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Review

Cite this article: Morgulchik N, Athanasopoulou F, Chu E, Lam Y, Kamaly N. 2021 Potential therapeutic approaches for targeted inhibition of inflammatory cytokines following COVID-19 infection-induced cytokine storm. *Interface Focus* **12**: 20210006. https://doi.org/10.1098/rsfs.2021.0006

Received: 20 January 2021
Accepted: 14 October 2021

One contribution of 7 to a theme issue 'Coronavirus and surfaces'.

Subject Areas:
biotechnology, nanotechnology

Keywords:
COVID-19, anti-inflammatory, targeted therapy, cytokine storm, biologics, multiorgan failure

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THE ROYAL SOCIETY PUBLISHING

Potential therapeutic approaches for targeted inhibition of inflammatory cytokines following COVID-19 infection-induced cytokine storm

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Coronavirus disease 2019 (COVID-19) is a deadly respiratory disease caused by severe acute respiratory syndrome coronavirus 2, which has caused a global pandemic since early 2020 and severely threatened people's livelihoods and health. Patients with pre-diagnosed conditions admitted to hospital often develop complications leading to mortality due to acute respiratory distress syndrome (ARDS) and associated multiorgan failure and blood clots. ARDS is associated with a cytokine storm. Cytokine storms arise due to elevated levels of circulating cytokines and are associated with infections. Targeting various pro-inflammatory cytokines in a specific manner can result in a potent therapeutic approach with minimal host collateral damage. Immunoregulatory therapies are now of interest in order to regulate the cytokine storm, and this review will summarize and discuss advances in targeted therapies against cytokine storms induced by COVID-19.

1. COVID-19 infection and the cytokine storm

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in the Chinese city of Wuhan in December 2019 and since then has spread across the globe rapidly, leading to over 4.9 million deaths and over 243 million infections (as of October 2021) [1]. COVID-19 infection leads to a hallmark hyper-inflammatory state, more commonly known as a 'cytokine storm' [2,3]. The onset of a cytokine storm leads to impaired oxygen-exchange and acute respiratory distress syndrome (ARDS), which is driven by a cytokine storm caused by upregulated levels of inflammatory mediators. ARDS is thought to be the cause of death in up to 70% of fatal COVID-19 cases where a cytokine storm has been detected [4]. Furthermore, continuous inflammation causes an imbalance in pro- and anti-coagulative factors, leading to microthrombosis, multiorgan injury and failure [5].

With a marked similarity to SARS and MERS, severely ill patients with COVID-19 demonstrate decreased CD4+ and CD8+ T lymphocyte counts, increased Th17 cell proliferation and abnormally elevated pro-inflammatory cytokine levels, notably interleukin-6 (IL-6), interferon-γ (IFN-γ), granulocyte-macrophage colony-stimulating factor (GM-CSF) and tumour necrosis factor-α (TNF-α) (figure 1) [6–8]. Moreover, post-mortem pathological examinations reported diffuse alveolar damage, mononuclear infiltration and pulmonary oedema, also characteristic of other highly pathogenic coronaviruses [8]. These findings altogether are indicative of a cytokine storm underlying ARDS and multiple organ failure (MOF) in most severe cases. Thus, targeting exaggerated cytokine response may be effective in improving outcomes in COVID-19 patients.

