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Review

Merits and culprits of immunotherapies for neurological diseases in times of COVID-19

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ABSTRACT

Immunosuppression and immunomodulation are valuable therapeutic approaches for managing neuroimmunological diseases. In times of the Coronavirus disease 2019 (COVID-19) pandemic, clinicians must deal with the question of whether immunotherapy should currently be initiated or discontinued in neurological patients. Uncertainty exists especially because different national medical associations publish different recommendations on the extent to which immunotherapies must be continued, monitored, or possibly switched during the current pandemic.

Based on the most recently available data both about the novel coronavirus and the approved immunotherapies for neurological diseases, we provide an updated overview that includes current treatment strategies and the associated COVID-19 risk, but also the potential of immunotherapies to treat COVID-19.

1. Introduction

The rapid pandemic outbreak of the Coronavirus disease 2019 (COVID-19) poses one of the most significant global challenges in the 21st century. The clinical presentations vary from asymptomatic and mild clinical symptoms to acute respiratory distress syndrome (ARDS) and associated death [1]. At the time of writing, more than three million people are officially infected worldwide, and more than 200,000 people died due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Unfortunately, there are no proven therapies, especially no vaccination, for SARS-CoV-2, and experiences with previous CoV epidemics reflect the ongoing and difficult challenge of finding effective treatment [2,3].

At present, there is a lack of data on how COVID-19 affects people with neuroimmunological diseases. In particular, neuromuscular disorders can affect respiratory muscles, and there is a heightened sense of concern for the potential risk of SARS-CoV-2 infections and the severity of manifestations [4]. Moreover, most patients with neuroinflammatory disorders are on immunosuppressive or immunomodulatory therapies. Due to its nature and previous evidence from other respiratory viral infections, immunosuppression appears to be another risk factor for both becoming infected with SARS-CoV-2 and developing serious complications [5]. However, stabilizing the neuroimmunological disorder with immunosuppression could hinder disease exacerbation and potentially outweighs the higher risks of infection [4]. Current uncertainty about applying immunotherapies is illustrated by numerous but inconsistent recommendations circulated by national and international societies for diverse neuroimmunological diseases.

Similar to other severe virus infections, the disease characteristics of COVID-19 comprise two critical phases in which the interplay between pro- and anti-inflammatory mechanisms of the host appear to play an important role in the disease-related outcome (Fig. 1a) [6,7]. Though an adequate and rapid immune response weakens virus replication and cytopathic tissue damage, the virus-induced increased host immunity, however, seems to conversely cause organ failure like ARDS and a cytokine storm (Fig. 1b) [8,9].

While the elevated risk of infection under immunomodulatory therapies is obvious, there is increasing evidence that the application of tailored immunotherapies may have beneficial effects in dampening excessive inflammation in late stages of infection [5]. Thus, experience in treating neuroinflammatory disorders could help to estimate the risk of infection with SARS-CoV-2 and to identify therapeutic strategies to minimize severe overactivation of the immune response following the viral phase of SARS-CoV-2 infection [9]

Here, we provide an overview covering the known and suspected SARS-CoV-2 induced immunological mechanisms and the related potential risks under currently recommended immunotherapies used

