THERAPEUTIC ADVANCES in
Infectious Disease

Review

Therapeutic advances in neuroinfectious diseases

Ther Adv Infect Dis

2024, Vol. 11: 1–18

DOI: 10.1177/20499361241274246

Rumyar Ardakani, Lucy Jia, Elizabeth Matthews and Kiran T. Thakur

***Abstract*:** There have been several major advances in therapeutic options for the treatment of neurological infections over the past two decades. These advances encompass both the development of new antimicrobial therapies and the repurposing of existing agents for new indications. In addition, advances in our understanding of the host immune response have allowed for the development of new immunomodulatory strategies in the treatment of neurological infections. This review focuses on the key advances in the treatment of neurological infections, including viral, bacterial, fungal, and prion diseases, with a particular focus on immunomodulatory treatment options. This review also highlights the process by which clinicians can request access to therapeutic agents on a compassionate or emergency basis when they may not be commercially available. While many therapeutic advances have been achieved in the past several years, there remains a pressing need for the continued development of additional therapeutic agents in the treatment of neurological infections.

Keywords: encephalitis, meningitis, neuroinfectious disease, neurologic infections, neurology, neuroinflammation, prion disease, therapeutics

Received: 10 January 2024; revised manuscript accepted: 5 July 2024.

Introduction

The sheer diversity and emergence of novel neurotropic pathogens pose unique challenges and opportunities in therapeutic drug development. Drugs targeting central nervous system (CNS) infections require unique properties, including the ability to enter the CNS through barriers, including the blood-cerebrospinal fluid (blood-CSF) barrier. Additionally, the impact of para and post-infectious neuroinflammation, which is often driving the neurological conditions seen, requires targeting inflammatory cascades rather than the primary infectious processes. Despite these challenges, there have been several important advances in therapeutic options for the treatment of neurotropic infectious diseases over the past two decades. These include the development of new therapeutic agents and repurposing of existing agents, particularly immunomodulatory treatments. These advances are especially important for immunocompromized patients, who often require unique therapeutic strategies.

In this review, we will highlight key therapeutic advances in the treatment of neurological infections, including viral, bacterial, fungal, and prion diseases. The first section of our review focuses on advances in direct antimicrobial agents, highlighting the discovery of novel agents and the repurposing of existing agents. The second section of our review focuses on advances in immunomodulatory treatments for the treatment of neurological infections, including steroids, intravenous immunoglobulin (IVIG), checkpoint inhibitor immunotherapy, viral-specific T-cells, and other immunomodulatory agents. While many of the described agents are commercially available, others may require an investigational new drug (IND) application for emergency compassionate use (see Figure 1).

Direct antivirals

Introduction

Viruses remain a frequent cause of neurological infections throughout the world. As bacterial meningitis has decreased in prevalence due to vaccinations, viral meningitis has emerged as the leading cause of meningitis in many regions of the world. Although many cases of viral meningitis and encephalitis are self-limited, there is still a

Correspondence to:
Kiran T. Thakur
Department of Neurology, Columbia University Irving Medical Center, 177 Fort Washington Avenue, Milstein Hospital, 8GS-300, New York, NY 10032, USA

Program in Neuroinfectious Diseases, Department of Neurology, Columbia University Irving Medical Center-New York Presbyterian Hospital
ktt2115@cumc.columbia.edu

Rumyar Ardakani
Elizabeth Matthews
Neuro-Infectious Diseases Group, Department of Neurology and Division of Infectious Diseases, University of Colorado School of Medicine, Aurora, CO, USA

Lucy Jia
Columbia University College of Physicians and Surgeons, New York, NY, USA

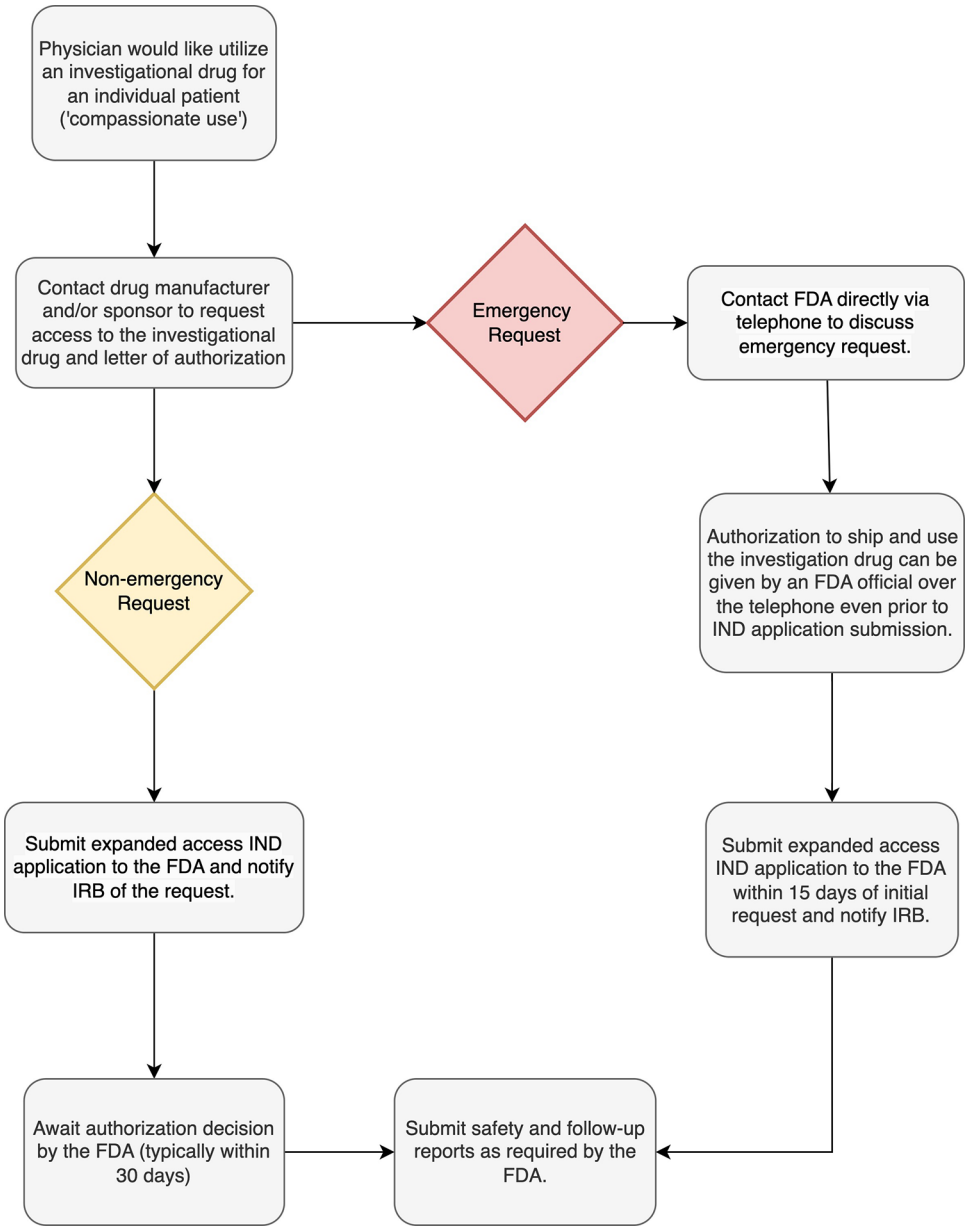

Figure 1. In many countries, physicians can request the use of unapproved investigational drugs for individual patients in certain circumstances. In the United States, this is completed by submitting an IND Application to the FDA. When an investigational drug is needed on an emergent basis, authorization can potentially be granted by an FDA official over telephone prior to a written IND submission. Some institutions may also have local IND offices that guide clinicians during the application process.
FDA, Food and Drug Administration; IND, investigational new drug.

risk of serious and potentially fatal complications associated with these infections, particularly in immunosuppressed patients.[1] Historically, antiviral treatments for viral meningitis and encephalitis have been largely limited to the use of acyclovir for infections involving herpes simplex virus and varicella-zoster virus (VZV). However, recent advances in the field have expanded therapeutic options for the treatment of viral infections of the nervous system, especially in those with underlying immunodeficiency.

Pleconaril

Pleconaril is an orally administered antiviral medication with activity against the picornaviruses

class of viruses, including enterovirus and rhinovirus.[2] It exerts its antiviral effect via binding to the viral capsid and interferes with viral uncoating. Additionally, pleconaril has excellent CNS penetration, achieving several-fold higher concentrations in the CNS compared to the serum.[3] It was originally evaluated for the treatment of rhinoviral respiratory infections, but did not receive approval from the Food and Drug Administration (FDA) due to potential drug interactions.[2] However, the drug was later studied in enterovirus infections with several reports of favorable outcomes in severe meningoencephalitis.[4] A placebo-controlled trial in infants with enterovirus meningitis did not demonstrate efficacy, but this was likely confounded by the small number of enrolled subjects and a relatively benign and short course of illness.[5] However, a review of two placebo-controlled trials did suggest a shortened duration of headaches in some patients with enterovirus meningitis.[2] In addition, there is at least one case report suggesting successful treatment of echovirus 6 associated chronic meningoencephalitis in a patient with underlying common variable immunodeficiency (CVID).[6]

Pocapavir

Pocapavir is also an orally administered viral capsid inhibitor that has more recently been developed as a potential treatment of enteroviruses, including poliovirus.[7] While extensive in vitro studies have been completed, the literature on its clinical use is largely limited to case reports. As examples, several case reports have been published demonstrating clinical improvement with pocapavir in immunocompromized patients. In one, pocapavir was associated with clinical stabilization in a patient with rituximab-associated, chronic enterovirus meningoencephalitis.[8] In another, treatment with pocapavir in a patient with chronic enteroviral meningoencephalitis in the setting of Good's syndrome was associated with a favorable outcome.[9] Although robust clinical trials for the use of pocapavir in neurological infections is lacking, these case reports suggest a potential role for its use in certain immunocompromized patients.

