acute GVHD and inducing its chronic form is necessary to achieve good clinical outcomes in HSCT. GVHD consists of inflammation induced by the conditioning regimen, the alloimmune response of the T lymphocytes, and organ damage due to the graft-*vs*-host reaction. Biological factors have been comprehensively analyzed to identify novel combinations of biomarkers that predict acute GVHD severity and prognosis more efficiently. Currently, there are no useful biomarkers that can predict the severity and prognosis of chronic GVHD or serve a practical clinical use.

Citation: Nagasawa M. Biomarkers of graft-*vs*-host disease: Understanding and applications for the future. *World J Transplant* 2021; 11(8): 335-343

Peer-review report's scientific quality classification
Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 16, 2021
Peer-review started: February 16, 2021
First decision: May 14, 2021
Revised: May 25, 2021
Accepted: August 10, 2021
Article in press: August 10, 2021
Published online: August 18, 2021

P-Reviewer: Aguilera I, Lei YC
S-Editor: Yan JP
L-Editor: A
P-Editor: Guo X

URL: https://www.wjgnet.com/2220-3230/full/v11/i8/335.htm
DOI: https://dx.doi.org/10.5500/wjt.v11.i8.335

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is widely performed as a treatment for malignant blood disorders, such as leukemia. Graft-*vs*-host disease (GVHD) is the most unfavorable complication of HSCT. Although the diagnostic process and management of GVHD are improving, GVHD remains a major clinical problem in transplantation medicine[1,2].

GVHD develops in the background of the immune response of the transplanted immune-competent cells against the alloantigens of the host, which is called the graft-*vs*-host (GVH) reaction. Such a reaction can cause allogeneic HSCT to induce GVHD. When the GVH reaction induces unfavorable symptoms, usually symptomatic organ damage, it is considered to be GVHD. When HSCT is performed as a treatment for malignant diseases in particular, the GVH reaction is therapeutically necessary, and it has been shown that a chronic GVH reaction (chronic GVHD) is correlated with the prevention of disease relapse and improved disease-free survival[3]. In acute GVHD, the relapse prevention effect is offset by its life-threatening complications, and a significant improvement in disease-free survival is difficult to prove in general[4]. Therefore, it is necessary to minimize the unfavorable effects of acute GVHD and induce tolerable chronic GVHD to achieve good clinical outcomes in HSCT for malignant diseases.

The severity of acute GVHD or the degree of organ damage is classically evaluated based on the clinical symptoms of three organs: the skin, liver, and intestine[5]. Therapeutic intervention for acute GVHD is usually considered in cases of grade 2 or above. It is difficult to predict responsiveness to treatment based on clinical severity and laboratory data before the intervention. It has been reported that the treatment response evaluated through clinical manifestations is rather important to predict prognosis. However, at least 4 wks of observation is necessary to determine the clinical improvement[6] and it is reported that 1 wk of clinical observation is not enough to predict the prognosis[7]. Therefore, a useful biomarker that can predict the responsiveness and prognosis of acute GVHD during a short interval has been intensively investigated. In addition, it must be considered that changes in the conditioning regimen, transplanted stem cells, and therapeutic immunosuppressive drugs may affect the utility of the rating system. Furthermore, we may have to re-consider the validity of conventional GVHD grading for the utility of novel biomarkers.

In this short review, acute GVHD-related biomarkers are discussed according to three divided phases: (1) An initiating proinflammatory period; (2) A GVH reaction induced by an immune response to alloantigens; and (3) The induction of organ damage as a result of GVHD (Figure 1). It is reasonable to expect that the biomarker of the GVH reaction is correlated with the intensity of GVHD. However, this is to be answered in terms of GVHD prognosis. Is the absolute value of the biomarker important? Is the duration of elevated biomarkers important? Otherwise, is responsiveness to the treatment important? Furthermore, the prognosis of GVHD is affected by host factors, which makes this problem more complicated.

THE BIOMARKERS OF EARLY INFLAMMATION

Inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and IL-6 are known to be released early in the transplant from the tissue or vascular endothelium damaged by the anticancer drugs or irradiation used in the conditioning regimens. These tissue-derived cytokines promote vascular endothelial damage and are thought to amplify the GVH reaction of transplanted lymphocytes through the activation of antigen-presenting cells[8]. When these cytokines are excessively produced, they are referred to as cytokine storms and are thought to be involved in hyperacute GVHD.

