ISSN 2220-3230 (online)

World Journal of *Transplantation*

World J Transplant 2020 March 31; 10(3): 47-78

Published by Baishideng Publishing Group Inc

W J T

World Journal of *Transplantation*

Contents

Irregular Volume 10 Number 3 March 31, 2020

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INDEXING/ABSTRACTING

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

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Lu-Lu Qi*

Proofing Production Department Director: *Yun-Xiaojian Wu*

NAME OF JOURNAL
World Journal of Transplantation

ISSN
ISSN 2220-3230 (online)

LAUNCH DATE
December 24, 2011

FREQUENCY
Irregular

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PUBLICATION DATE
March 31, 2020

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World J Transplant 2020 March 31; 10(3): 47-63

DOI: 10.5500/wjt.v10.i3.47

ISSN 2220-3230 (online)

REVIEW

Emerging and neglected zoonoses in transplant population

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Author contributions: Mrzljak A and Vilibic-Cavlek T made contributions to conception and design of the study, involved in drafting and revising the manuscript critically; Novak R, Pandak N, Tabain I, Franusic L, Bogdanic M, Barbic L, Savic V, Mikulic D, Pavicic-Saric J and Stevanovic V were involved in collecting data and drafting the manuscript; all authors read and approved the final manuscript.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

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Abstract

Zoonoses represent a problem of rising importance in the transplant population. A close relationship and changes between human, animal and environmental health ("One Health" concept) significantly influence the transmission and distribution of zoonotic diseases. The aim of this manuscript is to perform a narrative review of the published literature on emerging and neglected zoonoses in the transplant population. Many reports on donor-derived or naturally acquired (re-)emerging arboviral infections such as dengue, chikungunya, West Nile, tick-borne encephalitis and Zika virus infection have demonstrated atypical or more complicated clinical course in immunocompromised hosts. Hepatitis E virus has emerged as a serious problem after solid organ transplantation (SOT), leading to diverse extrahepatic manifestations and chronic hepatitis with unfavorable outcomes. Some neglected pathogens such as lymphocytic choriomeningitis virus can cause severe infection with multi-organ failure and

Manuscript source: Invited manuscript

Received: December 22, 2019
Peer-review started: December 22, 2019
First decision: February 20, 2020
Revised: March 15, 2020
Accepted: March 22, 2020
Article in press: March 22, 2020
Published online: March 31, 2020

P-Reviewer: Hibberd AD, Maggi F
S-Editor: Wang YQ
L-Editor: A
E-Editor: Qi LL

high mortality. In addition, ehrlichiosis may be more severe with higher case-fatality rates in SOT recipients. Some unusual or severe presentations of borreliosis, anaplasmosis and rickettsioses were also reported among transplant patients. Moreover, toxoplasmosis as infectious complication is a well-recognized zoonosis in this population. Although rabies transmission through SOT transplantation has rarely been reported, it has become a notable problem in some countries. Since the spreading trends of zoonoses are likely to continue, the awareness, recognition and treatment of zoonotic infections among transplant professionals should be imperative.

Key words: Zoonoses; Solid-organ transplant; Vector-borne diseases; Non-vector borne diseases; Viruses; Bacteria; Parasites

Core tip: The importance of zoonotic diseases in the transplant population is rising. Given the current diversity and extent of zoonotic pathogens, modes of transmission and clinical presentation in immunocompromised hosts, this manuscript aims to summarize the published literature on emerging and neglected zoonoses in the transplant population.

Citation: Mrzljak A, Novak R, Pandak N, Tabain I, Franusic L, Barbic L, Bogdanic M, Savic V, Mikulic D, Pavicic-Saric J, Stevanovic V, Vilibic-Cavlek T. Emerging and neglected zoonoses in transplant population. *World J Transplant* 2020; 10(3): 47-63
URL: https://www.wjgnet.com/2220-3230/full/v10/i3/47.htm
DOI: https://dx.doi.org/10.5500/wjt.v10.i3.47

INTRODUCTION

Zoonotic diseases - transmitted and shared between animals and humans, are nowadays receiving increased recognition. WHO estimates that more than 60% of all human pathogens are zoonotic, and that they represent 75% of all emerging pathogens during the past decade[1]. They encompass a wide range of pathogens (viruses, bacteria, parasites) and modes of transmission: *via* direct contact with infected animals or their secretions, the bite of arthropod vectors or indirect contact *via* the environment[2]. Given a close relationship between human, animal and environmental health (the "One Health" concept), human activities, climate and landscape changes influence significantly transmission and distribution of zoonoses[3,4]. The number of zoonotic diseases has been increasing in the last two decades and the spreading trends are likely to continue in future years. For example, West Nile virus (WNV), one of the most widely distributed arboviruses has expanded its area of circulation in many European countries[5]. In 2018, a large outbreak occurred across Southern and Central Europe with the number of confirmed human cases increasing up to 7.2-fold from the previous transmission season[6]. A total of 2083 human cases and 285 outbreaks among equids were reported, including previously virus-free regions[7]. In addition, geographical distribution of Zika virus (ZIKV) has steadily expanded. In 2015 and 2016, large outbreaks of ZIKA occurred in the Americas. In the USA and US Territories, 5168 and 36512 symptomatic ZIKV disease cases were reported in 2016[8]. Hepatitis E virus (HEV) is an important cause of acute viral hepatitis worldwide, with an increasing incidence in Europe since 2010. The reported incidence over 10 years has grown by ten times: From 514 cases in 2005 to 5617 cases in 2015[9]. On the other hand, solid-organ transplant (SOT) population is expanding as a result of increasing transplant rates, improved post-transplant management and survival[10,11]. In comparison to immunocompetent hosts, immunocompromised state of SOT recipients is an inevitable additional risk for the infection and unfavorable outcomes due to atypical presentation, possible delay in diagnostic tests (serology), more frequent presence of disseminated/advanced disease and prolonged treatment. Although majority of zoonotic infections develop in the post-transplant period, donor or transfusion transmitted zoonotic infections have been increasingly acknowledged as well. Therefore, the increasing trend of reports on zoonotic diseases in the transplant population over the past decade substantiates a need for a comprehensive review. This narrative review will cover two main groups of zoonotic infections; vector and non-vector borne infections and focus on major pathogens and their clinical manifestations in the transplant population (Table 1).

VECTOR-BORNE ZOONOSES

Tick-borne encephalitis virus

Tick-borne encephalitis virus (TBEV) is a tick-borne flavivirus widely distributed from Europe through far-eastern Russia to Japan. The virus is maintained in cycles involving *Ixodid* ticks (*Ixodes ricinus* and *Ixodes persulcatus*) and wild vertebrate hosts (mainly rodents)[12]. Transmission to humans occurs most commonly through a bite of an infected tick, however approximately 1% of all TBE cases are thought to be caused by food-borne TBEV (consumption of raw goat milk)[13,14]. TBEV can cause a wide spectrum of the disease, ranging from asymptomatic infection to severe encephalitis and even death[14]. Diagnosis is usually confirmed by the detection of TBEV IgM and IgG antibodies in serum and cerebrospinal fluid (CSF) samples. Determination of IgG avidity may be helpful in cases of atypical antibody response[15]. There are very few data on the transplant-transmitted TBEV infection. In 2012, a cluster of fatal TBEV infection was reported in Poland. Transmission of TBEV occurred through the transplanted organs (liver, kidneys) from a single donor to three recipients. The donor lived in an endemic area and the presence of TBEV was confirmed by the same viral strain detected in all recipients and in the donor[16]. Although transmission of TBEV through organ transplantation is rare, clinicians should consider screening donors who live or have recently visited endemic areas for TBEV, particularly during the arbovirus transmission season.

Borrelia burgdorferi (Lyme disease)

Borrelia burgdorferi is a tick-borne zoonosis widely distributed in North America and Europe. All three pathogenic species, *B. burgdorferi*, *B. afzelii* and *B. garinii* occur in Europe, and the latter two have been identified in Asia. *Borrelia burgdorferi* circulates between *Ixodes* ticks and vertebrate hosts in an enzootic cycle. Ticks can transmit borrelia to humans, but humans are dead-end hosts, unlikely to continue the life cycle of the spirochete[17]. Lyme disease (LD) has a broad spectrum of clinical manifestations. Primary infection presents as erythema migrans (EM). Late stages occur weeks to years following infection and include arthritis, peripheral neuropathy, and skin findings such as acrodermatitis chronica atrophicans[18]. Neuroborreliosis is one of the manifestations of LD involving the central nervous system (CNS)[19]. The role of immunosuppression in the development and progression of LD is not well understood. An analysis of SOT recipients on immunosuppressive treatment who presented with solitary EM did not reveal any significant differences in the clinical course of infection as compared with the general population[20]. The first case of LD in a transplanted patient was described in 1993 in a kidney transplant recipient in whom the disease progressed into the disseminated stage with severe neurological signs[21]. A study from Slovenia presented a case series of six SOT recipients with EM. All six patients had solitary skin lesions with clinical characteristics comparable to those of the skin lesions in immunocompetent patients. No clinical signs or symptoms suggesting borrelia dissemination were present or were reported either during the initial course of the illness or during the one-year follow-up period after antibiotic treatment and persistence of borrelia organisms in the skin after treatment was not established[20]. A case report of Lyme carditis after liver transplant that progressed to disseminated illness with a concomitant heart block and deterioration of mental status has also been described[22].