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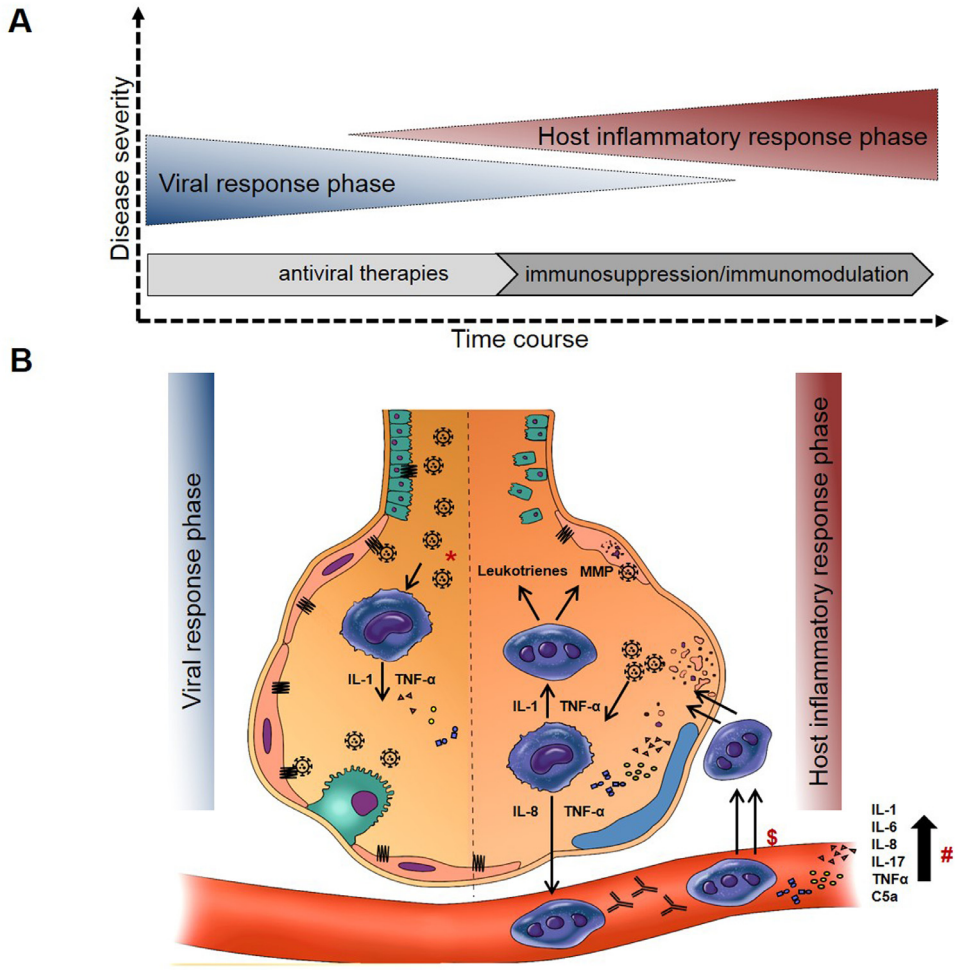

Fig. 1. Implication of inflammation during the viral and host response phase (adapted from Abbas et al. [116]) A: In the early stages of COVID-19 disease, antiviral treatment approaches may be effective, whereas immunosuppressive/immunomodulating therapies are an option in the inflammatory phase. B: Affected alveolus during both phases of COVID-19. Left: immune mechanisms during the viral response phase; right: several immune-mediated mechanisms in acute lung injury during the inflammatory host stage; * potential target of immunotherapies with antiviral potential; $ leukocyte trafficking as a potential target; inhibition of cytokine production and release during the phase of cytokine storm as a treatment target. MMP = matrix metalloproteinases; TNF-α = tumor necrosis factor-α; IL-1 = interleukin 1.

in neuroinflammatory disorders, but also opportunities of those approaches to treat the second phase of COVID-19.

2. Search strategy and selection criteria

References for this narrative review were identified by searches of PubMed for articles published between 1990 and 15th April 2020. The first and the last authors used combinations of the terms “coronavirus”, “COVID-19″, “SARS”, “MERS”, “multiple sclerosis”, “neuroimmunological disorder”, “neuroinflammatory disorder”, “immunosuppression”, “cytokine storm”, “disease modifying therapy” and “vaccination”, and applied no language restrictions.

3. COVID-19 and the role of inflammation

SARS-CoV-2 belongs to the group of highly diverse, enveloped, positive-sense, single-stranded RNA viruses and is the third known highly pathogenic zoonotic CoV after the SARS-CoV and the Middle East respiratory syndrome CoV (MERS-CoV) [2]. Despite the large number of current publications on COVID-19, conclusions regarding the pathogenesis are mainly drawn from clinical observations and experimental studies with SARS-CoV and MERS-CoV [2,10,11]. Unfortunately, the persistent lack of treatment options and the associated high mortality rates of these two CoVs underline the current challenge to treat COVID-19 successfully [2,3]. With regard to the two different disease stages of COVID-19, different immunological pathways are emerging that offer potential treatment targets (Fig. 1b).

In the viral response phase, receptor-mediated viral attachment and entry of SARS-CoV2 into the target cells are realized by the host angiotensin II converting enzyme (ACE-II) receptor binding to the viral spike glycoprotein [12]. Cells with high ACE-II expression are present in the salivary glands of the mouth, the whole respiratory tract and lung epithelial cells [13]. Moreover, SARS-CoV particles and viral genome have been detected in macrophages and lymphocytes as well as vascular endothelial cells [14].

