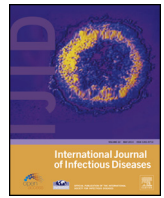




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Editorial

Host-directed therapies for improving poor treatment outcomes associated with the middle east respiratory syndrome coronavirus infections



SUMMARY

Three years after its first discovery in Jeddah Saudi Arabia, the novel zoonotic pathogen of humans, the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) continues to be a major threat to global health security.¹ Sporadic community acquired cases of MERS continue to be reported from the Middle East. The recent nosocomial outbreaks in hospitals in Seoul, Korea and at the National Guard Hospital in Riyadh, Saudi Arabia indicate the epidemic potential of MERS-CoV. Currently there are no effective anti-MERS-CoV anti-viral agents or therapeutics and MERS is associated with a high mortality rate (40%) in hospitalised patients. A large proportion of MERS patients who die have a range of pulmonary pathology ranging from pneumonia to adult respiratory distress syndrome with multi-organ failure, compounded by co-morbidities, reflecting a precarious balance of interactions between the host-immune system and MERS-CoV. Whilst we wait for new MERS-CoV specific drugs, therapeutics and vaccines to be developed, there is a need to advance a range of Host-Directed Therapies. A range of HDTs are available, including commonly used drugs with good safety profiles, which could augment host innate and adaptive immune mechanisms to MERS-CoV, modulate excessive inflammation and reduce lung tissue destruction. We discuss the rationale and potential of using Host-Directed Therapies for improving the poor treatment outcomes associated with MERS. Carefully designed randomized controlled trials will be needed to determine whether HDTs could benefit patients with MERS. The recurrent outbreaks of MERS-CoV infections at hospitals in the Middle East present unique opportunities to conduct randomized clinical trials. The time has come for a more coordinated global response to MERS and a multidisciplinary global MERS-CoV response group is required to take forward priority research agendas.

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1. Introduction and background

The past two decades has seen the emergence and spread of novel viral respiratory tract pathogens of humans, such as severe acute respiratory syndrome coronavirus (SARS-CoV), H7N9 avian strain of influenza A virus, swine influenza A H1N1, and Middle East respiratory syndrome coronavirus (MERS-CoV), for which no specific treatment options are available and carry a high morbidity and mortality rate.^{1–5} MERS-CoV was first reported from Jeddah in September 2012 when it was isolated from a Saudi patient who died of a severe respiratory illness and multi-organ failure.⁶ Since then community and hospital acquired MERS cases have been reported from twenty-nine countries from the Middle East, Africa, Europe, North America and Asia.⁷ Three years since its first discovery, many fundamental questions regarding the epidemiology, pathogenesis, immune responses and optimal treatment regimens of MERS-CoV remain unanswered.^{8–10} MERS-CoV continues to be of global concern as illustrated by recent nosocomial outbreaks at the National Guard Hospital in Riyadh, Saudi Arabia^{11–13} and at hospitals in Seoul, Republic of Korea.^{14–16} The Korean outbreak which resulted in 186 confirmed MERS cases with 35 deaths arose from a Korean traveler who imported MERS-CoV from the Middle East.¹⁷ As of 21 August 2015, there have been 1432 laboratory confirmed cases of human infection with 507 deaths (40% mortality).¹⁸

2. Current deficiencies of MERS-CoV treatment

Current clinical management of seriously ill MERS patients is fraught with difficulties.^{19,20} There are no MERS-CoV-specific antiviral, other therapeutic or immune based treatments approved for treating patients. Thus supportive care is the main stay of treatment and is focused on prevention of complications, particularly organ failure, ARDS, and secondary bacterial infections.²¹ Due to the high mortality in hospitalized MERS cases, empiric treatment has been tried on an ad hoc patient basis. Reports of the empiric individual or combination use of steroids, interferons (IFN- α and IFN- β), other generic anti-viral drugs have been tried have been used to treat MERS patients with no significant effects on clinical outcome.^{22–28} There have been no controlled randomized clinical trials of any treatment intervention performed to date. The use of convalescence plasma, monoclonal antibodies and mycophenolic acid are further options available and require evaluation in controlled clinical trials. There are several anti-MERS-CoV drugs in development but to date no anti-MERS-CoV therapeutics have been developed or approved by regulatory authorities. The unacceptable high mortality rate associated with MERS-CoV and its epidemic potential, indicates an urgent need for development of newer anti-MERS-CoV drugs, vaccines and alternate treatment approaches.^{29,30}

3. MERS-CoV pathogenesis and host immune responses

Infection with MERS-CoV presents as a spectrum of clinical manifestations from asymptomatic, mild to severe disease which progresses to multi-organ failure and death. A large proportion of patients infected with MERS-CoV are either asymptomatic or have mild illness and complete recovery occurs due to effective innate and acquired immune responses which eradicates the infection.³¹ No comprehensive immunopathogenesis studies have been conducted to date. The protective and deleterious human response to MERS-CoV remains to be determined. Pneumonia and multi-organ involvement is a common feature in patients with MERS.³² The high mortality seen in MERS-CoV could be attributed to acute lung injury, development of acute respiratory distress syndrome (ARDS).³³ ARDS is associated with leaky alveolar-capillary interfaces with pulmonary oedema, hypoxia, polymorphonuclear leucocytic or lymphocytic cells with upregulation of pro-inflammatory cytokines and gamma interferon and an aberrant immune response, which results in further tissue damage and deterioration of lung function. Sixty percent of MERS patients with acute lung injury or ARDS either recover after receiving intensive care and 40% of MERS patients succumb to the disease.³⁴

