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Short Communication

Immunotherapy for ANCA-associated vasculitis during the COVID-19 pandemic

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Abstract

Since the first description of infections with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in China in December 2019, it has evolved into a pandemic and emerged as an unprecedented worldwide crisis overwhelming healthcare systems globally. Analysis of the available literature to date suggests that, in addition to older age, patients with underlying co-morbidities including hypertension, diabetes, heart disease are at higher risk for severe disease with increased mortality. Practitioners around the world also have become increasingly concerned that immunosuppressed patients including those with autoimmune diseases may be at increased risk for developing Coronavirus Disease 2019 (COVID-19) with serious complications. Very little is known about how anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis modifies the susceptibility, clinical presentation and disease course of COVID-19. In this review, we discuss the mechanism of action and challenges of the current therapeutic armamentarium of ANCA-associated vasculitis and outline approaches to management of ANCA-associated vasculitis during the COVID-19 pandemic.

Keywords: ANCA-associated vasculitis, immunosuppression, COVID-19

Introduction

The ANCA-associated vasculitides (AAV) are a family of systemic autoimmune diseases characterized by systemic necrotizing inflammation. Three different AAV clinical entities have been described: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA). AAV is often seen in middle aged and older individuals, who must endure both disease- and treatment-related co-morbidities. Renal involvement with consequential CKD is common in AAV. Current guidelines for the management of AAV recommend use of high dose glucocorticoids with B cell depleting therapy or cytotoxic therapy for induction of remission followed by long-term use of low dose prednisone with or without B cell depleting therapy or anti-metabolite therapy to maintain remission. These aforementioned factors place AAV patients at increased risk for SARS-CoV-2 infection potentially with a more severe course and worse outcomes (1). Infections in general also often trigger relapses of vasculitis.

At the time of this writing in June 2020, we do not know how AAV can affect the susceptibility, clinical presentation and disease course of SARS-CoV-2 infection. Clinical and experimental data suggest a role for neutrophil extracellular traps, IL-6 and complement pathways in SARS-CoV-2 infection (2-4). These same pathways also have known pathogenic roles in AAV (5, 6). In this review, we discuss the mechanism of action and challenges of the current therapeutic armamentarium of AAV with a focus on GPA and MPA and outline approaches for the management of AAV during the COVID-19 pandemic based on personal opinion.

Glucocorticoids

Glucocorticoid use is one of the central pillars of AAV induction therapy. The immunomodulatory effects of glucocorticoids are mediated by the inhibition of the nuclear translocation of pro-transcription factors and disruption of the expression and downstream functional effects pro-inflammatory cytokines. These mechanisms converge on broad suppression of cell effector functions, anergy and the induction of apoptosis in T cell, B cell, and monocyte/macrophage subsets. Though the combination of glucocorticoids and high intensity agents like rituximab or cyclophosphamide is effective in inducing disease remission, this strategy is also associated with increased risk of infections, an important cause of early mortality in AAV (7).

There is, however, a lack of consensus on the need for pulse methylprednisolone, dosing regimens and the total duration of glucocorticoid therapy in AAV. One retrospective multi-center cohort study report-

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ed that the use of pulse methylprednisolone was associated with more episodes of infection and higher incidence of diabetes without clinical benefit (8). The RAVE trial demonstrated that prednisone can be safely stopped by 5 months during remission induction phase (9). The PEXIVAS trial demonstrated that reduced dose prednisone can be safely adopted into mainstream practice. The CLEAR study investigating the C5a receptor blocker avacopan provided evidence that disease remission could be achieved with avoidance of glucocorticoids altogether (10, 11).

In the setting of COVID-19, the interim guidance from the World Health Organization (WHO) on management of suspected COVID-19 advises against the use of glucocorticoids if possible because of concerns that this could delay viral clearance (12). In contrast, a recent press release from the RECOVERY trial indicated that low-dose dexamethasone (6 mg once daily, 2,104 patients; equivalent to 40 prednisone or 32 mg methylprednisolone) in comparison to "usual care" (4,321 patients) reduced deaths in ventilated patients by 35% and in those receiving oxygen by 20% (13). Given the recommendations by the WHO and consideration of available evidence, we advise against the use of high-dose steroids (i.e. pulse methylprednisolone) for remission induction in AAV and instead suggest initiation of oral prednisone following the reduced dose protocol of PEXIVAS with a fast taper by 3 months during COVID-19 pandemic (Table 1). In AAV patients who are on maintenance dose of prednisone, we recommend maintaining the same dose in uninfected individuals and initiating a slow taper if diagnosed with COVID-19.