The early cytopathic and inflammatory effects are related to rapid viral replication interfering with protein synthesis and function in infected cells leading to progressive dysfunction and finally apoptosis. Additionally, the virus induces a downregulation and shedding of the ACE-II receptor, causing pulmonary injury and the release of exuberant pro-inflammatory mediators [7,15,16]. Certain innate and adaptive immune cells provide important immune counterparts during the first stage of inflammation. Early-on synthesized and released viral proteins are recognized by the endosomal toll-like receptor 7 of infected tissue or innate immune cells (macrophages, neutrophils, and dendritic cells), leading to activation of intracellular pattern recognition receptors and transmembrane proteins [6,17]. The latter mechanisms converge on the activation of protein kinases, which in turn activate interferon (IFN) regulatory transcription factors that stimulate tumor necrosis factor-α (TNF-α) as well as interleukin

(IL)−1, IL-6, IL-8, and IL-12 transcription and secretion. In addition to the inhibitory effects against viral replication in both infected and non-infected cells, chemokine secretion induces an adaptive immune response primarily driven by T cells [6,18,19]. T cell differentiation and stimulation are supported by antigen presentation due to dendritic cells and cytokine release of $CD4^+$ *T* cells [20,21]. Cytotoxic T cells recognize cytosolic viral peptides presented by MHC class I molecules. $CD8^+$ *T* cells directly kill infected cells, activate nucleases that degrade viral genomes, and initiate further cytokine secretion that activates phagocytosis by pulmonary macrophages [22]. In terms of virus-induced shutoff of MHC class I expression on the infected cells, natural killer (NK) cells can recognize and kill virus-infected tissue cells as well [18,20,23].

In most COVID-19 patients the primary inflammatory reaction results in a reduction of viral activity followed by decremental dampening of inflammation [7]. The more significant challenge represent the secondary phase of inflammation in some patients, characterized by a cytokine storm and leukocyte infiltration into pulmonary tissue (Fig. 1b) [9]. Currently, various inadequate virus-induced immune defense mechanisms are being discussed. During the viral response phase, virus-neutralizing antibodies do not play a major role due to the lack of memory B cell clones. However, after B cell activation and proliferation, anti-spike-protein-neutralizing antibodies might promote proinflammatory macrophage accumulation and production of matrix metalloproteinases, leukotrienes, and IL-8 in the lungs by binding to Fc receptors [24]. IL-8 has a negative impact on T cell priming by dendritic cells, thereby providing an important mechanism for SARS-CoV2 to evade host immune responses. The continuous circle of viral replication and death leads to cell pyroptosis, which subsequently triggers massive cytokine release and immune cell migration into the lung [24,25]. Moreover, antibody-mediated activation of the complement system leads to chemokine production and invasion of granulocytes and lymphocytes that further increase pulmonary tissue damage (Fig. 1b) [10].

Overall, it can be concluded that different mechanisms of the innate and adaptive immune response to SARS-CoV-2 infection are self-perpetuating indicating potential detrimental but also beneficial effects of anti-inflammatory treatment approaches against COVID-19.

4. Mode of action of immune therapies and implications for COVID-19 infection

4.1. Interference with DNA synthesis

Azathioprine, methotrexate, and cyclophosphamide are long-established therapies in myasthenia gravis (MG), neuromyelitis optica spectrum disorders (NMOSD), idiopathic inflammatory myopathies (IIM), primary angiitis of the central nervous system (PACNS), inflammatory neuropathies and autoimmune encephalitis. While azathioprine and methotrexate are mainly used at disease onset and over a longer time, cyclophosphamide is mainly indicated in severe disease exacerbations aiming at a preferably low small cumulative dose [26]. Mitoxantrone, a type II topoisomerase inhibitor, is another immunosuppressive drug that was commonly used in secondary progressive multiple sclerosis (SPMS) and in treatment-refractory relapsing remitting MS (RRMS) as well as in NMOSD [27]. All drugs are characterized by long-term lymphopenia and neutropenia, resulting in higher infection rates [26].

Teriflunomide is a recently approved immunosuppressive drug for RRMS. It reversibly inhibits the dihydroorotate dehydrogenase that is expressed in lymphocytes [28]. Though, a notable decrease in peripheral lymphocyte counts of approximately 15% was observed, the incidence of infections was comparable between placebo- and teriflunomide-treated RRMS patients in both phase III trials [29,30]. However, the long-term risk of lymphopenia and infections in teriflunomide treated RRMS patients seems to be low [31]. Besides the anti-inflammatory effect, the inhibition of the de novo pyrimidine biosynthetic pathway promotes antiviral properties as was already shown for various DNA and RNA viruses [32].

Mycophenolate mofetil (MMF), currently used in MG, IIM, PACNS, and NMOSD, reversibly inhibits inosine monophosphate dehydrogenase and the synthesis of guanine monophosphate, disrupting the de novo purine synthesis [33]. Consequently, MMF mainly curtails the proliferation of T and B lymphocytes. Moreover, MMF reduces the production of lymphocyte-derived proinflammatory cytokines such as IFN-γ and TNF-α. Due to the mode of action, MMF increases the possibility of infections through reactivating latent viruses [34]. Interestingly, the active compound, mycophenolic acid, exhibits antiviral activity in vitro against various viruses, including MERS-CoV [35,36]. An in vivo study with MERS-CoV infected marmosets, however, showed high viral loads with more severe or even fatal disease outcome [37]. A case series of 8 patients treated with MMF and IFN-β revealed an overall survival [38]. Nevertheless, renal transplant recipients who were on maintenance MMF therapy also developed severe or fatal MERS-CoV infections [3]. In conclusion, continuous MMF therapy might increase the risk of infection, while the antiviral properties could be exploited as an acute treatment approach against COVID-19. However, the previous results must be interpreted with caution, since the usual dosage of MMF is unlikely to be a guarantee for prophylaxis or treatment of CoV infections [39].

