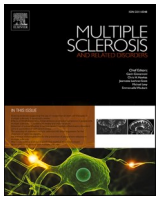
Multiple Sclerosis and Related Disorders 83 (2024) 105436

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard



Correspondence

Antiviral therapy with tenofovir in MS

A B S T R A C T

Infection by the Epstein-Barr virus (EBV) is implicated as the leading cause of multiple sclerosis (MS). We have previously published a case description of a person with MS (pwMS) who was also HIV positive and treated with a combination of antiretrovirals (ART) containing tenofovir, a potent inhibitor of EBV replication. In the years following this publication, the patient had no new relapses, even though she did not use any MS disease-modifying therapy for nearly five years. After switching to another ART with no known efficacy against EBV, her MS-disease activity gradually re-emerged. This finding further emphasizes that targeting EBV lytic reactivation should be explored further in clinical trials as a potential treatment option for MS.

1. Introduction

Recent evidence strongly implicates infection by the Epstein-Barr virus (EBV) as the leading cause of multiple sclerosis (MS), indicating that it is virtually impossible to get the disease without first being infected by EBV (Bjørnevik et al., 2022). This could have major implications for the development of new treatment strategies. Tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF) are used to treat hepatitis B and human immunodeficiency virus (HIV) infection in combination with other antiretrovirals (ARTs). TAF and TDF have also been demonstrated to be potent inhibitors of EBV lytic reactivation, raising the question of whether tenofovir could be a treatment option for EBV-associated diseases (Drosu et al., 2020).

2. Case report

In 2020, we published a case description of a person with MS (pwMS), treated with a combination treatment containing tenofovir (Torkildsen et al., 2020). The patient was a 34-year-old woman with relapsing-remitting MS (RRMS) since 2015. Based on high disease activity, she was started on disease-modifying therapy (DMT) with fingolimod at the time of diagnosis. She was later infected with HIV in 2017. Her initial HIV treatment was an integrase strand transfer inhibitor (INSTI)-based single-tablet regimen with three active agents consisting of a combination of elvitegravir, cobicistat, emtricitabine, and TAF. After the HIV infection was diagnosed and treated, the fingolimod treatment was terminated. Discontinuation of fingolimod is frequently associated with rebound-disease activity (Cerda-Fuertes et al., 2023; Nygaard et al., 2022), but our patient remained stable without any new disease activity. A follow-up magnetic resonance imaging (MRI) was performed in 2017, three months after stopping fingolimod, and again in 2018, without signs of new MRI disease activity. She switched to an HIV treatment with TDF in 2019. TDF has less potency against EBV replication than TAF, although its antiviral activity still is 7–10 fold the antiviral activity of acyclovir and penciclovir (Drosu et al., 2020). After the switch, she had one gadolinium-enhancing lesion on MRI, but no new clinical relapses. Following the initiation of HIV therapy, she reported that two of her previous MS-symptoms, pain and fatigue, decreased. She especially experienced that her neuropathic pain that she had experienced since 2015 resolved, a symptom that commonly persists in pwMS, even after DMT initiation.

We have been following this patient for new disease activity since the publication of our initial case report. During the subsequent years, while on the combination treatment with raltegravir, emtricitabine, and TDF, she had no evidence of new relapses, EDSS progression, or MRI lesions (Fig. 1). For convenience, she was in 2022, switched to a one-tablet dosing regimen consisting of dolutegravir and rilpivirin, a non-nucleoside-reverse transcription inhibitor with no known effect on EBV-replication. Her HIV infection remained well-controlled during this switch, and her HIV viral load in serum has stayed at zero throughout the observation period. After about five months with this new combination, her MRI showed new signs of disease activity, including new gadolinium-enhancing lesions. She was hospitalized with an MRI-verified relapse in October 2022 and treated with steroids. A subsequent MRI performed in June 2023 revealed new MS lesions, leading to the initiation of MS treatment with rituximab in June 2023.