B-cell depletion agents

Rituximab

Rituximab (RTX), a chimeric monoclonal antibody directed against CD20 surface antigen

Main Points

- Patients with ANCA-associated vasculitis require immunosuppressive treatment to prevent life threatening organ damage and may be at increased risk of COVID-19.
- The choice of immunosuppressive therapy for ANCA-associated vasculitis in the setting of SARS-CoV-2 infection should take into account the overlapping pathogenesis of ANCA-associated vasculitis and COVID-19 in addition to the risks and benefits of immunosuppressive therapy.

Table 1. Treatment recommendations for AAV management during COVID-19 pandemic.

Disease severity	Disease activity	COVID-19 positive	COVID-19 negative
Early systemic (no organ threatening or life-threatening disease)	Active disease	Oral GC*: prednisone 30 mg daily, tapered to 5 mg daily by week 15 HCQ 5 mg/kg/day to a maximum dose of 400 mg daily	Oral GC*: prednisone 30 mg daily, tapered to 5 mg daily by week 15 plus MTX 15 to 25 mg per week adjusted for GFR or MMF 2000 mg daily
	Remission	If on AZA/MMF/MTX: would discontinue them If on RTX: hold RTX If on GC: taper prednisone to 5 mg daily and continue	If on AZA/MMF/MTX: would continue them If on RTX: postpone RTX by 3 months If on low dose GC: continue
Generalized disease (Renal or other organ threatening disease, serum creatinine <5.6 mg/dL)	Active disease	Plasma exchange, 7 sessions of 60 mL/kg (within 14 days), use convalescent plasma (if available) Oral GC*: prednisone 30 mg daily, tapered to 5 mg daily by weeks 15 1st option: IVIG 0.4 gram/kg/day for 5 days 2nd option: Intravenous CYC 500 mg◊ every 2 to 3 weeks for 6 doses may be used at physician discretion 3rd option: TCZ 8 mg/kg body weight (day 1), re-dose (day 8 and day 15) due to plasma exchange	Oral GC*: prednisone 30 mg daily, tapered to 5 mg daily by week 15 Intravenous CYC 500 mg◊ every 2 to 3 weeks for 6 doses*
	Remission	If using AZA/MMF/MTX: would discontinue them If using RTX, hold RTX infusion If on low dose GC, taper prednisone to 5 mg daily and continue	If using AZA/MMF/MTX: would continue them If using RTX, postpone RTX infusion by 3 months in PR3 ANCA patients and hold in MPO ANCA patients If on low dose GC, continue GC
Severe disease (Renal or other vital organ failure, serum creatinine >5.6 mg/dL)	Active disease	Plasma exchange, 7 sessions of 60 mL/kg Oral GC*: prednisone 30 mg daily, tapered to 5 mg daily by week 15 1st option: Intravenous CYC 500 mg◊ every 2 to 3 weeks for 6 doses may be used at physician discretion 2nd option: IVIG 0.4 gram/kg/day for 5 days 3rd option: TCZ 8 mg/kg body weight (day 1), re-dose (day 8 and day 15) due to plasma exchange	Plasma exchange, 6 sessions of 60 mL/kg Oral GC*: prednisone 30 mg daily, tapered to 5 mg daily by week 15 Intravenous CYC 500 mg◊ every 2 to 3 weeks for 6 doses**
	Remission	If using AZA/MMF/MTX: would discontinue them If using RTX, hold RTX infusion If on low dose GC, taper prednisone to 5 mg daily and continue	If using AZA/MMF/MTX: would continue them If using RTX, postpone RTX infusion by 3 months If on low dose GC, continue GC

* PEXIVAS (Plasma exchange and glucocorticoid dosing in the treatment of ANCA associated vasculitis) reduced dose protocol.
◊ CORTAGE (CORTicosteroid and cyclophosphamide based induction therapy trial dosing of CYC for systemic necrotizing vasculitis patients AGEd >65.
** If infusion center is considered a place with low transmission risk.
GC: glucocorticoids; HCQ: hydroxychloroquine; MTX: methotrexate; GFR: glomerular filtration rate; MMF: mycophenolate mofetil; RTX: rituximab; IVIG: intravenous immunoglobulin; TCZ: tocilizumab; CYC: cyclophosphamide; AZA: azathioprine.