Cladribine is a synthetic purine analog that disrupts DNA synthesis and repair, specifically in lymphocytes. Up to 4 months after application, cladribine leads to a preferential decrease of circulating $CD4^+$T cells, and for a shorter period to a reduction of NK cells, mature and memory B cells, and $CD8^+$ *T* cells [40]. The resulting lymphopenia renders patients transiently more susceptible towards infections, especially viral infections and reactivation [41]. Of note, the pulsed immunosuppression shortly after administration is associated with a higher infectious risk but could be beneficial due to the long-term anti-inflammatory effect without associated immunosuppression.

4.2. Pulsed depletion of immune cells

Monoclonal antibodies (mAb) targeting B cells are frequently applied in neuroinflammatory disorders. Especially rituximab, a chimeric anti-CD20 mAb, has shown promising effects in a wide range of inflammatory neurological disorders, including MG, NMOSD, autoimmune encephalitis, inflammatory neuropathies as well as RRMS [42]. For RRMS and primary progressive MS, the humanized CD20 mAb ocrelizumab received approval in 2018 [43,44]. The CD20 molecule is expressed throughout B cell maturation. Thus, both compounds effectively deplete late pre-B cells up to and including memory B cells but not early pro-B cells, plasma cells, or plasmablasts. Moreover, the CD20 antigen is also expressed on a subset of $CD4^+$ *T* cells [42,43].

Inebilizumab is a mAb against the CD19 antigen and has recently shown positive results in NMOSD patients [45]. Compared to CD20 mAb, inebilizumab has a more pronounced impact on B-cell depletion, since CD19 expression starts at the pro-B cell stage, and CD19 is expressed on the majority of plasma cells [46]. B-cell depletion is associated with a slightly increased frequency of upper respiratory tract infections and certain influenza and pneumonia cases [43–45]. In particular, the associated interference with $CD4^+$ *T* cells might reduce the acute defense against SARS-CoV2. Concerning the repeated application of mAb against CD19 and CD20 antigens, the long-term absence of a B cell immune response appears to be the main issue. In general, all three drugs often show persistent B cell depletion even before the planned reapplication [43–45]. However, despite a recovery of the total B cell account, the repopulated B cell compartment consists largely of naive B cells, while memory B cells remain almost absent in peripheral blood for several years after the last administration [47]. The lack of memory B cells might be relevant

in the future for COVID-19 since low vaccination response rates during B cell depletion treatment approaches are reported [48]. However, long-lived plasma cells, themselves unaffected by CD20 mAb and persisting after depletion of the B cell precursors, suggests vaccination before treatment initiation. Contrary, inebilizumab might predict a higher infectious risk due to the relevant depletion of long-lived plasma cells in peripheral blood and bone marrow [49]. Another risk factor for COVID-19 is thought to be the treatment-related late-onset neutropenia, which commonly occurs along with hypogammaglobinemia [50].

Alemtuzumab is a humanized anti-CD52 mAb approved for the therapy of active RRMS. The CD52 antigen is highly expressed on the surface of B and T cells and at lower levels on monocytes and macrophages [51]. The rapid and profound lymphopenia in the first months following alemtuzumab administration results in a small but definite increase in the risk of infection [51,52].

The repopulation dynamics of immune cells derived from hematopoietic stem cells are distinct for different immune cell types. Since T cell recovery is slower than B cell repopulation, opportunistic infections are more likely to be associated with T cell depletion [53]. However, pneumonia and upper respiratory tract infections might be related to the additionally documented hypogammaglobulinemia after T and B cell recovery [54]. Notably, after the critical phase of lymphopenia induced by alemtuzumab, there is both sufficient immunocompetence and corresponding inhibition of MS-related inflammatory activity in the further course of disease [51]. Moreover, the pulsed nature of this treatment approach provides the opportunity to delay further therapy courses without a detectable impact on efficacy [55].