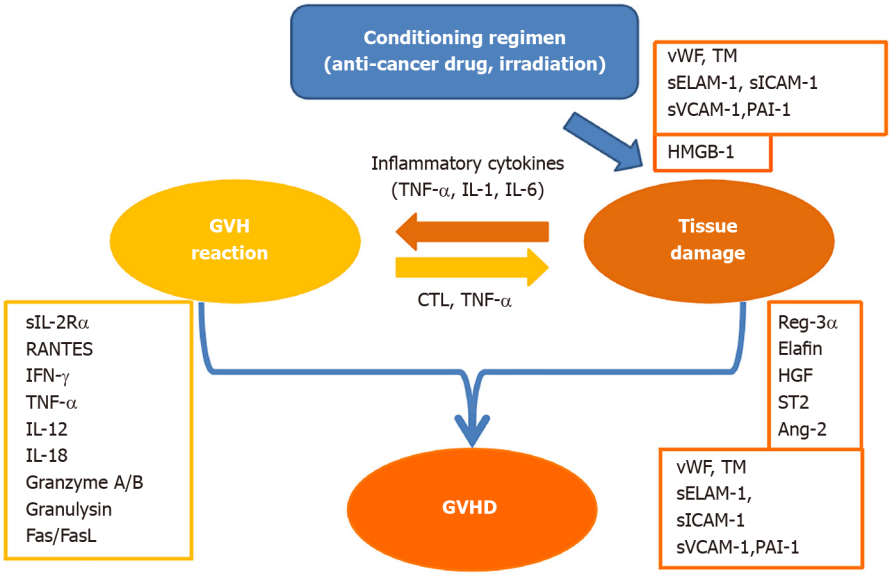

Figure 1 Simplified schema of the graft-*vs*-host reaction and graft-*vs*-host disease, and related biomarkers. Biomarkers of endothelial injury are presented separately from other tissue damage-related biomarkers in graft-*vs*-host disease (refer to the main text). Ang-2: Angiopoietin-2; CTL: Cytotoxic T lymphocyte; Fas-FasL: Fas and Fas Ligand; GVH: Graft-*vs*-host; GVHD: Graft-*vs*-host disease; HGF: Hepatocyte growth factor; HMGB-1: High-mobility group box 1; IFN-γ: Interferon-γ; IL: Interleukin; PAI-1: Plasminogen activator inhibitor-1; RANTES: Regulated upon activation, normal T cell expressed and secreted; Reg-3α: Regenerating islet-derived 3α; sELAM-1: Serum endothelial leucocyte adhesion molecule-1; sICAM-1: Soluble intercellular adhesion molecule-1; sIL-2R: Soluble IL-2 receptor; ST2: Suppression of tumorigenicity 2; sVCAM-1: Soluble vascular cell adhesion molecule-1; TM: Thrombomodulin; TNF-α: Tumor necrosis factor-α; vWF: von Willebrand factor.

THE BIOMARKERS OF THE GVH REACTION

The GVH reaction appears as an alloimmune response of T lymphocytes, inducing the activation of T lymphocytes, overproduction of cytokines, and development of primarily CD8-positive cytotoxic T lymphocytes (CTLs).

The most frequently used biomarker of T cell activation is a soluble IL-2 receptor (sIL-2R)[9]. regulated upon activation, normal T cell expressed and secreted (RANTES) is also used[10]. Recently, a sensitive assay system has been developed for several T cell derived extracellular vesicles (TDEVs), which are triggered for release by activation[11]. It was found that TDEVs accurately reflect the GVH reaction and acute GVHD specifically[12]. In addition, interferon-g (IFN-g) released by activated T lymphocytes activates macrophages to produce TNF-α, which promotes tissue injury [13] and is reported to be a useful biomarker of GVHD[14,15]. In contrast, ferritin and soluble CD163, which are also produced by activated macrophages in this phase, are reported to be associated with the prognosis of HSCT rather than GVHD[16]. It has been reported that type 1 T helper (Th1) immunity is the main component of acute GVHD, and that Th1 cytokines, IL-12, and IL-18 are biomarkers of GVHD[17].

The activated biomarkers of CTLs include granzyme A/B[18] and granulysin[19]. The former exhibits direct killing activity against all target cells in the presence of perforin, while the latter displays direct killing activity towards all target cells by itself [20]. Additionally, there is the Fas and Fas Ligand (Fas-FasL) system, which exhibits killing activity against only the target cells expressing Fas[21], such as that of hepatocytes and the epidermis[22].

The abovementioned biomarkers are indicators of the GVH reaction but are not directly related to the severity of GVHD, which is based on organ injury, damage, or dysfunction. A component of the biomarkers produced by the GVH reaction is the so-called inflammatory cytokine that induces fever[23], but the fever does not necessarily correlate with the severity of GVHD.

THE BIOMARKERS THAT REFLECT ORGAN DAMAGE DUE TO GVHD

Gastrointestinal tract

Regenerating islet-derived 3α (Reg-3α) is a C-type lectin that was discovered in regenerating islet cells. Reg-3α has antibacterial activity against gram-positive bacteria and is thought to be produced during the destruction and repair of intestinal tissue. It has been reported that the level of Reg-3α on days 7 and 14 of HSCT predicts acute GVHD and non-relapse mortality (NRM) very well[24,25].

Skin

Elafin, also known as skin-derived antileukoprotease or peptidase inhibitor 3, correlates well with skin symptoms due to GVHD[26]. It is thought to be produced as part of the tissue repair process for skin lesions caused by GVHD.

Hepatocytes

Hepatocyte growth factor (HGF) regenerates hepatocytes, and serum HGF levels are high in acute GVHD[27]. It is considered to reflect the regeneration response of hepatocytes damaged by GVHD. Interestingly, HGF has the ability to relieve acute GVHD in mice[28].

Vascular endothelium

Vascular endothelial injury related to GVHD is a complicated problem associated with HSCT. There are no characteristic clinical manifestations of vascular endothelial injury, such as with GVHD of the skin (rash), liver (jaundice), and intestine (diarrhea), and differentiation from other complications such as thrombotic microangiopathy or veno-occlusive disease that develop in the background of endothelial injury during the process of HSCT is quite difficult. GVHD-related vascular endothelial injury usually spans across various organs.

The presence of vascular endothelial injury has been reported to influence the onset and prognosis of acute GVHD[29]. The following biomarkers of vascular endothelial injury have been reported: von Willebrand factor (vWF)[30], thrombomodulin (TM)[31], soluble adhesion molecules (sELAM-1, sICAM-1, and sVCAM-1)[32], plasminogen activator inhibitor-1 (PAI-1)[33], endothelial-derived microparticles (EDMPs)[21], and platelet-derived microparticles (PDMPs)[30]. Microthrombi arise through the activation of vascular endothelial cells, migration of inflammatory cells, and platelet activation and aggregation, resulting in circulation disturbance and organ damage. D-dimer, which is commonly used as a marker of thrombi, is a sensitive nonspecific biomarker of endothelial injury[29]. Angiopoietin-2 (Ang-2), associated with angiogenic activity, has also been reported as a biomarker[34].

At present, it is considered that GVHD is an exacerbating factor of vascular endothelial injury, and intractable vascular endothelial disorder and the elevated vascular injury biomarker are thought to be associated with refractory GVHD[35] and poor prognosis[36,37] rather than a predictor of GVHD.