A large majority of patients who die due to infection with MERS-CoV may have some form of immunosuppression due to old age or having co-morbid conditions (diabetes, chronic lung, renal, cardiac or liver disease or have an underlying immunosuppressive condition).³⁵ It appears that the outcome of MERS patients may represent a precarious balance of both host- and MERS-CoV-induced immune signaling events.³⁶ It is not known whether mortality is a reflection of an ineffective host response to MERS-CoV or whether an aberrant host immune response contributes to pathogenesis and poor prognosis. Interventions that could manipulate this host-pathogen relationship via modulation of the host response to MERS-CoV infection may help improve mortality rates in patients with MERS.³⁷ For instance, genome analysis suggest that immune signaling modulation may affect outcome,³⁸ and adenosine deaminase may prevent MERS-CoV entry into host cells.³⁹ A range of Host-Directed Therapies (HDTs) have the potential for improving the treatment outcomes of severe lung infections.⁴⁰

4. Host-directed therapies for MERS

The general principles of using HDTs are to augment anti-MERS-CoV protective immune mechanisms, modulate destructive immune-mediated inflammatory responses, and protect tissues from inflammatory damage. A range of HDT interventions are available^{41,42} which require evaluation for treatment of patients with MERS:

- 1) 'Repurposed' commonly used drugs with excellent safety profiles include those being used for lowering cholesterol, diabetes, arthritis, antibiotics, epilepsy and cancer, which can modulate autophagy, promote other immune effector mechanisms, antimicrobial peptide production and repair of damaged tissues,
- 2) Micronutrient products with immune-modulatory effects,
- 3) Cellular therapy using mesenchymal stromal cells obtained from patient's own bone marrow to reduce aberrant inflammation, regenerating tissues and inducing anti-MERS-CoV immune responses.

4.1. Repurposed drugs

Several commonly available products with a longstanding safety record which are readily available and require evaluation as

treatments for severe MERS, and for which open label clinical trials should be considered.⁴³ Statins have shown potential for treatment of influenza⁴⁴ and other diseases with lung injury.⁴⁵ They induce autophagy and maturation of phagosome and have anti-inflammatory effects through peroxisome proliferator-activated receptor- γ and transforming growth factor- β . Non-steroidal anti-inflammatory drugs such as Indomethacin, Ibuprofen and Acetylsalicylic acid inhibit cyclooxygenase and reduce inflammation and tissue pathology;⁴⁶ overt inflammatory immune responses, have been curbed using etoposide in patients with severe influenza infection,⁴⁷ which may in part be due to differential susceptibility of Treg (regulatory T-cells).⁴⁸ The diabetes drug Metformin increases mitochondrial ROS production and enhances macrophage autophagy.⁴⁹ Several cancer drugs such as Gleevac (Imatinib)-a tyrosine kinase inhibitor, activate autophagy and reduce inflammatory responses.⁵⁰ Doxycycline has potential for protection against destruction and degradation of tissue collagen and other structural proteins through its matrix metalloproteinase (MMP) inhibitor effect.⁵¹ A recent study describes a library of 290 compounds screened for antiviral activity against MERS-CoV and severe acute respiratory syndrome coronavirus (SARS-CoV). Of these 27 compounds with activity against both MERS-CoV and SARS-CoV were identified.⁵² These compounds include inhibitors of dopamine receptor used as anti-psychotic drugs and inhibitors of estrogen receptors used for cancer treatment.

4.2. Autologous bone-marrow derived stromal cells

Mesenchymal stromal cells (MSCs) derived from the patient's own bone marrow may have the potential to modulate aberrant immune responses through their anti-inflammatory and tissue-repairing effects for severe viral and bacterial infections of the lung.^{58,59} The use of adjunct therapy using MSCs derived from the patient's own bone marrow and expanded *ex vivo* before re-infusion, is currently under evaluation for range of infectious and non-communicable diseases and should be evaluated for improving treatment outcome of MERS-CoV in hospitalized cases, with very encouraging and life-saving results in the MSCs treatment of patients with ARDS.⁵³

5. Advancing host-directed therapies for MERS

Repurposed drugs have well-defined safety and pharmacokinetic profiles their individual evaluations through controlled clinical trials are required to define their effectiveness in treatment of severe cases of MERS and patients with co-morbidities. Treatment outcome measures would be effect on mortality, lung function, and long term sequelae, immune responses, and resolution of lung inflammation and tissue regeneration. To achieve optimal treatment several variables need to be explored when trialing these agents including patient's age, the presence of co-morbid illness, the extent of disease and the timing of the intervention. Carefully designed randomized controlled trials will be needed to determine whether HDTs could benefit patients with MERS, and optimally these studies. HDT trials in MERS could benefit from experience in managing life-threatening clinical situations, where overt inflammation caused by a 'cytokine storm' in the context of T-cell based therapies of malignant diseases, can be controlled. Highly activated T-cells are not responsive to glucocorticosteroids,^{54–56} and yet may respond to newer drugs, such as anti-TNF reagents (e.g. etanercept), anti-IL-6 and anti-IL-1beta.⁵⁷

Many fundamental questions regarding MERS epidemiology, pathogenesis, protective immune responses, viral kinetics, and optimal treatment remain unanswered three years into its first discovery. A MERS-CoV response group is required and the recurrent outbreaks of MERS-CoV infections at hospitals present unique challenges for control of MERS-CoV and at the same time

provides an opportunity to conduct randomized clinical trials and answer priority research questions. The time has come for a more coordinated global response to take forward important priority epidemiological, translational clinical and basic science research forward. The establishment of clinical trials capability within a global consortia will develop infrastructure and build local capacity to take forward further evaluations of new drugs, therapeutics and vaccines

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