Anaplasma phagocytophilum (Human granulocytic anaplasmosis)

Human granulocytic anaplasmosis (HGA) is a tick-borne infection caused by *Anaplasma phagocytophilum*, an intracellular bacterium, which commonly infects neutrophils[23]. The infection is mostly spread through a bite of *Ixodes* ticks in Europe (*Ixodes ricinus* and *Ix. persulcatus*) and in North America (*Ix. scapularis* and *Ix. pacificus*) after feeding on infected animals such as domestic (dog, horse) and wild ruminants, hedgehogs and wild boars[24,25]. However, there are reports of transmission through infected blood as well as of perinatal transmission[25]. Immunocompetent individuals with HGA develop high-grade fever, malaise, nausea, headache, myalgia, arthralgia, CNS and gastrointestinal symptoms. Rarely individuals present with an erythematous rash[26]. Whereas anaplasmosis is mostly a self-limiting disease, predictors of a more severe course include advanced age, immunosuppression, and comorbidities such as diabetes[26]. Severe course includes the development of acute respiratory distress syndrome, peripheral neuropathies, DIC-like coagulopathies,

Table 1 Clinical manifestations of emerging and neglected zoonoses in non-transplant and transplant population

Pathogen	Clinical presentation		Laboratory diagnosis	Ref.
	Immunocompetent patients	Immunocompromised patients		
Vector-borne zoonoses				
Tick-borne encephalitis virus	Asymptomatic infection to severe encephalitis	Few data: One cluster of fatal TBE	ELISA (IgM, IgG), Avidity; VNT; RT-PCR	[4,14-16]
Borrelia burgdorferi	Erythema migrans, arthritis, peripheral neuropathy, acrodermatitis chronica atrophicans, neuroborreliosis	Possible dissemination with severe neurological and cardiac symptoms	ELISA (IgM, IgG); IFA (IgM, IgG); Immunoblot (IgM, IgG); PCR	[4,18-20]
Anaplasma phagocytophilum	Mostly self-limiting disease, non-specific symptoms, rash, gastrointestinal and CNS involvement	Unusual presentations: Acute respiratory distress syndrome, haemorrhagic manifestations, pancreatitis, acute renal failure, orchitis	Microscopy of peripheral blood (morulae); IFA (seroconversion of 4-fold increase in IgG titer); PCR	[4,26,32,33,43]
Ehrlichia spp.	Self-limiting febrile illness to fatal multi-organ failure	More frequently severe manifestations: Fatal multiorgan failure, acute respiratory distress syndrome meningoencephalitis, toxic and septic-like syndromes	Microscopy of peripheral blood (morulae); IFA (seroconversion of 4-fold increase in IgG titer); PCR	[4,25,36,37,42]
Rickettsia spp.	Self-limiting disease, flu-like symptoms, with or without eschar and rash; vasculitis-mediated organ failure	Few data: More frequently severe manifestations, splenic rupture	IFA (IgM, IgG); PCR	[4,49,51]
Orientia tsutsugamushi	Nonspecific febrile illness to fatal multiorgan failure, eschar, CNS involvement	Few data: Only one case with eschar and renal graft dysfunction	IFA (IgM, IgG); PCR	[4,53,54]
Rift Valley Fever virus	Subclinical to severe febrile illness, fatal haemorrhagic fever	Few data: Only one case with meningoencephalitis	ELISA (IgM, IgG); VNT; RT-PCR	[4,59,61]
St. Louis encephalitis virus	Majority asymptomatic, febrile illness, aseptic meningitis and encephalitis	Few data: Meningoencephalitis	ELISA (IgM, IgG); VNT; RT-PCR	[4,63,65]
Zika virus	Asymptomatic infection to severe neurological disorders	Infectious complications and graft rejection	ELISA (IgM, IgG); VNT; RT-PCR	[4,69-71]
Chikungunya virus	Mild febrile illness and polyarthralgia, rarely meningoencephalitis, myocarditis	No impact on graft function	ELISA (IgM, IgG); VNT; RT-PCR	[4,74,75,77,79,80]
Dengue virus	Asymptomatic infection to severe fatal illness	More commonly prolonged course with complications and graft rejection	ELISA (IgM, IgG); VNT; NS1 antigen; RT-PCR	[4,82,84-86]
West Nile virus	Asymptomatic infection, mild febrile disease, neuroinvasive disease (elderly)	Fatal neuroinvasive disease more frequent	ELISA (IgM, IgG); VNT; Avidity; VNT; RT-PCR	[4,87,96,97,108,109]
Usutu virus	Asymptomatic infection, neuroinvasive disease (elderly)	Fatal neuroinvasive disease more frequent	ELISA (IgM, IgG); VNT; RT-PCR	[4,114-119]
Eastern equine encephalitis virus	Asymptomatic, neuroinvasive disease (meningitis, encephalitis)	Few data: Neuroinvasive disease	ELISA (IgM, IgG); VNT; RT-PCR	[4,123,124]
Leishmania spp.	Cutaneous, mucocutaneus and visceral leishmaniasis	The same as in immunocompetent; organomegaly may be less frequent in visceral leishmaniasis	Microscopy; Culture; PCR; IFA (IgM, IgG)	[4,129,130]
Non-vector-borne zoonoses				
Hepatitis E virus	Asymptomatic infection, fulminant hepatitis, acute-on-chronic liver failure, extrahepatic manifestations	Chronic hepatitis, cirrhosis, extrahepatic manifestations	ELISA (IgM, IgG); Immunoblot (IgM, IgG); RT-PCR	[4,131-133,135,136]
Rabies virus	Fatal encephalitis	Fatal encephalitis	Microscopy (Negri bodies); DFA (antigen detection); IHC (antigen detection); RT-PCR, RFFIT, FAVN	[4,143-146]

Lymphocytic choriomeningitis virus	Asymptomatic infection, nonspecific febrile illness, aseptic meningitis	More severe clinical presentation, hepatitis, meningoencephalitis, multiorgan failure	ELISA (IgM, IgG); IFA (IgM, IgG); RT-PCR	[4,99,151,152]
Toxoplasma gondii	Asymptomatic, mononucleosis-like symptoms	More severe clinical presentation, cerebral toxoplasmosis, fatal disseminated disease	ELISA (IgM, IgG); IFA (IgM, IgG); Avidity, Immunoblot (IgM, IgG); PCR	[4,156-158]

CNS: Central nervous system; DFA: Direct immunofluorescence assay; ELISA: Enzyme-linked immunosorbent assay; FAVN: Fluorescent antibody virus neutralization test; IFA: Indirect immunofluorescence assay; IgG: Immunoglobulin G; IgM: Immunoglobulin M; IHC: Immunohistochemistry; NS1: Non-structural protein 1; PCR: Polymerase chain reaction; RT-PCR: Reverse-transcriptase polymerase chain reaction; TBE: Tick-borne encephalitis; RFFIT: Rapid fluorescent focus inhibition test; VNT: Virus neutralization test.

hemorrhagic manifestations, rhabdomyolysis, pancreatitis and acute renal failure[26]. The diagnosis can be confirmed by microscopic identification of morulae in neutrophils on peripheral blood smear or in buffy coat, PCR or serology[27]. Based on the few case reports of anaplasmosis in recipients of kidney, pancreas or liver[28-32] the incidence of anaplasmosis in transplant recipients does not appear to be high and manifestations of the disease seem to be similar to non-transplant patients. In transplant patients, the clinical presentation commonly involved non-specific systemic symptoms. However, there was also a rather unusual presentation in a kidney recipient in the form of orchitis[33]. It was observed that immunosuppressive therapy does not seem to alter acute or convalescent antibody titers[34]. Solid organ transplant (SOT) recipients with anaplasmosis usually also have a good initial response to treatment with doxycycline[33].

Ehrlichia spp. (Human monocytic ehrlichiosis)

Human monocytic ehrlichiosis (HME) is a tick-borne zoonosis caused by *Ehrlichia chaffeensis* and less commonly, *E. ewingii*. HME occurs across the south-central, south-eastern, and mid-Atlantic states, corresponding to areas where their reservoirs (white-tailed deer) and vectors (*Amblyomma americanum* ticks) both exist[35]. The clinical manifestations of HME vary from a self-limited febrile illness to fatal multi-organ failure[25]. Severe manifestations such as acute respiratory distress syndrome, pulmonary hemorrhages, meningoencephalitis, toxic shock-like, and septic shock-like syndromes have also been described[25,36,37]. The diagnosis can be confirmed by PCR or serology[25,38]. In some cases, morulae may be observed in leukocytes on Wright stained peripheral blood smear, particularly in immunocompromised hosts[25,39]. There have been reports of HME transmission through SOT[37], as well as through blood product transfusions[25]. Ehrlichiosis was described in kidney[37,40-44], liver[36,43,45], lung[38,42,43,46] and heart transplant recipients[42,43]. Immunocompromised persons, particularly SOT recipients, more frequently develop severe and prolonged manifestations of ehrlichiosis with higher case-fatality rates[25,37,42]. Furthermore, SOT recipients showed having a higher risk to develop acute lung injury and acute respiratory distress syndrome[42]. However, one report showed that 15 transplant patients with ehrlichiosis had similar and favorable outcomes compared with immunocompetent patients[43]. Among SOT recipients, infected lung recipients showed more severe and progressive clinical course[42]. Some reports, have also described re-infections in liver transplant recipients, suggesting that initial infection may not provide long-lasting immunity in patients on immunosuppressive therapy[45].

Rickettsia spp.