Suppression of tumorigenicity 2 (ST2) belongs to the IL-1 receptor family, binds to IL-33, and induces a Th2 immune response. Soluble ST2 inhibits IL-33 as a decoy receptor, and it is said to act on a Th1 deviated response[38]. ST2 has been reported as a biomarker of cardiovascular diseases and is thought to reflect myocardial repair and remodeling. When ST2 is high, myocardial damage is considered severe, and the prognosis of cardiovascular diseases is poor[39].

ST2 is reported to reflect refractory GVHD in the examination of acute GVHD[40]. It has been reported that the ST2 value on day 28 post-transplantation is associated with grade 3–4 GVHD with a much better NRM rate than TNF-α, IL-8, Reg-3a, sIL-2Ra, elafin, and HGF in the cord blood transplantation cohort[41]. It is speculated that ST2 is elevated along with tissue damage in refractory GVHD, and then the increased ST2 may induce a Th1 response by inhibiting IL-33, thus further aggravating the acute GVHD.

High-mobility group box 1 (HMGB-1) is a ubiquitous nuclear protein that regulates chromatin function, similar to histones. HMGB-1 is released from activated macrophages or damaged tissues and induces inflammation *via* interactions with toll-like receptors (TLR2 or TLR4). Therefore, HMGB-1 is considered a damage-associated molecular pattern (DAMP). In a mouse model, HMGB-1 has been reported to be involved in the pathogenesis of GVHD[42,43]. In humans, increased HMGB-1 levels on day 0 are reported to be associated with vascular injury, but not necessarily with GVHD[44].

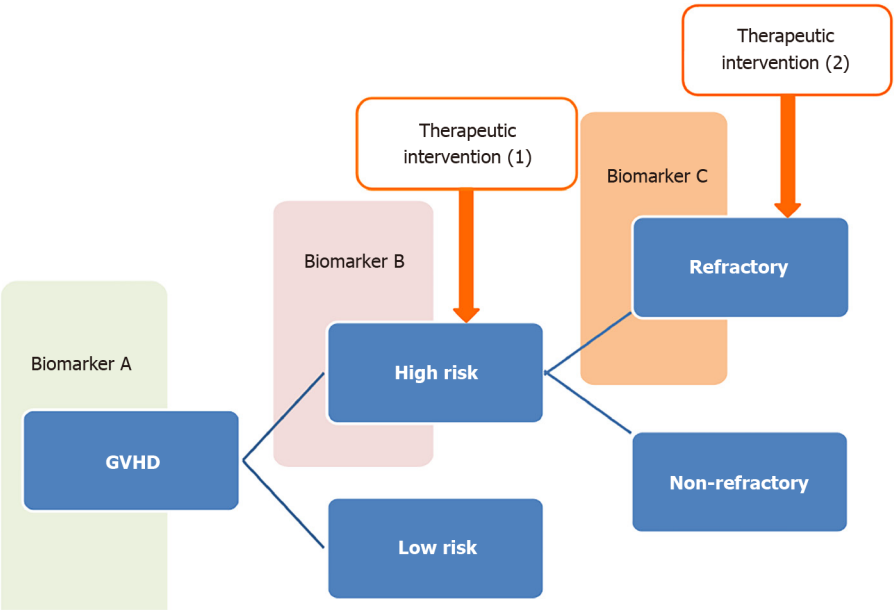

Figure 2 An overview of tentative stratification for graft-*vs*-host disease biomarkers. Biomarker A: Predicts graft-*vs*-host disease (GVHD); Biomarker B: Predicts a high risk of GVHD; Biomarker C: Predicts responsiveness to therapeutic intervention (1). GVHD: Graft-*vs*-host disease.

DO GVH REACTION BIOMARKERS BECOME A PREDICTOR OF GVHD?

It is reasonable that the GVH reaction biomarkers are related to GVHD because the latter is fundamentally based on the former. However, it is also true that it is quite difficult for one or a few biomarkers to predict GVHD prognosis precisely, because there are numerous and diverse pathological factors involved in the process of HSCT, in addition to the heterogeneity of the donor and recipient.

Recently, a comprehensive analysis of biological factors has been performed using proteomics, transcriptomics, genomics, cytomics, and tandem mass spectrometry methods to identify novel combinations of biomarkers that predict the severity and prognosis of GVHD more efficiently rather than searching useful biomarkers by disclosing the basic pathogenesis of GVHD[45].

IS IT BETTER TO MAKE PREDICTIONS BEFORE OR AFTER TREATMENT?

In the treatment of pediatric acute lymphocytic leukemia, a remarkable improvement in prognosis has been achieved under the two-step stratification of therapy by pre-treatment and steroid-sensitive factors, without the introduction of new anticancer drugs between 1960 and 1995[46].

Based on a similar concept, it will be necessary to stratify therapeutic strategies by considering both the severity of GVHD and responsiveness to treatment according to the proper combination of biomarkers to overcome refractory GVHD (Figure 2). There are several reports of biomarkers that predict responsiveness to GVHD therapy in a short observation period[47,48]. However, it must also be taken into consideration that the clinical outcomes of GVHD are affected by the progress of preventive and targeted therapy for GVHD.

IS THERE A GOOD BIOMARKER FOR CHRONIC GVHD?

Chronic GVHD is similar to collagen disease in that its pathological essence is based on immune dysregulation[49]. In chronic GVHD, a high level of soluble B cell-activating factor, an abnormality of the B lymphocyte subset[50], and a decrease in regulatory T cells (CD4+CD25+FOXP+/CD4 ratio)[51] have been reported. matrix metalloproteinase-3 (MMP-3) has been reported to be associated with non-infectious obstructive bronchiolitis[52], which is one of the most intractable and lethal complic-

ations of chronic GVHD. Currently, there are no useful biomarkers that can predict the severity and prognosis of chronic GVHD or serve a practical clinical use.