3. Discussion

Our patient experienced no new clinical relapses during her nearly five-year treatment period with TAF or TDF, despite having had highly active MS disease before starting this treatment. After switching to another ART, her MS disease activity gradually re-emerged. It is interesting to note that the MS disease activity appears to have been suppressed while the patient was on an ART that included tenofovir, which is known to have an effect against EBV lytic activation. The patient then experienced new inflammatory activity after changing treatments.

There is an ongoing debate about whether EBV acts as a trigger or a driver of MS disease activity (Sollid et al., 2022). If EBV acts only as a trigger, causing MS but not contributing further, EBV-directed treatment would not alter subsequent disease activity. Conversely, if the EBV infection acts as the driver of the disease, both initiating the disease process and being necessary for successive flairs of inflammation, targeting EBV activity could also lead to ceased autoimmunity and, thus, reduced inflammatory disease activity (Sollid et al., 2022). Since TAF and TDF mainly prevent the lytic reactivation of EBV, this could indicate

https://doi.org/10.1016/j.msard.2024.105436
Received 14 August 2023; Received in revised form 20 December 2023; Accepted 6 January 2024
Available online 7 January 2024

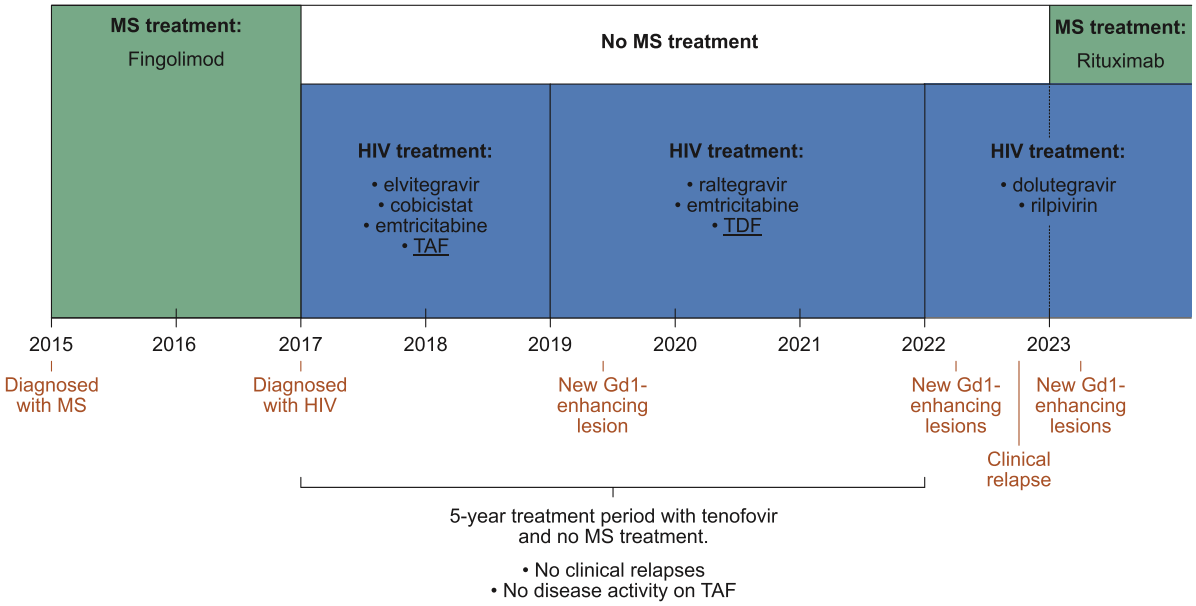


Fig. 1. Disease evolution, HIV- and MS-treatment in our patient. The EDSS of the patient was stable throughout the observation period, except for a transient increase during the relapse in 2022. The serum HIV viral load has stayed at zero throughout the observation period and T-cell levels within normal ranges. * TAF; Tenofovir alafenamide, TDF; Tenofovir disoproxil fumarateis.

