

A perspective on modern advances for COVID-19 (SARS-CoV-2) therapeutics

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Introduction

To date, no therapeutics have been clearly established to be successful in the prevention or treatment of COVID-19. A variety of approaches targeting different aspects of the clinically heterogeneous syndrome - including the initiation and maintenance of the viral infection itself, the hyper-inflammatory state that characterizes a subset of severe cases, and the pro-thrombotic phenotype observed in some patients - have been proposed. Several of these are familiar to the rheumatology community from their use in autoimmune disease. Here is a discussion of several of these potential treatments, current evidence from limited clinical reports regarding their efficacy in COVID-19, and a snapshot of the evolving guidelines from professional societies regarding their role in clinical practice.

Antiviral/antibody approaches

Passive antibody therapy as a treatment or prophylactic modality for infectious disease has a long history usually considered to have been inaugurated by efforts against tetanus and diphtheria in the 1890s, when the serum of rabbits who had survived infection was protective in rabbits who were later exposed (1, 2). In the pre-antibiotic era techniques for purifying the antibody component of serum improved the safety profile of such treatment against multiple common bacteria with (for the time) good effect, although after antibiotics came into use the approach fell out of favor in most cases (3). As the field of immunology advanced, it was appreciated that the affinity purification process in the B cell response to infection was responsible for producing antibodies against a given pathogen, although along with these were found non-specific antibodies. In more recent times, the potential for convalescent plasma to serve as a rapidly accessible anti-infective agent against novel pathogens has been appreciated (4). Convalescent plasma has reportedly been effective in a few COVID-19 patients (5-7), and over 50 clinical trials are registered to evaluate its use. Studies have reported encouraging results on the antibody and cellular immunity profiles of recovered COVID-19 patients. In one study 14 patients (whose extent of illness was unclear, requiring hospitalization for between 11 and 45 days) were assayed for antibodies and T cell responses to COVID-19 nucleoprotein and spike protein, along with assays for virus-neutralizing antibody titers (8). Among five of eight recently-discharged patients, and three of four who were two weeks post-discharge, there were high neutralizing antibody titers, which correlated with both anti-spike titers and T cell activation by spike protein in the post-discharge patients.

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Methods of producing monoclonal antibodies, which may inhibit the initiation and maintenance of viral infection, have been pursued as a means of essentially scaling up and standardizing passive immunization. In the setting of the Ebola virus outbreak in 2018 there was success in a trial of REGN-EB3 (Regeneron), which was developed by immunizing mice engineered to encode fully-human antibody variable regions, selecting a subset of antibodies that among other properties bound a site of interest on the virus in question, and then producing those antibodies at scale in cell culture (9). In the Ebola context, 28-day mortality was reduced by approximately 40% (10). For COVID-19, the process of selecting the candidate antibodies was underway in mid-March 2020, and trials of efficacy in prophylaxis and treatment are reportedly anticipated to begin in the summer. Other antibody treatments are in development by AstraZeneca and Vir Biotechnology/Eli Lilly.

Many antiviral drugs repurposed from other illnesses are being considered or trialed against COVID-19. The HIV-1 protease inhibitor combination of lopinavir-ritonavir (Kaletra, Abbvie) has been the subject of one non-blinded RCT with no significant effect on mortality, and is included in the protocols for the UK RECOVERY (11) and WHO Solidarity (12) trials (in the latter case along with interferon beta-1α (Rebif, EMD Serono)). An open-label randomized trial in a less ill population comparing lopinavir-ritonavir alone or in combination with ribavirin and interferon beta-1β reported a decrease in duration of detectable viral RNA in the na-

sopharynx, with all patients in the control and experimental groups surviving (13). There is a report of compassionate-use RNA polymerase inhibitor remdesivir (Gilead) in a population of US patients (14). One published RCT showed a non-statistically-significant trend toward improved time to clinical improvement (15) without change in 28-day mortality (many of these patients also received steroids, antibiotics, interferon alfa 2 β , and lopinovir-ritonavir), although the authors suggest a subgroup of patients with less severe disease at the time of treatment may benefit. A second study, which is in progress, has publicized an interim analysis that reports a significant decrease in time to recovery and an almost-significant mortality benefit (16). As a consequence, remdesivir received emergency FDA approval. The influenza treatment favipiravir (Avigan, Fujifilm) is being used experimentally in Japan with an ongoing Phase III trial.