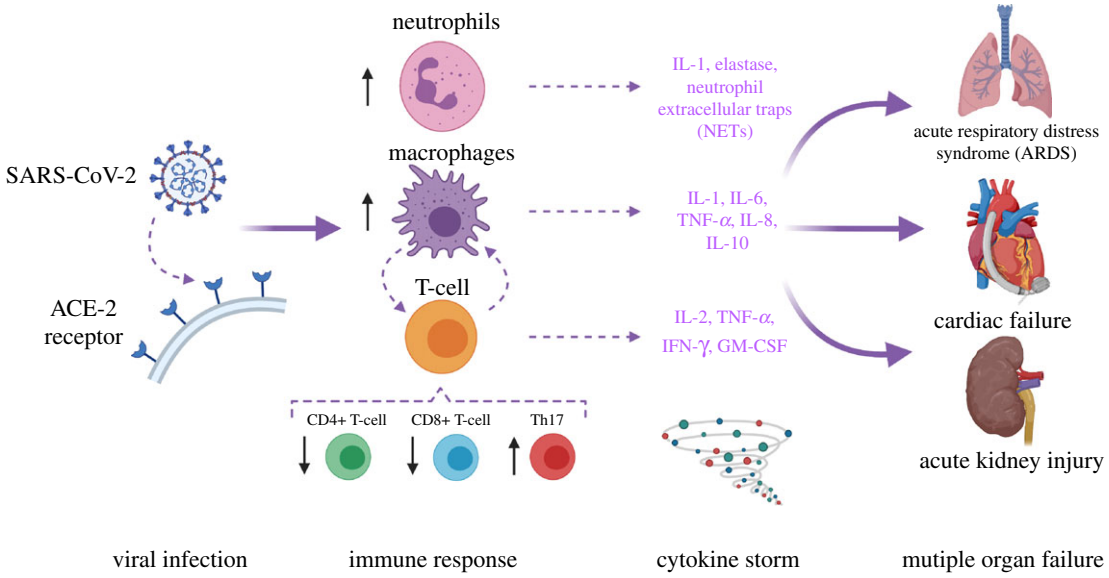

Figure 1. SARS-CoV-2 immune response and outcomes. SARS-CoV-2 infection of host cells via the ACE-2 receptors triggers an immune response, notably activation of neutrophils, macrophages and Th17 cells, downregulation of CD4+ and CD8+ T cells and increased cytokine production. The abnormally elevated pro-inflammatory cytokines, known as cytokine storm, can cause cell death and tissue damage across the body that may lead to MOF and death.

2. Anti-inflammatory therapeutic approaches used to date to combat COVID-19

Multiple anti-inflammatory therapies have been used to diminish high cytokine levels and to mitigate the cytokine storm-related morbidity and mortality in COVID-19 patients (tables 1 and 2). However, none of the existing therapeutic approaches has demonstrated desired efficacy, and no consensus has been reached yet with regard to timing, duration and type of regimen. Untargeted immunosuppression of cytokine storm in COVID-19 with corticosteroids and anti-malarials has been associated with mixed success so far. While anti-inflammatory corticosteroids, such as dexamethasone, have been successfully used for the treatment of critically ill SARS and MERS patients, these drugs failed to deliver on their promise for long-term use in COVID-19 treatment of patients with mild-to-moderate symptoms due to increased risk of co-infections [38]. However, a randomized, open-label clinical trial, RECOVERY, showed that dexamethasone could decrease mortality in hospitalized patients with COVID-19 who require respiratory support [39]. The short-term use of low-dose methylprednisolone was reported to improve clinical outcomes for severely ill patients, but further clinical investigations are required for confirmation [40,41]. The clinical performance of anti-malarials, chloroquine and its derivative hydroxychloroquine is also inconsistent. While it has been suggested that chloroquine inhibits production and release of IL-6 and TNF-α [42] and hydroxychloroquine modulates antigen processing in antigen-presenting cells [43], thus both suppressing cytokine storm, major clinical trials with these drugs have been halted due to suboptimal efficacy and prominent adverse effects [44,45]. Intravenous immunoglobulin (IVIG), derived from pooled human plasma, has been used for the treatment of various immune diseases [46]. As an immunomodulator, IVIG can suppress inflammation [9,47], and in a recent multi-centre retrospective cohort study proved that when administered early, IVIG improves prognosis for critically ill COVID-19 patients [48].