4.3. Peripheral sequestration of leukocytes

Natalizumab is a recombinant humanized mAb directed against alpha4-integrin molecules on leukocytes and blocks transmigration of peripheral immune cells into the CNS [56]. Natalizumab is currently available for RRMS treatment. Since focal immunosuppression rather increases the risk of serious opportunistic infections of the brain, respiratory infections are rarely reported [57]. Alpha4-integrin also serves as a retention signal for mainly lymphoid progenitor cells in the bone marrow. Thus, natalizumab treatment results in an increase of NK cells, T lymphocytes, and especially B cells in the peripheral blood [58,59]. The higher B cell-mediated inflammatory state might be favorable against infectious disease. Moreover, a decreased migration of lymphocytes after blocking alpha4-integrin was reported in inflammatory lung disease suggesting a possible protective effect of natalizumab in COVID-19 infection [60].

Favorable effects of peripheral sequestration of leukocytes are assumed for oral sphingosine 1-phosphate receptor (S1PR) modulators in MS therapy. Fingolimod is effective in treating RRMS, whereas siponomid was recently approved for secondary progressive (by EMA) and relapsing forms (by FDA). Both medications inhibit lymphocyte egress out of secondary lymphoid organs, resulting in a profound diminution of naive and central memory T cells and memory B cells in the periphery [61,62]. S1PR modulators lead to a peripheral lymphopenia up to 20−30% compared to baseline with implications for infection rates. Although various reports underline pulmonary complications occurring during treatment with fingolimod, modulation of S1PR was protective against experimental asthma, and documented to inhibit pulmonary vascular leakage in murine models of acute lung injury [63−65]. Moreover, fingolimod suppresses the IL-6 and IL-8 mRNA expression and protein secretion from lung epithelial cells [66].

To date, one clinical trial has examined changes of pneumonia severity on X-ray images in severe COVID-19 cases under fingolimod (Table 1).

4.4. Pleiotropic immunomodulation

Glatiramer acetate is a mixture of synthetic polymers consisting of four amino acids and competes with myelin antigens for presentation to T cells. There is no increased risk of infections observed in RRMS patients [67].

Like glatiramer acetate, dimethyl fumarate is approved for RRMS. The mode of action has not been fully elucidated but may include anti-inflammatory and cytoprotective aspects. Dimethyl fumarate can lead to pronounced lymphopenia below 500/μl that may persist for several months. Importantly, patients > 55 years of age appeared to be at a higher risk of lymphopenia [68].

4.5. Cytokine targeted agents

IFN-β is approved for RRMS and secondary progressive MS for more than 20 years [69]. IFN-β shifts cytokine production in favor of anti-inflammatory cytokines and modulates the antigen-presenting

Table 1
Current clinical trials on COVID-19 with approved or recommended immunotherapies for neuroinflammatory diseases. COVID-19 = Coronavirus disease 2019; *d* = days; IL-6 = interleukin 6; IVIG = intravenous immunoglobulins; n/*a* = not applicable; RCT = randomized controlled trial.

Drug(s)	Study title	Phase	Study design	Subjects	Primary endpoints	NCT number	(Assumed) mechanism of action
Fingolimod	Efficacy of Fingolimod in the Treatment of New Coronavirus Pneumonia (COVID-19)	II	single-arm	30	The change of pneumonia severity on X-ray images (5d after fingolimod treatment)	NCT04280588	Leucocyte sequestration
Eculizumab	Soliris to Stop Immune Mediated Death In Covid 19 Infected Patients. A Trial of Distal Complement Inhibition.	II	single-arm	n/a	Mortality Time in the ICU Time on a ventilator	NCT04288713	Complement inhibition
Tocilizumab	Multicenter Study on the Efficacy and Tolerability of Tocilizumab in the Treatment of Patients With COVID-19 Pneumonia	II	single-arm	400	One-month mortality rate	NCT04317092	Il-6 inhibition
IVIG	The Efficacy of Intravenous Immunoglobulin Therapy for Severe 2019-nCoV Infected Pneumonia	II	RCT (standard care)	80	Clinical improvement based on the 7-point scale	NCT04261426	Pleiotropic immunomodulation
Glucocorticosteroids	Efficacy and Safety of Corticosteroids in COVID-19	II	RCT (placebo)	400	The incidence of treatment failure in 14d	NCT04273321	Downregulation of inflammatory cytokines

function of dendritic cells and promotes anti-inflammatory B-cell functions [67,69]. There is no heightened risk of infection during IFN-β treatment. Only a few patients experience mild leukopenia or lymphopenia [67]. IFN-β is naturally secreted by fibroblasts and binds to the IFN receptor, which activates the Janus kinase/signal transducer and activator of the transcription pathway and consequently leads to increased gene expression of antiviral and antiproliferative molecules. During a viral infection, the extensive release of IFNs is triggered by innate immune players [70]. Interestingly, studies evaluating the antiviral activity of IFNs have reported IFN-β as the most potent of them in reducing MERS-CoV replication in vitro [71,72]. Therefore, combining IFN-β with other antiviral agents is investigated in MERS-CoV, both in vitro studies and clinical trials (Table 1) [73,74].

