Review

A Mechanistic Model of Primary Progressive Multiple Sclerosis Pathogenesis: Integrating Genetics, Epstein-Barr Virus, and Potential Tenofovir Intervention

Richard Cipian *

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A Mechanistic Model of Primary Progressive Multiple Sclerosis Pathogenesis: Integrating Genetics, Epstein-Barr Virus, and Potential Tenofovir Intervention

Richard Cipian

California State University, Los Angeles. Department of Philosophy. Los Angeles, CA; richardchristopher679@gmail.com

Abstract

Primary Progressive Multiple Sclerosis (PPMS), is an aggressive form of Multiple Sclerosis which affects up to 10–15 percent of MS cases. There is a sustained decline in neurological functions with rare inflammatory relapses. This paper addresses the role of shared MS immune—risk genes (HLA-DRB1*15:01 and non- HLS loci), (2) PPMS based CNS—intrinsic variants affecting neuronal resilience) and Epstein -Barr virus (EBV) infection which induces compartmentalized B- cell inflammation within the CNS (1-4) and the potential of halting (PPMS) progression with use of Tenofovir disoproxil/ alafenamide fumarate (TDF/TAF).

Keywords: relapsing remitting multiple sclerosis; primary progressive multiple sclerosis (PPMS); epstein barr virus (EBV); HLA-DRB1*15:01; 1q21.1-CHDL/PRKAB2; tenofovir disoproxil/ alafenamide fumarate (TDF/TAF)

Introduction

Multiple Sclerosis is a disorder which manifests as a chronic one which causes inflammation, and neurodegeneration. Clinical courses include relapsing- remitting (RRMS) , Secondary Progressive MS (SPMS), and Primary Progressive MS (PPMS) [1,2]. PPMS is characterized by spinal predominance, presence of diffuse lesions and meningeal B-cell aggregates. There is chronic microglial activation at lesion rims. This characteristic is linked to steady disability without prominent relapses [3,4] Primary progressive multiple sclerosis (PPMS) is characterized by neurological decline with limited response to existing disease-modifying therapies. There is strong epidemiological association with Epstein–Barr virus (EBV) infection [1,2]. Growing evidence implicates EBV-infected B cells and their lytic reactivation are implicated in MS pathogenesis [3–5].

Tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF), are used as nucleotide reverse transcriptase inhibitors in HIV and hepatitis B therapy. They have the feature of inhibiting EBV DNA polymerase and lytic replication in vitro. TAF displays higher potency than TDF against EBV in some assays [31,32]. Case reports of MS patients on tenofovir-containing antiretroviral regimens describe prolonged clinical and MRI stability. There is renewed disease activity after tenofovir withdrawal. This suggests a possible disease-modifying effect mediated by EBV suppression [31–34]. TAF is being tested as an add-on to existing Multiple Sclerosis therapies in early-phase clinical trials in relapsing–remitting MS (RRMS) with virologic and neuroaxonal endpoints, but no trials specifically target PPMS [35–37].

There are >200 MS susceptibility loci, primarily immune-related and shared across subtypes identified by genome-wide association studies (GWAS). HLA-DRB1*15:01 confers the strongest risk [5,6]. Progression-focused analyses examine severity loci which are enriched in neuronal/synaptic/mitochondrial pathways. It is possible that PPMS induces amplified

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neurodegeneration on top of a foundation where there is increased genetic susceptibility [7,8]. EBV infection and seroconversion is linked with increased risk due to B-cell dysregulation and molecular mimicry [9–11]. TDF/TAF may be a targeted intervention in reducing progression and potentially halting PPMS.

Genetic Architecture of PPMS

Shared polygenic risk in PPMS and RRMS is present because of shared polygenic risk where there is due presence of susceptibility loci, with similar HLA-DRB1*15:01 effecting sizes and polygenic scores [6,13]. T/B-cell activation is modulated by Non-HLA loci (e.g., IL2RA, IL7R, CD40). This creates a common autoimmune predisposition [5,6].

Loci which influences disability accrual that is independent of relapses is identified by severity GWAS. Synaptic integrity (e.g., GRIN2A), mitochondrial function (e.g., MT-ND genes), and lipid metabolism are targeted [7,8]. The 1q21.1 locus shows PPMS bias because hypermethylation alters CHD1L (chromatin remodeler, DNA repair) and PRKAB2 (AMPK subunit, energy sensing) expression. Impairing of neuronal stress responses in iPSC/zebrafish models is observed [14].

EBV as Pathogenic Trigger

There is disruption of EBV latency in memory B cells. HLA-DRB1*15:01 promotes molecular mimicry. There is EBV peptide presentation which mimics myelin (e.g., EBNA1 cross-reacts with GlialCAM). Variants in TNFRSF1A/CD40 weaken control of viral replication. This yields exhausted CD8+ T cells and expanded EBV+ autoreactive B cells [9–11,15]. Mononucleosis amplifies risk 32-fold [9].