The complexity of the immune system as a whole and in particular the immune response to SARS-CoV-2 with elevated levels of both pro-inflammatory and anti-inflammatory cytokines such as IL-6 and IL-10, respectively [49], may underpin the mixed outcomes of general immunosuppressive anti-COVID-19 treatments so far. However, targeted immunomodulating therapies have been explored on par and hold promise to become a potential first-line COVID-19 therapy.

Most widely, blocking cytokine receptors to suppress their activity is explored as a COVID-19-related cytokine storm treatment avenue. IL-6 has a fundamental role in the cytokine storm, and its elevated levels tend to be correlated with the disease severity [50–52]. A recombinant humanized antibody, tocilizumab, binds to soluble and membrane-bound IL-6 receptors, and inhibits IL-6 mediated inflammatory response by blocking its signal transduction [53]. Multiple studies suggest that tocilizumab could effectively improve symptoms and outcome in severe and critical COVID-19 patients [54–58]. However, tocilizumab has been previously linked to increased risk of opportunistic infections for other indications such as rheumatoid arthritis [59], and a major clinical trial has recently demonstrated that this drug was not effective in preventing intubation or death in moderately ill hospitalized COVID-19 patients [60]. Analogously, another rheumatoid arthritis drug, IL-1 receptor antagonist protein, anakinra, which inhibits the activity of pro-inflammatory IL-1α and IL-1β cytokines, has been repurposed for COVID-19 [61]. A retrospective cohort study of patients with COVID-19 and ARDS showed that intravenous administration of a high-dose anakinra improved the clinical status of the participants [61]. Furthermore, anakinra was found to reduce the need for oxygen therapy and the mortality among severe COVID-19 patients [62].

Alternatively, downstream inhibition of major inflammation-associated signalling pathway could provide an alternative approach to cytokine storm suppression, for instance, targeting Janus kinase-signal transducer and activator of transcription proteins (JAK-STAT) pathway [63]. Early clinical data suggest that the use of currently available JAK inhibitors such as baricitinib

Table 1. Small-molecule-based targeted anti-inflammatory approaches in patients with COVID-19. RA = rheumatoid arthritis; MF = myelofibrosis; cGVHD = graft-versus-host disease; MCL = mantle cell lymphoma; CLL = chronic lymphocytic leukaemia; WM = Waldenström macroglobulinemia; MZL = marginal zone lymphoma; LAM = lymphangioleiomyomatosis; PsA = psoriatic arthritis; Ps = plaque psoriasis.

drug	cytokine regulation	study type (identification number), status	study aim	original indication
JAK inhibitors				
baricitinib	IL-6: JAK1, JAK2, TYK2; IFN-γ: JAK1, JAK2; IL-2, IL-4, IL-7: JAK1, JAK3 [9]	Phase III (NCT04421027), recruiting [10]	to assess effectiveness in hospitalized patients with COVID-19	RA
ruxolitinib	IL-6: JAK1, JAK2, TYK2; IFN-γ: JAK1, JAK2; IL-2, IL-4, IL-7: JAK1, JAK3 [9]	Phase II and III (NCT04359290), recruiting [11]	to evaluate safety and efficacy in patients with COVID-19 severe pneumonia	MF, cGVHD
BTK inhibitors				
acalabrutinib	IL-6, IL-10, TNF-α, MCP-1 [12]	Phase II (EudraCT 2020-001736-95), active [13]	to evaluate efficacy and safety of multiple candidate agents for treatment of COVID-19 in hospitalized patients	MCL
ibrutinib	IL-6, IL-10, TNF-α, MCP-1 [14]	Phase II (NCT04439006), recruiting [15]	to study side effects, best dose and its efficacy in treating COVID-19 patients who require hospitalization	MCL, CLL, WM, MZL, cGVHD
mTOR inhibitor				
rapamycin/ sirolimus	IL-1β, IL-6 [16]	Phase II (NCT04341675), recruiting [17]	to assess clinical outcomes and improvement in hospitalized patients with COVID-19	LAM
PDE4 inhibitors				
apremilast	IFN-γ, TNF-α, IL-2, IL-12, IL-17, IL-23, IL-10 [18]	Phase II (NCT04488081), recruiting [19]	to evaluate efficacy for treatment of critically ill COVID-19 patients	PsA, Ps