Rickettsioses are bacterial infectious diseases that occur in endemic areas across the world. They are classified into two main groups: The spotted fever group with the main representatives; *Rickettsia rickettsii* (Rocky Mountain spotted fever; RMSF) transmitted by the ticks in the USA, Mexico and South America[47]; *R. conorii* (Mediterranean spotted fever; MSF) transmitted by dog ticks in Southern and Eastern Europe, Africa, India, Russia[47,48] and the typhus group which includes *R. prowazekii* (epidemic typhus) and *R. typhi* (murine typhus)[48]. Following a tick exposure, clinically significant rickettsial infections present with flu-like symptoms with or without eschar at the site of the tick bite, accompanied by rash. The clinical course is highly variable and ranges from self-limited to vasculitis-mediated organ failure and death[49]. The diagnosis of rickettsioses is most often established by serology. Indirect immunofluorescence assay (IFA) has been considered the gold standard. The test has limited utility in species determination within a serogroup due to extensive cross-reactivity and as any immunoglobulin-based assay in the context immunocompromised patient should be interpreted with caution[49]. Rickettsioses have been rarely reported in the transplant population. The scarcity of the data implies that even in immunocompromised hosts majority of the infections are mild and rarely result in a malignant vasculitis-associated form. A case of RMSF in a cardiac transplant recipient from southern Utah demonstrated a prompt clinical response after empirical treatment with doxycycline and delayed development of rickettsia antibodies (5 mo after the infection)[50]. Only one case demonstrated the development of complications. Severe MSF infection has been reported in a kidney transplant recipient from Southern France, who developed flu-like symptoms, maculopapular rash and splenic rupture requiring splenectomy. Doxycycline therapy resulted in rapid improvement and favorable outcome[51]. Rickettsial infections are probably underrecognized and underreported in the transplant population.

Orientia tsutsugamushi (Scrub typhus)

Scrub typhus is a zoonosis caused by *Orientia tsutsugamushi*, an obligate intracellular bacterium. It is a common re-emerging rickettsial infection in India and many other countries in Southeast Asia, the Pacific Islands, and Northern Australia (the "tsutsugamushi triangle")[52]. *Orientia tsutsugamushi* is transmitted to humans by the bites of the larval life stage of infected *Leptotrombidium* mites (*Leptotrombidium deliense* and *Leptotrombidium akamushi*) while field rodents serve as reservoirs. The clinical presentation of scrub typhus ranges from nonspecific febrile illness to potentially fatal multi-organ involvement such as liver, kidney, or lung[53]. In some patients, an eschar may develop at the site of mite feeding. CNS involvement (meningitis, encephalitis) has also been observed[54]. The diagnosis of scrub typhus is usually made by a single IFA titer against *O. tsutsugamushi* of 400, a seroconversion or a 4-fold increase in IgG titer using paired serum samples[55]. So far, only one study described scrub typhus in a renal transplant recipient in India. The patient presented with fever, headache, meningeal signs, graft dysfunction, and eschar and responded well to intravenous azithromycin and became afebrile within 24 h[53]. Since many cases of scrub typhus are underdiagnosed, clinicians should consider in differential diagnosis this potentially fatal zoonosis in regions of endemicity.

Rift Valley fever virus

Rift Valley fever virus (RVFV) is a mosquito-borne phlebovirus. RVFV outbreaks in humans have been reported in Africa, the Indian Ocean islands, and the Arabian Peninsula[56]. Cattle, sheep, goats, and camels are particularly susceptible to RVF and serve as amplifying hosts for the virus[57]. RVFV transmission to humans occurs by direct contact with infected animals or their body fluids, consumption of raw milk or meat or by mosquito bites (*Culex, Aedes*)[58]. Human infections are usually subclinical or presenting as moderate to severe febrile illness while 1-2% of RVFV infections result in fatal haemorrhagic fever[59]. RVFV can be diagnosed by RNA detection, antigen detection or serology[60]. In 2015, an imported case of RVF in a kidney transplant recipient was reported in France. The initial clinical presentation was characteristic for acute hepatitis and four weeks later, the patient presented with a meningoencephalitis. IgM and IgG antibodies were detected in CSF and blood up to 2 mo after symptoms onset, whereas in urine and semen, RVFV RNA was detected by RT-PCR up to three and four mo, respectively. The severity of clinical presentation may have been related to immunosuppression, which might also have slowed down the clearance of the virus[61].

St. Louis encephalitis virus

St. Louis encephalitis virus (SLEV) is a mosquito-borne flavivirus. The virus can be found in the Western Hemisphere, but epidemics typically occur in the Ohio River-Mississippi River basin. Humans are dead-end hosts of a mosquito–bird–mosquito cycle[62]. While mostly asymptomatic, less than 1% of all SLEV infections lead to symptomatic disease ranging from febrile illness to aseptic meningitis or encephalitis[63]. Diagnosis is based on serology[64]. The prevalence of SLEV infections in transplant recipients is largely unknown. During the 2015 outbreak, three SOT recipients were hospitalized with confirmed neuroinvasive SLEV infection (meningoencephalitis) in Phoenix, Arizona. One patient died, whereas two other patients survived but required prolonged hospitalization. One patient recovered fully; the other patient had residual dysarthria[65].

ZIKV

ZIKV is an emerging mosquito-borne flavivirus. Before the large outbreak of ZIKV infection on Yap Island (Federated States of Micronesia), only sporadic cases were reported in Africa and Asia, but in 2007 ZIKV emerged as an important human pathogen[66,67]. Human infections mainly occur through the bite of *Aedes* mosquitoes (*Ae. aegypti* and *Ae. albopictus*), however, non-vector borne transmission of ZIKV such as sexual and transplacental transmission was also reported[68]. Although symptoms associated with ZIKV infection are generally mild and the majority of infected persons do not develop any symptoms, ZIKV is also associated with severe neurological disorders, mainly Guillain-Barré syndrome. Diagnostic testing for ZIKV infection can be accomplished using molecular and serologic methods[69,70]. Case reports describing ZIKV infection in transplant patients are limited. In 2015 and 2016, ZIKV infection was confirmed among 129 kidney transplants and 58 liver transplants tested in Brazil. All ZIKV-infected SOT recipients presented with complications, notably bacterial infections, and required hospitalization. Based on this small case series, it was not possible to assess the potential impact of ZIKV in the immunosuppressed SOT recipients, including infectious complications and graft rejection[71]. Therefore, further studies are needed to evaluate the impact of ZIKV infection in this population group.

Chikungunya virus

Chikungunya virus (CHIKV) is an emerging mosquito-borne alphavirus. Since 2004, CHIKV caused several large outbreaks in Africa, the Indian Ocean islands, Asia, Europe, and the Americas[72]. In an urban transmission cycle, humans are the major hosts and mosquitoes of the genus *Aedes* are vectors[73]. Although chikungunya fever is usually benign, prolonged polyarthralgia may lead to considerable disability in a significant proportion of patients[72]. Atypical manifestations include meningoencephalitis, myocarditis, respiratory, renal and hepatic failure[74,75]. Laboratory diagnosis is accomplished by detection of CHIKV RNA and/or detection of IgM and IgG antibodies[72]. Few data exist regarding the clinical characteristics of CHIKV infections in the transplant population[76-79]. In one case series of SOT recipients from Colombia with confirmed CHIKV infection, most patients had a benign clinical course with no severe complications[78]. A study from Brazil analyzed clinical symptoms of chikungunya in four kidney transplant recipients. The clinical picture was typical, none of patients developed any severe manifestations and all recovered fully with no complications[77]. Another Brazilian study showed similar results. SOT recipients with CHIKV infection seem to have a clinical presentation and course similar to those seen in the general population, with no apparent damage to the graft. Among liver transplant recipients, elevation of liver enzymes was not observed, and there was no clinical impact on graft function. Among kidney transplant recipients, only a few had a slight increase of serum creatinine levels, without acute kidney failure or dialytic support[80]. Although reports on the chikungunya in the transplant population are rare, the transplant community must be reminded that the risk of CHIKV infection should be considered in deceased organ donor candidates recently returned from travel to endemic areas[76].

Dengue virus

Dengue virus (DENV) is a mosquito-borne flavivirus widely distributed in the tropics and subtropics. In an urban cycle, the virus is transmitted from human to human by the bite of *Ae. aegypti* and *Ae. albopictus* mosquitoes. Non-vectorial DENV transmission through SOT can also occur[81]. The clinical presentations of DENV infection range from asymptomatic to severe illness with fatal outcome. The symptomatic cases are categorized as undifferentiated febrile illness, dengue fever, dengue hemorrhagic fever and dengue shock syndrome[82]. Etiologic diagnosis can be obtained by virus isolation, detection of NS1 antigen, DENV RNA or specific IgM and IgG antibodies[83]. SOT recipients showed a spectrum of clinical manifestations similar to the non-transplant population. However, the course of the illness can be prolonged with complications such as graft dysfunction. Fatal cases were also reported[84-86]. A Thai study analyzed outcomes of DENV infection in a large cohort of kidney transplant recipients. Although a transient decline in allograft function occurs in some patients, the overall clinical and allograft outcomes seemed to be favorable[87]. A Colombian study on retrospective case series of SOT recipients with DENV infection showed that regarding the clinical course, 75% of patients had at least one warning sign, 45% were managed in the intensive care unit, and 30% had severe dengue. However, all patients had a full recovery after the infection[88]. In contrast, a study from India showed that early post-transplant DENV infection appears to be severe and associated with more complications in kidney transplant recipients[89]. There have been limited descriptions of possible DENV transmission through SOT, of which the majority are classified as possible transmission due to the lack of DENV RNA confirmation in the donor[81,90,91]. A case of DENV transmission from donor to the recipient after liver transplantation was described in India. The recipient developed dengue fever without showing any features of severe graft dysfunction and recovered fully[81]. Several studies in SOT recipients who developed dengue through organ transplantation showed that the liver was the main target organ in all patients, even in subjects that received heart and kidney transplantation. Transplant patients were more likely to present with elevated liver transaminases and hyperbilirubinemia, suggesting that the liver could be more susceptible to DENV or is generally more compromised in transplant recipients[81,91,92]. A recently published study from India presented the first report on the detection of DENV in the donor cornea indicating the risk of iatrogenic DENV transmission through corneal transplantation[93]. To avoid DENV transmission by organ or tissue transplantation, the donors should be screened in endemic areas.