on B cells has become a mainstay of AAV management during the past decade. RTX causes B cell depletion through the direct induction of apoptosis, antibody dependent cytotoxicity and complement dependent cytotoxicity. In addition to decreasing pathogenic autoantibody production, depletion of B cells has additional effects on the secretion of proinflammatory cytokines, antigen presentation, and T cell activation and effector differentiation, all of which have established pathophysiologic roles in AAV (14). Randomized controlled trials have confirmed the efficacy of RTX for remission induction and maintenance, which has greatly advanced mainstream practices in AAV (9, 15, 16).

Although antibody-producing plasma cells are not targeted directly by rituximab, hypogammaglobulinemia is often seen with long-term use due to the depletion of plasma cell precursors. In rheumatoid arthritis (RA) patients treated with RTX, low IgG levels have been associated with an increased infection signature (17). Although, similar association between the extent of IgG decrease and overall rates of infection was not clear in two observational studies if AAV patients (18, 19), severe infections were reported in randomized controlled trials affecting 7%, 8% and 12% of subjects after 6, 12 and 18 months after RTX was administered (9, 15, 20). Rates of opportunistic infection with cytomegalovirus and varicella zoster were also increased. Specific risk factors for infection following RTX use included glucocorticoid therapy in addition to classic risk factors of older age and diabetes. We also would be remiss not to mention the long-lasting effects of RTX on antibody response against several vaccines (21).

Review of the literature at the time of this review was written identified three AAV cases on a background of RTX therapy who developed COVID-19 with variable clinical course, one required mechanical ventilation, one required 100% non-rebreather and the remaining patient had a mild disease course (22-24). How do we use this limited information to guide RTX use in active vasculitis where the risk of mortality from active disease exceeds the risk of mortality from COVID-19? Most RTX based regimens use high doses of glucocorticoids in the beginning to achieve rapid disease control. Compared to RTX, cyclophosphamide (CYC) affects autoantibody-producing plasmablasts and short-lived plasma cells and allows for rapid tapering of glucocorticoids. Rapid tapering of glucocorticoids is paramount to enhance viral clearance in SARS-CoV-2 infection. In the setting of active AAV in a COVID-19 patient, we suggest using a combination of reduced dose CYC and glucocorticoids with rapid taper and avoidance of RTX unless there is a contraindication for the use of CYC. In AAV patients who are maintained on scheduled RTX for remission maintenance, we suggest delaying any redosing of RTX.

Cytotoxic and anti-metabolite agents

Cyclophosphamide

The cytotoxic agent cyclophosphamide (CYC) has been used for over half a century as an AAV induction agent. As an alkylating agent, CYC acts as a genotoxin by forming irreparable covalent inter- and intra-strand crosslinks within DNA. The lethal accumulation of this DNA damage leads to apoptotic death in proliferative lymphocytes. Dose-dependent bone marrow toxicity is also well described (25). Real-life data from two centers revealed that 86 of 100 patients received CYC as part of their induction regimen. During a cumulative follow-up of 212 patient-years with 112 infectious complications, moderate (0.31-1.0x10^9/L) and severe lymphopenia (≤0.3x10^9/L) were recorded in 73% and 8% of the follow-up time. Severe lymphopenia was associated with serious infectious complications, with a rate of infections of 2.23 events/person-year in the presence of severe lymphopenia compared to 0.41 and 0.19 in moderate and in those with no lymphopenia. Low initial estimated glomerular filtration rate, duration of glucocorticoids, and duration of immunosuppression were predictors of severe lymphopenia (26). The addition of CYC to hydrocortisone enhanced reduction of lymphocytes in *in vivo* experiments (27).

Preservation of cellular immunity is key in the management of SARS-CoV-2 infections. Virally induced lymphopenia is common in COVID-19 cases, and superimposing this effect on the baseline lymphopenia often seen with CYC likely results in even greater risk for a severe disease course. At the time of this writing, there is a single case report of a 25 year old male presenting with a new diagnosis of AAV with concurrent COVID-19 (28). His initial treatment regimen included methylprednisolone, plasma exchange, intravenous immunoglobulin for AAV and hydroxychloroquine and levofloxacin for COVID-19. A week later, his PCR test for COVID-19 was negative. He was started on CYC for his AAV and discharged home with stable renal function. If CYC must be used in a COVID-19 patient with severe active AAV, we recommend low-dose administration, either per oral or intravenous route, be initiated with caution based on evidence from the CORTAGE comparator trial (29). Here patients aged ≥65 were randomized to receive a fixed scheduled CYC dosed at 500 mg every 2 to 3 weeks together with reduced duration of oral glucocorticoids versus higher doses of intravenous CYC and longer glucocorticoid exposure. Similar remission rates with were achieved in both arms, but with a significant reduction of serious adverse events including infections in patients who received low dose of CYC.