and ruxolitinib is associated with improved clinical and laboratory parameters, or faster clinical improvement of severe COVID-19 patients [64,65]. However, the risks may outweigh the benefits for JAK inhibitors in COVID-19 treatment as these drugs may increase the chance of viral reactivation by blocking anti-viral IFN-α production [66], and baricitinib, in particular, has been linked to lower lymphocyte counts, which is already a critical concern for COVID-19 patients [67].

3. Potential targeted therapeutic approaches against the COVID-19 cytokine storm

There are as yet few anti-inflammatory therapeutic approaches that have been deliberated upon in a clinical trial setting. However, as more evidence on COVID-19 pathogenesis comes to light, targeting cytokine storm appears more promising, and more therapeutic approaches with different molecular entities such as small-molecule therapeutics, biologics and nanomedicines are investigated (figure 2).

3.1. Small-molecule therapeutics

The main advantage of small-molecule drugs over any higher molecular weight therapeutic agents is oral availability and predictable pharmacokinetic profiles due to their simple chemical structures [68]. In addition to well-known JAK inhibitors such as baricitinib and ruxolitinib that are currently undergoing clinical trials for COVID-19 repurposing (table 1), other kinase inhibitors are now also being considered in response to the pressing need to mitigate the fatal consequences of COVID-19-related cytokine storm.

Small-molecule inhibitors specific to Bruton's tyrosine kinases (BTK) such as acalabrutinib and ibrutinib are considered for the treatment of COVID-19 due to their ability to inhibit B-cell signalling pathway and suppress subsequent production of pro-inflammatory cytokines such as TNF-α, IL-6, IL-10 and chemokine (C-C motif) ligand 2 (CCL2) [69,70]. Both BTK inhibitors showed improvements in symptoms and outcomes in preliminary studies with acalabrutinib substantially reducing key pro-inflammatory IL-6 cytokine levels [12,14] and are now in the middle of Phase II clinical trials to further evaluate their effectiveness [13,15].

Moreover, a few studies have suggested using sirolimus (also known as rapamycin), a selective mammalian target of rapamycin (mTOR) inhibitor, to tame the cytokine storm by inhibiting the mTOR pathway that plays a key role in downstream T-cell differentiation and cytokine production [71–74]. The immunosuppressant has previously been shown to shorten the duration of ventilator usage and improved clinical

Table 2. Biologic-based targeted anti-inflammatory approaches in patients with COVID-19. RA, rheumatoid arthritis; CRS, cytokine release syndrome; GCA, giant cell arteritis; SJIA, systemic juvenile idiopathic arthritis; iMCD, idiopathic multicentric Castleman disease; CAPS, cryopyrin-associated periodic syndromes; TRAPS, tumour necrosis factor receptor-associated periodic syndrome; HID, hyperimmunoglobulin D syndrome; FMF, familial Mediterranean fever; JIA, juvenile idiopathic arthritis; PsA, psoriatic arthritis; AS, ankylosing spondylitis; CD, Crohn's disease; UC, ulcerative colitis; Ps, plaque psoriasis; HS, hidradenitis suppurativa; UV, uveitis; HLH, hemophagocytic lymphohistocytosis; AIDS, acquired immunodeficiency syndrome.