WNV

WNV is one of the most widely distributed emerging mosquito-borne flaviviruses. In a natural cycle, the virus is maintained in a bird-mosquito-bird cycle. Transmission to humans occurs through the bite of *Culex* mosquitoes[94]. Approximately 80% of immunocompetent individuals infected with WNV remain asymptomatic while 20% develop mild febrile disease (WNV fever). Less than 1% of infected individuals, mainly immunocompromised and elderly develop neuroinvasive disease (meningitis, encephalitis, myelitis)[95]. Diagnosis is confirmed by the detection of WNV IgM and IgG antibodies in serum/CSF with confirmation by virus neutralization test in samples with cross-reactive antibodies[96]. Since WNV IgM antibodies may persist up to 500 d in some patients, IgG avidity differentiates current/recent WNV infection from persistent IgM seropositivity from the previous WNV transmission season[97]. WNV RNA can be detected in blood, CSF and urine samples using RT-PCR, but molecular methods are less sensitive than serology[98]. WNV has been identified as a cause of both donor-derived and post-transplant infection[99]. WNV transmission by organ transplantation was first reported in 2002[100]. Thereafter, there are many reports on donor-derived or naturally acquired WNV infection in the adult transplant population[101-108]. Although WNV infection is associated with higher mortality in the transplant patients[105,108,109] there are some reports on WNV in SOT recipients with a complete recovery as well as asymptomatic infections[108,110]. Few reports describing post-transplant WNV neuroinvasive disease in pediatric patients showed a complete recovery in all patients[104,111,112]. In the light of the WNV (re-) emergence, clinicians should be aware that SOT recipients could be exposed to WNV *via* multiple sources. Therefore, WNV should be included in the differential diagnosis in all patients presenting with fever and neurological symptoms after transplantation during the arbovirus transmission season.

Usutu virus

Usutu virus (USUV) is a mosquito-borne flavivirus that emerged in Europe in 1996[113]. The natural cycle, geographic distribution and clinical symptoms of USUV overlap with WNV. Although human clinical cases of USUV infection are rarely reported, several recently published reports highlight its role in the etiology of neuroinvasive diseases[114-117]. Like WNV, the majority of USUV infections are asymptomatic or present as a non-specific febrile disease (USUV fever)[117]. Neuroinvasive disease was reported in both immunocompetent and immunocompromised patients in Italy, Croatia, and Hungary[114,116,118,119]. In addition, some atypical presentations such as facial paresis have also described[120]. However, there is only one published report on USUV infection in a transplanted patient in Italy. The patient who underwent an orthotopic liver transplant developed neuroinvasive disease in the post-transplant period[121]. Since many of USUV cases remain underdiagnosed or misdiagnosed as WNV due to similar clinical symptoms and serological cross-reactivity, clinicians should keep in mind this viral zoonosis, especially during the arbovirus transmission season.

Eastern equine encephalitis virus

Eastern equine encephalitis virus (EEEV) is a mosquito-borne alphavirus endemic to eastern North America. In nature, the virus spreads between *Culiseta melanura* mosquitoes found in forested wetlands. Mosquitoes of *Aedes* and *Culex* genera may transmit EEEV to humans[122]. Most persons infected with EEEV are asymptomatic or they present with a non-specific febrile illness, while less than < 5% develop neuroinvasive disease (meningitis, encephalitis). The case fatality rate is around 50% and many survivors suffer residual neurological sequelae[123]. There is only one report of organ-derived EEEV. In autumn 2017, three SOT recipients (lung, heart, liver) from a common donor developed encephalitis one week after transplantation. Lung and liver recipients died, while the heart recipient survived but had residual tremor. The donor and all organ recipients showed laboratory evidence of EEEV. The fact that all SOT recipients developed encephalitis suggests that the risk of neuroinvasive disease may be increased with this route of transmission. EEEV should be considered in SOT recipients who develop encephalitis after transplantation, particularly if donors and recipients reside in endemic areas of the USA[124].

Leishmania spp.

Leishmaniasis is a cosmopolitan zoonosis caused by the protozoan parasite of the genus *Leishmania*. It is transmitted by the bite of phlebotomine sandflies of the genus *Phlebotomus* (in the Old World) or *Lutzomyia* (in the New World). So far, at least 20 different *Leishmania* species have been associated with human infection. Clinical presentation of leishmaniasis includes cutaneous (CL), mucocutaneous (MCL), or visceral leishmaniasis (VL)[125]. CL occur in three different forms: Localized, diffuse and disseminated. CL is characterized by single or multiple skin ulcers, satellite lesions, or nodular lymphangitis. MCL present with mucosal tissue metastasis in the mouth and upper respiratory tract *via* lymphatic or hematogenous dissemination. VL is the most severe form of leishmaniasis and if untreated it is fatal in 95% of patients[125,126]. VL is usually caused by *Leishmania donovani* or *L. infantum* although other *Leishmania* species that usually cause CL have been described causing VL too[125]. Clinical presentation of VL is nonspecific with prolonged fever, anorexia, weight loss and overall poor health status. Typically the patients have hepatosplenomegaly and lymphadenopathy and in laboratory examination pancytopenia is frequently found[127]. The worldwide number of VL cases in SOT recipients has steadily increased since the 1990s, although VL is still a rare disease among transplant recipients[128]. VL is the most frequently observed clinical presentation in this population, followed by MCL and more rarely CL. Fever is the most common symptom of VL in SOT recipients, whereas organomegaly may be less frequent in SOT recipients than in immunocompetent individuals. Immunosuppression seems to predispose to development of MCL caused by viscerotropic strains[128-130]. Clinical presentation in these patients is almost the same as in immunocompetent persons although sometimes it can be atypical making it much more difficult for the diagnosis, therefore it is frequently overlooked or delayed in transplant patients. The combination of conventional and molecular diagnostic methods may serve as the best approach[130].

NON-VECTOR-BORNE ZOONOSES

Hepatitis E virus

HEV is a non-enveloped RNA virus that belongs to the family *Hepeviridae*. Genotypes 1 and 2 are restricted to humans only, while 3 to 8 are zoonotic genotypes. In fragile sanitary infrastructure (*e.g.* Asia, Africa, Mexico) genotypes 1 and 2 usually cause human diseases, whereas genotypes 3 and 4 are nowadays found to be the most common genotypes in high-income countries[131]. Waterborne, zoonotic and foodborne transmissions are the most common routes of infection, with the primary reservoirs (Europe) being domestic pigs, wild boars, and deer[131]. Parenteral transmission, transmission *via* solid organs and blood components has been increasingly recognized[131,132]. HEV is diagnosed through serology and nucleic acid amplification test, although, only HEV RNA testing is recommended for the immunocompromised population[131]. Hepatitis E virus infection typically manifests as an acute self-limiting hepatitis, but may also present as fulminant hepatitis (pregnant women) or acute-on–chronic liver failure in patients with pre-existing liver diseases or extra-hepatic manifestations[131,132]. After solid-organ transplantation, genotype 3 and 4 HEV can be responsible for chronic hepatitis (positive HEV RNA > 6 mo) where the majority of cases are asymptomatic accompanied by mild liver test abnormalities. Chronic infections may rapidly progress to liver fibrosis and cirrhosis[133]. Thus far, there have been numerous reports of chronic hepatitis E in the liver, kidney, heart, lungs, liver-kidney, kidney-pancreas, islet cell recipients[133,134]. Furthermore, extrahepatic manifestations are also common in SOT recipients, including neurological (neuralgic amyotrophy, Guillain-Barré syndrome, encephalitis, myelitis)[135], renal manifestations (membranoproliferative and membranous glomerulonephritis)[136], as well as thrombocytopenia[135] and cryoglobulinemia[136]. After an acute infection, one third of the patients will clear the virus after the reduction of immunosuppression[131]. In other patients (about 60%), the infection will typically progress to chronic forms and lead to the need for additional treatments[131,133]. A recent multi-center study which included 255 solid organ transplant recipients, confirmed that ribavirin is highly efficient for treating chronic HEV infection and that HEV RNA polymerase mutations do not play a role in HEV clearance[137].

