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COVID-19 pandemic: what can pharmaceutical formulation and drug delivery experts offer?

The current COVID-19 pandemic caused by SARS-CoV-2 is undoubtedly the biggest and most detrimental health crisis the world has ever seen since the 1918 Spanish flu pandemic caused by the H1N1 virus. Ever since the first case report back in Dec. 2019, the number of those affected has risen to well over 3 million infection cases and well over 200,000 deaths worldwide to date[1].

The last two months (March and April 2020) have witnessed an unsurpassed increase in the number of clinical trials worldwide, their aim is to find a solution either in the form of an effective drug(s) to eradicate the virus, manage the acute phase of the disease, in particular the complications of the ''Cytokine storm'', or as prophylaxis i.e. to develop safe and effective vaccines. Clinical trials that are sponsored by governments, World Health Organization (WHO), the Big Pharma, with the involvement of and in collaboration with universities, charities, hospitals, NGOs and research centres worldwide have reached over 1000 trials (recruiting and non-recruiting) according to *the National Institute of Health database of privately and publicly funded clinical studies conducted around the world*[2]. According to the Global Coronavirus COVID-19 Clinical Trial Tracker, there are currently over 650 trials running worldwide with the majority taking place in China (over 300 trials) followed by the USA (over 100 trials)[3].

A search of the recruiting clinical trials reveals a list of old and new drugs that are being ''repurposed'' where they are tested as potential treatments either for their direct anti-viral activity, or for their ability to provide management of selected debilitating respiratory and cardiovascular symptoms and complications, characteristic of COVID-19.

Several relatively new anti-viral drugs including the fixed-dose combination of Lopinavir/Ritonavir, Favipiravir, Umifenovir and Remdesivir are being tested either on their own or in combination with other measures. Amongst the conventional small (molecular weight of less than 1000 $g.mol^{-1}$) drug molecules tested are the anti-malarial drugs Hydroxychoroquine and Chloroquine, the macrolide antibiotic Azithromycin, the angiotensin II receptor antagonist Losartan, the statin Simvastatin, the corticosteroids Dexamethasone and Methylprednisolone, vitamins C and D, the anti-parasitic drugs Nitazoxanide and Ivermectin (lab-based evidence of anti-viral activity, not yet in clinical trials), the anti-gout/anti-micro-tubule agent Colchicine, the NSAIDs Celecoxib, Ibuprofen, Naproxen and Tranexamic acid, the acetylcholinesterase inhibitor Pyridostigmine Bromide and the aldosterone antagonist and potassium-sparing diuretic Spironolactone.

Trials involving the use of plasma therapy, stem cells and repurposing biologics including monoclonal antibodies such as Sarilumab (rheumatoid arthritis treatment), Tocilizumab (rheumatoid arthritis treatment), Siltuximab (multicentric Castleman's disease treatment), Bivacizumab (anti-VEGF treatment) are all underway.

The approach of clinically testing, approving and using registered and investigational drugs for clinical applications beyond their original indication (so called repurposing, repositioning or retasking) is currently happening at a large and unprecedented scale in an attempt to control the COVID-19 pandemic. Such a strategy is likely to give rise to a range of safety and efficacy challenges that could be addressed through a pharmaceutical formulation/drug delivery approach. Reformulating already approved drugs to overcome issues of instability, poor membrane permeability, compromised bioavailability, inadequate duration of action, side effects and developing alternative dosage forms to administer via more appropriate routes of administration

(e.g. pulmonary instead of oral or oral instead of subcutaneous) are indeed within the realm of pharmaceutical formulation and drug development research.

Development of an effective prophylaxis in the form of a vaccine for COVID-19 is another area of research interest where pharmaceutical scientists have already made a difference. mRNA-1273 (in Phase 1 trials) is an mRNA-based vaccine formulated by encapsulating the mRNA molecule in lipid nanoparticles[4]. Formulation and development of gene silencing molecules based on RNA interference, DNA plasmid, viral vectors, recombinant proteins and new adjuvants, microneedles and nanotechnology are areas of active research that could help further advance current knowledge, leading to new modalities with better therapeutic outcomes.

The current COVID-19 pandemic poses a new challenge to pharmaceutical scientists, one that could be harnessed and translated to new and exciting research projects leading to novel medicines that would make a difference by addressing an unmet, yet urgent clinical need. Despite the global lockdown, we are experiencing unprecedented level of collaboration and data sharing amongst research communities that is changing the landscape and further facilitating and advancing developments.

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