Global co-operation results in cellular therapies aimed at treating patients with COVID-19

Introduction

Worldwide, the pharmaceutical and healthcare industries in collaboration with research establishments are working at an unprecedented rate to develop treatments to deal with the global threat from COVID-19. Even in the last few weeks, the international involvement and output are growing, with vaccines, drugs, stem cells and other cellular therapies being investigated. As part of this program, regulators are cutting the red tape and rapidly reviewing proposals from companies, scientists and clinical teams who are working toward innovative therapies.

As far as cellular therapies are concerned, mesenchymal stromal/stem cells (MSCs) are emerging as a promising therapeutic option for exploitation in the treatment of patients suffering from virus related respiratory damage. The use of modified Natural Killer (NK) cells, which are a critical component of the body's repertoire of immune cells, is also an evolving contender in the drive to find ways to tackle COVID-19 related organ damage.

Although there may well be a potential role for MSCs and other cell-based therapies in treatment of patients with COVID-19, these need to be investigated using well designed and controlled trials to ensure patient safety and reliability of results. A balance must be achieved between rapid investigation, communication and robust analysis of clinical outcome data.

This mini review aims to highlight a few of the key advances focussing on MSCs and NK cells.

Mesenchymal Stem/Stromal Cells (MSCs)

MSCs have already proven to be effective at reducing inflammation and ameliorating cytokine storms in various clinical settings. Cytokines are small proteins produced by many cells in the body and the term "cytokine storm" relates to the dramatic release of these proteins when cells are damaged by infection including COVID-19, chemotherapy or even in transplantation where donor cells react with the patient's immune cells. Uncontrolled cytokine release can cause overwhelming activation of many immune cells resulting in devastating inflammation, organ damage and even death.

Studies looking at the possible role of MSC based therapies in COVID-19 indicate that these cells may exert beneficial effects, potentially by inhibiting over activation of the immune system thus helping to prevent lung damage due to Acute Respiratory Distress Syndrome (ARDS). This respiratory complication results in the lung lining becoming leaky so the lungs fill with fluid, causing difficulty breathing and patients may require support on a ventilator. MSCs have previously been shown to be able to secrete beneficial proteins that can promote tissue repair so may be capable of preventing pulmonary fibrosis and improving lung function.

ARDS has significant resource implications, prolonging Intensive Care Unit (ICU) and hospital stay and requiring rehabilitation in the community, all of which impact on healthcare providers and social care services. There are currently no treatments for ARDS and a

therapeutic intervention that could improve the outcome for sufferers would be of major benefit.

As part of the global initiative to co-ordinate efforts to combat the effects of COVID-19, it is encouraging to note that an international team of scientists has recently been granted immediate US Food and Drug Administration (FDA) authorisation for a 24-patient clinical trial to test the safety and explore the efficacy of intravenously administered unrelated donor umbilical cord-derived MSCs to help prevent the life-threatening lung inflammation that accompanies severe cases of COVID-19.

Dr Camillo Ricordi, the principal investigator based at the University of Miami Miller School of Medicine, commented: "There is no time to waste. Patients who die from COVID-19 have a median time of just 10 days between first symptoms and death. In severe cases oxygen levels in the bloodstream drop and the inability to breathe pushes patients towards their end very quickly; any intervention that might prevent that trajectory would be highly desirable."

This trial will be based at the University of Miami Health System and Jackson Health System in Miami and the clinical protocol has been already shared with other institutions throughout the world so that they may participate in testing similar treatment strategies in the fastest and most efficient way possible.
https://www.europeanpharmaceuticalreview.com/news/116794/us-researchers-to-study-stem-cell-therapy-in-COVID-19-patients/
https://www.trialsitenews.com/university-of-miami-cure-alliance-launch-mesenchymal-stem-cell-study-for-at-risk-COVID-19-patients/

Another formal collaboration is underway between Aspire, a US based biotech company specialising in cellular therapeutics, the U.S. FDA and Health Canada regarding development of the Aspire's cellular therapy product ACT-20, for the treatment of severe COVID-19 Pneumonia.

ACT-20 is a pooled donor derived preparation of MSCs that are expanded in cell culture from donated human umbilical cord tissue. The expanded MSCs are frozen, so are effectively an "off the shelf" product. MSCs have been previously used in clinical studies for immune modulation of inflammatory diseases such as graft-versus-host disease (GVHD), systemic lupus erythematosus (SLE), stroke and ARDS. It is therefore a logical step to consider the use of this product in COVID-19 patients who have virally induced ARDS.
https://bioinformant.com/aspire-act-20-covid19/

Athersys, is another US based company that is an established player in the field of "off the shelf" MSC production from donated bone marrow. The company is now focusing on launching a new trial of MultiStem®, its MSC product, for the treatment of COVID-19 induced ARDS. This proposed clinical program has received a "Highly Relevant" designation from the Biomedical Advanced Research and Development Authority (BARDA).

The MultiStem® product may be expanded on a large scale using Athersys's technology for future clinical use and stored frozen until needed. Cells obtained from a single bone marrow donor may be used to produce hundreds of thousands to millions of doses of the MultiStem product.