In addition to treatment of enterovirus-associated meningoencephalitis, pocapavir is also being studied for the clearance of immunodeficiency-associated vaccine-derived poliovirus infections (iVDPVs).[10] In one randomized, blinded, placebo-controlled study, pocapavir was well-tolerated and significantly reduced time to virus clearance in immunocompetent patients challenged with the oral poliovirus vaccine.[7] In 2020, the first case of successful clearance of iVDPV by pocapavir was reported in an infant with X-linked agammaglobulinemia.[10] In 2021, pocapavir was utilized in the coordinated response to vaccine-derived poliovirus infection in Barcelona, Spain in a patient with CVID.[11]

Fluoxetine

Fluoxetine, a selective serotonin reuptake inhibitor used in the treatment of depression and anxiety disorders, has been proposed as a potential treatment option for enterovirus infections.[12] Initial in vitro studies identified fluoxetine as a potent inhibitor of enteroviruses through stereoselective binding to the highly conserved enterovirus 2C protein.[12] The exact function of the enterovirus 2C protein is yet to be determined, but is it has been proposed to be integral to viral replication and may be involved in viral evasion of the host immune response.[13] Additionally, fluoxetine has high CNS penetration, reaching concentrations 20-fold higher in the CNS compared to the serum.[14] Given evidence of in vitro antiviral effects, it has been proposed as a potential treatment strategy for enterovirus D68-associated acute flaccid myelitis.[12] A multicenter retrospective observational cohort study in 2019 demonstrated that fluoxetine was well-tolerated in patients with Enterovirus D68 (EVD68) AFM but failed to show efficacy.[14] However, the authors propose that fluoxetine may have been preferentially provided to patients with more severe disease related to AFM, resulting in selection bias that may have confounded ability to prove efficacy.

Since the identification of fluoxetine as a potential antiviral agent, several case reports also followed suggesting potential efficacy in the treatment of enterovirus meningoencephalitis in immunocompromized patients, though this was usually in combination with IVIG.[15,16] A more recent case report involving rituximab-associated chronic echovirus 13 meningoencephalitis and myofascitis demonstrated treatment failure to IVIG followed by clinical improvement and CSF viral clearance after treatment with fluoxetine.[17] These studies suggest a potential role for fluoxetine in some patients with enterovirus infection of the nervous system.

Amenamevir

Amenamevir is an anti-herpetic drug with a unique mechanism of action directed toward the helicase-primase complex.[18] It was approved for the treatment of herpes zoster in Japan in 2017.[18] Compared to acyclovir and valacyclovir, amenamevir has the benefit of once-daily dosing and does not require dosing adjustment based on renal function. The current indication for amenamevir is restricted to herpes zoster and not for central nervous system infections due to poor CNS penetration of the drug.[19] Related to this, it is relevant to note that there have been several reports of VZV meningitis and/or vasculitis after treatment of herpes zoster with amenamevir.[20–22] Notably, most of these cases were related to treatment of herpes zoster with trigeminal nerve involvement. Therefore, caution should be exercised in using amenamevir for the treatment of herpes zoster with trigeminal involvement or in immunocompromized patients.

Mirtazapine

Mirtazapine is a serotonin $5HT_{2a}$ receptor antagonist used primarily for treatment of depression. As in vitro studies have demonstrated that John Cunningham virus (JCV) infects oligodendrocytes through the $5HT_{2a}$ receptor, there has been interest in mirtazapine as a potential treatment for progressive multifocal leukoencephalopathy (PML), especially as the drug is known to have good CNS penetration.[23,24] While there are no robust clinical trials to demonstrate its efficacy, there are numerous case reports and case series that suggest potential benefits. For example, one case series of four patients with human immunodeficiency virus (HIV) infection and PML suggested clinical improvement in three of four patients after treatment with mirtazepine.[25] Over the past decade, several additional case reports of clinical benefit with mirtazapine in PML have been published, some of which involved concurrent use of the antimalarial agent mefloquine.[26,27] While evidence on efficacy is currently limited, it is reasonable to consider mirtazapine in the treatment of PML given its overall safety and tolerability.

Direct antibacterials and antimycobacterials

Meropenem and fluroquinolones

Community-acquired bacterial meningitis (CABM) continues to cause epidemics across the African Sahel region and is a growing burden in immunologically susceptible populations worldwide. Specific bacterial pathogens responsible for CABM may vary depending on epidemiology, risk factors, and vaccination status of specific communities but may include *Streptococcus pneumoniae*, *Neisseria meningiditis*, *Haemophilus influenza*, *S. agalactiae*, and *Listeria monocytogenes*. Outcomes in CABM depend on the prompt initiation of antibiotics. Additionally, the selection of a specific antibiotic regimen is dependent on the regional drug susceptibility patterns, though data is often incomplete with regard to epidemiological patterns of resistance. Over the decade, few new antibiotics have emerged, though there are growing scientific efforts to evaluate the use of novel immunomodulatory therapies in CABM (discussed further in the immunomodulatory section of this paper below).

Meropenem is a promising drug that was studied in a randomized study in children and shown to be as bactericidal as cefotaxime in this patient population.[28] Another class of drugs is fluoroquinolones, with moxifloxacin effective in models of penicillin-resistant *S. pneumoniae* and *L. monocytogenes* meningitis.[29,30] A variety of antibacterial treatments have been utilized for intrathecal therapy (including vancomycin and aminoglycosides) and are typically simultaneously used with intravenous therapy. Intraventricular (IVT) administration of antibiotics has been only documented by case reports with no major randomized controlled studies to date. Therefore, there is a lack of conclusive data regarding optimal use of intrathecal therapy.[31]

Rifampin, isoniazid, pyrazinamide, and levofloxacin

Tuberculous meningitis (TBM) remains a major cause of global morbidity and mortality, and the leading cause of death due to extrapulmonary tuberculosis (TB). Though current World Health Organization (WHO) guidelines recommend the use of the same drug regimen for pulmonary and extrapulmonary TB (rifampicin, isoniazid, pyrazinamide, and ethambutol) with differences in length of treatment time, data suggests that this regimen is not optimal for CNS disease. The evidence showing that there was a lack of optimization in CNS drug treatment was highlighted in phase II trials evaluating the safety of higher dosing rifampicin in Indonesia.[32,33] Additionally, an

open-lab randomized controlled trial (RCT) in Uganda (ISRCTN42218549) compared high-dose rifampicin (35 mg/kg/day orally or 20 mg/kg/day intravenously) to standard-of-care rifampicin dosing in people living with HIV (PLWH).[34] In patients who received rifampicin at the standard-of-care dosing, approximately one-third had undetectable rifampicin concentrations in the CSF while those receiving high-dose rifampicin had CSF concentrations above the minimum inhibitor concentration. The ongoing short intensive treatment for children with tuberculous meningitis trial is an RCT investigating whether higher dose rifampin (30 mg/kg vs 15 mg/kg), isoniazid (20 mg/kg), and pyrazinamide (40 mg/kg) in combination with levofloxacin (20 mg/kg) for 6 months is a safe and effective alternative to 12 months of standard-of-care treatment.[35]

Linezolid

Another strategy of treatment for TBM has included the use of adjunctive linezolid, leveraged for treatment in drug-resistant TB. As an example, the adjunctive linezolid for treatment of TBM (ALTER study) is an ongoing phase II randomized open-label trial (NCT04021121) investigating the pharmacodynamics and tolerability of adjunctive linezolid in TBM in Uganda. Additionally, the ongoing intensified trial (INTENSE) is a phase III RCT assessing both the role of adjunctive linezolid and high-dose rifampin and aspirin 200 mg in the first 8 weeks for treatment of TBM (NCT04145258). Although the results of these studies are pending, they may prove to be promising strategies in the treatment of drug-resistant TBM.

Bedaquiline

Bedaquiline is a relatively new anti-TB medication used in multidrug resistant tuberculosis with a unique mechanism of action involving inhibition of Adenosine Triphosphate (ATP) synthase in mycobacteria.[36] The drug was approved for use in the United States and the European Union in 2012, making it the first targeted TB medicine with a novel mechanism of action in over 40 years.[37] Although bedaquiline has not historically been utilized specifically for the treatment of TBM, a recent pharmacodynamic study has demonstrated that bedaquiline freely penetrates into the CSF of patients with pulmonary TB at concentrations similar to plasma.[38] However, further studies are needed to investigate clinical benefit.