Compartmentalized Inflammation in PPMS

There is EBV+ B cellular infiltration across the blood-meningeal barrier. This causes development of follicle-like aggregates. There is then production of oligoclonal bands and cytokines [3,16]. Microglia/astrocyte activation is observed which influences paramagnetic rim lesion development with iron/complement-mediated axonal loss. There is remyelination failure due to the EBV+ B cells infiltration [4,17]. CHD1L-deficient neurons exhibit oxidative/mitochondrial stress that accelerates "smoldering" damage. Perhaps this is behind PPMS's insidious course [14,18].

EBV establishes lifelong latency in B cells. There is periodic lytic reactivation of EBV from latently infected B cells and is linked to B-cell activation and differentiation into plasmablasts and plasma cells [3–5,13]. EBV-infected B cells appear to be over-represented or dysregulated in peripheral blood. This is also observed in meningeal and perivascular aggregates in the CNS. Such cells act as antigen-presenting cells, cytokine sources, and antibody producers [3–5]. Chronic, low-grade EBV activity in reservoirs is hypothesized to provide continuous antigenic stimulation for autoreactive T cells. There is driving of local microglial activation and oxidative injury. This sustains compartmentalized inflammation in progressive stages [28–30].

This model is consistent with the relative success of B-cell–depleting therapies in both RRMS and PPMS, but also with their limitations: anti-CD20 antibodies spare long-lived plasma cells and some CD20-negative memory subsets that may continue to harbor EBV [1,14,38]

PPMS pathology is dominated by diffuse microglial activation in normal-appearing white and grey matter. There is meningeal inflammation with cortical demyelination, and slowly expanding lesions. Inactive rims develop rather than frequent gadolinium-enhancing foci [7,26,40]. These observations fit a scenario where ongoing local immune activation driven by EBV-infected B-cell/plasma-cell populations damages axons and neurons over time without frequent large relapses [28–30,140]. It is hoped that a drug that specifically reduces EBV lytic activity in those cells could attenuate this chronic neuroinflammatory drive.

Integrated Mechanistic Model

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An integrated model suggests that there is Genetic priming due to Immune-risk alleles and added CNS vulnerability (1q21.1 etc.) [5–8,14]. Then there is the EBV hit where EBV latency expands EBV+ autoreactive B cells [9–11]. CNS seeding would occur where meningeal niches develop and there is sustaining of low-grade inflammation [3,16]. Neurodegeneration occurs as a function of microglial oxidative bursts which erode genetically fragile axons [4,17,18].

PPMS phenotype: Continuous progression sans relapses characterizes PPMS [1,2].

Tenofovir Fumarate: Mechanistic Rationale

TDF/TAF's metabolite (tenofovir-diphosphate) inhibits EBV DNA polymerase (Ki ~0.5 μM, clinically achievable), blocking lytic reactivation and late-gene expression in B cells [19]. This may curtail EBV reservoir replenishment [19,20] and lead to contracting of pathogenic B-cell clones feeding meningeal niches [10,15] There could be an expected attenuation of smoldering inflammation and microglial activation [3,4].

TDF stabilized RRMS according to an anecdotal case series report. A clinical TAF-MS trial (NCT04880577) testing EBV suppression is ongoing [20,21]. In PPMS, synergy with ocrelizumab/BTKi is possible, treating MS patients with high-EBV genetic vulnerability [12,22].

Tenofovir prodrugs (TDF and TAF) are converted intracellularly to tenofovir diphosphate. It then competes with natural nucleotides and there is termination of DNA synthesis by viral polymerases [32]. Tenofovir also inhibits EBV DNA polymerase and viral DNA replication in cell culture. TAF is reported to be roughly twice as potent as ganciclovir in some in-vitro assays [38]. There is improvement of the therapeutic index because TAF achieves higher intracellular levels in lymphoid cells than TDF at lower plasma concentrations, [32].

EBV lytic reactivation leads to plasmablast and plasma cell differentiation .These cells are not adequately targeted by anti-CD20 therapies in that depletion does not occur[28,39]. Eliminating EBV lytic DNA replication in these cells by tenofovir use could decrease viral antigen load, virion release, and EBV-driven inflammatory signaling within CNS-associated B-cell niches [31,38].

There is a case report of a woman who sustained clinical and MRI remission with no new lesion development due to Tenofovir use over several years. After the patient stopped tenofovir use she experienced renewed inflammatory disease activity [31,33].

There are other reports of HIV-positive MS patients on tenofovir-containing regimens that have shown long-term clinical and MRI stability. This could mean that such treatment is compatible with an anti-EBV effect [8,9,16]. There is a rationale paper explicitly proposing tenofovir as a treatment option for MS, and calling for dedicated clinical trials [32]. These observations have contributed to the design of RRMS trials testing TAF as add-on therapy. There are endpoints including EBV shedding, neurofilament light chain (NfL), and microglial activation [35–37].

Reduction of EBV Lytic Activity in CNS-Associated B Cells

Chronic, compartmentalized immune activation within the CNS is believed to perpetuate PPMS [27,42]. Repeated cycles of EBV lytic reactivation in plasmablasts/plasma cells and CD20-negative memory B cells could continuously promote local antigen presentation (EBV and cross-reactive self-antigens), pro-inflammatory cytokine production, and recruitment and activation of microglia and astrocytes [28,29].