that lytic reactivation is the primary driver of the disease process in MS. Several alternative explanations could also account for this potential effect. First, it is possible that the combined effect of CD4+ *T* cell repertoire depletion followed by sustained TAF-mediated suppression of the EBV-infected B cell compartment delayed priming and re-emergence of potentially pathogenic EBV-specific or autoreactive CD4+ *T* cells. We therefore cannot know if the remission was primary due to the effect of TAF on EBV lytic replication, and not due to HIV-mediated depletion of the CD4+ *T* cell compartment itself. Secondly, an alternative hypothesis could be that TAF works primarily by inhibiting human endogenous retroviruses (HERV) which have been previously linked to MS disease pathogenesis (Morandi et al., 2019).

The incidence of MS has been reported to be lower in HIV positive individuals (Gold et al., 2015, McKay et al., 2023), and HIV-positive individuals exposed to ART (McKay et al., 2023). Taken together, these studies raise the question of whether it was the HIV infection per se, or the ART, that was the protective factor against MS, and if the ARTs were preventing MS because they were working against EBV or HERVs. Our findings align with earlier case reports on pwMS treated with tenofovir, showing improvement in disease activity and MS symptoms (Delgado et al., 2014; Chalkley et al., 2014; Maruszak et al., 2011; Skarlis et al., 2017). In addition, clinical stabilisation has been reported in one MS-patient without HIV, treated with a combination regime containing TAF (Drosu et al., 2018). Interestingly, an improvement in MS-symptoms were reported in two of these cases (Delagado et al., 2014; Drosu et al., 2018). Drosu et al. (2018), especially reported an improvement in fatigue and neuropatic pain, the same as for our patient. We were not able to find any data on whether elvitegravir, cobicistat, or emtricitabine have any effects on EBV lytic activation or MS-disease activity. The rationale for why TAF should stabilize or improve MS-symptoms, is not known. One possibility could be that the expression of EBV proteins are downregulated by blocking lytic DNA replication, thus eliminating the causal antigens driving the inflammation in MS (Drosu et al., 2020; Sollid et al., 2022).

Tenofovir has excellent safety and tolerability profile and is also used as a pre-exposure prophylaxis (PrEP) in high-risk individuals to prevent HIV infection, making it a particularly strong candidate as a drug for primary prevention of virally acquired diseases. Since EBV mainly resides in the latent phase in infected individuals, the observations on the use of TAF in pwMS could help answer the question of whether lytic reactivation is necessary for disease activity in MS. Currently one study on TDF (clilinicaltrials.gov: NCT05957913) and one study on TAF (EUCT number: 2023–503,814–62–00) are being performed in pwMS, where the main goal is to determine the effect on EBV shedding. Hopefully, these studies will determine whether tenofovir should be explored further as a treatment in MS.

Role of funding source

The funding source had no role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

CRediT authorship contribution statement

Øivind Torkildsen: Conceptualization, Data curation, Funding acquisition, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Kjell-Morten Myhr:** Conceptualization, Funding acquisition, Project administration, Resources, Writing – review & editing. **Pascal Brugger-Synnes:** Data curation, Investigation, Writing – review & editing. **Kjetil Bjørnevik:** Conceptualization, Methodology, Resources, Writing – review & editing.

Declaration of competing interest

Øivind Torkildsen has received speaker honoraria from or and served on scientific advisory boards for Biogen, Sanofi-Aventis, Merck, Teva, Gilead and Novartis; and has participated in clinical trials organized by Biogen, Merck, Novartis, and Roche. Kjell-Morten Myhr has received unrestricted research grants to his institution and scientific advisory board, and speaker honoraria from Almirall, Biogen, Genzyme, Merck, Novartis, Roche and Teva; and has participated in clinical trials organized by Biogen, Merck, Novartis, and Roche. Pascal Brugger-Synnes has no declarations relevant to the field of multiple sclerosis. Kjetil Bjørnevik has no declarations relevant to the field of multiple sclerosis.

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