Delamanid and pretomanid

Drugs used for second- or third-line treatment in drug-resistant TB may also be another important therapeutic target for CNS disease. For example, Delamanid and Pretomanid are novel anti-TB medications that exert their effect via inhibiting the synthesis of mycobacterial cell wall components, including methoxy mycolic acid and keto-mycolic acid. They have significant bactericidal activity with a pharmacodynamic profile that achieves adequate concentrations in the CNS, making them attractive agents for evaluation in TBM regimens.[39–42]

Direct anti-fungals

Current antifungal drugs used for invasive fungal infections (IFIs) include polyenes, azoles, pyrimidines, and echinocandins.[43] However, even with first-line treatment, mortality is high in patients with CNS fungal infections.[44] Limitations with current therapies include drug toxicity, drug-drug interactions, limited spectrum of activity, and increased drug resistance over the years.[43,45] There is also the additional challenge of achieving adequate CNS penetration, which has limited the use of the echinocandin class in treatment of neuroinfectious diseases.[46,47] While existing drugs such as sertraline and tamoxifen have shown promise as potential antifungal agents in preclinical studies, recently completed clinical trials for adjunctive use of these drugs in the treatment of HIV-associated cryptococcal meningitis did not demonstrate clinical benefits.[48–50] There remains a pressing demand for novel therapeutic drugs and improvements in current antifungal treatment regimens.

Fosmanogepix

Fosmanogepix (FMGX) is a first-in-class small-molecule drug targeting the Gwt1 enzyme in the glycosylphosphatidylinositol (GPI) anchor biosynthesis pathway that has demonstrated broad-spectrum activity against invasive yeast and mold infections. FMGX is currently under development for treatment of invasive candidiasis, aspergillosis, scedosporiosis, fusariosis, mucormycosis, cryptococcosis, and coccidioidomycosis.[43,51,52] This new drug offers several advantages that make it a particularly exciting new treatment for CNS fungal infections. It has wide tissue distribution including penetration of the CNS, unlike the echinocandin class, and its new mechanism of

action makes it a promising therapy against drug-resistant fungal strains. It also boasts a favorable drug-drug interaction profile, good drug tolerability, and high oral availability, allowing for the development of both intravenous (IV) and oral formulations.[53,54]

Significant progress has been made in clinical trials of FMGX with successful completion of two phase II studies for the treatment of candidemia and invasive candidiasis with treatment success rates over 80%, as defined by clearance of candidemia (NCT03604705, NCT04148287). A phase III trial for the potential treatment of candidemia and/or invasive candidiasis is currently underway and is scheduled for completion in 2026 (NCT05421858). In this two-arm study, the safety and efficacy of FMGX will be compared to standard-of-care therapy (caspofungin plus fluconazole). FMGX has also been trialed as a potential treatment of invasive aspergillus or rare mold infections in a phase II study (NCT04240886), which was recently terminated early to prioritize a randomized comparative phase III trial for the same indication, though phase III trial plans have not yet been posted on ClinicalTrials.gov. In addition to clinical trials, some patients have been able to access FMGX through Pfizer's expanded access program, with demonstrated success in several cases of drug-resistant or invasive *Fusarium* infections.[55,56]

Olorofim

Another drug under development, olorofim (formerly F901318), is the first of the novel orotomide drug class to reach clinical trials. Inhibiting the fungal enzyme dihydroorotate dehydrogenase, olorofim has selective activity against molds and dimorphic fungi.[43] Early models have also shown some penetration to the CNS, including high in vitro and in vivo activity against CNS *Coccidioides*, and the drug has received breakthrough therapy designation from the FDA for treatment of CNS coccidioidomycosis.[43,51,57,58] It has now completed enrollment in a single-arm phase IIb trial for treatment of IFIs, including *Aspergillus* spp. In addition, other resistant fungi in patients without other treatment options (NCT03583164). Though results are not yet published from this trial, parent company F2G reported preliminary results of the first 100 patients, showing favorable drug tolerability and a 44% treatment response rate at day 42.[59] With these promising results, F2G submitted a New Drug Application to the FDA for treatment of drug-resistant IFIs, but the FDA recently denied approval, requesting additional data.[60] A multicenter phase III trial for treatment of invasive aspergillosis comparing olorofim with AmBisome (liposomal amphotericin B) followed by standard-of-care is also actively ongoing (NCT05101187), with estimated completion in 2025. F2G also has a managed access program (MAP) for the compassionate use of olorofim, though at the time of this publication, it is temporarily closed to new patients due to problems matching supply to demand.[61]

New formulations of amphotericin B

In addition to these new drug classes, advances have been made in the formulation of amphotericin B to reduce its toxicity and enhance the medication delivery process. In the AmBisome Therapy Induction Optimization (AMBITION) trial in HIV-positive patients with cryptococcal meningitis, single high-dose liposomal amphotericin B (AmBisome) combined with flucytosine (5-FC) and fluconazole was found to be noninferior compared to the current WHO recommended regimen (7 days of amphotericin B deoxycholate with flucytosine). The ability to administer higher doses with fewer adverse effects may lead to reductions in hospital stay length, a particularly advantageous feature in resource-limited settings.[62,63] A new nanoparticle-based encochleated form of amphotericin B, MAT2203, similarly offers potentially reduced toxicity and lower costs compared to the traditional intravenous formulation. Developed by Martinas Biopharma, MAT2203 is the first oral formulation to reach clinical development.[51,57,64] The phase I/II EnACT trial evaluating the treatment of cryptococcal meningitis in patients infected with HIV was completed in February 2023 (NCT04031833), and preliminary analyses showed a >90% early survival rate in patients receiving MAT2203 and 5-FC, which was noninferior, if not improved, compared to the patient group receiving IV-administered amphotericin B and 5-FC.[65] A phase III trial (EnACT3) is currently being planned for the same indication (NCT05541107).

Advances in treatment of prion diseases

Prion diseases, also known as transmissible spongiform encephalopathies, are neurodegenerative diseases that progress rapidly, are universally

fatal, and are currently incurable.[66] Current standard-of-care consists of supportive measures due to limited efficacy of disease-modifying treatments. Despite several repurposed drugs such as quinacrine, pentose polysulfate, doxycycline, and flupirtine advancing to clinical trials, none have shown significant improvement in human survival rates.[67–70] New anti-prion mechanisms being investigated target the reduction or neutralization of cellular prion protein (PrP^{C}) and its pathogenic isoform, scrapie prion protein (PrP^{Sc}).[66,71]

PRN100

A notable advancement in the field is PRN100, a newly developed fully humanized PrP^{C} monoclonal antibody. Created by the Medical Research Council (MRC) Prion Unit at University College London (UCL), PRN100 was administered as compassionate use treatment to six patients with probable sporadic or iatrogenic Creutzfeldt-Jakob disease (CJD) at University College London Hospital in 2018 to 2019.[72] Intravenously administered through a cautious dose-escalation approach, treatment was well-tolerated and reached target CSF drug concentrations. PRN100 did not significantly impact survival or disease progression when compared to historical data of untreated patients; however, the MRC Prion Disease Rating Scale score, a functional status scale designed to measure disease severity, appeared to stabilize in three patients once CSF drug concentrations reached target levels. In addition, autopsy results of two patients showed altered patterns of PrP labeling in the brain, suggesting potential disease-modifying effects in target tissue.[72,73] These results show promise, and it will be of great interest to observe whether a larger clinical trial, along with earlier administration of the antibody during the disease process, might yield more favorable outcomes.

Anle138b

Another novel therapeutic candidate is anle138b, an oligomer modulator that inhibits PrP^{Sc} formation. Preclinical studies have demonstrated anti-prion activity with excellent penetration of the blood-brain barrier (BBB) and oral bioavailability, and it has been found to improve survival outcomes in late prion infections in murine models.[74–76] While not yet the subject of specific clinical trials for prion diseases, anle138b has been investigated as a therapeutic agent for Parkinson's disease due to its ability to inhibit alpha-synuclein aggregation. Initial evaluations in a phase Ia trial involving healthy volunteers demonstrated a favorable safety profile (NCT04208152), and a subsequent phase Ib study in patients with mild and moderate Parkinson's disease has recently been completed (NCT04685265). While results from this study are pending, confirmation of anle138b's safety and efficacy could prompt a broader exploration and application of this therapeutic to patients with prion diseases.

Immunomodulatory therapies

Immunomodulatory therapies are increasingly being used in the treatment of neuroinfectious diseases in several somewhat distinct contexts. The first is the use of immunomodulation in the direct treatment of infections, via increased immune system activation against the infectious pathogen. The second is to limit the deleterious effects of the host inflammatory response against the infection. Within this second context is the specific role of immunomodulation in the prevention and treatment of immune reconstitution inflammatory syndrome (IRIS).

Steroids for bacterial meningitis

Corticosteroids have been investigated in bacterial, tuberculous, and cryptococcal meningitis as well as neurocysticercosis and viral encephalitis. The most recent robust data on the use of corticosteroids in CABM was a 2015 meta-analysis of 25 RCTs which found that corticosteroids had no impact on overall mortality but were associated with the following: (1) decreased mortality in *S. pneumoniae* meningitis in high-income countries, (2) decreased morbidity (hearing loss and neurologic sequelae) for adults and children with any pathogens in high-income countries, and (3) decreased hearing loss for children with *H. influenzae* meningitis in any income country.[77] While earlier studies had shown that the benefit of steroids was dependent on timing (benefit only seen if steroids were given before or with antimicrobials) this study did not find variability with timing.