Hydroxychloroquine (HCQ)/chloroquine

There has been substantial interest in HCQ since data was reported to suggest a reduction of the viral load of COVID-19 in infected patients treated with HCQ and azithromycin (17). The theoretical interest in HCQ as an anti-viral agent is not novel. As a proposed mechanism, HCQ increases the lysosomal pH and thereby interferes with post-translational modifications of cell surface proteins such as the ACE2 and Sigma-1 receptors. These are involved in viral ingress (in particular ACE2 and COVID-19), and inspired *in vitro* studies suggestive of a potential effect (18). However, it should be noted that in spite of well-established *in vitro* inhibition of a wide variety of viruses, HCQ is not an effective treatment for any of them. The only indexed public data claiming a positive finding are reports from the same group that presented the viral load findings (19). In one series, outcomes for 80 patients treated with HCQ and azithromycin (without any comparison control group) were reviewed. Of these, 85% were discharged at the time of its conclusion (which would seem like a high proportion) but only 15% of the sample required oxygen therapy. This implies an unusually healthy sample. Although HCQ was adopted much more widely than the very tenuous evidence for its effectiveness would seem to warrant, there is no robust signal of effectiveness in treatment. A retrospective study from the US Veterans Health Administration, currently in preprint form, compared HCQ versus HCQ and azithromycin. Neither treatment found any evidence for a protective effect of HCQ (20). Nonetheless, there is a large-scale US clinical trial in progress to compare 15-day outcomes in patients with and without HCQ treatment. HCQ

is also one of the treatments being assessed in the WHO Solidarity and UK RECOVERY trials. There are additionally efforts to test HCQ for pre- or post-prophylactic effectiveness (21-23).

Agents used in rheumatologic practice

The worst manifestations in the subset of particularly severe COVID-19 cases appear to involve an excessive immunological response with elevated cytokines correlating with end-organ dysfunction (24), the so-called cytokine storm syndrome (CSS). Being characterized by either or both of excess pro-inflammatory stimulus and insufficient anti-inflammatory regulation. CSS manifests in a variety of different profiles that have been distinguished by the nature of the inciting stimulus, host factors shaping the subsequent response, and the biochemical details of the linkage between the two. CSS has been appreciated in certain infectious contexts, for instance in H1N1 influenza, where the notion of immunosuppression at the appropriate disease stage has been proposed as a treatment (25). Elevated pro-inflammatory cytokines had been noted in prior epidemic coronaviruses *in vitro* (26). With COVID-19 in particular, elevations have been reported in both pro-inflammatory (IL-1 β , IFN- γ , IP-10, MCP-1) and anti-inflammatory (higher IL-4 and IL-10) cytokines, with correlation between IL-2R, IL-6 and disease severity (27). With evidence of complement associated injury in biopsies of severely-ill COVID-19 patients (28), the ability of medicinal chemists to tune the extent to which targeted immunomodulatory therapies fix complement, by varying the IgG subclass or removing the Fc domain completely, provides another axis (29, 30).

Clinically, these patients bear similarity to secondary hemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome (MAS). They are febrile, frequently with acute respiratory distress syndrome, and may present with cytopenias as well as elevated ferritin. Occasional cases have been reported of patients with repeatedly negative viral swabs who nonetheless remained in a sustained hyper-inflammatory state. These observations have led to the suggestion that interventions, either individually or in combination, targeted to reduce the magnitude of the immune response to COVID-19, may be beneficial (31).