The inhibition of IL-6 is an intensively investigated treatment approach for inflammatory diseases. Tocilizumab and satralizumab are mAbs against the IL-6 receptor and currently used in NMOSD [75,76].

IL-6 production has been associated with predominantly pro-inflammatory effects. IL-6 is immediately produced in response to infections but also upregulated in chronic autoimmune processes [77]. Although potential antiviral properties of exogenous IL-6 have been suggested, mostly detrimental consequences of increased IL-6 levels in infections have been reported [78]. The increased expression of T cell-regulating molecules such as programmed cell death-1 and its ligand, as well as synergistic interaction with IL-17, lead to an increased inflammatory host stage. Subsequently, IL-6 is a key player in cytokine release syndromes (CRS) seen in infections or after adoptive T cell therapy [79,80]. Elevated systemic levels of IL-6 were frequently reported with the exacerbation of clinical outcomes involving viral pathogens [78,81]. With respect to COVID-19, CRS are commonly reported in severe and fatal disease cases with corresponding high IL-6 levels in the blood [9,82–84]. Interestingly, tocilizumab is approved for the treatment of a chimeric antigen receptor T cell-induced CRS [85]. Subsequently, various reports also suggested a favorable outcome of tocilizumab treatment in severe CRS in COVID-19 cases [86,87]. In a non-randomized, open-label, clinical trial, 21 patients with severe COVID-19 received tocilizumab in addition to lopinavir and methylprednisolone. All patients survived without side effects [88]. The early signals of clinical improvement and the relatively low rate of side effects due to IL-6 inhibition prompted initiation of an ongoing clinical trial (Table 1).

4.6. Complement inhibition

The humanized mAB Eculizumab blocks the cleavage and activity of complement factor 5 (C5), ultimately inhibiting complement-mediated cell lysis. It became the first mAb approved for aquaporin-4-antibody-positive NMOSD and for severe MG [89,90]. Eculizumab is associated with a heightened risk of pneumococcal and meningococcal infections, but also reports about viral infections are available at present, possibly due to the complement-dependent regulation of T cell activation [91,92]. Although the complement system plays a crucial role in the antiviral response of the host, the increased complement activation during the inflammatory phase in COVID-19 sheds new light on its possible destructive potential [93]. In SARS-CoV-infected mice, the complement system may not play a key role in controlling virus replication but mediates lung tissue damage by upregulation of inflammatory cytokines and neutrophil activation [94]. Interestingly, C3a and C5a blockade has been proposed as a treatment option for virus-induced acute lung injury, and the anti-C5a antibody has been shown to weaken sever lung tissues injury in SARS-CoV infected mice [10,93]. To date, a clinical trial with eculizumab in COVID-19 is under investigation (Table 1).

4.7. Blockade of intracellular signaling pathways

Cyclosporine A (CsA) is an immunosuppressive drug that is commonly used in MG and IIM cases [95,96]. CsA therapy does not seem to render patients with neuroinflammatory disorders more susceptible to infections [97]. CsA binds to cellular cyclophilins to inhibit calcineurin. The inhibition of calcineurin blocks the translocation of the nuclear factor of activated T cells from the cytosol into the nucleus, thereby reducing the transcription of pro-inflammatory genes encoding e.g. cytokines such as IL-2. Although CsA mainly targets T cell activation, accumulating evidence supports a crucial regulatory impact on innate immune cells, including dendritic cells, macrophages, and neutrophils [98]. In vitro studies have shown that CsA inhibits the replication of diverse CoVs [11]. However, studies in humans are still lacking and might be limited due to the very close margin between therapeutic and toxic blood concentrations [99].

4.8. Acute treatment approaches

Glucocorticosteroids (GCS) are widely used in various neuroinflammatory diseases.

GCS restrict the production of numerous inflammatory mediators and inhibit the migration of immune cells across the blood-brain barrier [100].

Long-term administration of GCS is associated with bacterial and viral infections. In contrast to continuous treatment, repeated pulse therapy does not increase the risk to develop bacterial infections, but severe viral infections are reported [101]. In terms of COVID-19, there is currently a controversy concerning the application of GCS application in cases of ARDS or severe respiratory failure, since previous data have shown increased mortality and secondary infection rates in CoV patients [102,103]. However, results from a clinical trial are still awaited (Table 1).