Following this 2015 meta-analysis, there have been several additional studies in high-income countries. The 2017 MONALISA prospective study of 212 patients with neurolisteriosis in France demonstrated increased mortality in

patients receiving dexamethasone.[78] While not a RCT, baseline characteristics between the two groups were relatively similar, pointing toward a true effect of dexamethasone as opposed to a biased treatment group. A 2016 prospective study in the Netherlands of 1412 patients showed mortality benefit of dexamethasone in both pneumococcal and non-pneumococcal species, though notably neurolisteriosis only made up a minority of the non-pneumococcal group.[79] Two studies out of Taiwan in 2019 and 2021 showed increased mortality with dexamethasone; however, neither was randomized and the dexamethasone groups were sicker at baseline, so it is difficult to draw conclusions about the impact of dexamethasone.[80,81] Two recent reviews recommend a 4-day course of dexamethasone for all adults in high-income regions with bacterial meningitis excluding those with confirmed neurolisteriosis.[82,83]

In low-income regions, data is limited to small series in specific countries. A 2022 prospective study in Afghanistan on 393 children with CABM found that dexamethasone was associated with a significant mortality benefit.[84] A 2017 prospective study in Ethiopia showed survival benefit in the subgroup of patients not receiving early antimicrobials.[85]

In summary, recent data mostly supports the findings in the 2015 meta-analysis that steroids provide a morbidity and mortality benefit in bacterial meningitis in high-income regions, though has added to our understanding that this benefit likely extends to non-pneumococcal species and that a notable exception is listeriosis where steroids are likely harmful. Some small studies also suggest a potential benefit in low-income regions, but these findings warrant confirmation in larger multinational studies.

Steroids in other neuroinfectious diseases

Corticosteroids have long been used in the treatment of TBM and are part of the official Infectious Disease Society of America (IDSA) guidelines as a strong recommendation but with only moderate certainty in the evidence.[86] A 2022 meta-analysis of 11 newer studies, most of which were RCTs, confirmed that dexamethasone in combination with antitubercular drugs was associated with improved effective rates and decreased adverse effects when compared to antitubercular drugs alone, adding to the evidence in support of dexamethasone use.[87]

Given the data supporting the use of corticosteroids in several forms of infectious meningitis, the CryptoDex trial was conducted to determine if corticosteroids were beneficial in HIV-associated cryptococcal meningitis.[88] Unlike bacterial and TBM, this trial was stopped early after interim analysis demonstrated a statistically significant increase in disability and adverse events in the dexamethasone arm compared to the control group. The mortality rate was also higher in the dexamethasone group (47% vs 41%) but this did not reach statistical significance. Based on this RCT, the WHO now recommends against the use of corticosteroids for cryptococcal meningitis as a strong recommendation with high certainty evidence.[89]

The most recent IDSA guidelines for viral encephalitis from 2008 recommend against the use of corticosteroids for most infectious encephalitis etiologies, including herpes encephalitis, citing insufficient data.[90] Two recent trials have attempted to provide data on the role of dexamethasone as an adjunct treatment in herpes encephalitis. The GACHE trial in the early 2000s was unfortunately closed due to slow recruitment.[91] The DexEnceph trial conducted in the UK recruited its final patient as of 2022, and study results are forthcoming.[92]

In the 2008 IDSA guidelines, the two pathogens where steroids could be considered were varicella-zoster and Epstein-Barr encephalitis based on limited, anecdotal reports.[90] Outside isolated case reports, no recent robust data exists to support or oppose these recommendations.

Steroids are routinely used in neurocysticercosis. The 2017 IDSA guidelines recommend the use of adjunctive corticosteroids for patients with viable parenchymal cysts and subarachnoid neurocysticercosis prior to receiving antiparasitic agents.[93] This is based on several case series and one prospective study in 2004 showing decreased rate of seizures in patients on steroids plus antiparasitics compared to either alone.[94]

Interleukins

Interleukins are signaling molecules (cytokines) that play a critical role in T-cell proliferation and function. They are particularly important in regulating the immune response to infectious diseases, facilitating activation and recruitment of lymphocytes (particularly T-cells) to aid in pathogen clearance.[95]

Interleukins may exert effects within the CNS both by transport of peripheral interleukins through the BBB or via direct cytokine production from resident microglia in the CNS.[96] Therefore, interleukins, specifically IL2, IL7, and IL15, have been proposed as a potential therapeutic to boost T-cell function and promote viral clearance.

PML due to JCV occurs almost exclusively in the setting of cellular immunodeficiency and thus interleukins have been explored as a potential therapeutic strategy for the treatment of PML. Numerous case reports in patients with PML have shown success with using IL7, reporting viral clearance from the CSF and clinical and/or radiographic stabilization with some rare cases even showing improvement.[97–107] A 2022 retrospective case series of 64 patients with PML receiving IL7 had mixed results.[108] For patients with HIV in this study, survival was similar to what has been reported with antiretroviral therapy (ART) alone (which patients in this study also received). This is not entirely surprising as ART itself leads to cellular immune reconstitution (i.e., improved CD4+ T-cell count). The non-HIV patients in this study had several mechanisms of cellular immunodeficiency (primary immunodeficiency syndrome, hematologic malignancy, and iatrogenic immunosuppression due to organ transplantation or autoimmune conditions). In the first two mechanisms, there are no feasible therapeutic options to allow immune reconstitution. For the iatrogenic immunosuppression patients, many of these patients require some degree of ongoing immunosuppression, again limiting full immune reconstitution. In these patient populations, survival was much better than reported outcomes in the literature. While not a controlled comparison study, this does provide encouraging evidence of potential benefits for the non-HIV-associated PML patient population. There are several case reports using IL2 that showed improvement in CSF viral load and clinical improvement (some with complete resolution of symptoms).[109] Finally, there is a single case report using an IL15 superagonist in a patient who developed PML after allogenic stem cell transplant, which resulted in clearance of JCV from the CSF as well as clinical and radiographic improvement.[110]

Immune checkpoint inhibitors

Along the same line as interleukins, immune checkpoint inhibitors (ICIs) have also been proposed to aid in JCV control. In a recent multicenter survey involving 79 patients with PML treated with ICIs, the mortality rate at 1 year was 48.1%.[111] Of note, this patient population included patients with HIV and patients without HIV, and mortality rates were similar regardless of the underlying condition. In HIV patients, where immune reconstitution can be achieved through the use of ART, mortality rates in the literature range from 25% to 50%.[112,113] However, in the non-HIV population, where immune reconstitution is impossible or highly unlikely, mortality rates remain as high as 85%–90%.[111] Thus, similar to interleukins, ICIs seem to offer possible mortality benefits in patients without HIV who are otherwise unable to achieve immune reconstitution.

Immune-related adverse events (irAEs) are a major concern with ICIs, both off-target irAEs as well as a potentially increased risk for severe PML-associated IRIS. In this same series of 79 patients mentioned above, 30% had irAEs, which were mostly dermatologic and gastrointestinal in nature. Of those, 30% had to discontinue ICI therapy, but it does not appear any of these irAEs were fatal. PML–IRIS occurred in 19% of patients, with the highest rates in the HIV population (41.7%) and patients with chronic inflammatory conditions (37.5%). PML–IRIS was fatal in 9% of patients. There is insufficient literature to know the rates of IRIS among patients with chronic inflammatory conditions not treated with ICIs. However, in the HIV population, in a prior study of 59 patients with HIV treated with ART alone, the rate of PML–IRIS was 30.5%, suggesting an increased rate when ICI therapy is added.[114]

In summary, while there is some convincing evidence that ICI may improve outcomes in PML, this is highly dependent on the underlying etiology of the IRIS. In the HIV population where immune reconstitution can be achieved through ART, there does not seem to be a benefit of adding ICI, and there is likely an increased risk of IRIS. For patients with chronic inflammatory conditions, there may be an increased risk of PML–IRIS, though the benefit remains unknown as there are no controlled studies or prior literature for comparison. While not discussed in the review above, patients with life-sustaining organ transplants similarly are likely at prohibitively high risk of immunotherapy-mediated organ rejection to consider ICI therapy. Thus, if

considering this therapy, patients must be carefully selected.

Viral-specific T-cells

Viral-specific T-cells (VSTs) are another proposed mechanism of immune augmentation to treat neuroinfectious diseases. Particularly given concerns about off-target irAEs with less specific treatments like ICIs, VSTs are appealing in their narrow action. Three small case series involving a total of 14 patients (1 HIV positive and 13 HIV negative) treated with VST have been published.[115–117] In the largest series of nine patients, six achieved PML control, while three died due to PML progression. In the series of three patients, two had clinical and radiographic improvement (including the 1 HIV positive patient), and one patient remained stably disabled and died while in hospice. Finally, in the series of two patients, both had clinical and radiographic improvement. Given the patient populations in these series were nearly all HIV-negative patients, the mortality rates are far better than those reported in the literature for similar populations. Importantly, one patient in this series was a lung transplant patient who would not have been a candidate for ICI, and she achieved control of her PML without any evidence of graft rejection.