Recently, there has been much progress in the understanding of acute and chronic inflammation based on basic immunology[53,54]. In these studies, it was reported that chromatin and DNA modifications in immune cells are significant in chronic inflammation. Based on a new approach towards and an understanding of chronic GVHD, it is expected that its essential pathology will be disclosed and the available biomarkers will be discovered in the near future.

CONCLUSION

The sensitive and specific biomarkers that predict the severity and prognosis of GVHD have been intensively investigated through using proteomics, transcriptomics, genomics, cytomics, and tandem mass spectrometry methods. Although the utility of available biomarkers have limitations for the clinical decisions, it is expected that its essential pathology will be disclosed and the more useful biomarkers will be discovered in the near future.

ACKNOWLEDGEMENTS

I appreciate all of the staff at the Tokyo Medical and Dental University Hospital who were involved in the medical care of patients with SCT.

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World Journal of Transplantation

Submit a Manuscript: https://www.f6publishing.com

World J Transplant 2021 August 18; 11(8): 344-355

DOI: 10.5500/wjt.v11.i8.344

ISSN 2220-3230 (online)

MINIREVIEWS

May mesenchymal stem cell transplantation be a solution for COVID-19 induced cytokine storm?

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Author contributions: Sütlüoğlu H performed the writing, created the figures and tables; Özdemir Ö designed the outline, and coordinated the writing of the paper.

Conflict-of-interest statement: The authors declare no conflict of interest regarding the publication of this paper.

Manuscript source: Invited manuscript

Specialty type: Transplantation

Country/Territory of origin: Turkey

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Abstract

The recently emergent disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), transmitted by droplets and aerosols, was named coronavirus disease 2019 (COVID-19) by World Health Organization. Predominantly, the disease progress is asymptomatic or mild, but one-fifth of the patients advance to severe or critical illness. In severe COVID-19 patients, type-2 T helper cells release numerous cytokines; this excessive immune response is named as cytokine storm. The cytokine storm, which is the hallmark of the COVID-19 induced by the disease and aggravates due to lack of proper immune response, similar to SARS and Middle East respiratory syndrome (MERS), and the disease status may progress forward to acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome, multi-organ dysfunction syndrome, and death. Mesenchymal stromal cell transplantation is up-and-coming in treating many diseases such as HIV, hepatitis B, influenza, coronavirus diseases (SARS, MERS), lung injuries, and ARDS. Upon closer inspection on respiratory diseases, COVID-19, influenza, SARS, and MERS have similarities in patho-genesis, especially cytokine and immune response profiles. These comparable features in terms of the cytokine storm will provide hints for the treatment of COVID-19.

Key Words: Mesenchymal stem cell; Mesenchymal stromal cell; COVID-19; Cytokine storm; Immunosuppression; Transplantation

Core Tip: Upon closer inspection on respiratory diseases, coronavirus disease 2019 (COVID-19), influenza, severe acute respiratory syndrome, and Middle East

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 22, 2021
Peer-review started: February 22, 2021
First decision: May 5, 2021
Revised: June 16, 2021
Accepted: August 10, 2021
Article in press: August 10, 2021
Published online: August 18, 2021

P-Reviewer: Wu LH
S-Editor: Yan JP
L-Editor: A
P-Editor: Li X

respiratory syndrome have similarities in pathogenesis, especially cytokine and immune response profiles. These comparable features in terms of the cytokine storm will provide hints for the treatment of COVID-19. Transplantation of mesenchymal stromal cells provides tissue regeneration and rejuvenation with immunotolerant and immunomodulant properties on damaged tissues by exerting their effects through immune cells.

Citation: Sütlüoğlu H, Özdemir Ö. May mesenchymal stem cell transplantation be a solution for COVID-19 induced cytokine storm? *World J Transplant* 2021; 11(8): 344-355
URL: https://www.wjgnet.com/2220-3230/full/v11/i8/344.htm
DOI: https://dx.doi.org/10.5500/wjt.v11.i8.344

INTRODUCTION

The substantial clues of a novel severe acute respiratory syndrome (SARS)-like coronavirus and possible outbreak were predicted with highlighting pandemic preparedness by Ge *et al*[1] from Wuhan in 2013. Two years after this study, Menachery *et al*[2] had been likewise drawing attention to a potential risk of SARS coronavirus (SARS-CoV) re-emergence from viruses circulating in bat populations. In late 2019, a few patients related to a seafood market in Wuhan province from China with the symptoms of fever, myalgia, dry cough, dyspnea, headache, sore throat, diarrhea, nausea, vomiting, and SARS-like viral pneumonia were reported[3,4]. Further analyses have shown a novel single-stranded enveloped RNA virus from the Coronaviridae family, and the genome sequence of the virus had 96.2% similarity with other bat betacoronaviruses causing previous diseases [79.6% with SARS, approximately 50% with Middle East respiratory syndrome (MERS)]. The recently emergent disease caused by the SARS-CoV-2 virus, transmitted by droplets and aerosols, was named coronavirus disease 2019 (COVID-19) by World Health Organization (WHO)[5-8]. As a consequence of increasing cases, WHO has announced that the outbreak would be assessed as a pandemic from March 11st, 2020, onward[9]. The disease differs from influenza-related pneumonia in that it is able to progress very seriously, even in young people without comorbidity. To date, mainly being in the first place thousands of bravely health workers like Li Wenliang, more than 4 million deaths and 200 million cases were confirmed, and the outbreak still has destructible impacts on economic and social circumstances[10-12]. The disease currently does not have any curable therapy. Recently discovered vaccines are being commenced to use in many countries with emergency use authorization[13,14]. Several new variants were reported, which are thought to be more infectious from the United Kingdom and numerous countries[15,16]. Due to this manner, the need for new and effective treatments continues.