Rabies virus

Rabies virus (RABV) is a neurotropic lyssavirus that belongs to the family *Rhabdoviridae*. With some exceptions (particularly islands), the RABV is found worldwide, however almost all human deaths caused by RABV occur in Asia and Africa. Typical reservoirs of RABV are domestic dog (Africa and Asia), jackal (Africa), mongoose (Africa), fox (Europe, Asia, America), raccoon (America), skunk, coyote (America) and bats (Europe, Australia, America). Humans become infected by the bite of infected animals or by contact with infectious saliva through mucous membranes or breaks in the skin[138]. Human-to-human RABV transmission may occur through tissue or organ transplantation. The first case of RABV transmitted through corneal transplantation was reported in 1978 in the USA[139], followed by several other reports[140-142]. However, rabies transmission through SOT transplantation has rarely been reported. In 2004 (USA), four recipients of a liver, kidneys and an arterial segment from a common organ donor with unrecognized rabies developed encephalitis within 30 d after transplantation. The patients presented with fever and altered mental status (confusion, agitation, tremors, and delirium). All patients died within 50 d after transplantation[143]. In 2013, a patient died of rabies 18 mo after receiving a deceased-donor kidney transplant in the USA. Three other recipients (kidney, heart, and liver) did not show symptoms consistent with rabies or encephalitis. All received post-exposure prophylaxis with rabies immune globulin and vaccine and remain asymptomatic[144]. The transmission of RABV through SOT has become a notable problem in China. In 2015, two patients who received kidney transplants from the same donor presented with typical symptoms of rabies and eventually died. In 2016, infected donor organs were transplanted to three patients. Two recipients that were diagnosed with rabies died[145]. In 2016, another two cases of RABV transmission through SOT were reported in China. Two kidney transplant recipients died, whereas a liver recipient did not show any signs or symptoms of rabies or encephalitis[146]. A case of RABV transmission through a kidney transplant was also reported in a child in Kuwait[147]. Since the mortality rate of rabies is extremely high, rabies should be considered in patients with acute progressive encephalitis of unexplained etiology, especially for potential organ donors[144].

Lymphocytic choriomeningitis virus

Lymphocytic choriomeningitis virus (LCMV) is an Old World arenavirus distributed in Europe and Americas. The main reservoir of LCMV is a house mouse (*Mus musculus, Mus domesticus*), but some other rodents including pet animals may also transmit the virus[148]. LCMV transmission to humans occurs by inhalation of aerosolized excreta/secreta of infected rodents (urine and saliva), bites and contact with rodent blood[149]. LCMV infection in immunocompetent individuals is typically asymptomatic or it presents as nonspecific febrile illness or aseptic meningitis[99]. In contrast, immunocompromised hosts such as transplant recipients develop severe infection with multisystem organ failure and high mortality rate. Several clusters of organ-transplant-associated LCMV infections have been reported in the USA from 2003 to 2013. Signs and symptoms suggestive of LCMV infection occurred in clusters of SOT recipients, in 2003 and 2005. Laboratory testing revealed the LCMV in all the recipients, however, the virus could not be detected in donors. Seven of eight recipients died, 9-76 d after transplantation. In the 2005 cluster, the donor reported contact with a hamster pet, infected with an LCMV strain identical to that detected in the organ recipients. No source of infection was found in the 2003 cluster[150]. In 2010-2011, four clusters of organ-transplant-associated LCMV transmissions have been reported; 11 of 14 recipients died[151]. The majority of patients with fatal donor-derived LCMV infection showed hepatitis as a prominent feature[99]. In a recently published study, a case of LCMV infection in a renal transplant recipient that was non-organ donor-derived was described. The patient presented with meningoencephalitis acquired by the exposure to mice excreta. The clinical course was complicated by the development of hydrocephalus, requiring a ventriculoperitoneal shunt[152]. Although the risk of LCMV among organ recipients is low, clinicians should be aware of the possibility of transplant-transmitted LCMV infection.

Toxoplasma gondii (Toxoplasmosis)

Toxoplasmosis is a zoonotic disease caused by a protozoan *Toxoplasma gondii*. It is an obligate intracellular parasite that is widely spread all over the world. Warm-blooded vertebrates are the intermediate hosts where asexual reproduction takes place. This results in the formation of tachyzoites and bradyzoites. Tachyzoites can invade various tissues *e.g.* lungs, CNS and heart but also, they can cause intrauterine infection with possible transplacental transmission to the fetus. Bradyzoites form the tissue cysts in the intermediate host. Felids are the only definite hosts where sexual reproduction occurs resulting in excretion of oocysts into the environment *via* feces. Transmission to humans occurs through the ingestion of water, vegetables, or soil contaminated with oocysts or raw or undercooked meat containing tissue cysts with bradyzoites[153]. The worldwide prevalence of toxoplasmosis in the human population varies from 10 to 80%[154,155]. The course of infection is generally benign and most infected individuals remain asymptomatic or mildly symptomatic. The disease may have an acute or chronic form. The presence of bradyzoites in tissue cysts represents the latent infection which can reactivate at any age. Prenatal transplacental infection can result in intrauterine fetal growth retardation, hepatosplenomegaly, eye and/or brain damage, fetal death or premature birth. If symptomatic, postnatal toxoplasmosis can present as fever with lymphadenopathy. Chorioretinitis as a manifestation of acquired toxoplasmosis is seen less frequently. Rarely, a potentially fatal disseminated disease, myocarditis, pneumonitis, hepatitis, myositis or encephalitis can be seen in an immunocompetent patients[156]. Toxoplasmosis as an infectious complication is a well-recognized entity in SOT recipients. If it presents in the first three post-transplant mo, the graft transmission is most likely, but if it presents after this early period, most often it is the result of the latent infection reactivation or the primary infection. Clinical presentation in SOT patients is more severe as cerebral, disseminated and pulmonary toxoplasmosis is seen more often than mild forms (fever and ocular toxoplasmosis). Even more severe forms with higher mortality are seen in graft transmission[157,158]. As toxoplasmosis in SOT patients might be a fatal disease and as at the same time it is a preventable infection, clinicians have to follow the screening and chemoprophylaxis guidelines to optimize the patient's outcome.

CONCLUSION

This article summarizes the most important emerging and neglected zoonotic pathogens and their clinical presentations in the transplant population. In recent decades, human activities along with climatic changes have led to the shifts in environmental conditions influencing among others, the transmission and distribution of zoonotic pathogens. As the number of zoonotic diseases is increasing, the spreading trends are likely to continue in the future. In parallel, the expanding transplant population worldwide imposes additional challenges for diagnostics and treatment of zoonotic infections. Immunosuppressed state may influence the serologic response and delay diagnosis, modify and aggravate clinical presentation and prolong treatment and recovery. Keeping that in mind is of particular importance in the context of emerging and neglected pathogens which may not be familiar to the wider community of transplant professionals in different geographical locations. The increasing trend of the pathogens transmitted and shared between animals and humans in global and especially transplant population, emphasizes the need for the multidisciplinary approach ("One Health") in the surveillance and control of zoonotic infections around the world.

ACKNOWLEDGEMENTS

This study was supported in part by the Croatian Science Foundation, project No. IP 2016-06-7456: Prevalence and molecular epidemiology of emerging and re-emerging neuroinvasive arboviral infections in Croatia; CRONEUROARBO (to TVC).

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World Journal of Transplantation

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

World J Transplant 2020 March 31; 10(3): 64-78

DOI: 10.5500/wjt.v10.i3.64

ISSN 2220-3230 (online)

SYSTEMATIC REVIEWS

Novel alternative transplantation therapy for orthotopic liver transplantation in liver failure: A systematic review

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Author contributions: Furuta T conceptualized and designed the review together with Furuya K and Zheng YW; Furuta T and Furuya K carried out the analysis; Furuta T drafted the initial manuscript; all authors reviewed and approved the final manuscript as submitted; Furuta T and Furuya K contributed equally to the work; Zheng YW and Oda T are senior authors.

Supported by National Natural Science Foundation of China, No. 81770621; Ministry of Education, Culture, Sports, Science, and Technology of Japan, KAKENHI, No. 18H02866; and Japan Science and Technology Agency-Japan International Cooperation Agency's (JST-JICA) Science and Technology Research Partnership for Sustainable Development (SATREPS) Project, No. JPMJSA1506.

Conflict-of-interest statement: The authors report no relevant conflicts of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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Abstract

BACKGROUND

Orthotopic liver transplantation (OLT) is the only treatment for end-stage liver failure; however, graft shortage impedes its applicability. Therefore, studies investigating alternative therapies are plenty. Nevertheless, no study has comprehensively analyzed these therapies from different perspectives.

AIM

To summarize the current status of alternative transplantation therapies for OLT and to support future research.

METHODS

A systematic literature search was performed using PubMed, Cochrane Library and EMBASE for articles published between January 2010 and 2018, using the following MeSH terms: [(liver transplantation) AND cell] OR [(liver transplantation) AND differentiation] OR [(liver transplantation) AND organoid] OR [(liver transplantation) AND xenotransplantation]. Various types of studies describing therapies to replace OLT were retrieved for full-text evaluation. Among them, we selected articles including *in vivo* transplantation.

RESULTS

A total of 89 studies were selected. There are three principle forms of treatment for liver failure: Xeno-organ transplantation, scaffold-based transplantation, and cell transplantation. Xeno-organ transplantation was covered in 14 articles,

Manuscript source: Invited manuscript

Received: December 4, 2019
Peer-review started: December 4, 2019
First decision: December 12, 2019
Revised: February 10, 2020
Accepted: March 23, 2020
Article in press: March 23, 2020
Published online: March 31, 2020

P-Reviewer: Gavriilidis P, Qin JM, Tao R
S-Editor: Tang JZ
L-Editor: A
E-Editor: Qi LL

scaffold-based transplantation was discussed in 22 articles, and cell transplantation was discussed in 53 articles. Various types of alternative therapies were discussed: Organ liver, 25 articles; adult hepatocytes, 31 articles; fetal hepatocytes, three articles; mesenchymal stem cells (MSCs), 25 articles; embryonic stem cells, one article; and induced pluripotent stem cells, three articles and other sources. Clinical applications were discussed in 12 studies: Cell transplantation using hepatocytes in four studies, five studies using umbilical cord-derived MSCs, three studies using bone marrow-derived MSCs, and two studies using hematopoietic stem cells.