Intravenous immunoglobulins:

IVIG has been trialed in the treatment of viral encephalitis, particularly in immunocompromized populations. Although generally considered safe with minimal adverse effects, assessing its efficacy has been challenging. Existing evidence primarily consists of case reports or series, and the inherent biases in patient selection as well as heterogeneity of cases make direct comparisons difficult.[118] Despite the completion of the IgNiTE trial (NCT02308982), a phase III RCT evaluating the effects of early treatment of IVIG in pediatric patients with all-cause encephalitis, no results are available, and there remains a need for higher quality evidence for clinical decision making.

While the decision to initiate IVIG treatment is case-dependent, the literature provides evidence of more consistent application of IVIG in patients with hypogammaglobulinemia due to immunosuppression. Notably, several cases of enteroviral meningoencephalitis in hypogammaglobulinemic patients have demonstrated symptomatic improvement and viral clearance following IVIG treatment.[8,15,119–121] A study further supports potential benefits by showing a dose-dependent effect on viral clearance.[122] However, the timing and threshold of immunosuppression necessitating IVIG initiation remain unclear. Moreover, a review of patients diagnosed with arboviral disease while on rituximab treatment found no significant difference in outcomes for those who received IVIG, raising uncertainties about the extension of benefits to immunosuppressed patients infected with other pathogens.[123]

Other immunomodulatory agents

Complement inhibitors, particularly drugs targeting C5a or C5aR, have been proposed as a possible method of reducing brain inflammation in bacterial meningitis. While adjunctive treatment with C5 antibodies has led to improved outcomes in a murine model of pneumococcal meningitis, the use of complement inhibitors for treatment of CNS infections has not yet been assessed in clinical trials.[124]

Tumor necrosis factor alpha (TNF-α) inhibitor use in CNS infections has also been explored. Thalidomide and its synthetic analogs have demonstrated improved survival and morbidity outcomes in rabbit models of TBM.[125,126] Though an earlier RCT of thalidomide use in children with TBM was terminated early due to adverse events, subsequent case reports indicate that administering thalidomide at lower doses may be associated with better drug tolerance and improved outcomes for certain clinical indications such as necrotizing tuberculous abscesses.[125,127,128] In addition, although TNF-α monoclonal antibodies are typically limited by poor CNS penetration, they may play a role in conditions where inflammation increases permeability of the BBB. Etanercept has been administered in cases of complicated neurocysticercosis with associated clinical improvement and a favorable safety profile.[129]

Teriflunomide, a dihydro-orotate dehydrogenase inhibitor primarily used in multiple sclerosis, has undergone testing in cell models for a variety of viral diseases, including JCV, HIV, and human T-lymphotropic virus 1 (HTLV-1).[130–133] It works by inhibiting de novo pyrimidine synthesis leading to a reduction in lymphocytic proliferation,

therefore moderating inflammatory processes and potentially inhibiting replication of viruses dependent on cell proliferation. Currently, there is an ongoing phase I/II study evaluating the effects of teriflunomide in adults with HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) (NCT04799288).

Therapeutic advances in CNS–IRIS

IRIS refers to a dysregulated inflammatory syndrome following reconstitution of the immune system in patients who were previously immunosuppressed. This is classically seen in HIV-infected individuals after initiation of ART and may manifest as either the "unmasking" of an occult infection or paradoxical worsening of a previously known infection. Examples of common pathogens associated with CNS–IRIS include, but are not limited to, tuberculosis, cryptococcus, and JC virus. Corticosteroids remain the mainstay of treatment of severe IRIS involving the CNS, especially when there are no antimicrobial agents available for treatment of the underlying infection or antimicrobial treatments fail to adequately control the inflammatory response.[134] However, steroids may also hinder pathogen-specific T-cell responses and compromise pathogen clearance. Therefore, there has been increasing interest in immunomodulatory strategies that reduce excessive neuroinflammation while preserving pathogen-specific T-cell responses. Maraviroc, a CC chemokine receptor 5 (CCR5) antagonist, was proposed to have indirect immunomodulatory properties that could be effective in managing PML–IRIS.[135] However, despite mechanistic plausibility, a recent multicenter retrospective cohort study involving 27 patients with PML–IRIS did not demonstrate the clear efficacy of this drug.[136] Similarly, TNF-α inhibitors have also been proposed as therapeutic strategy in patients with CNS–IRIS in the setting of cryptococcal meningitis or tuberculosis, with several case reports and case series suggesting favorable response, usually in conjunction with steroids.[137–139] However, there are not yet any controlled trials to demonstrate efficacy of TNF-α inhibitors for the management of CNS–IRIS.

Conclusion

There have been several important and clinically relevant advances in the treatment of neurological infections in the past two decades. This includes the development of several new direct antimicrobial agents and the repurposing of existing agents. In addition, immunomodulatory strategies targeting the host immune response are increasingly being utilized for the treatment of neurological infections. These advances are particularly relevant to immunocompromized patients with impaired immune responses to pathogens. Fortunately, many of these agents have already been approved for commercial use. However, when specific agents are not commercially available, physicians should be aware that they may be able to secure such agents through an IND application for emergency compassionate use (Figure 1). While many therapeutic advances have been achieved in the past several years, there remains a pressing need for the development of additional therapeutic agents in the treatment of neurological infections. With the increasing use of immunosuppressive medications for the treatment of chronic autoimmune conditions and organ transplantation, the number of patients at risk for serious neurological infections is expected to rise. Therefore, a better understanding of pathogen and host immune responses will be key for developing new agents and therapeutic strategies in this patient population. The COVID-19 pandemic has demonstrated that the rapid development of antimicrobial treatments and vaccines is possible in times of urgency.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Rumyar Ardakani: Conceptualization, Writing and reviewing; Writing – original draft.

Lucy Jia: Conceptualization, Writing and reviewing; Writing – original draft.

Elizabeth Matthews: Conceptualization, Writing and reviewing; Writing – original draft.

Kiran T. Thakur: Conceptualization; Writing and reviewing; Writing – original draft; Writing – review & editing.

Acknowledgements

None.

Funding
The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Kiran T Thakur (NIH/NINDS K23 1K23NS105935-01).

Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
Data supporting this paper are included within the article and/or supporting materials.

ORCID iD
Kiran T. Thakur https://orcid.org/0000-0003-0050-0323

References

1. Pruitt AA. Central nervous system infections in immunocompromised patients. *Curr Neurol Neurosci Rep* 2021; 21: 37.
2. Desmond RA, Accortt NA, Talley L, et al. Enteroviral meningitis: natural history and outcome of pleconaril therapy. *Antimicrob Agents Chemother* 2006; 50: 2409–2414.
3. Romero JR. Pleconaril: a novel antipicornaviral drug. *Expert Opin Invest Drugs* 2001; 10: 369–379.
4. Rotbart HA and Webster AD. Treatment of potentially life-threatening enterovirus infections with pleconaril. *Clin Infect Dis* 2001; 32: 228–235.
5. Abzug MJ, Cloud G, Bradley J, et al. Double blind placebo-controlled trial of pleconaril in infants with enterovirus meningitis. *Pediatric Infect Dis J* 2003; 22: 335–340.
6. Radanović I, Rkman D, Zekan P, et al. Chronic meningoencephalitis caused by Echo virus 6 in a patient with common variable immunodeficiency: successful treatment with pleconaril. *Wien Klin Wochenschr* 2018; 130: 70–72.
7. Collett MS, Hincks JR, Benschop K, et al. Antiviral activity of pocapavir in a randomized, blinded, placebo-controlled human oral poliovirus vaccine challenge model. *J Infect Dis* 2017; 215(3): 335–343.
8. Epstein S, Thakkar R, Fong KT, et al. Compassionate-use pocapavir and immunoglobulin therapy for treatment of rituximab-associated enterovirus meningoencephalitis. *J Neurovirol* 2022; 28: 329–334.
9. Grammatikos A, Bright P, Pearson J, et al. Chronic enteroviral meningoencephalitis in a patient with good's syndrome treated with pocapavir. *J Clin Immunol* 2022; 42: 1611–1613.
10. Copelyn J, Hincks JR, Wilmshurst JM, et al. Clearance of Immunodeficiency-associated vaccine-derived poliovirus infection with pocapavir. *Pediatric Infect Dis J* 2020; 39: 435–437.
11. Álamo-Junquera D, Politi J, Simón P, et al. Coordinated response to imported vaccine-derived poliovirus infection, Barcelona, Spain, 2019–2020. *Emerg Infect Dis* 2021; 27: 1513–1516.
12. Tyler KL. Rationale for the evaluation of fluoxetine in the treatment of enterovirus D68-associated acute flaccid myelitis. *JAMA Neurol* 2015; 72: 493.
13. Wang S-H, Wang K, Zhao K, et al. The structure, function, and mechanisms of action of enterovirus non-structural protein 2C. *Front Microbiol* 2020; 11: 615965.
14. Messacar K, Sillau S, Hopkins SE, et al. Safety, tolerability, and efficacy of fluoxetine as an antiviral for acute flaccid myelitis. *Neurology* 2019; 92: e2118–e2126.
15. Sham L, Bitnun A, Branson H, et al. Treatment of rituximab-associated chronic CNS enterovirus using IVIg and fluoxetine. *Neurology* 2019; 92: 916–918.
16. Gofshteyn J, Cárdenas AM and Bearden D. Treatment of chronic enterovirus encephalitis with fluoxetine in a patient with X-linked agammaglobulinemia. *Pediatric Neurol* 2016; 64: 94–98.
17. Vermeersch G, Laenen L, Lens G, et al. Antiviral treatment with fluoxetine for rituximab-associated chronic echovirus 13 meningoencephalitis and myofasciitis. *Euro J Neurology* 2022; 29: 3117–3123.
18. Shiraki K, Yasumoto S, Toyama N, et al. Amenamevir, a helicase-primase inhibitor, for the optimal treatment of herpes zoster. *Viruses* 2021; 13: 1547.
19. Ohtsu Y, Susaki Y and Noguchi K. Absorption, distribution, metabolism, and excretion of the novel helicase-primase inhibitor, amenamevir (ASP2151), in rodents. *Eur J Drug Metab Pharmacokinet* 2018; 43: 693–706.
20. Itoh K, Mitsuke Y, Wakahara M, et al. Aseptic meningitis after amenamevir treatment for herpes zoster in the first branch of the trigeminal nerve. *Intern Med* 2022; 61: 2809–2811.