name	drug type	study type (identification number), status	study aim	original indication
IL-6/IL-6R targeting				
tocilizumab	anti-IL-6R human IgG1 mAb	Phase III (NCT04320615), completed [20]	to evaluate safety, efficacy, pharmacodynamics and pharmacokinetics in patients with severe COVID-19 pneumonia	RA, CRS, GCA, PJIA
sarilumab	anti-IL-6R human IgG1 mAb	Phase III (NCT04327388), completed [21]	to evaluate clinical efficacy in patients with severe or critical COVID-19	RA
clazakizumab	anti-IL-6 human IgG1 mAb	Phase II (NCT04348500), active [22]	to evaluate safety and adverse events in patients with COVID-19	RA
siltuximab	anti-IL-6 chimeric human–mouse IgG1 mAb	Phase III (NCT04330638), active [23]	to evaluate safety and efficacy individual or in combination with IL-1 blocker (anakinra) in patients with COVID-19 and systemic cytokine release syndrome	iMCD
IL-1R targeting				
anakinra	recombinant human IL-1Rα antagonist	Phase III (NCT04362111), recruiting [24]	to determine effect of early treatment with COVID-19-induced pneumonia	RA, CAPS
canakinumab	anti-IL-1β human IgG1κ mAb	Phase III (NCT04362813), active [25]	to evaluate the safety and efficacy with COVID-19-induced pneumonia	CAPS, TRAPS, HIDS/MKD, FMF, SJIA
GM-CSF/GM-CSF-R targeting				
mavrilimumab	anti-GM-CSF-R human IgG4 mAb	Phase II and Phase III (NCT04447469), recruiting [26]	to evaluate the safety and efficacy of two dose levels in patients with severe COVID-19 pneumonia and hyperinflammation	RA
otilimab	anti-GM-CSF human IgG1 mAb	Phase II (NCT04376684), active [27]	to evaluate benefit–risk in patients with severe pulmonary COVID-19 related diseases	RA
lenzilumab	anti-GM-CSF human IgG1κ mAb	Phase III (NCT04351152), recruiting [28]	to evaluate the impact on time to recovery in hospitalized patients with severe or critical COVID-19 pneumonia	RA
TJ003234	anti-GM-CSF human IgG1 mAb	Phase II and III (NCT04341116), recruiting [29]	to evaluate the safety and efficacy in patients with severe COVID-19 disease	RA
gimsilumab	anti-GM-CSF human IgG1 mAb	Phase II (NCT04351243), active [30]	to evaluate the safety and efficacy in patients with lung injury or acute respiratory distress syndrome secondary to COVID-19	RA
TNFα targeting				
adalimumab	anti-TNFα human recombinant IgG1 mAb	Phase IV (ChiCTR2000030089), recruiting [31]	to evaluate the safety and efficacy in patients with severe COVID-19	RA, JIA, PsA, AS, CD, UC, Ps, HS, UV
		Phase II (ISRCTN33260034), recruiting [32]	to evaluate effectiveness in preventing or reducing severity of COVID19 disease	
infliximab	anti-TNFα recombinant chimeric human–mouse IgG1 mAb	Phase II (NCT04425538), active [33]	to assess efficacy in patients with severe or critical COVID-19 disease	RA, CD, UC, AS, PsA, Ps

(*Continued.*)

Table 2. (*Continued.*)

name	drug type	study type (identification number), status	study aim	original indication
IFN-γ targeting				
emapalumab	anti-IFN-ɣ human IgG1 mAb	Phase II and III (NCT04324021), terminated [34]	to assess safety and efficacy in patients with severe COVID-19 disease	HLH
IL-8 targeting				
BMS-986253	anti-IL-8 human IgG1κ mAb	Phase II (NCT04347226), recruiting [35]	to evaluate time-to-improvement following treatment compared to standard of care in patients with COVID-19 respiratory disease	BRAF V600 mutation-positive unresectable or metastatic melanoma
CCR5 targeting				
leronlimab	anti-CCR5 human IgG4 mAb	Phase II (NCT04343651), active [36]	to evaluate safety and efficacy in patients with mild-to-moderate symptoms of COVID-19 infection	AIDS
		Phase II (NCT04347239), recruiting [37]	to evaluate safety and efficacy in patients with severe or critical symptoms of COVID-19 infection	

Figure 2. Therapeutic approaches targeting COVID-19-induced cytokine storm with small-molecule, biologic and nanomedicine therapies.

outcomes in patients with severe H1N1 pneumonia by inhibiting T and B cells activation [16]. However, whether its efficacy in influenza treatment can be replicated in COVID-19 is yet to be seen as Phase II clinical trials for sirolimus are soon to begin upon completion of recruitment [75].