CONCLUSION

The clinical applications are present only for cell transplantation. Scaffold-based transplantation is a comprehensive treatment combining organ and cell transplantations, which warrants future research to find relevant clinical applications.

Key words: Cell transplantation; Liver transplantation; Organ transplantation; Xenotransplantation; Tissue engineering; Scaffold

Core tip: This systematic review analyzes the current status of transplantation treatments in place of liver organ transplantation from multiple viewpoints. We classified reports into three types: Xeno-organ transplantation, scaffold-based transplantation, and cell transplantation. Clinical application occurred for cell transplantation with hepatocytes and mesenchymal stem cells; however, the effect was limited. On the other hand, scaffold-based transplantation is a comprehensive treatment that combines organ transplantation and cell transplantation. Future research for clinical application is expected. The present article provides researchers with a summary and updated information on recent trends in alternatives to liver transplantation and support for future research.

Citation: Furuta T, Furuya K, Zheng YW, Oda T. Novel alternative transplantation therapy for orthotopic liver transplantation in liver failure: A systematic review. *World J Transplant* 2020; 10(3): 64-78
URL: https://www.wjgnet.com/2220-3230/full/v10/i3/64.htm
DOI: https://dx.doi.org/10.5500/wjt.v10.i3.64

INTRODUCTION

Liver diseases lead the causes of mortality worldwide, accounting for approximately 1-2 million deaths per annum according to the World Health Organization[1]. Orthotopic liver transplantation (OLT) remains as the only curative therapy for end-stage liver diseases. However, the shortage of donor organs limits its application.

Alternatives to OLT such as liver support systems, including bioartificial livers, and hepatocyte transplantation have been extensively explored; however, none could be adopted in clinical practice[2]. Thus, to overcome the organ shortage, many researchers attempted to find alternatives to the traditional solid-organ transplantation method[3].

Various alternative treatments are available, including organ transplantations from other human beings, transplanting cells from other species, or transplanting processed cells from humans or transplanting processed cells from other species.

Alternative therapies investigated in the past include xenotransplantation, scaffold-based transplantation, and cell transplantation therapies. In particular, the use of animal livers for human patients, *i.e.*, xenotransplantation, has been deemed as a solution for donor shortage. If the organ of other species could be transplanted, there are many advantages about the supply of organ[4]. Although this approach has still several problems, such as immune rejection and coagulopathy, α-1,3-galactosyltransferase gene-knockout (GT-KO) pigs that do not express the α1,3Gal (Gal) antigens have improved the potential of this therapy[5,6]. In fact, it underwent many advancements through genome editing technologies[7].

Scaffold-based transplantation is a novel method, which aims to generate tissues and organs *ex vivo* or *in vivo* with biological materials that can be used to repair, regenerate, or even replace malfunctioning tissues and organs. Essentially, to create scaffolds, all the cells from animal organs are removed while retaining the structural, mechanical, and chemical attributes of the native tissue[8]. Then, the human-derived cells are embedded in the scaffold that serves as an ideal container to generate humanized organs.

In parallel, cell transplantation research has undergone vast advancements with the establishment of induced pluripotent stem cells (iPSCs). Clinical human-to-human hepatocyte transplantation following host conditioning has been reported[9]. However, hepatocytes have limitations with respect to proliferation, function, and immunity. Recently, pluripotent or somatic stem cells were used as new sources in place of hepatocytes[10]. Further, researchers tried to direct pluripotent or somatic stem cells toward differentiation into hepatocytes in various studies[11].

Thus, alternative therapies manifest various combinations depending on different resources. Still, no study has comprehensively analyzed these different viewpoints yet, although such studies are instrumental while considering novel alternatives for the future regarding the utility of these kinds of treatments.

Therefore, we aimed to discuss the current status of alternative transplantation therapies to replace liver organ transplantation and to support their research and development.

MATERIALS AND METHODS

The methodological approach included the development of selection criteria, defining the search strategies, assessing the study quality, and abstracting the relevant data. The PRISMA statements checklist for reporting a systematic review was followed[12].

Identification and selection of the studies

This systematic literature review was performed to select articles discussing alternatives to liver organ transplantation. The PubMed, Cochrane Library, and EMBASE were electronically searched for articles published between January 2010 and December 2018, using the following MeSH terms: [(liver transplantation) AND cell] OR [(liver transplantation) AND differentiation] OR [(liver transplantation) AND organoid] OR [(liver transplantation) AND xenotransplantation].

Inclusion and exclusion criteria

The study selection criteria were defined before initiating data collection to identify eligible studies for the analysis. Only studies written in English were selected. We retrieved all studies in which the primary objective was to evaluate new transplantation therapies in place of OLT for our analysis.

Exclusion criteria were as follows: (1) Studies not including *in vivo* transplantation; (2) Studies lacking sufficient details; (3) Review articles; (4) Expert opinions; (5) Letters; and (6) Conference summaries.

Study selection and quality assessment

The titles and abstracts of the retrieved studies were independently and blindly screened for relevance by two reviewers (Furuta T and Furuya K), who assessed the study quality and extracted data. To enhance sensitivity, records were removed only in case both reviewers judged them to be inappropriate. All disagreements were resolved by discussion and consensus. The study design, quality, level of evidence, and the relevance of the studies were analyzed according to the objective of this study.

Analysis

We classified the reports into three types: Xeno-organ transplantation, scaffold-based transplantation, and cell transplantation. Further, we categorized the source of donor or donor species, recipients, and the clinical applications.

RESULTS

Literature search and selection

The combined search identified 2821 articles. Of these, 2630 were removed after evaluating the title and abstract. By checking the full text, 89 articles were considered eligible for the systematic review and were analyzed qualitatively and quantitatively. The entire study selection process is summarized in Figure 1.

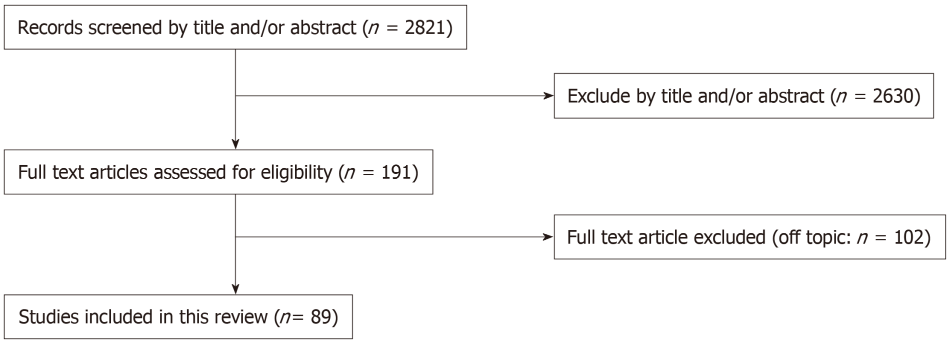

Figure 1 Flowchart of the study selection.

Treatment modalities and clinical application

From our qualitative analysis on the selected articles, there were 14 xeno-organ transplantation studies, 22 scaffold-based transplantation studies, and 53 cell transplantation studies. The study selection is displayed in Tables 1-3[2,5,13-99]. There were various sources of alternative therapy, including organ liver (25 studies), adult hepatocytes (31 studies), fetal hepatocytes (three studies), mesenchymal stem cells (MSCs; 25 studies), embryonic stem cells (ESCs; one study), and iPSCs (three studies) and others (Table 4)[2,5,13-45,48-70,72-99]. Clinical application was discussed in 12 studies. In particular, hepatocyte transplantation was discussed in four studies, umbilical cord derived MSCs (UC-MSCs) transplantation was described in five studies, bone marrow derived MSCs (BM- MSCs) was described three studies and hematopoietic stem cells was described two studies.

DISCUSSION

Among various alternative OLT therapies, only cell transplantation has been adopted in clinical practice. However, its long-term improvement effects are yet to be proven. In particular, few studies report that it can become a bridge for OLT. Considering the viewpoint of cell transplantation, cell processing strategies such as proliferation or hepatic differentiation might assume paramount significance. On the other hand, although scaffold-based transplantation is far from being applied clinically, it is deemed as attractive and promising. This approach has been devised as a treatment method that combines the efficiency of solid organ transplantation with the control of rejection. It is also a comprehensive treatment incorporating cell processing technologies.

Although many patients die from liver failure, there is no other curative treatment other than OLT. However, organ shortage remains as the major shortcoming for transplantation globally. Because of graft shortages, alternative treatments for OLT have received significant research attention.

The concept of scaffold-based transplantation was developed to substitute for the damaged human liver requiring immediate transplantation. In particular, many studies discussed xeno-organ transplantation using decellularized liver scaffolds from other species embedded with human derived hepatic cells.

Our search revealed articles on xeno-organ transplantation (*n* = 14), scaffold-based transplantation (*n* = 22), and cell transplantation (*n* = 53), with the majority being related to “cell therapy”.