MultiStem® is already being used to treat stroke and ARDS and this therapy has also received Fast Track designation from the FDA. It has the potential to make a significant improvement in patients' lives and in the use of resources needed to treat COVID-19 related respiratory conditions.
https://www.genengnews.com/gen-edge/athersys-stem-cell-therapy-targets-top-cause-of-COVID-19-deaths/
https://www.clinicaltrialsarena.com/news/athersys-multistem-COVID-19-trial/

In Israel, Pluristem Therapeutics Inc., a leading regenerative medicine company developing novel biological therapeutic products, announced on April 13th that it has treated a patient suffering from COVID-19 respiratory complications in the United States. The treatment was undertaken under the U.S. FDA's Single Patient Expanded Access Program, also called a compassionate use program. This is part of the U.S. Coronavirus Treatment Acceleration Program (CTAP), an emergency scheme for possible therapies that aims to accelerate new treatments to patients as quickly as possible. The company's PLacental eXpanded (PLX) cells are donor placenta-derived, MSC-like cells that are designed to be administered to patients without the need for tissue or genetic matching so they are readily accessible. These cells release soluble biomolecules, such as cytokines and other key proteins, which act to facilitate healing of damaged tissue by stimulating the body's own regenerative mechanisms. PLX cells have immunomodulatory properties that may prevent or reverse the dangerous over activation of the immune system due to a COVID-19 induced cytokine storm.

Because PLX cells are available off-the-shelf and can be manufactured in large-scale quantities, they offer the possibility of addressing the global pandemic. PLX cells may potentially reduce the incidence and/or severity of COVID-19 pneumonia and pneumonitis leading hopefully to a better prognosis for patients. Pluristem's main aim is to start a multinational clinical trial as soon as possible for PLX cells in the treatment of patients suffering from complications associated with COVID-19. The company will release data on the status and progress of its planned clinical trial program in due course.
https://www.pluristem.com/wp-content/uploads/2020/04/PSTI-COVID-19-First-Patient-in-US-FINAL-FOR-RELEASE.pdf
https://www.pluristem.com/placental-expanded-plx-products/

A new Wellcome Trust funded trial titled "Repair of Acute Respiratory Distress Syndrome by Stromal Cell Administration" (REALIST) has been instigated in Queen's University Hospital, Belfast. The trial will test if treatment with a preparation of MSCs, called REALIST ORBCEL-C, which is derived from umbilical cord tissue and produced under licence by the UK NHS Blood and Transplant Service, can improve outcomes in patients with ARDS. Patients will be recruited to the REALIST trial in one of two phases. Phase 1 will recruit up to 18 patients to receive increasing doses of REALIST ORBCEL-C to confirm which dose is best tolerated. Phase 2 of the trial will recruit a further 60 patients who will be randomly allocated to either a group which receives treatment with REALIST ORBCEL-C or a group that receives a dummy version (placebo). Patients will have a 1:1 chance of receiving MSCs or placebo. The REALIST trial will determine the safest tolerated dose of REALIST ORBCEL-C as well as analyse the effects of the therapy on patients with ARDS.
https://www.qub.ac.uk/News/Allnews/QueensUniversityleadingcelltherapyclinicaltrialtohelpimproveoutcomesinCOVID-19patients.html
https://www.clinicaltrialsarena.com/news/queens-university-covid-therapy-trial/

Natural Killer cells

Natural Killer (NK) cells play a key role in defence against viral infections by recognising infected cells, attaching to them and destroying them. This in turn helps to prevent the virus replicating as it needs to be inside an intact host cell to do so. Other immune cells are involved fighting a virus but the entire immune response takes time. In the case of COVID-19 infection, a proportion of patients can become very rapidly overwhelmed by the virus, so upregulating the immune response by introducing NK cells that are capable of recognising infected cells and destroying them would be a potentially significant therapeutic development.

Celularity, a New Jersey-based biotech company, has been given the go ahead from the FDA to start a clinical trial of CYNK-001, it's allogeneic, off-the-shelf, cryopreserved natural killer cell therapy to be used in a study in up to 86 patients with COVID-19. CYNK-001 cells which are derived from the donated placental tissue have already been shown to be well tolerated in early clinical trials and are currently being investigated as a treatment for some haematological cancers and a particular brain malignancy. The safety of CYNK-001 has already been established and the aim now is to gain an insight into the potential impact of treatment on patients diagnosed with COVID-19. It is well recognised that NK cells become activated during viral infections regardless of the virus class involved. CYNK-001 is capable of a range of biological activities similar to those observed in NK cells in the body, including the ability to bind to virally infected cells. If this occurs in patients then CYNK-001 could be beneficial in terms of limiting viral replication and help prevent disease progression by eliminating infected cells.
https://www.fiercebiotech.com/biotech/rudy-giuliani-backed-COVID-19-therapy-from-celularity-nabs-fda-speedy-trial-start
https://www.prnewswire.com/news-releases/celularity-expands-strategic-collaboration-with-united-therapeutics-corporation-to-COVID-19-infection-and-acute-respiratory-distress-syndrome-301038319.html
https://www.cancernetwork.com/immuno-oncology/fda-accepts-ind-nk-cell-therapy-cynk-001-treat-patients-COVID-19