Another potential target of interest is phosphodiesterase 4 (PDE-4), which regulates the production of pro-inflammatory cytokines through cyclic adenosine monophosphate activation [18]. Apremilast was originally proposed as an auto-immune disease treatment and shown to diminish pro-inflammatory cytokine TNF-α, IFN-γ, IL-2, IL-4, IL-6 and IL-13 expression and *vice versa* to increase anti-inflammatory IL-10 expression [76]. Treatment with the selective PDE-4 inhibitor at early phases of SARS-CoV-2 pneumonia resulted in a significant reduction in IL-6 across all four patients with minimal side effects [77]. The early success and excellent safety profile led to further investigation, and apremilast has been accepted for a Phase II clinical trial [19].

3.2. Biologics

The use of monoclonal antibodies (mAbs) in the treatment of inflammation has been widely accepted for the last decade, with immunomodulatory mAbs generally proven safe and in many cases effective [78]. Most therapeutic approaches for suppressing cytokine storm are based on targeting either the cytokine itself or its receptor. Together with widely investigated tocilizumab, other mAbs targeting IL-6 such as siltuximab and IL-6 receptor such as sarilumab are being considered as promising anti-inflammatory therapies for COVID-19, and both are currently evaluated in Phase III clinical trials in hospitalized COVID-19 patients [23,79]. Another mAb targeting IL-1β cytokine has now also reached Phase III clinical trials [25], previously demonstrating a

reduction in serum inflammatory biomarkers in COVID-19 patients upon subcutaneous administration [80].

Anti-TNF-α mAbs have been associated with not only reduced activity of TNF-α but also downregulation of key pro-inflammatory cytokines IL-1 and IL-6, offering a 'double-whammy' therapeutic approach [81,82]. Observational clinical data in patients on anti-TNF therapy for rheumatoid arthritis have shown to be inversely associated with death and hospital admission for COVID-19 [83]; however, no effect on intensive care admission was observed [84]. While the potential use of anti-TNF-α mAbs is backed up by a holistic understanding of the mechanisms of a cytokine storm and observational clinical data, very few clinical studies are currently investigating these therapies for the prevention of cytokine storm progression and overall COVID-19 treatment (table 2) [31,32].

Targeting other pro-inflammatory cytokines such as GM-CSF has also been pursued to curb hyperinflammation [85,86]. Anti-GM-CSF mAb lenzilumab and anti-GM-CSF receptor mAb mavrilimumab, alongside other mAbs used in the treatment of COVID-19, have been associated with earlier clinical improvement in respiratory parameters, demonstrating potential efficacy of this therapeutic approach [28,86,87]. While IFN-γ, IL-8 and C-C chemokine receptor type 5 (CCR5) mAbs are investigated as anti-cytokine storm therapies in COVID-19 [34,35,37], a few cytokines and chemokines upregulated in a cytokine storm such as C-X-C motif chemokine ligand 10 (CXCL10) and CCL2 are not yet targeted directly by any therapeutic approaches and in light of the urgent need for a viable COVID-19 treatment, drugs against these targets should be evaluated as well.