Azathioprine

Azathioprine (AZA) is a purine analogue that blocks deoxyribonucleic acid (DNA) repair mechanisms. This activity leads to cumulative lethal genotoxicity predominantly in fast-dividing cell populations. T-cells and granulocyte lineages giving rise to neutrophils and others are particularly susceptible to this mechanism of action. In AAV, AZA is prescribed primarily for remission maintenance. Data from randomized controlled trials have indicated AZA is comparable in efficacy to methotrexate (MTX) and superior to mycophenolate mofetil for this indication (30, 31).

No information exists about coronaviruses outcomes in patients using AZA at the time that this review was prepared. We recommend, however, that AZA be reduced or withheld altogether in AAV patients who are in remission, but test positive for COVID-19. Lymphopenia especially is a common toxic effect of AZA use, and, like other thiopurine drugs, AZA has a very narrow therapeutic index. Pharmacokinetic genetic variation is also critical determinant of toxicity with thiopurine S-methyltransferase (TPMT)-deficiency portends a high risk of AZA-induced bone marrow toxicity (32). In one prospective 14-month follow-up study of patients with inflammatory bowel disease (IBD) and using AZA, roughly one-third of patients presented with lymphopenia (<1.0x10^9/L) (33). 19.2% had severe lymphopenia, defined as a count <0.6x10^9/L. Lymphopenia also was more frequently observed in patients concomitantly using steroids (33). Interestingly, though lymphopenia and especially severe forms (<0.5x10^9/L) are more frequent in IBD patients, the rate of opportunistic infections seems to be low and is associated with the simultaneous use of additional immunosuppressive agents (34).

Methotrexate

Methotrexate (MTX) was initially used as an anti-neoplastic anti-folate anti-metabolite that acts to disrupt DNA synthesis by poisoning of the enzyme dihydrofolate reductase (DHFR). Aside from folate metabolism disruption, MTX also suppresses the pro-immune functions of T-cells, monocytes/macrophages, endothelial cells via several other mechanisms including the augmentation of adenosine signaling, de-

creased reactive oxygen species (ROS) synthesis, down-regulation of surface adhesion molecules, alteration of pro-inflammatory cytokine profiles, and polyamine inhibition (35, 36). The effect on adenosine signaling, which drives an intracellular cascade promoting an overall anti-inflammatory state in T-cells, seem to be the most important mode of action of MTX.

MTX is used as both an induction and maintenance agent for sinus-limited AAV and as a long-term remission maintenance agent for patients with severe multi-organ disease after induction with CYC or RTX. A French Vasculitis Study Group randomized head-to-head comparator trial found that the efficacy for remission maintenance is roughly equivalent for AZA with a roughly equal overall adverse event rate (30). The rates and extent of lymphopenia and neutropenia respectively were not statistically different for the AZA and MTX treatment arms.

As with AZA, we recommend that MTX be reduced or withheld altogether in AAV patients in remission who test positive for COVID-19 and especially in cases complicated by acutely progressive renal failure. Whether or not this maneuver would, however, have a positive impact on the clinical course of COVID-19 patients is unclear. Short drug holidays have been found to enhance the immunogenicity of seasonal influenza vaccinations, suggesting that MTX does impair anti-viral immune responses (37). Yet, MTX use in non-RA populations with autoimmune disease has not been associated with any specific risk increase in either total or serious infections to date (38). Still, we would err on the side of caution as the full spectrum of SARS-CoV-2 complications in critically ill patients and the impact of adenosine signaling modulation remain unknown.