21. Omiya M, Nishiguchi S, Moriya H, et al. Aseptic meningitis after amenamevir treatment for herpes zoster ophthalmicus with oculomotor nerve palsy in a patient taking immunosuppressant. *J Infect Chemotherapy* 2023; 29: 519–522.
22. Taniguchi Y, Kano Y, Kitamura T, et al. Varicella-zoster meningoencephalitis and vasculitis after treatment with amenamevir to herpes zoster in the trigeminal nerve area. *Rinsho Shinkeigaku* 2021; 61: 239–242.
23. Elphick GF, Querbes W, Jordan JA, et al. The human polyomavirus, JCV, uses serotonin receptors to infect cells. *Science* 2004; 306: 1380–1383.
24. Paulzen M, Gründer G, Tauber SC, et al. Distribution pattern of mirtazapine and normirtazapine in blood and CSF. *Psychopharmacology (Berl)* 2015; 232: 807–813.
25. Cettomai D and McArthur JC. Mirtazapine use in human immunodeficiency virus–infected patients with progressive multifocal leukoencephalopathy. *Arch Neurol*. Epub ahead of print 1 February 2009. DOI: 10.1001/archneurol.2008.557.
26. Alwehaibi AI, AlJaber MI and Nahrir S. Favorable response to mirtazapine in john cunningham virus-related gray matter lesion in a patient with human immunodeficiency virus. *Cureus*. Epub ahead of print 14 March 2019. DOI: 10.7759/cureus.4255.
27. Hamaguchi M, Suzuki K, Fujita H, et al. Successful treatment of non-HIV progressive multifocal leukoencephalopathy: case report and literature review. *J Neurol* 2020; 267: 731–738.
28. Klugman KP and Dagan R. Randomized comparison of meropenem with cefotaxime for treatment of bacterial meningitis. meropenem Meningitis Study Group. *Antimicrob Agents Chemother* 1995; 39: 1140–1146.
29. Sipahi OR, Turhan T, Pullukcu H, et al. Moxifloxacin versus ampicillin + gentamicin in the therapy of experimental Listeria monocytogenes meningitis. *J Antimicrob Chemother* 2008; 61: 670–673.
30. Ostergaard C, Sørensen TK, Knudsen JD, et al. Evaluation of moxifloxacin, a new 8-methoxyquinolone, for treatment of meningitis caused by a penicillin-resistant pneumococcus in rabbits. *Antimicrob Agents Chemother* 1998; 42: 1706–1712.
31. Lewin JJ, Cook AM, Gonzales C, et al. Current practices of intraventricular antibiotic therapy in the treatment of meningitis and ventriculitis: results from a multicenter retrospective cohort study. *Neurocrit Care* 2019; 30: 609–616.
32. Ruslami R, Ganiem AR, Dian S, et al. Intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis: an open-label, randomised controlled phase 2 trial. *Lancet Infect Dis* 2013; 13: 27–35.
33. Svensson EM, Dian S, Te Brake L, et al. Model-based meta-analysis of rifampicin exposure and mortality in Indonesian tuberculous meningitis trials. *Clin Infect Dis* 2020; 71: 1817–1823.
34. Cresswell FV, Ssebambulidde K, Grint D, et al. High dose oral and intravenous rifampicin for improved survival from adult tuberculous meningitis: a phase II open-label randomised controlled trial (the RifT study). *Wellcome Open Res* 2018; 3: 83.
35. Thomason M. SURE: short intensive treatment for children with tuberculous meningitis.
36. Khoshnood S, Goudarzi M, Taki E, et al. Bedaquiline: current status and future perspectives. *J Glob Antimicrob Resist* 2021; 25: 48–59.
37. Traoré AN, Rikhotso MC, Banda NT, et al. Effectiveness of the novel Anti-TB bedaquiline against drug-resistant TB in Africa: a systematic review of the literature. *Pathogens* 2022; 11: 636.
38. Upton CM, Steele CI, Maartens G, et al. Pharmacokinetics of bedaquiline in cerebrospinal fluid (CSF) in patients with pulmonary tuberculosis (TB). *J Antimicrob Chemother* 2022; 77: 1720–1724.
39. Tucker EW, Pieterse L, Zimmerman MD, et al. Delamanid central nervous system pharmacokinetics in tuberculous meningitis in rabbits and humans. *Antimicrob Agents Chemother* 2019; 63: e00913-19.
40. Shibata M, Shimokawa Y, Sasahara K, et al. Absorption, distribution and excretion of the anti-tuberculosis drug delamanid in rats: extensive tissue distribution suggests potential therapeutic value for extrapulmonary tuberculosis. *Biopharm Drug Dispos* 2017; 38: 301–312.
41. Bratkowska D, Shobo A, Singh S, et al. Determination of the antitubercular drug PA-824 in rat plasma, lung and brain tissues by liquid chromatography tandem mass spectrometry: application to a pharmacokinetic study. *J Chromatogr B Analyt Technol Biomed Life Sci* 2015; 988: 187–194.
42. Shobo A, Bratkowska D, Baijnath S, et al. Tissue distribution of pretomanid in rat brain via mass spectrometry imaging. *Xenobiotica* 2016; 46: 247–252.

43. Mota Fernandes C, Dasilva D, Haranahalli K, et al. The future of antifungal drug therapy: novel compounds and targets. *Antimicrob Agents Chemother* 2021; 65: e01719-20.

44. Jia DT and Thakur K. Fungal infections of the central nervous system. *Semin Neurol* 2019; 39: 343–357.

45. Góralska K, Blaszkowska J and Dzikowiec M. Neuroinfections caused by fungi. *Infection* 2018; 46: 443–459.

46. Schwartz S, Kontoyiannis DP, Harrison T, et al. Advances in the diagnosis and treatment of fungal infections of the CNS. *Lancet Neurol* 2018; 17: 362–372.

47. Wirth F and Ishida K. Antifungal drugs: an updated review of central nervous system pharmacokinetics. *Mycoses* 2020; 63: 1047–1059.

48. Li W, Yun Z, Ji C, et al. Discovery of novel sertraline derivatives as potent anti-*Cryptococcus* agents. *J Med Chem* 2022; 65: 6541–6554.

49. Rhein J, Huppler Hullsiek K, Tugume L, et al. Adjunctive sertraline for HIV-associated cryptococcal meningitis: a randomised, placebo-controlled, double-blind phase 3 trial. *Lancet Infect Dis* 2019; 19: 843–851.

50. Ngan NTT, Thanh Hoang, Le N, Vi Vi NN, et al. An open label randomized controlled trial of tamoxifen combined with amphotericin B and fluconazole for cryptococcal meningitis. *eLife* 2021; 10: e68929.

51. Rauseo AM, Coler-Reilly A, Larson L, et al. Hope on the horizon: novel fungal treatments in development. *Open Forum Infect Dis* 2020; 7: ofaa016.

52. Gintjee TJ, Donnelley MA and Thompson GR. Aspiring antifungals: review of current antifungal pipeline developments. *J Fungi* 2020; 6: 28.

53. Hodges MR, Ople E, Wedel P, et al. Safety and pharmacokinetics of intravenous and oral fosmanogepix, a first-in-class antifungal agent, in healthy volunteers. *Antimicrob Agents Chemother* 2023; 67: e01623-22.

54. Shaw KJ and Ibrahim AS. Fosmanogepix: a review of the first-in-class broad spectrum agent for the treatment of invasive fungal infections. *J Fungi* 2020; 6: 239.

55. Winston DJ, Young PA, Schlamm HT, et al. Fosmanogepix therapy of disseminated *fusarium* infection. *Clin Infect Dis* 2023; 77: 848–850.

56. Goggin KP, Londeree J, Freeman AF, et al. Successful use of fosmanogepix for treatment of rare highly resistant cutaneous fusariosis in a pediatric patient with STAT3 hyper-immunoglobulin e syndrome and end-stage kidney disease. *Open Forum Infect Dis* 2023; 10: ofad285.