3.3. Nanomedicine

Although useful in combating the cytokine storm, the use of immunosuppressants will result in systemic reduction in patients' immunity and pose an increased risk of secondary infection or sepsis. Moreover, the short half-lives of small molecules limit the ability to achieve sustained drug delivery and therapeutic benefits. On the other hand, biologics usually suffer from poor bioavailability and, therefore, a higher dose might be required, resulting in an increased risk of unforeseen adverse effects. Encapsulating these therapeutic agents into smart nanocarriers would allow targeted delivery, increased bioavailability and circulation stability as well as optimization of pharmacokinetic profiles of combination therapies as multiple therapeutic agents can be encapsulated into nanoparticles.

A few nanomedicine approaches have emerged as anti-inflammatory COVID-19 treatments. Rao *et al.* demonstrate decoy nanoparticles formulated by fusing two cellular membrane nanovesicles to protect host cells by competing with virus [88]. Alongside angiotensin-converting enzyme 2 (ACE-2) receptors that bind SARS-CoV-2 virus itself, the nanodecoy possesses IL-6 and GM-CSF receptors on its surface that efficiently bind and neutralize pro-inflammatory cytokines IL-6 and GM-CSF [88]. Thus, nanodecoys have been shown to effectively suppress cytokine levels in acute pneumonia mouse model *in vivo* [88].

Other nanoparticle-based approaches so far have focused on delivery of non-specific anti-inflammatory agents such as adenosine and corticosteroids. Dormoont *et al.* reported the development of squalene-based multidrug nanoparticles consisting of adenosine and the antioxidant α-tocopherol as a potential targeted approach for cytokine storm mitigation [89]. Adenosine, a non-specific immunomodulator, has been shown to inhibit TNF-α, IL-6 and IL-12 production and promote the release of anti-inflammatory IL-10 [90]. This nanoformulation exploits the enhanced permeability and retention effect to achieve site-targeted delivery. The multidrug nanoparticle has been shown to accumulate at the site of inflammation and was associated with a significant reduction in TNF-α alongside an increase in IL-10 in endotoxemia mouse model [89]. To avoid systemic immunosuppression and increased risk of secondary infection, nanoformulations of dexamethasone have been previously developed to treat other inflammatory diseases such as cancer, inflammatory bowel disease and inflammatory arthritis and proposed for COVID-19 treatment to improve specificity, stability and efficacy of dexamethasone [91]. However, the idea is still at its early stages, and more research has to be done to find the optimal formulation and evaluate its efficacy.

While nanomedicine has been centre-stage in vaccine development recently, it is so far underused in therapeutic development to combat viral infections in general and COVID-19 in particular [92]. However, more evidence is being amassed on potential benefits of nanomedicine in developing COVID-19 therapies and how nanomedicine can address limitations of repurposed anti-inflammatory agents and improve their specificity, bioavailability and *in situ* release kinetics [93,94].

4. Challenges and perspectives

As cytokine storm has been convincingly linked to fatal outcomes in SARS-CoV-2 infections, targeted approaches to curb hyperinflammation have been widely explored and hold promise of improving prognoses and reducing COVID-19-associated mortality. However, complexity of the immune response in general and specific patterns linked to COVID-19 are yet to be fully comprehended. As the understanding of origins, patterns and consequences of SARS-CoV-2-induced cytokine storm grows, it will become more apparent what subset of patients and at what disease stage could benefit the most from anti-inflammatory therapies. In parallel to the vaccine rollout, it is critical to continue investing efforts into novel treatment developments given the likelihood of variation in vaccine protection due to continuous mutations in the virus. Moreover, integrating nanoscience into re-purposing of existing targeted drugs and the development of novel molecular entities can help overcome safety and efficacy shortcomings currently associated with these therapeutics—by targeting drugs to a particular tissue in the body or by boosting synergy of combination therapies through concurrent delivery.

Data accessibility. This article does not contain any data.

Authors' contributions. N.M., F.A., E.C. and Y.O. and N.K. devised, planned, wrote and edited the paper.

Competing interests. We declare that we have no competing interests.

Funding. This work was supported by the Department of Chemistry, Imperial College London.

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