Mycophenolate mofetil and mycophenolate sodium

Mycophenolic acid (MPA), either in form of its salt mycophenolate sodium (MS) or its prodrug mycophenolate mofetil (MMF), is a selective, non-competitive, and reversible inosine 5'-monophosphate dehydrogenase (IMPDH) inhibitor. Inhibition of IMPDH and eventually lymphocyte proliferation explains the immunosuppressive mode of MPA, used to prevent transplant rejection and in autoimmunity. IMPDH2 interacts with the SARS-CoV-2 viral protein nsp14, which might be implicated in an antiviral mechanism. Moreover, MMF docked to potential target proteins of SARS-CoV-2 with involvement of dihydroorotate dehydrogenase, which is required for pyrimidine biosynthesis and thus replication of SARS-CoV-2. These findings confirm previous investigations highlighting *in vitro* efficacy against Middle East Respiratory Syndrome (MERS)-CoV, while *in vivo* data suggested more harm than benefit (39). No such experience has been published in COVID-19. In the transplant setting, MMF or MPA are stopped in most cases with SARS-CoV-2 infection, given its potential to aggravate lymphopenia and causing a more severe disease course (40).

MMF has been used in the management of AAV. The MYCYC trial revealed that MMF is effective in the induction of remission but more relapses are observed in the follow-up, especially when patients are proteinase 3 (PR3)-ANCA positive (41). In line, a significant increase in disease relapses was reported in the IMPROVE trial, testing a maintenance strategy containing MMF or AZA (31). In MYCYC, more patients receiving MMF had serious adverse events compared to CYC-based induction therapy, and numerically more had serious infections (41). This argues that from a safety profile perspective and the current evidence as discussed above MMF plays no or only a limited role in the current situation.

Agents that target pathways also implicated in COVID-19 pathogenesis

In addition to direct cytopathic affects, increasing evidence indicates that poor outcomes in SARS-CoV-2 infection are also driven by immune-mediated mechanisms mediated by dysregulated cytokine activities (42). These dysregulated activities can result in a cytokine storm syndrome similar to that reported with other serious viral infections including influenza, SARS, and MERS-CoV, in macrophage-activating syndrome and hemophagocytic lymphohistiocytosis. This has been described in several critically ill patients and fatal cases. Clinical and experimental data suggest roles for neutrophil extracellular traps, IL-6, antibody effects, and the complement pathways in these cases (43-47). These same mechanisms also have known pathogenic roles in AAV. We discuss below AAV treatment approaches that affect these pathways and which could also reduce viral replication and infectivity.

Intravenous immunoglobulin (IVIG)

IVIG is a biologic product prepared from pooled serum of healthy individuals and enriched for polyclonal immunoglobulin IgG. Originally developed for antibody replacement in primary immunodeficiency states, recognition of its immunomodulatory effects has expanded the therapeutic use of IVIG in managing autoimmune diseases. IVIG has been shown to inhibit ANCA-induced neutrophil activation and cytokine release *in vitro*, and anti-idiotypic antibodies against ANCAs have been detected in IVIG preparations (48, 49). IVIG has been used successfully in AAV for relapsing disease and refractory disease and for patients who are profoundly immunosuppressed (50). A recent meta-analysis of nine studies demonstrated that IVIG was associated with rapid improvement in disease activity regardless of modifications of background immunosuppressive therapy (51).

We suggest IVIG be considered for remission induction in patients without COVID-19 infection, especially in situations when rapid withdrawal of glucocorticoids is warranted. In previous studies in patients infected with MERS-CoV and SARS-CoV-1, IVIG demonstrated clinical benefits with good tolerance, suggesting a possible role in managing infection with by the closely related SARS-CoV-2 (52). A small case series of 3 patients with deteriorating COVID-19 infected from Wuhan, demonstrated clinical and radiographic recovery with initiation of IVIG (53). The immunomodulatory effects of IVIG combined with its potential to enhance passive immunity in a manner similar to convalescent plasmas suggest that IVIG could be a first line therapy for remission induction in AAV patients with COVID-19 disease.

Hydroxychloroquine

The anti-malarial drug chloroquine and its safer derivative hydroxychloroquine (HCQ) have been used to treat autoimmune disease since the 1940s due to its immunomodulatory effects. HCQ has effects on several immune mediators which play a role in pathogenesis of AAV. These effects include decrease in serum B cell activating factor, induction of apoptosis of autoreactive memory T cells, inhibition of high mobility group box inflammatory signaling, inhibition of matrix metalloproteinase (MMP)-9 and tissue inhibitor of matrix metalloproteinase (TIMP)-1 and suppression of macrophage mediated production of cytokines as well as decrease in platelet aggregation. HCQ was used in 8 AAV patients with improved clinical outcomes in a single center study (54). A clinical trial to evaluate the effect of adding HCQ to maintenance immunosuppression on disease activity and quality of life in AAV patients has been launched.