Repeated administration of intravenous immunoglobulins (IVIG) is a well-established immune-modulating therapy, particularly in inflammatory neuropathies as well as MG. Besides their favorable role in pathogen recognition and clearance in immunodeficient patients, IVIG might have promising effects on pathogen-induced host inflammation. Regarding myeloid cell activation in the inflammatory phase, IVIG saturate the IgG recycling capacity of neonatal Fc receptors and consequently reduce the levels of antiviral neutralizing antibodies responsible for activation of macrophages and NK cells [104,105]. Moreover, IVIG inhibit both TNF-α-induced NF-κB activation in neutrophils and endothelial cells [104]. IVIG also reduce pro-inflammatory cytokine production by mononuclear cells while they increase the production of the anti-inflammatory IL-1 receptor antagonist [106]. IVIG can also expand regulatory T cells and suppress pathogenic Th1 and Th17 subsets [107]. As dysregulated excessive complement activity is likely to be a key molecular mechanism in the acute inflammatory phase, IVIG-mediated neutralization of complement factors could be beneficial [108]. IVIG also inhibit endothelial cell proliferation and downregulate mRNA expression of adhesion molecules such as vascular cell adhesion protein 1 [109]. In addition, IVIG attenuate IL-1α-dependent leukocyte adhesion to endothelium, activation, and tissue injury [106]. The endothelial effects of IVIG are thus potentially useful in ameliorating disease severity or possibly preventing the onset of acute inflammatory lung injury. Since only a few cases of IVIG treatment for COVID-19 have been reported to date, but further immunotherapies have been administered, conclusions about its efficacy could not be drawn. However, previous studies in septic patients showed a favorable outcome upon IVIG administration, and a clinical trial in COVID-19 is still ongoing (Table 1) [110].

Therapeutic apheresis is considered as a treatment option in disease exacerbation of several neuroinflammatory disorders [111]. Higher infection rates are observed during and after treatment but mainly include catheter-associated infections. With regard to the

inflammatory host phase, the removal of circulating inflammatory cytokines and the replacement of protective plasma proteins may counteract inflammation and vascular leakage [112]. Due to the small number of randomized trials in septic patients, however, only weak evidence exists to recommend plasma exchange.

5. Implications for the application of immunotherapies in the age of COVID-19

Although respective data are still lacking, we believe that classical immunosuppressive agents such as azathioprine, methotrexate, mitoxantrone, and cyclophosphamide might be associated with a higher risk of infection due to the caused long-lasting lymphopenia. Unfortunately, such compounds are still continuously used for numerous neurological diseases as the corresponding approval studies for new selective therapies, especially for orphan diseases, are rarely conducted. However, a treatment cessation due to the COVID-19 pandemic may both worsen the disease and increase the risk of poor outcome in case of a COVID-19 infection. In particular, disease exacerbation might result in the need for acute therapy intervention with GCS, which could also result in longer-lasting immunosuppression. Furthermore, hospitalization could lead to a higher probability of exposure to already infected patients. Thus, the associated risk of infection might be offset by the improvement in neurological function in severe disease cases by controlling the inflammation. For long-term disease stability, de-escalating strategies, e.g., dose reduction, could be considered. For treatment initiation in orphan diseases such as MG or IIM, the off-label compounds MMF or CsA might be more advisable than the therapies described above. Fortunately, there are currently several selective immunotherapies for MS that offer more options in times of COVID-19. In modest MS, self-injected therapies (glatiramer acetate, IFN-β), dimethyl fumarate, and teriflunomide do not seem to be associated with an increased risk of COVID-19 infection or complications due to their low level of immunosuppression and should therefore be initiated or continued.

Regarding active RRMS, the inhibition of leukocyte trafficking using fingolimod is related to a mildly increased risk of viral infections and complications. In the context of natalizumab, opportunistic CNS infections are more relevant than systemic virus spread. Nevertheless, treatment with natalizumab may offer more flexibility, as a recent retrospective evaluation showed that extending the dosing interval to up to 6 weeks appeared to be associated with a lower progressive multifocal leukoencephalopathy risk [113]. The initiation and continuation of both drugs, however, do not pose an additional risk of developing more severe COVID-19 to RRMS patients. In contrast, treatment cessation might result in MS reactivation. Pulsed immunosuppressive therapies, including mAbs against CD19/20 as well as CD52 and cladribine, are associated with an increased infectious risk over a limited period after initiation. However, the extent of immunosuppression and the repopulation dynamics differ fundamentally between such therapeutic agents and should be considered in treatment decisions. Especially after B cell depletion with rituximab, ocrelizumab, or inebilizumab, a reduced humoral immunity develops over the next 6–12 months and is maintained by the subsequent reapplication. Thus, for repeated applications, it seems to be advisable to use serological markers, such as the CD19 B cell status, to avoid long-term side effects like hypogammaglobinemia [50].