Cell transplantation

Cell transplantation is an attractive alternative to conventional organ transplantation. Hepatocyte transplantation has also been applied clinically, however, with limited effect. To obtain better transplantation efficiency, studies were conducted to evaluate the differentiation quality and administration methods.

In this study, regarding transplantation cell sources, we found that adult hepatocytes, fetal hepatocytes, stem cells such as iPSCs, ESCs, MSCs, and differentiated hepatocytes-like cells (HLCs) have been used and most report used hepatocytes as the cell source. In addition, our article showed that only cell transplantation was clinically applied.

Lee *et al*[13] reported the application of neonatal hepatocytes encapsulated in alginate microbeads transplanted in three patients with acute liver failure from error of sulfite metabolism. Hansel *et al*[100] reported hepatocyte transplantation applied in 100

Table 1 Cell transplantation

Donor			Recipients (disease, strain *etc.*)	Outcomes	Year
Cells	Species	Treatments [co-culture (Co), organoid generated]			
Hepatocytes	Human	-	Human (ALF)	Hepatic function	2018[13]
		-	Human (ACLF)	Hepatic function	2014[22]
		-	Human (metabolic disease)	Engraftment, hepatic function	2012[23]
		-	Human (oxalosis)	Hepatic function	2012[24]
		-	Rat (SD)	Hepatic function, survival extension	2017[25]
		-	Mouse (NOD/SCID)	Alb secretion, engraftment	2017[26]
		-	Mouse (FRG)	Engraftment, hepatic function	2013[27]
		-	Mouse (SCID/Alb-uPA)	Analysis of NK cell	2010[28]
		UC-MSC (human)	Mouse (BALB/c)	Engraftment, hepatic function	2018[29]
	Rat	-	Mouse (C57BL/6 FRG)		2018[30]
		-	Rat (Wistar)	Engraftment	2015[31]
		-	Rat (SD)	Engraftment, hepatic function	2015[32]
		-	Rat	Engraftment	2014[33]
		-	Rat (DPP4-)	Engraftment, repopulation	2014[34]
		-	Rat (An alb)	Engraftment, hepatic function	2014[35]
		HSCs (Rat), SECs (Rat)/Co	Mouse (C57BL/6)	Engraftment, survival extension	2014[36]
		-	Rat (SD)	Hepatic function	2010[37]
	Mouse	Organoid	Mouse (C57BL/6)	Engraftment	2017[38]
		-	Mouse (emdr2$^{-/-}$)	Engraftment, Repopulation	2015[39]
		-	Mouse (Fah-/-)	Hepatic function	2010[40]
		-	Mouse (FVB/N)	Engraftment, analysis of metabolite	2010[41]
		-	Mouse (C57BL/6)	Engraftment	2010[42]
Hepatocytes (fetal)	Rat	-	Rat (DPPIV^{-})	Engraftment, repopulation	2018[43]
	Mouse	-	Mouse (C57BL/6)	Engraftment, hepatic function	2012[44]
Liver cells	Rabbit	-	Rabbit (New Zealand)	Hepatic function	2012[45]
Hepatic oval cells	Rat	-	Rat (Lewis)	Hepatic function, survival extension	2013[46]
Hepatoma cell line		-	Rat (SD)	Hepatic function, survival extension	2013[47]
UC-MSCs	Human	-	Human after OLT	Hepatic function, intervention rate	2017[48]
		-	Human after OLT	Hepatic function	2017[49]
BM-MSCs/BM-MNCs	Human	-	Human (LC)	Hepatic function	2017[50]
		-			2016[51]
		-	Human (Liver failure)	Hepatic function	2013[52]
	Rabbit	-	Rabbit	Remodeling	2011[53]
BM-MSCs/HSCs	Human	-	Human (EPP)	Engraftment	2010[54]
BM-MSC	Human	-	Human (LC)	Engraftment, hepatic function	2011[55]
		-	Rat (Wistar)	Hepatic function	2014[56]
		-	Mouse (SCID)	Engraftment, analysis of glucose	2017[57]

		-	Mouse (Pfp/Rag2$^{-/-}$)	Engraftment	2010[58]
	Rhesus macaque	-	Mouse	Hepatic function	2018[59]
	Rat	-	Rat (SD)	Hepatic function	2014[60]
BM-MNC-EPC	Rat	-	Rat (SD)	Remodeling	2012[61]
Liver-MSCs	Human	-	Mouse (NOD/SCID)	Engraftment, repopulation	2011[62]
AD-MSCs	Human	-	Mouse (c57/B6)	Analysis of IRI	2014[63]
	Mouse	-	Mouse (Swiss CD1)	Repopulation	2012[64]
AD-MSC-Hep	Mouse	-	Mouse (C57BL/6)	Engraftment	2015[65]
CD34+ cells	Human	-	Human (LC)	Hepatic function	2015[66]
ESCs-Hep	Mouse	-	Mouse (BALB/c)	Engraftment, hepatic function	2012[67]
iPSC-Hep	Human	Organoid	Mouse (Alb-Tk-NOG)	Survival extension, hepatic function	2017[68]
		Organoid	Mouse (NOD/SCID)	Engraftment	2013[69]
	Mouse	-	Mouse (Fah-/- C57Bl/6)	Engraftment	2010[70]
iMPC-Hep	Human	-	Mouse (FRG)	Engraftment	2014[71]
GPSCs-Hep	Mouse	-	Mouse (Hfe-null)	Engraftment	2015[72]
Liver stem cells	Rat	Organoid	Rat (Fah$^{-/-}$Il2rg$^{-/-}$)	Engraftment, hepatic function	2016[73]

"-" means negative treatment. ALF: Acute liver failure; ACLF: Acute on chronic liver failure; SD: Sprague dawley; UC-MSCs: Umbilical cord deriver mesenchymal stem cells; BM-MSCs: Bone marrow derived mesenchymal stem cells; MNCs: Mononuclear cells; HSCs: Hematopoietic stem cells; LC: Liver cirrhosis; EPP: Erythropoietic protoporphyria; BM-MNC-EPC: BM-MNC derived endothelial progenitor cell; AD-MSCs: Adipose derived MSCs; IRI: Ischemia-reperfusion injury; AD-MSC-Hep: AD-MSC derived hepatocyte; iMPC: Induced multipotent progenitor cell; GPSCs: Germ line cell-derived pluripotent stem cells.

patients with errors of metabolism and acute-on-chronic liver failure (ACLF). Nevertheless, the use of human hepatocytes has limitations including limited organ availability, limited cell proliferation, loss of function, and risk for immune rejection[101,102]. Previous studies have explored the application of not only hepatocytes but other cell sources as well. Xue *et al*[103] performed a meta-analysis of cell transplantation for ACLF including nine RCTs. In this report, UC-MSCs and bone marrow-derived MSCs (BM-MSCs) were used as the cell source, which improved the survival period and liver function.

MSCs, especially BM-MSCs, have shown immunomodulatory and antifibrotic effects in other organ systems, and MSC transplantation has shown positive results in the treatment of liver fibrosis[104,105]. We also found 2 reports of hematopoietic stem cell transplantation, but they were relatively less applied than UC-MSCs and BM-MSCs.

Most importantly, MSCs can secure more sources than hepatocytes, but the problem of cell quality still remains. As a stem cell therapy, iPSCs attract considerable attention in the field of transplantation. iPSCs were established from adult fibroblasts by introducing dierent transcription factors[106]. They overcame the ethical aspects of ESCs and have the self-renewal properties and pluripotency, the ability to differentiate into various somatic cells, including hepatocytes[107].

HLCs derived from human iPSCs have been researched as a potential alternative to hepatocytes for cell therapy, disease models, and evaluating drugs[108,109]

Takebe *et al*[3] succeeded in creating a liver bud with iPSCs derived HLCs. This study demonstrated a three-dimensional liver bud produced by co-culturing with Human Umbilical Vein Endothelial Cells and MSCs was able to improve the liver function of recipient following transplantation.

A 3 dimensional (3D) culture is effective for hepatocyte functionality[110], and using a method combining iPSCs and 3D culture may eventually assure high cell quality and quantity.

Nevertheless, because of potential tumorigenicity, the risks of developing teratomas, and the lack of long-term safety and ecacy, 3D cultures and iPSCs have not been clinically applied yet[111,112]. In our search, we did not find many studies elucidating the *in vivo* application of iPSCs.

Cell transplantation also suffers from these above-mentioned challenges. Moreover, in the recent years, *in vitro* expansion of human hepatocytes has been explored[113] to overcome the challenges with iPSCs. The improvements in these approaches may lead to the development of alternative therapies.

Xeno-organ transplantation

Table 2 Xeno-organ transplantation

Donor organ	Recipients	Outcomes	Year
GTKO pig	Tibetan macaques	Cytokine profile	2017[74]
	Baboon	Survival extension	2018[5]; 2017[14]; 2014[75]; 2012[76]; 2010[77]
		Analysis of thrombotic microangiopathy	2016[78]
		Analysis of platelet	2014[79]
		Analysis of rejection	2012[80]
		Platelet aggregation	2012[81]
		Analysis of coagulopathy	2012 [82]
		Hepatic function	2010[83]
Pig	Baboon	Analysis of immunoglobulin	2018 [84]
Rabbit	Porcine, rabbit	Analysis of IgG	2012[85]

GTKO: Alpha 1-3 galactosyltransferase gene knockout; IgG: Immunoglobulin G.