HCQ has also been suggested to exert broad anti-viral effects mediated by several mechanisms. These include the inhibition of host receptor glycosylation required for viral entry; intracellular disruption proteolytic processing of viral proteins; and endosomal acidification, which interferes with viral replication and assembly. HCQ was also shown to inhibit SARS-CoV-2 replication *in vitro*.

At the time this manuscript was written, there were >100 ongoing clinical trials testing the safety and efficacy of HCQ in COVID-19. The results of three big studies published recently dim hopes that HCQ can treat COVID-19 infection, both for hospitalized patients as well as for post-exposure prophylaxis (55, 56). Based on this, the U.S Food and Drug Administration revoked the emergency use of chloroquine phosphate and hydroxychloroquine to treat hospitalized COVID-19 positive patients. Still, considering the immunomodulatory benefits of HCQ in AAV, we recommend initiation of HCQ in AAV patients with persistent arthralgia who are COVID-19 positive (57). A dose of 5 mg/kg body weight and a total dose of 400 mg should not be exceeded, and overall adaptation appropriate for the degree of kidney function impairment should to be made. If higher doses are used as described in, the rate of serious cardiovascular events may be increased given the high frequency of underlying cardiac involvement in patients with AAV (58).

Plasma exchange (PLEX)

The rationale for PLEX derives from the pathogenic role that ANCAs are thought to play in AAV. A rapid decline in pathogenic ANCA is thought to translate to swift resolution of inflammation and decrease consequential damage. Trial evidence that removal of ANCAs from the plasma of patients with active disease, however, has been mixed. The MEPEX trial in which patients with severe AAV and serum creatinine ≥500 µmol/L (≥5.7 mg/dL) were randomized to receive pulse intravenous methylprednisolone or 7 sessions of PLEX over 14 days on a background of CYC found improved renal survival in PLEX-treated cases at 3 months and 12 months (59). There was, however, no difference in mortality between the two groups at 12 months, and no renal survival benefit during the long term follow up phase (median of 3.95 years) (60). The more recent multi-center PEXIVAS trial, which enrolled 704 AAV patients with alveolar hemorrhage or moderate renal failure, found no evidence that adjuvant PLEX decreases the risk of all-cause mortality or end stage renal disease at a median follow up of 2.9 years (10). The PEXIVAS trial, despite its large size, however, was underpowered to make a definitive conclusion about renal outcomes. Limitations included a lack of information on estimated GFR over time and no review of renal histology. PEXIVAS also did not evaluate early renal outcomes, which is especially germane to management of AAV in COVID-19 positive patients.

We suggest, however, that PLEX be considered as an adjunct for remission induction therapy in severe AAV patients with COVID-19 (61). The host response to SARS-CoV-2 in critically ill patients is characterized by cytokine storm, inflammation, endothelial dysfunction and a hypercoagulable state (42, 45). PLEX could be useful for removing inflammatory cytokines and stabilizing endothelial membranes. Therapeutic PLEX has been shown to improve mortality in in sepsis and severe cases of H1N1 influenza A, which share many features in common with severe COVID-19 disease (62-64). Thus, the potential benefits of PLEX for both AAV and severe COVID-19 infection make it attractive treatment strategy especially when glucocorticoids and CYC, which have far broader immunosuppressive effects, cannot be optimally dosed or because B cell depleting therapy cannot be initiated due to the need preserve an anti-viral humoral response. We suggest using fresh frozen plasma as the replacement fluid, and the specific use or addition of convalescent plasma can be considered if available (65, 66). The interest in the use of convalescent plasma lead to the initiation of almost 100 registered trials at the time of writing, and a combination of cytokine removal by PLEX and reconstitution with convalescent plasma seems an elegant option.