57. Houšť J, Spížek J and Havlíček V. Antifungal drugs. *Metabolites* 2020; 10: 106.

58. Wiederhold NP, Najvar LK, Jaramillo R, et al. The orotomide olorofim is efficacious in an experimental model of central nervous system coccidioidomycosis. *Antimicrob Agents Chemother* 2018; 62: e00999-18.

59. F2G Announces Data from Phase 2b Study at ID Week 2022 showing positive therapeutic response in patients with invasive fungal infections treated with olorofim, https://www.globenewswire.com/news-release/2022/10/21/2539410/0/en/F2G-Announces-Data-from-Phase-2b-Study-at-ID-Week-2022-Showing-Positive-Therapeutic-Response-in-Patients-with-Invasive-Fungal-Infections-Treated-with-Olorofim.html (2023, accessed 14 September 2023).

60. F2G receives complete response letter from FDA for new drug application for Olorofim for the treatment of invasive fungal infections; plans resubmission with additional data and analyses, https://www.globenewswire.com/news-release/2023/06/19/2690251/0/en/F2G-Receives-Complete-Response-Letter-from-FDA-for-New-Drug-Application-for-Olorofim-for-The-Treatment-of-Invasive-Fungal-Infections-Plans-Resubmission-With-Additional-Data-and-Ana.html (2023, accessed 14 September 2023).

61. Access to Olorofim, including Expanded Access (Compassionate Use), https://www.f2g.com/access_olorofim (2023, accessed 24 September 2023).

62. Harrison TS, Lawrence DS, Mwandumba HC, et al. How Applicable is the single-dose AMBITION regimen for human immunodeficiency virus–associated cryptococcal meningitis to high-income settings? *Clin Infect Dis* 2023; 76: 944–949.

63. Jarvis JN, Lawrence DS, Meya DB, et al. Single-dose liposomal amphotericin B treatment for cryptococcal meningitis. *N Engl J Med* 2022; 386: 1109–1120.

64. Aigner M and Lass-Flörl C. Encochleated Amphotericin B: is the oral availability of amphotericin B finally reached? *J Fungi* 2020; 6: 66.

65. MAT2203: Enabling a safe delivery of a top antifungal treatment, https://www.matina

sbiopharma.com/lnc-technology/mat2203 (2023, accessed 24 September 2023).

66. Zafar S, Noor A and Zerr I. Therapies for prion diseases. *Handb Clin Neurol* 2019; 165: 47–58.
67. Vallabh SM, Minikel EV, Schreiber SL, et al. Towards a treatment for genetic prion disease: trials and biomarkers. *Lancet Neurol* 2020; 19: 361–368.
68. Geschwind MD, Kuo AL, Wong KS, et al. Quinacrine treatment trial for sporadic Creutzfeldt-Jakob disease. *Neurology* 2013; 81: 2015–2023.
69. Haïk S, Marcon G, Mallet A, et al. Doxycycline in Creutzfeldt-Jakob disease: a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2014; 13: 150–158.
70. Otto M, Cepek L, Ratzka P, et al. Efficacy of flupirtine on cognitive function in patients with CJD: a double-blind study. *Neurology* 2004; 62: 714–718.
71. Zhu C and Aguzzi A. Prion protein and prion disease at a glance. *J Cell Sci* 2021; 134: jcs245605.
72. Mead S, Khalili-Shirazi A, Potter C, et al. Prion protein monoclonal antibody (PRN100) therapy for Creutzfeldt–Jakob disease: evaluation of a first-in-human treatment programme. *Lancet Neurol* 2022; 21: 342–354.
73. Zerr I. Investigating new treatments for Creutzfeldt–Jakob disease. *Lancet Neurol* 2022; 21: 299–300.
74. Shim KH, Sharma N and An SSA. Prion therapeutics: lessons from the past. *Prion* 2022; 16: 265–294.
75. Levin J, Sing N, Melbourne S, et al. Safety, tolerability and pharmacokinetics of the oligomer modulator anle138b with exposure levels sufficient for therapeutic efficacy in a murine Parkinson model: a randomised, double-blind, placebo-controlled phase 1a trial. *EBioMedicine* 2022; 80: 104021.
76. Wagner J, Ryazanov S, Leonov A, et al. Anle138b: a novel oligomer modulator for disease-modifying therapy of neurodegenerative diseases such as prion and Parkinson's disease. *Acta Neuropathol* 2013; 125: 795–813.
77. Brouwer MC, McIntyre P, Prasad K, et al. Corticosteroids for acute bacterial meningitis. *Cochrane Database Syst Rev* 2015; 2015: CD004405.
78. Charlier C, Perrodeau É, Leclercq A, et al. Clinical features and prognostic factors of listeriosis: the MONALISA national prospective cohort study. *Lancet Infect Dis* 2017; 17: 510–519.
79. Bijlsma MW, Brouwer MC, Kasanmoentalib ES, et al. Community-acquired bacterial meningitis in adults in the Netherlands, 2006-14: a prospective cohort study. *Lancet Infect Dis* 2016; 16: 339–347.
80. Hsieh D-Y, Lai Y-R, Lien C-Y, et al. Nationwide population-based epidemiological study for outcomes of adjunctive steroid therapy in pediatric patients with bacterial meningitis in Taiwan. *Int J Environ Res Public Health* 2021; 18: 6386.
81. Lai Y-R, Lin J-R, Chang W-N, et al. Outcomes of adjunctive steroid therapy in adult patients with bacterial meningitis in Taiwan: a nationwide population-based epidemiologic study. *J Clin Neurosci* 2019; 61: 54–58.
82. van de Beek D, Brouwer MC, Koedel U, et al. Community-acquired bacterial meningitis. *Lancet* 2021; 398: 1171–1183.
83. Hasbun R. Progress and challenges in bacterial meningitis: a review. *JAMA* 2022; 328: 2147–2154.
84. Rahimi BA, Ishaq N, Mudaser GM, et al. Outcome of acute bacterial meningitis among children in Kandahar, Afghanistan: a prospective observational cohort study. *PLoS One* 2022; 17: e0265487.
85. Tadesse BT, Foster BA, Shibeshi MS, et al. Empiric treatment of acute meningitis syndrome in a resource-limited setting: clinical outcomes and predictors of survival or death. *Ethiop J Health Sci* 2017; 27: 581–588.
86. Nahid P, Dorman SE, Alipanah N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: treatment of drug-susceptible tuberculosis. *Clin Infect Dis* 2016; 63: e147–e195.
87. Wang W, Gao J, Liu J, et al. Clinical efficacy of dexamethasone in the treatment of patients with tuberculous meningitis: a meta-analysis. *Contrast Media Mol Imaging* 2022; 2022: 2180374.
88. Beardsley J, Wolbers M, Kibengo FM, et al. Adjunctive dexamethasone in HIV-associated cryptococcal meningitis. *N Engl J Med* 2016; 374: 542–554.

89. WHO. Guidelines for diagnosing, preventing and managing cryptococcal disease among adults, adolescents and children living with HIV, https://iris.who.int/bitstream/handle/10665/357088/9789240052178-eng.pdf?sequence=1 (2022, accessed 12 October 2023).

90. Tunkel AR, Glaser CA, Bloch KC, et al. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2008; 47: 303–327.

91. Meyding-Lamadé U, Jacobi C, Martinez-Torres F, et al. The German trial on Aciclovir and Corticosteroids in Herpes-simplex-virus-Encephalitis (GACHE): a multicenter, randomized, double-blind, placebo-controlled trial. *Neurol Res Pract* 2019; 1: 26.

92. Whitfield T, Fernandez C, Davies K, et al. Protocol for DexEnceph: a randomised controlled trial of dexamethasone therapy in adults with herpes simplex virus encephalitis. *BMJ Open* 2021; 11: e041808.

93. White AC, Coyle CM, Rajshekhar V, et al. Diagnosis and treatment of neurocysticercosis: 2017 clinical practice guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH). *Clin Infect Dis* 2018; 66: e49–e75.

94. Singhi P, Jain V and Khandelwal N. Corticosteroids versus albendazole for treatment of single small enhancing computed tomographic lesions in children with neurocysticercosis. *J Child Neurol* 2004; 19: 323–327.

95. Al-Qahtani AA, Alhamlan FS and Al-Qahtani AA. Pro-inflammatory and anti-inflammatory interleukins in infectious diseases: a comprehensive review. *Trop Med Infect Dis* 2024; 9: 13.

96. Kennedy RH and Silver R. Neuroimmune signaling: cytokines and the CNS. In: Pfaff DW and Volkow ND (eds) *Neuroscience in the 21st century*. New York, NY: Springer New York, pp. 1–41.

97. Alstadhaug KB, Croughs T, Henriksen S, et al. Treatment of progressive multifocal leukoencephalopathy with interleukin 7. *JAMA Neurol* 2014; 71: 1030–1035.

98. Alstadhaug KB, Rinaldo CH, Osnes L, et al. Progressive multifocal leukoencephalopathy treated with interleukin-7. *Clin Infect Practice* 2020; 7–8: 100049.