Predominantly, the disease progress is asymptomatic or mild, but one-fifth of the patients advance to severe or critical illness[17]. In severe COVID-19 patients, type-2 T helper (Th) cells release numerous cytokines; this excessive immune response is named as 'cytokine storm', which is the leading cause of lung injury, acute respiratory distress syndrome (ARDS), multi-organ dysfunction syndrome (MODS), and death[18,19]. In this review, we aim to outline the usage of mesenchymal stem cells (MSCs) or, in other words, mesenchymal stromal cells, which have immunosuppressant and immunomodulatory benefits in countless diseases such as graft-*vs*-host disease, Crohn's disease, and some type of lung injuries, on severe or critically ill COVID-19 patients[20-24].

INTRODUCTION TO COVID-19 PATHOGENESIS AND PRESENT THERAPIES

In the eighty percent of the people who have been exposed to the SARS-CoV-2 *via* droplets and aerosols from an infected person, the disease remains limited in the upper respiratory tract. However, in the rest of the patients, the virus proceeds to the lower respiratory tract, and with pulmonary involvement, it causes more severe

illness. Disease mortality was reported between 0.5 and 2 percent in different studies and changes with obesity, older age, hypertension, and underlying chronic medical conditions[25-27]. The infectious process might occur progressively in a wide range of manifestations with life-threatening cardiovascular, thromboembolic, neurological, and respiratory complications[4,19,28,29]. As compatible with virus-cell invasion pathophysiology, organ involvement is correlated with the expression of host cells' angiotensin-converting enzyme 2 (ACE2) receptor and transmembrane protease, serine 2 (TMPRSS2) enzyme[30,31]. Unfortunately, the ACE2 receptor is widely distributed on the human cell surface, like lung, intestine, liver, kidney, brain, especially the alveolar type II (AT2) cells, capillary endothelium, and the AT2 cells highly express TMPRSS2[32-34]. On the grounds of that, the primary target of the virus is the lung. Moreover, the maladaptive immune response in severely ill patients damages the airways and causes a terrible cytokine storm characterized by elevated blood cytokine levels as a consequence of hyperactivation of the immune cells and impaired feedback mechanism. However, it leads to excessive infiltration of monocytes, macrophages, and T cells in the lungs. Therefore, disease severity in patients is due to not only the viral infection but also the host response. A notable example of this condition might be multisystem inflammatory syndrome in children and multisystem inflammatory syndrome in adults[35,36]. This uncontrolled hyperinflammatory response catalyzes multi-organ damage leading to multi-organ failure, especially of the cardiac, hepatic, and renal systems[18,29]. These organ failures raise the mortality rate, such as most patients with SARS-CoV-2 infection who developed acute kidney injury or have existing chronic kidney disease eventually died[37]. At present, no curative and effective COVID-19 treatment available, and the primary approach to patients is supportive care such as oxygen therapy (such as high flow nasal cannula oxygen therapy, mechanic ventilation), antipyretics, or venous thromboembolism prophylaxis[38,39]. Various drugs and supplementary therapies like antivirals (remdesivir, lopinavir/ritonavir, oseltamivir, favipiravir), antibiotics (azithromycin), immunomodulatory drugs (tocilizumab, hydroxychloroquine, convalescent plasma, anakinra, *etc.*) are being still investigated, but none of the therapies have reliable evidence[17]. To date, the only drug which is evidenced to decrease the mortality rate in severe and critically ill patients is corticosteroids[40]. Also, a specific agent to alleviate the SARS-CoV-2 induced cytokine storm is not developed as yet, and drugs that are aimed at this phenomenon are non-specific. Suppressing the excessive immune response is the key difficulty of the therapy options [41]. It is thought that people who overcome COVID-19 might have long-term sequels and different organ damages, notably lung and heart[42,43]. Multipotent MSC transplantation could promote lung and other damaged tissue repairs with its differentiation and paracrine secretory properties (exosomes/extracellular vesicles) and may prevent morbidities[44-47].

IMMUNO-PATHOGENESIS OF THE DISEASE AND PATIENT SELECTION FOR MSC TRANSPLANTATION

The virus that reaches the lungs from the upper respiratory tract *via* the ACE2 receptor infects AT2 cells here. After intracellular replication, it spreads to the parenchyma by exocytosis and causes epithelial and endothelial damage. The alveolar macrophages recognize damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) that arise from infected both AT-1 and AT-2 type dead cells, and the initiation of the inflammation is triggered (Figure 1). Thus, numerous chemokines and cytokines are started to secret excessively by lung and peripheral immune cells[18]. The cytokine storm, which is the hallmark of the COVID-19 induced by the disease and aggravates due to lack of proper immune response, similar to SARS and MERS, and the clinical status may progress forward ARDS, systemic inflammatory response syndrome, MODS, and death[48,49].

When the severe patients' laboratory results were analyzed, decreased lymphocyte count, elevated leukocyte count, neutrophils-lymphocytes ratio, a low percentage of monocyte, eosinophils, and basophils have been observed. Besides, Th, T suppressor (Ts), and regulatory T (Treg) cell count were determined as more obviously decreased in severe cases[50]. While studies on the pathophysiology of the disease are continuing, the following substances were found high in patients who suffer from cytokine storm: interleukin (IL)-1β, IL-2, IL-6, IL-7, IL-8, IL-9, IL-10, and IL-17; granulocyte-macrophage colony-stimulating factor (GM-CSF); TNF-α, IFN-γ, and IFN-γ inducible protein 10 (IP10); monocyte chemoattractant protein 1 (MCP-1);