Several approaches are in varying degrees of use and evaluation. One, a more mechanical type of approach, involves the Oxiris membrane (Baxter International) which has been shown in small studies to reduce pro-inflammatory cytokine levels (TNF- α , IL-6, IL-8, and IFN- γ) in septic patients (32). It is currently be-

ing tested under an FDA Emergency Use Authorization in COVID-19 patients.

Steroids are controversial in the critically-ill infectious context in general, and in particular at the beginning of the COVID-19 epidemic based on evidence of no beneficial effect and delay in viral clearance in SARS and MERS (33). There was a reluctance to employ them, although how well-founded this avoidance may be is difficult to establish (34) and in practice they are widely used. Among the Infectious Disease Society of America's recommendations, the only concrete entry is against steroids in COVID-19 pneumonia, although conditional and with very low certainty (35). Part of the concern is that in prior viruses, steroid treatment seemed to delay viral clearance. It is not clear that this is the case in COVID-19, as one report (36) found that "low dose" corticosteroid (median 40 mg of methylprednisolone) did not delay viral clearance. The optimal use of steroids in COVID-19 patients remains enigmatic.

Given the double-edged nature of immunosuppression in an infectious disease context, rheumatologists have sought guidance regarding safe practices for administration of the medications they use during the time of the COVID-19 pandemic. Data is scant, but expert opinion has been compiled into the ACR COVID-19 Clinical Guidance for Adult Patients with Rheumatic Diseases that is pending journal review (37). In general, absent risk of exposure, the guideline suggests maintaining patients on their usual medications, and for newly diagnosed patients to be treated in the same manner as usual. If exposure is suspected, aside from HCQ, sulfasalazine, and non-steroidal anti-inflammatories (NSAIDs) other agents should be held until either testing verifies absence of infection or two weeks without infectious symptoms have passed. The possible exception is IL-6 inhibition which may be continued. If infection is known or highly likely, all agents except HCQ and possibly NSAIDs should be held, again with the possible exception of IL-6 inhibition.

Many of the more specific immunosuppressant agents, which are employed in rheumatologic diseases, have been used or proposed for use in COVID-19 patients. The first and perhaps most widely targeted approach is IL-6 axis inhibition, with the early experience in China with tocilizumab (Actemra, Genentech) and ongoing US trials of Sarilumab (Kevzara, Regeneron/Sanofi). In seven critically-ill patients given tocilizumab (38) (according to a protocol of up to two doses depending on response

to the first, and in variable combinations with steroids) three died within seven days, although it is not clear whether this reflects any difference relative to patients in similarly poor condition who were not treated. Among eight moderately- to severely-ill tocilizumab-treated patients, none died in that timespan (again without comparison to matched controls). Of note a CRP cutoff of 170 mg/L in that population of 15 patients would have predicted the outcome reasonably well, with two patients above that cutoff stabilizing and one below developing worsening disease. A second retrospective cohort of severe cases treated with tocilizumab after one week of “standard of care” reported improvement in all 21 patients analyzed. There appear additionally to be six case reports of improvement after tocilizumab treatment. Two trials (39, 40) are underway for tocilizumab. Another IL-6 axis agent, sarilumab, is also currently in two trials motivated by the preliminary tocilizumab findings. To date, there are no accessible published reports of preliminary effectiveness.

IL-1, being upstream of IL-6, has also been proposed as a target in COVID-19. The similarity of severe COVID-19 to cytokine storm, as seen in macrophage activation syndrome, has also suggested a role for IL-1 inhibition (41). Autopsy findings of a neutrophilic pulmonary capillaritis, and the negative prognostic value of the neutrophil-to-lymphocyte ratio, have raised the possibility of NETosis (the generation of pathogen-binding DNA-protein aggregates from degenerated neutrophils). This could contribute to widespread downstream organ damage in COVID-19 and might also be ameliorated by IL-1 blockade (42). There are several ongoing studies to determine if anakinra (Kineret, Sobi) influences COVID-19 progression, with one published case series of nine patients reporting safety of the medication (43).