By inhibiting EBV DNA polymerase, tenofovir could reduce lytic cycles. There would be a reduction in the frequency and magnitude of local EBV antigen bursts and the release of EBV virions capable of infecting additional B cells. Downstream microglial activation and oxidative stress would also be reduced [27,32,35,36]. This could slow further neuroaxonal loss, translating clinically into reduced progression rates though it may not replace lost myelin to a full extent.

Synergy with B-Cell–Depleting Therapy

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Ocrelizumab is approved for PPMS. It significantly slows disability progression. Though there are incomplete responses [26,28]. CD20-negative plasma cells and some tissue-resident memory B cells survive and an EBV reservoir is maintained [39]. Combining tenofovir with anti-CD20 therapy could, in theory, target the entire EBV reservoir by affecting peripheral B cell EBV niches while tenofovir reduces lytic CNS EBV replication [6,7,13,14].

Modulation of Innate Immune Activation

EBV lytic products, including viral DNA and proteins, can activate innate sensors in microglia and astrocytes (e.g., TLR9, cGAS–STING), driving chronic production of pro-inflammatory mediators and reactive oxygen/nitrogen species [28–30,40]. By reducing EBV replication and virion production, tenofovir could indirectly lower microglial translocator protein (TSPO) expression.[28–30,35–37]. This would reduce cortical pathology. Neurofilament light proteins (NfL) levels and TSPO-PET imaging, already planned as endpoints in RRMS TAF trials, are appropriate biomarkers to test this mechanism in PPMS [35–47].

Alternative or Complementary Mechanisms

Tenofovir may inhibit reverse transcriptase activity of human endogenous retrovirus (HERV) elements. Such elements have been suggested to have a role in MS pathogenesis. The idea is that reducing HERV expression could reduce innate immune activation and autoimmunity [32,42]. In HIV-positive individuals, antiretroviral therapy also alters T-cell subsets and systemic immune activation. There could also be immune modulatory effects in those without HIV disease [32,42,48].

Relevance to PPMS Versus RRMS

Since PPMS is more strongly associated with spinal cord and diffuse grey matter damage [26,27,40], compartmentalized CNS inflammation and meningeal aggregates which do not respond fully to systemic immunosuppression, makes a direct antiviral intervention attractive [28–30,45]. Reducing EBV lytic reactivation which is behind smoldering damage might have a stronger effect on reducing MS pathology than just combating traditional relapses since relapses are T cell driven [28–30,38]. Data on tenofovir use for PPMS is unavailable [31–34,41]. It is unknown if EBV lytic activity is higher in PPMS versus RRMS even though PPMS involves chronic neurodegeneration. [26,28,32].

Hypothesis to Evidence

Quantifying EBV lytic and latent gene expression in CSF cells is justified in clinical trials. CNS tissue from PPMS versus RRMS patients should be assessed to see if there is a reduction of EBV-infected B-cell subsets in blood and CSF. This should be correlated with markers of progression (EDSS, NfL, imaging) [3–5,13]. In vitro work should be done where EBV-infected B cells derived from PPMS patients are assessed for TDF/TAF effects on lytic reactivation, cytokine profiles, and interactions with microglia [32,38]. TSPO-PET measures of microglial activation, spinal cord and brain atrophy rates, and clinical progression could be used as endpoints [26,28,35–37].

A multicenter, placebo-controlled trial of TAF add-ons to ocrelizumab or best standard care in PPMS could be justified. Stratification by EBV activity markers and relevant genetic determinants (e.g., HLA, KIR) could help identify responder subgroups. This would use composite progression endpoints with imaging and fluid biomarkers [26–28,35–37]. Adoptive EBV-specific CD8 T cells infused to target infected B cells—could be considered [30,42].

Discussion

This model suggests that primary infection with EBV in genetically susceptible individuals with haplotypes associated with PPMS can be treated with tenofovir and use of ocrelizumab as adjunct. Tenofovir would act on both peripheral and CNS derived EBV lytic replication while ocrelizumab

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would assist in reducing the EBV reservoir in the periphery. Hopefully there would be a reduction of smoldering activity in the CNS and a halting of MS progression [25].

Conclusion

This model of PPMS pathogenesis integrates shared genetics, EBV-driven B-cell pathology, and CNS fragility. TDF/TAF offers a testable adjunct by disrupting viral perpetuation of smoldering inflammation consistent with the relative success of B-cell–depleting therapies in both RRMS and PPMS, but also with their limitations: anti-CD20 antibodies spare long-lived plasma cells and some CD20-negative memory subsets that may continue to harbor EBV [1,14,38]

These features fit a scenario where ongoing local immune activation, possibly driven by EBV-infected B-cell/plasma-cell populations, gradually damages axons and neurons without frequent large relapses [7,26,28–30,40]. Tenofovir would target EBV lytic activity and attenuate reduce chronic neuroinflammation

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