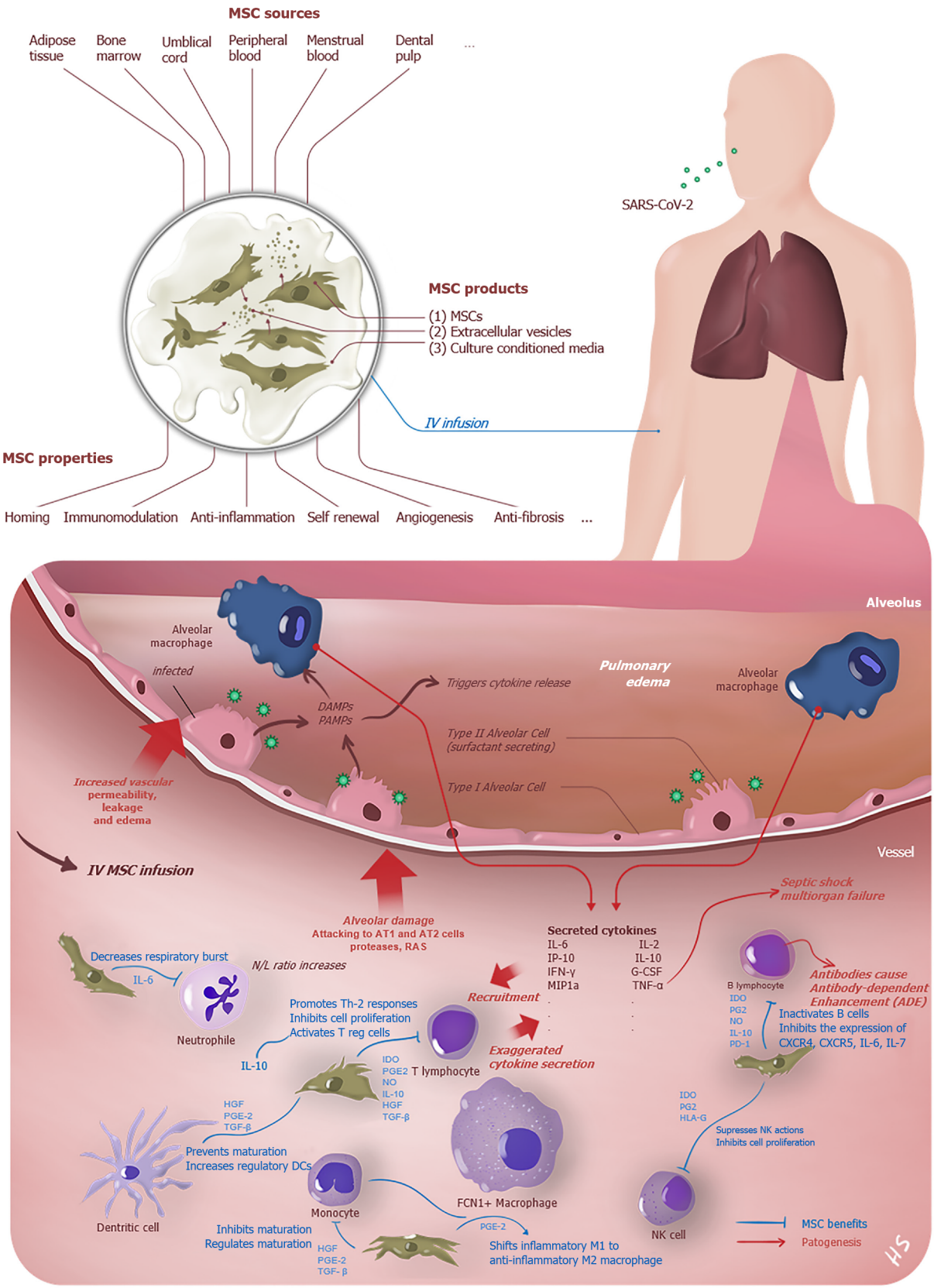

Figure 1 Summary of coronavirus disease 2019 pathogenesis and mesenchymal stem cells benefits. IL: Interleukin; PAMP: Pathogen-associated molecular patterns; DAMP: Damage-associated molecular patterns; IP-10: Interferon gamma-induced protein 10; IFN: Interferon; MIP1a: Macrophage inflammatory protein-1a; TNF-α: Tumor necrosis factor α; IDO: Indoleamine 2,3-dioxygenase; G-CSF: Granulocyte colony-stimulating factor; PG: Prostaglandin; PD-1: Programmed cell death protein 1; HGF: Hepatocyte growth factor; TGF-β: Transforming growth factor-β; FCN1+: Ficolin-1 (highly inflammatory monocyte-derived macrophage); AT: Adipose tissue; DC: Dendritic cell; T reg: regulatory T lymphocytes; NK cells: Natural killer cells; CXCR: CXC motif chemokine receptors; IV: Intravenous; RAS: Renin-angiotensin system; N/L: Neutrophil/lymphocyte; MSC: Mesenchymal stem cells.

macrophage inflammatory protein 1α (MIP-1α) and MIP-1β; chemokines like CC

chemokine ligand 2 (CCL2), CCL3, and CCL5; and C-X-C motif chemokine ligand 8 (CXCL8), CXCL9, and CXCL10[4,51]. In the detailed clustering analyses of the patients, higher C-reactive-protein (CRP), D-Dimer, ferritin, IP-10 (CXCL10), IL-10, IL-6 were founded to strongly correlated with poor clinical prognosis[52,53].

Together with these results, it is thought immunosuppression might be harmful in the early stages but helpful late stages of the disease. For this reason, the timing of the immunomodulatory therapies is essential[19]. Mortality rate reductive effects of the corticosteroids in patients who are intubated or only taken oxygen support can be explained with their potent anti-inflammatory effects[54]. Immunosuppression is a two-sided sword, and selective application is fundamental. Nevertheless, the ideal candidates for the immunomodulatory therapy in COVID-19 are still unspecified. Even only cytokine-specific therapies like IL-6 inhibitor tocilizumab might cause increasing the risk of sepsis, bacterial pneumonia, gastrointestinal perforation, and hepatotoxicity as a possible consequence of profound immunosuppression[55]. Additionally, indiscriminative and long-lasting immunosuppression has some disadvantages as SARS-CoV-2 progression and secondary infections. Therefore, administration of the short half-live immunosuppressant drugs will be more appropriate management.