99. Gasnault J, de Goër de Herve M-G, Michot J-M, et al. Efficacy of recombinant human interleukin 7 in a patient with severe lymphopenia-related progressive multifocal leukoencephalopathy. *Open Forum Infect Dis* 2014; 1: ofu074.

100. Guffroy A, Solis M, Gies V, et al. Progressive multifocal leukoencephalopathy and sarcoidosis under interleukin 7: the price of healing. *Neurol Neuroimmunol Neuroinflamm* 2020; 7: e862.

101. Guille M, Rousset S, Bonneville F, et al. IL-7 immunotherapy for progressive multifocal leukoencephalopathy in a patient with already controlled HIV-1 infection on antiretroviral therapy. *AIDS* 2019; 33: 1954–1956.

102. Harel A, Horng S, Gustafson T, et al. Successful treatment of progressive multifocal leukoencephalopathy with recombinant interleukin-7 and maraviroc in a patient with idiopathic CD4 lymphocytopenia. *J Neurovirol* 2018; 24: 652–655.

103. Miskin DP, Chalkias SG, Dang X, et al. Interleukin-7 treatment of PML in a patient with idiopathic lymphocytopenia. *Neurol Neuroimmunol Neuroinflamm* 2016; 3: e213.

104. Patel A, Patel J and Ikwuagwu J. A case of progressive multifocal leukoencephalopathy and idiopathic CD4+ lymphocytopenia. *J Antimicrob Chemother* 2010; 65: 2697–2698.

105. Ray U, Cinque P, Gerevini S, et al. JC polyomavirus mutants escape antibody-mediated neutralization. *Sci Transl Med* 2015; 7: 306ra151.

106. Soleimani-Meigooni DN, Schwetye KE, Angeles MR, et al. JC virus granule cell neuronopathy in the setting of chronic lymphopenia treated with recombinant interleukin-7. *J Neurovirol* 2017; 23: 141–146.

107. Sospedra M, Schippling S, Yousef S, et al. Treating progressive multifocal leukoencephalopathy with interleukin 7 and vaccination with JC virus capsid protein VP1. *Clin Infect Dis* 2014; 59: 1588–1592.

108. Lajaunie R, Mainardi I, Gasnault J, et al. Outcome of progressive multifocal leukoencephalopathy treated by interleukin-7. *Ann Neurol* 2022; 91: 496–505.

109. Dubey D, Zhang Y, Graves D, et al. Use of interleukin-2 for management of natalizumab-associated progressive multifocal leukoencephalopathy: case report and review of literature. *Ther Adv Neurol Disord* 2016; 9: 211–215.

110. Oza A, Rettig MP, Powell P, et al. Interleukin-15 superagonist (N-803) treatment

of PML and JCV in a post-allogeneic hematopoietic stem cell transplant patient. *Blood Adv* 2020; 4: 2387–2391.

111. Boumaza X, Bonneau B, Roos-Weil D, et al. Progressive multifocal leukoencephalopathy treated by immune checkpoint inhibitors. *Ann Neurol* 2023; 93: 257–270.

112. Gasnault J, Costagliola D, Hendel-Chavez H, et al. Improved survival of HIV-1-infected patients with progressive multifocal leukoencephalopathy receiving early 5-drug combination antiretroviral therapy. *PLoS One* 2011; 6: e20967.

113. Marzocchetti A, Tompkins T, Clifford DB, et al. Determinants of survival in progressive multifocal leukoencephalopathy. *Neurology* 2009; 73: 1551–1558.

114. Sainz-de-la-Maza S, Casado JL, Pérez-Elías MJ, et al. Incidence and prognosis of immune reconstitution inflammatory syndrome in HIV-associated progressive multifocal leucoencephalopathy. *Eur J Neurol* 2016; 23: 919–925.

115. Hopfner F, Möhn N, Eiz-Vesper B, et al. Allogeneic BK virus-specific T-cell treatment in 2 patients with progressive multifocal leukoencephalopathy. *Neurol Neuroimmunol Neuroinflamm* 2021; 8: e1020.

116. Muftuoglu M, Olson A, Marin D, et al. Allogeneic BK virus-specific T cells for progressive multifocal leukoencephalopathy. *N Engl J Med* 2018; 379: 1443–1451.

117. Berzero G, Basso S, Stoppini L, et al. Adoptive transfer of JC virus-specific T lymphocytes for the treatment of progressive multifocal leukoencephalopathy. *Ann Neurol* 2021; 89: 769–779.

118. Wagner JN, Leibetseder A, Troescher A, et al. Efficacy and safety of intravenous immunoglobulins for the treatment of viral encephalitis: a systematic literature review. *J Neurol* 2022; 269: 712–724.

119. Cook SG, Ford AW, Lindholm DA, et al. Enteroviral meningoencephalitis as a complication of rituximab therapy for rheumatoid arthritis. *Cureus*. Epub ahead of print 22 September 2021. DOI: 10.7759/cureus.18189.

120. Higer M, Cana D, Podlech J, et al. Life-threatening disseminated enterovirus infection during combined rituximab and ibrutinib maintenance treatment for mantle cell lymphoma: a case report. *J Med Case Rep* 2020; 14: 135.

121. Wagner JN, Leibetseder A, Troescher A, et al. Characteristics and therapy of enteroviral encephalitis: case report and systematic literature review. *Int J Infect Dis* 2021; 113: 93–102.

122. Moschovi MA, Katsibardi K, Theodoridou M, et al. Enteroviral infections in children with malignant disease: a 5-year study in a single institution. *J Infect* 2007; 54: 387–392.

123. Kapadia RK, Staples JE, Gill CM, et al. Severe arboviral neuroinvasive disease in patients on rituximab therapy: a review. *Clin Infect Dis* 2023; 76: 1142–1148.

124. Koelman DLH, Brouwer MC and Van De Beek D. Targeting the complement system in bacterial meningitis. *Brain* 2019; 142: 3325–3337.

125. Van Toorn R, Zaharie S-D, Seddon JA, et al. The use of thalidomide to treat children with tuberculosis meningitis: a review. *Tuberculosis* 2021; 130: 102125.

126. Kumar R, Kolloli A, Singh P, et al. Thalidomide and phosphodiesterase 4 inhibitors as host directed therapeutics for tuberculous meningitis: insights from the rabbit model. *Front Cell Infect Microbiol* 2020; 9: 450.

127. Van Toorn R, Solomons RS, Seddon JA, et al. Thalidomide use for complicated central nervous system tuberculosis in children: insights from an observational cohort. *Clin Infect Dis* 2021; 72: e136–e145.

128. Schoeman JF, Springer P, Van Rensburg AJ, et al. Adjunctive thalidomide therapy for childhood tuberculous meningitis: results of a randomized study. *J Child Neurol* 2004; 19: 250–257.

129. Nash TE, Ware JM, Coyle CM, et al. Etanercept to control inflammation in the treatment of complicated neurocysticercosis. *Am J Trop Med Hygiene* 2019; 100: 609–616.

130. Enose-Akahata Y, Ngouth N, Ohayon J, et al. Effect of teriflunomide on cells from patients with human T-cell lymphotropic virus type 1-associated neurologic disease. *Neurol Neuroimmunol Neuroinflamm* 2021; 8: e986.

131. O'Hara BA, Gee GV, Haley SA, et al. Teriflunomide Inhibits JCPyV infection and spread in glial cells and choroid plexus epithelial cells. *IJMS* 2021; 22: 9809.

132. Ambrosius B, Faissner S, Guse K, et al. Teriflunomide and monomethylfumarate target HIV-induced neuroinflammation and neurotoxicity. *J Neuroinflammation* 2017; 14: 51.

133. Ambrosius B, Gold R, Chan A, et al. Antineuroinflammatory drugs in HIV-associated

neurocognitive disorders as potential therapy. *Neurol Neuroimmunol Neuroinflamm* 2019; 6: e551.

134. Bowen L, Nath A and Smith B. CNS immune reconstitution inflammatory syndrome. *Handb Clin Neurol* 2018; 152: 167–176.

135. Hodecker SC, Stürner KH, Becker V, et al. Maraviroc as possible treatment for PML-IRIS in natalizumab-treated patients with MS. *Neurol Neuroimmunol Neuroinflamm* 2017; 4: e325.

136. Bernard-Valnet R, Moisset X, Maubeuge N, et al. CCR5 Blockade in inflammatory PML and PML-IRIS associated with chronic inflammatory diseases' treatments. *Neurol Neuroimmunol Neuroinflamm* 2022; 9: e1097.

137. Brienze VMS, André JC, Liso E, et al. Cryptococcal immune reconstitution inflammatory syndrome: from blood and cerebrospinal fluid biomarkers to treatment approaches. *Life* 2021; 11: 95.

138. Armange L, Lacroix A, Petitgas P, et al. The use of TNF-α antagonists in tuberculosis to control severe paradoxical reaction or immune reconstitution inflammatory syndrome: a case series and literature review. *Eur J Clin Microbiol Infect Dis* 2023; 42: 413–422.

139. Scarpazza C, Prosperini L, Mancinelli CR, et al. Is maraviroc useful in multiple sclerosis patients with natalizumab-related progressive multifocal leukoencephalopathy? *J Neurological Sci* 2017; 378: 233–237.