Complement-targeted therapy

The role of the alternative complement pathway in AAV pathogenesis has become clear in the past decade. The complement system is a part of the innate immune system also critically involved in antibody-mediated immunity. Three main physiologic activities have been described, including defense mechanisms against infectious agents, bridging innate and adaptive immunity, and disposing of immune complexes (67). Patients with AAV are prone to thrombosis, and complement C5a is key in this process (68). AAV lung and renal sections exhibit evidence of increased alternative and lectin pathway activation. Immunostains typically reveal prominent terminal complex, C4d, and mannose binding lectin (MBL)-associated serine protease (MASP)2 deposition (69). These findings suggest that inhibition of complement activation would be useful therapeutically. In agreement, the ADVOCATE phase 3 trial of avacopan (Vynpenta®), an oral C5aR inhibitor, recently reported that complement inhibition is a safe and efficacious glucocorticoid-free induction approach for AAV (ancavasculitisnews.com/2019/11/27/pivotal-advocate-trial-shows-superiority-of-avacopan-to-treat-aav). Similarly, eculizumab, a monoclonal antibody directed against C5, has been used in single cases with AAV after failure of commonly prescribed immunosuppressive measures (70).

The alternative complement pathway is also likely pathogenically relevant in SARS-CoV-2 infection and COVID-19 disease. Studies in mice infected with the closely related MERS-CoV found that the C5a-C5aR1 axis is critical in propagation of inflammation (46). Blocking activation of alternative complement reduced lung injury and broadly suppressed inflammatory responses (47). Avacopan is currently used in early access programs but given the involvement of C5a in the pathogenesis of coronaviruses-induced lung damage, it should be considered as standard in the contemporary era once licensed or broadly available. Eculizumab is currently tested in three registered clinical trials involving patients with COVID-19. Preliminary experience with eculizumab or ravulizumab in paroxysmal nocturnal hemoglobinuria point towards their safety, and further studies are necessary (71). Again, terminal complement complex inhibition might be considered an option in patients presenting with a new diagnosis or relapsing AAV and concomitant SARS-CoV-2 infection (71).

IL-6-targeting agents

IL-6 inhibition has not been studied in formal clinical trials as an approach for managing AAV. Increased IL-6 serum levels, however, were detected in AAV patients enrolled in the RAVE trial, and these increased levels correlated with active disease features and predicted the risk of relapse for patients in remission (72). Case reports and series have also documented treatment benefit with tocilizumab (73).

IL-6 inhibition has also gained attention as an attractive potential treatment strategy for severe COVID-19 disease manifestations like the cytokine storm. Increased IL-6 serum levels are present in COVID-19 patients (42, 44, 45). In agreement, an open label, non-controlled, non-peer reviewed study conducted in China in 21 patients with severe respiratory symptoms related to COVID-19 suggested that benefit (74). Experience from Brescia revealed that if there was a response observed following tocilizumab, this was rapid, sustained and associated with significant clinical improvement (75). At the time that this manuscript was prepared, 32 clinical trials evaluating the efficacy of the anti-IL-6 receptor monoclonal antibodies tocilizumab and sarilumab in COVID-19 patients were either planned or in progress.

Should these trials provide evidence of benefit for managing critically ill COVID-19 disease, IL-6 inhibition could be considered as AAV induction therapy in infected patients. At this time, however, given the paucity of formal trial evidence of benefit for IL-6 agents in either dis-

ease, we recommend considering IVIG or PLEX first before tocilizumab or sarilumab in patients with active AAV and COVID-19.

Additional measures to minimize risk of COVID-19 infection in AAV

Strict adherence to social distancing protocols, hand hygiene and encouraging use of face mask in public places should be discussed with each patient. AAV patients require regular clinic visits and laboratory work to monitor disease course and therapy-related adverse effects. Many institutions have transitioned from in-person clinic visits to telephone or video visits to minimize exposures. In stable patients, the interval between regular blood draws can be extended. AAV patients should be advised to complete recommended vaccinations for influenza and pneumococcus.

Conclusion

The natural history of AAV is relapsing-remitting course resulting in cumulative multi-organ injury. Infections and infection-related mortality are not uncommon adverse consequences seen with current standard-of-care treatment approaches for AAV. When considering the impact of immunosuppressive therapy on the risk and severity of COVID-19 disease, we should also account for the risks of uncontrolled vasculitis activity if hold or decrease the dose of immunosuppressive medications. A strong understanding of the features of immune dysregulation shared by AAV and SARS-CoV-2 therapies should help practitioners select immunomodulatory approaches with the best chance of providing the best possible outcomes for AAV patients infected with SARS-CoV-2 virus. The framework for AAV management provided in this review reflects our latest understanding of these mechanisms and is submitted as a potentially useful tool for management of AAV patients during COVID-19 pandemic.

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