There is still no consensus about the biomarkers that can be used for patient selection. However, besides the being need for further studies, it is thought that severe and critically ill patients might benefit from immunomodulatory options including MSC transplantation. Focusing on potential cytokine storm predictors, cytokine level measurement, especially IL-6, is not routine and usually is a "send-out" test. Instead of that, there are more accessible tests such as CRP, D-Dimer, and Ferritin, but their cut-off values vary in different studies. Another disease, hemophagocytic lymphohistiocytosis (HLH), which is induced cytokine storm, has a diagnostic score H score, (it assets temperature, organomegaly, number of cytopenias, triglycerides, fibrinogen, ferritin, aspartate aminotransferase, hemophagocytes on bone marrow aspirate, and known immunosuppression), and modified or a redesigned version of the score will be helpful not only in the management of MSC transplantation but, including other immunomodulatory therapies[56]. Further studies, which take these variables into account, need to be undertaken.

BENEFITS AND MECHANISMS OF MSC TRANSPLANTATION AND LIMITATIONS OF THE STUDIES

MSCs were firstly described in 1968 by Friedenstein *et al*[58] with a cluster of cells from bone marrow as colony-forming unit-fibroblasts[57]. Multipotent MSCs were defined by the International Society for Gene & Gene Therapy with three minimal criteria; being plastic adherent, specific surface antigen expression (expressing CD73, CD90, and CD105, lacking the expression of hematopoietic and endothelial markers CD11b, CD14, CD19, CD34, CD45, CD79α, and HLA-DR) and multipotent differentiation potential (capable of *in vitro* differentiation into adipocyte, chondrocyte and osteoblast lineages)[59]. Recently, The International Society for Cell & Gene Therapy (ISCT) Mesenchymal Stromal Cell (ISCT MSC) committee has advised naming these extraordinary cells as "Mesenchymal Stromal Cells" instead of "Mesenchymal Stem Cells" to clarify nomenclature[60]. In this review, we use the terms as synonyms. These cells derived from limited tissues like adipose, umbilical cord, placenta, synovium, and menstrual blood has such properties as priming, self-renewal, differentiation, immunomodulation & immunoprivilege, angiogenesis & repair, homing mechanism, anti-apoptosis, anti-inflammation & anti-fibrosis, and clinical trials about the benefits on COVID-19 patients continue[61].

MSC transplantation is up-and-coming in treating many diseases such as HIV, Hepatitis B, Influenza, coronaviruses (SARS, MERS), lung injuries, and ARDS. The only treatment of the HLH disease that causes the cytokine storm is stem cell transplantation[62]. Upon closer inspection on respiratory diseases, COVID-19, influenza, SARS, and MERS have similarities in pathogenesis, especially cytokine and immune response profiles. These comparable features in terms of the cytokine storm will provide hints for COVID-19 treatment[56,63]. In influenza A (H5N1) infection-induced lung injury, which acts similar to COVID-19 pro-inflammatory cytokine release, the significant benefits of MSCs in both cytokine profile and alveolar clearance are evidenced[23,64]. Menstrual-blood-derived MSC transplantation has significantly reduced mortality in influenza A (H7N9)-induced ARDS[22]. Mahendiratta *et al*[65] recently published a systematic review and reported pooled evidence on MSC therapy

benefits in SARS-CoV-2, SARS-CoV, MERS-CoV, and ARDS.

While MHC-1 expression of the MSCs provides the escape from Natural killer cells response, minimal MHC-2 expression or absence of this surface protein hampers the $CD4^+$ T cell response. For this reason, they are assumed as hypoimmunogenic[66]. MSCs, provide tissue regeneration and rejuvenation with immunotolerant and immunomodulant properties on damaged tissues by exerting their effects through immune cells[67]. Also, young MSCs might be useful in older adults because aged MSCs contribute to inflammaging and immunosenescence, which may explain the high mortality rate in this population due to COVID-19[68,69]. As well as numerous mechanisms are continuing to be investigated, some of them can be summarized as follows: (1) Inhibition of T cell (significantly cytotoxic $CD8^+$ T cells, Th 1 , Th 17)[61,70-72], B cell proliferation to plasma cell (thus MSCs can reduce the secretion of immunoglobulin), Dendritic cell activation, and apoptosis of T cells; (2) Differentiation of the cytokine profile and cell type of T cells and B cells into anti-inflammatory cytokines such as induces the production of IL-10 and regulatory T cell, regulatory B cell[61,67]; (3) Reduction of production in cytokine storm-related inflammatory factors, such as IL-1α, IL-6, IFN-γ, IL-17, TNF-α (Figure 1)[73]; (4) Promoting the transformation of inflammation-related M1 macrophages to regeneration-related M2 macrophages[74,75]; and (5) MSC products like exosomes and extracellular vesicles that do not contain any cell are thought to have similar effects to MSC transplantation, owing to the soluble mediator profiles they secrete[67,76].

Besides being encouraging and promising, the previous studies had some limitations, and one crucial of them is the small sample size. Also, the outcomes of the studies were not standardized, and most of the outcomes are observatory. Commonly evaluated parameters are CRP, D-dimer, IL-6, IL-10, TNF-α, blood lymphocyte, neutrophil counts, pulmonary involvements in thorax computed tomography, and radiography imaging. Another point is that some studies were assumed as successful, despite having already an ameliorative trend in parameters before transplantation[77,78]. In almost all of the studies, patients had received antibiotics, antivirals, antipyretics, corticosteroids, and supportive treatments (Table 1).