Concerning the mode of action of cladribine and alemtuzumab, a normalization of the total lymphocyte count due to immune reconstitution can be expected 6–12 months after application and, at most, leads to a slightly increased risk of severe virus infections. The pulsed nature of these compounds provides the opportunity to delay therapy until the peak of the pandemic is over.

For eculizumab, there is currently no evidence of increased susceptibility to COVID-19 infection or its outcome. In light of its indication for active MG and NMOSD cases, therapy should, therefore, be initiated and continued. The same applies to the use of mAbs against IL-6 in patients with NMOSD.

With regard to acute treatment approaches, including IVIG and therapeutic apheresis, there is currently no sufficient evidence that either intervention poses an additional risk of COVID-19 infection. Due to the increased risk of infection, intravenous GCS therapies should only be conducted if there is a clear clinical indication such as relapses or as a required premedication in pulsed immunotherapy regimens

6. Implications for treatment continuation in the case of an acute COVID-19 infection

In the event of an acute COVID-19 infection, the continuation of immunotherapy should be questioned critically, especially considering the previous course of the neuroimmunological disease. In particular with immunosuppressive therapies, a sustained therapeutic effect can be expected for weeks and months even after the therapy has been discontinued. These therapies should therefore be suspended. In contrast, selective immunotherapies such as glatiramer acetate, IFN-β, teriflunomide or dimethyl fumarate seems to be safe in case of COVID-19 infection. However, in severe lymphopenia resulting from the latter therapy, treatment should also be interrupted.

With respect to immunotherapies for active RRMS, both natalizumab and fingolimod could be continued or stopped for few weeks before a disease reactivation or rebound are expected. Pulsed immunotherapies including treatment approaches with exclusive B-cell depletion, alemtuzumab and cladribine should be delayed in case of an acute infection. In view of both the safety data and the current indications, especially in severe refractory cases, mAbs against IL-6, complement inhibitors and CsA should be continued.

7. Implications for vaccination under immunotherapies in the age of COVID-19

Regarding the intensive search for vaccines, the question arises to what extent an adequate vaccination response can be expected among recipients of immunotherapies. Whether vaccination is as effective under immunotherapies in neurological disorders as in the general population is not well studied. Unfortunately, the few existing studies gave contradicting results [48,114]. While a sufficient vaccination response is more probable with immunomodulatory and selective treatment strategies, immunosuppressants and especially B-cell depletion approaches might be unfavorable in such a situation. Overall, immune reconstitution after pulsed cell depletion might be a determining factor for a successful vaccination with few side effects [114]. On the other hand, theoretically an increased immune response against different types of vaccines, such as live attenuated viruses or inactive viruses as well as adjuvanted-containing vaccines, could trigger immune response to self-antigen with increased relapse rates after vaccination [115].

Furthermore, the restriction on vaccines with live attenuated viruses, especially under diseases modifying treatments must be observed [114].

8. Outstanding questions and concluding remarks

In general, immunotherapies are a mainstay in the management of neuroimmunological diseases, while it is still unclear whether and how they increase the risk of COVID-19 and its complications. The risks of treatment cessation can be higher than the risk of a worsened COVID-19 disease course under ongoing immunotherapy. In this context, factors such as the local prevalence rate for COVID-19 might also play a role regarding future therapeutic decisions.

Moreover, the current lockdown in various countries around the world has led to limited availability of healthcare services. Future

studies should therefore also investigate the relationship between such treatment delay and disease activity. In general, the potential long-term risk of infection must be considered in future treatment decisions. Hence, approved selective immunotherapies from other indications should also be investigated for their use in rare neuroinflammatory diseases. It is, therefore, appropriate to amend the off-label use regulations and, in particular, to consider immunological investigations. In this review, we have outlined several beneficial aspects of immunotherapies in COVID-19 cases: antiviral effects of IFN-ß, CsA, and teriflunomide; leukocyte sequestration by natalizumab or S1PR modulators; complement inhibition by eculizumab; as well as potential immunoregulatory effects in terms of a cytokine storm by IVIG or GCS. So far, however, the experience is limited to therapies that target IL-6. This is mainly explained by previous successful observations with tocilizumab in CRS, which seems to be a hallmark in severe COVID-19 cases [87,88]. The major challenge of the current and future COVID-19 studies investigating the above-mentioned therapies could be to determine the right time for starting and discontinuing treatment. Several biomarkers are available to identify the beginning of the host response phase and should be considered as regular inclusion criteria in clinical trials [9]. The use of immunotherapies other than tocilizumab beyond clinical trials or without using a standardized definition for the inflammatory host phase should be avoided, as neither success nor failure will allow conclusions to be drawn.

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