A novel approach to repurposing existing drugs in new settings, by using machine learning techniques on a database of structured medical information, has identified baricitinib (Olumiant, Eli Lilly) as a possible COVID-19 treatment (44). Although it is a Janus kinase (JAK) inhibitor that downregulates inflammation in rheumatologic diseases, baricitinib is also known to have a high affinity for the Adaptor-associated protein kinase 1 (AAK1), which promotes viral entry by upregulating endocytosis. Although the JAK inhibition property might be expected to diminish the host ability to clear virus, the team advocating for trials of baricitinib point out that by the time of the hyper-inflammatory phase of illness in most cases, the viral load is already decreasing

and that this is when they propose to administer the drug. It is not clear then in what sense the AAK1 effect would be relevant. Two trials are underway to assess baricitinib.

Vaccination

The long-term burden of COVID-19 will be determined by a number of factors relating to the virus itself that are not yet understood. The ability to achieve population-level protection against recurrent explosive pandemics will ultimately depend on successful and timely production of a vaccine. In light of the magnitude of the global disease burden, vaccine development attempts are underway even in the absence of disease-specific knowledge that is usually established beforehand, such as the threshold for protective antibody titers (the quantity of the antibody generated by the vaccination that is sufficient to prevent disease). There is also uncertainty regarding the duration of a potential vaccination effect. Antibody-mediated protection may wane relatively quickly although a T-cell component of immunity might be more durable. Even the target for what fraction of the population must be effectively immunized to achieve “herd” immunity is uncertain given its dependence on the viral basic reproductive number, with estimates in the vicinity of 60% (45).

One approach, with an existing agent, is based on the observation made in some preprints that BCG vaccination may inversely correlate with rates of COVID-19 infection, although difficult to assess causality in light of significant confounding factors. Expectations should be significantly tempered by prior studies indicating no protective effect of BCG against influenza (46), although there are ongoing trials to determine what benefit, if any, there may be in COVID-19 (47, 48).

A multitude of research programs developing a COVID-19-specific vaccine are under accelerated development (summarized in a regularly updated list on the WHO website). One particularly novel approach, which was previously under development targeting epidemic coronaviruses in a collaboration between NIH and Moderna, involves administering an mRNA coding a desired pathogenic antigen target (for the COVID-19 spike protein). It is optimized for uptake by encapsulation with a lipid nanoparticle, so that host cells produce the antigen and induce an immune response to it. In a Stage I trial of this approach against two strains of influenza, this study showed seroconversion to protective titers in 80-100% of subjects (49). This is currently undergoing safety and immunogenicity testing in the US (50).

Additional mRNA-based approaches are under development in Germany (Curevac, Biontech) and one is under development in the UK (Imperial). Adenoviral vector approaches are in a combined phase 1 and 2 trial in the UK, phase 1 trial in China, and an intranasal agent in Belgium. DNA-based vaccines are in phase 1 trials in the UK (Oxford), US (INOVI0) and in production by an Italy/US collaboration. Protein-based efforts are underway in France, UK, US, and Canada, although none yet in trials. None of these have been assessed for effectiveness in humans, and only a few [a DNA vaccine (51) (INOVI0) and a spike protein fusion (52)] have animal data indicating induction of virus-recognizing antibodies.

Conclusion

At this still-early stage in our understanding of COVID-19, which therapeutic or preventive approaches will prove effective, if any, remains unclear. Lessons learned and technologies developed in the context of recent epidemics and other novel pathogens, although arguably under-resourced, have nonetheless provided a basis for a variety of approaches to COVID-19. It may be that the standard of care develops into a multi-faceted approach - for instance a combination of passive antibody therapy and antiviral chemotherapy for one disease phenotype, immunologic modulation of one or more types for others, and ultimately vaccination to minimize the need for either. Major programs to transition the state of knowledge from the present, dominated by uncontrolled and/or small studies, to sufficiently well-designed randomized control trials, will require time. Long-term data safety will be limited if compressed time-lines are approved for clinical trials.

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