The first successful animal-to-animal liver xenotransplantation was reported in 1968[114]. Because of the development of immunosuppressive drugs, various studies were conducted that targeted the applicability of harvested organs from other species. Among animals, pigs were proved as useful in terms of size and rejection strength; therefore, genetically modified porcine organs hold enormous potential for this purpose. Although the cornea and skin of pig have been clinically applied, for OLT, the survival period is so short that liver xenotransplantation could not been applied clinically. To solve the problem of severe rejection, GT-KO pig was developed, intending to reduce the risk of GVHD[115]. The recent development of CRISPR/Cas9 has made this animal model more suitable[116].

Regarding xenotransplantation, 12 of 14 articles in our search used GT-KO pigs. Shah *et al*[14] reported that a human prothrombin-concentrate complex and immunosuppression was used on GT-KO pigs and that the survival was improved. Even then, it is necessary to improve physiological problems such as rejection, coagulation factors, and complementary species specific for application in humans.

Scaffold-based transplantation

Regarding rejection and infection, decellularization of tissue is an attractive method. Decellularization of tissues and even whole organs represents a novel approach for developing perfusable extracellular matrix (ECM)-derived scaffolds with preserved vascular integrity. Decellularized tissue is rarely rejected and is used for tissue reconstruction as scaffold material[117]. This decellularized scaffold is transplanted orthotopically or ectopically. The decellularization of whole organ was first introduced by Ott *et al*[118] in 2008 with the aim of developing acellular hearts from mice. Bovine heart valves and corneas or those from pigs have already been commercialized and clinically applied[119]. In recent years, research has been conducted on human liver and hepatocytes. Mazza *et al*[2] reported in 2015 that human liver was decellularized and re-cellularized with a liver cell line to create engineered livers.

KaKabadze *et al*[15] engrafted sheep liver cells on decellularized human placenta and transplanted them into sheep that underwent partial hepatectomy. Human placenta was considered as an attractive source because it has a well-developed vascular network and ECM for tissue engineering. Moreover, it is usually discarded and widely available.

In addition, many articles exhibited the application of decellularized tissues and biomaterial-based scaffold.

As biomaterials, natural biomaterials are applied such as collagen and hyaluronic acid, and synthetic materials such as polymers based on polylactic acid and polyglycolic acid, among others[16-18]. Previous reports show that after transplanting these scaffolds, the liver function in recipients improved[19-21].

More recently, bio-printed scaffolds have been developed that mimic the tissue using these biomaterials[120]. However, they have problems of vascularization for tissue engraftment and repopulation, which warrant further research.

Meanwhile, scaffold-based transplantation with an ECM was proven effective, and further research is underway with an aim to select ideal cells for humans[119].

iPSCs and few other cell sources are seeded and cultured in decellularized tissue and other scaffolds such that tissue regeneration *in vitro* can be performed. Therefore,

Table 3 Scaffold-based transplantation

Donor			Recipients (strain)	Outcomes	Year
Scaffold	Species	Seeding cell			
Decellularized organ liver	Human		Mouse (C57BL/6J)	Immunogenicity	2015[2]
	Porcine		Rat (F344)	Immunogenicity	2013[86]
			Porcine	Immunogenicity	2013[87]
			Porcine	Engraftment	2012[88]
	Sheep, rat		Sheep, rat	Engraftment	2015[89]
	Rat	Hepatocytes (rat), BM-MSCs (Rat)	Rat (Lewis)	Engraftment	2014[90]
		Hepatocytes (rat)	Rat (Lewis)	Engraftment, Hepatic function	2010[91], 2011[92]
	Mouse	Hematopoietic progenitor cells (mouse)	Mouse (C57Bl/6)	Hepatic function, metabolic function	2018 [93]
		BM-MSCs (mouse)	Mouse (NOD-SCID)	Survival extension, hepatic function	2014[94]
Placenta	Human	Liver cells (sheep)	Sheep	Survival extension, hepatic function	2018[15]
Amniotic membrane	Human	AD-MSCs (human)	Mouse	Survival extension, hepatic function	2015[95]
Nonwoven polyglycolic acid scaffolds		Liver cells (human, mouse)	Mouse (NOD/SCID)	Analysis of human metabolite	2017[19]
3D hydrogel		Hepatocytes (human)	Mouse (nude)	Engraftment, hepatic function	2016[16]
Hyaluronan tube		Hepatocytes (rat), adipose-MSCs (human)	Rat (nude)	Engraftment, hepatic function	2016[17]
Polyethylene glycol hydrogels		Hepatocytes (rat)	Mouse (Nude)	Engraftment	2015[20]
Microbeads		Hepatocytes (rat)	Rat (SD)	Hepatic function	2014 [96]
Poly-L-glycolic acid		Hepatocytes (mouse)	Mouse (NOD/SCID)	Engraftment	2014[21]
Hyaluronan hydrogels		Hepatic stem cells (human)	Mouse (Athymic nude)	Engraftment	2013[97]
Apatite-fiber scaffold		Hepatocytes (mouse) + HSC + SECs	Mouse (BALB/CA nu)	Hepatic function	2011[98]
Chitosan-alginate fibrous scaffolds		BM-MSCs (human)	Rat (Wistar)	Hepatic function	2010[99]
Hyaluronic acid sponge		Fetal hepatocyte (rat)	Rat (LEC)	Engraftment, hepatic function	2010[18]

3D: Three dimensional; SD: Sprague dawley; HSCs: Hematopoietic stem cells; BM-MSCs: Bone marrow derived mesenchymal stem cells.

further research should aim to solve this problem for actualizing its application clinically.

Conclusion and future perspectives

Our study summarized alternative therapies for OLT. Alternative therapies have been deeply researched, particularly xeno-organ, scaffold-based, and cell transplantations. Clinically, only cell transplantation with hepatocytes or MSCs has been applied.

Scaffold-based transplantation is a comprehensive treatment that combines xeno-organ and cell transplantations. Future research on the clinical application of scaffold-based transplantation is expected.

Table 4 Sources of alternative therapy

Donors	Species	Numbers
Organ liver	Total	25
	Human	1[2]
	Porcine	16[5,14,74-84,86-88]
	Sheep	1[89]
	Rabbit	1[85]
	Rat	4[89-92]
	Mouse	2[93,94]
Hepatocytes (adult)	Total	31
	Human	10[13,16,22-29]
	Rat	14[17,20,30-37,90-92,96]
	Mouse	7[21,38-42,98]
Hepatocytes (fetal)	Total	3
	Rat	2[18,43]
	Mouse	1[44]
Liver cells	Total	3
	Human	1[19]
	Sheep	1[15]
	Rabbit	1[45]
MSCs (umbilical cord)	Human	3[29,48,49]
MSCs (bone marrow)	Total	15
	Human	9[50-52,54-58,99]
	Macaques	1[59]
	Rabbit	1[53]
	Rat	3[60,61,90]
	Mouse	1[94]
MSCs (Adipose)	Total	4
	Human	2[17,63]
	Mouse	2[64,65]
MSCs (liver)	Human	1[62]
Hematopoietic stem cells	Human	2[54,66]
ESCs	Mouse	1[67]
iPSCs	Total	3
	Human	2[68,69]
	Mouse	1[70]
GPSCs	Mouse	1[72]
Liver stem cells	Total	2
	Human	1[97]
	Rat	1[73]

MSCs: Mesenchymal stem cells; ESCs: Embryonic stem cells; iPSCs: Induced pluripotent stem cells; GPSCs: Germ line cell-derived pluripotent stem cells.

ARTICLE HIGHLIGHTS

Research background

Orthotopic liver transplantation (OLT) is the only treatment for end-stage liver failure; however, the shortage of donor organs limits its application. To overcome this problem, many researchers have attempted to develop alternatives to OLT.

Research motivation

There are several reports of alternative therapies. Nevertheless, no study has comprehensively analyzed these therapies from varying perspectives.

Research objectives

This systematic review aims to summarize the current status of alternative transplantation therapies for OLT and to support future research.

Research methods

A systematic review was performed by searching the PubMed, Cochrane Library and EMBASE databases for studies concerning alternative transplantation therapy for OLT. We used the following MeSH terms: "liver transplantation", "cell", "differentiation", "organoid", and "xenotransplantation". Various types of studies were retrieved for full-text evaluation. Of these, we selected articles involving *in vivo* transplantation.

Research results

A total of 89 studies were selected. There are three principle forms of treatment: Xeno-organ transplantation (14 articles), scaffold-based transplantation (22 articles), and cell transplantation (53 articles). Various types of sources for transplantation were discussed: Organ liver, 25 articles; adult hepatocytes, 31 articles; mesenchymal stem cells (MSCs), 25 articles; induced pluripotent stem cells, three articles and other sources. Clinical applications were discussed only for cell transplantation (12 studies; four studies using hepatocytes, five studies using umbilical cord-derived MSCs, three studies using bone marrow-derived MSCs, and two studies using hematopoietic stem cells).

Research conclusions

This systematic review summarized alternative therapies for OLT from varying perspectives. Alternative therapies have been deeply researched, particularly xeno-organ, scaffold-based, and cell transplantation. Clinically, only cell transplantation with hepatocytes and MSCs have been applied. Scaffold-based transplantation is a comprehensive treatment that combines xeno-organ and cell transplantations. Future research on the clinical application of scaffold-based transplantation is expected.

Research perspectives

This systematic review describes the current status of alternative therapy for OLT in end-stage liver failure. Further studies are needed for clinical applications in the future.

ACKNOWLEDGEMENTS

We would like to thank Vikas Narang for English language editing.

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