ISSUES OF THE MSC TRANSPLANTATION

Although clinical research is still ongoing, strict 'Good Manufacturing' rules are applied in the preparation of MSCs for clinical use[79]. It is seen that these rules are rigorously followed in the studies. The frequently preferred IV MSC dose is 10^6 cells per kilogram, and the infusion rate is 60 min, but the total dose calculation (*e.g.*, 15 × 10^7 cells) and multiple injection choices varied in different studies (Table 1). MSCs reach the lungs about venous vascular anatomy through IV administration and have been shown clearance from injured and inflamed lung tissue within 24-48 h[80]. Most of the studies to date have not contained any information about the ACE2 expression of administered MSCs or supposed as lack of ACE2 expression. Nevertheless, Derkeste *et al*[81] reported that adult bone marrow, adipose tissue, and umbilical-cord derived MSCs highly express ACE2. The same study has shown that placenta-derived MSCs and human-induced pluripotent stem cells are the best sources for COVID-19 treatment because of very low or absence ACE2 expression. Another significant aspect of MSC products is the contained pro-inflammatory cytokine amount. There are concerns regarding the possibility of worsened the cytokine storm by this situation. Moreover, the inflammatory response within the first two hours was reported due to IV MSC infusion[82]. About that, it has been seen a single shot corticosteroid application before the MSC infusion in previous studies. A recent systematic review from Thompson *et al*[83] has indicated intravascular (IV) MSC transplantation safety. The study has shown an association with fever but not non-fever acute infusional toxicity, infection, thrombotic/embolic events, or malignancy. However, Moll *et al*[84] have drawn attention to that MSCs highly express the procoagulant tissue factor and could trigger blood clotting in COVID-19 patients already in a hypercoagulable state. Finally, while cell-based strategies have tremendous benefits, it should be kept in mind that treatment costs are still very high, and the developing countries will have difficulties meeting these therapies[85].

Table 1 Promising mesenchymal stem cells studies

Ref.	MSC type	Sample size	Dose	Outcome
Leng *et al* [86]	ACE2$^-$ MSC	10 patients (7 MSC + 3 Placebo)	Single infusion 10^6 cells/kg cells IV, 40 min	A decrease of TNF-α and an increase of anti-inflammatory IL-10 were significant ($P < 0.05$). Other outcome data consisted of one critically ill patient. Three of the 7 patients who taken MSC discharged in the follow-up period
Zhang *et al* [77]	Human umbilical cord Wharton's jelly-derived MSCs (hWJCs)	One critically ill patient	Single infusion 10^6 cells/kg cells IV, 40 min	The patient was discharged 6 d after the administration. They suggested that remarkable amelioration in imaging, laboratory, and clinical test outcomes
Sánchez-Guijo *et al* [87]	Adipose tissue-derived MSC (AT-MSC)	13 severe ill patients	More than 1 infusion approximately 10^6 cells/kg cells IV	Two patients died during the follow-up period. They detected a decrease in inflammatory parameters and an increase in total lymphocyte counts 5 d after administration
Sengupta *et al*[88]	Bone marrow MSCs derived exosomes	24 patients	Single infusion 15 ml ExoFlo^{TM} IV	The study's survival rate is 83%, and 71% of the patients were recovered in the study interval. The outcome of the study is a clinical improvement with an average PaO_2/FiO_2 rate increase of 192% ($P < 0.001$)
Peng *et al* [89]	UC-MSCs and CP	1 severe ill patient	Two times infusion plasma volume 400 mL (Total) (1:160 titer SARS-CoV-2 specific IgG); 3 times infusion 10^6 cells/kg (Total) IV 30-40 min	Lack of response to CP treatment, MSCs were administrated to the patient. After the clinical improvement, the patient was discharged
Liang *et al* [78]	UC-MSCs	1 critically ill patient	3 times infusion 5×10^7 cell (each time) with thymosin-a1 IV	Clinical and laboratory improvement had been seen; The patient was discharged 17 d after the first MSC infusion
Tang *et al* [90]	Menstrual blood-derived MSCs	2 patients	3 times infusion 10^6/kg cells	Imaging and laboratory improvement had been seen
Shu *et al* [91]	UC-MSCs	41 severe ill patients (12 MSC treatment + 29 Placebo)	Single infusion 2×10^6 cells/kg IV 60 min	In treatment arm progression from severe to critical illness and 28-d mortality rate were 0, while 4 patients deteriorated to critical condition and 3 of them died, 28 d mortality rate was 10.34%. The treatment arm's clinical and laboratory improvements were significantly faster than the placebo group
Tao *et al* [92]	Human umbilical cord blood-derived MSCs	1 critically ill patient	5-times infusion 1.5×10^6 cells/kg (each time) IV 60-80 min	After the MSC treatment, related to the clinical condition, the patient had undergone lung transplantation. The patient died 6 d after the transplantation because of the rejection
Feng *et al* [93]	UC-MSCs	16 severe and critically ill patients	4 times with one-day intervals 1×10^8 cells once 90 min	The primary outcome was oxygenation index on day 14, and it has improved after UC-MSCs transplantation. On day 28, there is no significant difference between severe and critical types' mortality rates (6.25%)
Guo *et al* [94]	UC-MSCs	31 severe and critically ill patients	10^6/kg cells in 100 mL saline 200 mL (median volume) for each patient	They reported a significant increase in lymphocyte count, PaO_2/FiO_2, and decrease CRP, D-Dimer, IL-6, procalcitonin

UC: Umbilical cord; MSC: Mesenchymal stem cell; AT: Adipose Tissue; CP: Convalescent plasma; IL: Interleukin; PaO_2: Partial pressure of oxygen; FiO_2: Fraction of inspired oxygen; CRP: C reactive protein.

CONCLUSION

Despite to be seen the benefits of MSC and its products in COVID-19, the mechanisms still need to be elucidated. Therefore, the need for the results of ongoing clinical trials and meta-analyses of randomized controlled trials continues. We think that if the costs, ethical, and storage problems of treatments are resolved over time, they might prevent COVID-19 related morbidity and mortality. We foresee that most of these problems will get over with advanced researches on MSC products. However, it should not be overlooked that MSC and MSC-based treatments are still experimental and have pros and cons.

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