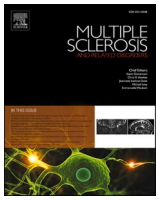
Multiple Sclerosis and Related Disorders 83 (2024) 105396

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

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



Correspondence

Radiologic and clinical stability in an HIV-negative MS patient after tenofovir: An updated case report

1. Introduction

In 2018, members of our team published an interesting case of a patient with newly diagnosed aggressive relapsing-remitting multiple sclerosis (RRMS) who experienced significant improvement in both neurological symptoms and fatigue after starting Combivir (zidovudine/lamivudine) in the absence of disease-modifying therapies (DMTs). (Drosu et al., 2018) Since this patient was negative for HIV, it prompted an intriguing hypothesis that the effect of treatment may be attributable to the known direct activity of zidovudine as an antiviral against EBV and, therefore, the larger question of whether MS could ultimately be treatable with drugs targeting EBV lytic reactivation. Given prior negative trials with acyclovir, (Lycke, 2017) we suggested that it might be prudent to avoid classical anti-herpesvirus drugs and instead use compounds that bypass the rate-limiting step of viral kinase-dependent drug metabolism, like those used for the treatment of HIV. (Drosu et al., 2018) Since circumstantial epidemiological evidence of a lower incidence of MS in patients with HIV supported the possible existence of other HIV drugs with anti-EBV effects, (Gold et al., 2015; Nexø et al., 2013) our team then screened these compounds for activity against EBV in vitro, which led to the identification of tenofovir prodrugs as compounds with superior anti-EBV activity. (Drosu et al., 2020) Here, we provide an update on that case and discuss implications for future clinical trials.

2. Case report

Briefly, this concerns the case of a patient with RRMS with spinal cold-predominant disease and severe fatigue diagnosed in 2014, who experienced both clinical and radiological improvement after treatment with Combivir (zidovudine/lamivudine). [1] Shortly after the previous publication in 2018, the decision was made by the patient to discontinue therapy with Combivir, citing MS symptomatic stability. At the end of that year, a follow-up MRI demonstrated a new sub-centimeter T2 hyperintense brain lesion. Symptomatic benefit continued, however, with no recurrence of fatigue or other MS symptoms. Although the patient was strongly advised to start a disease-modifying therapy (DMT), she opted for watchful waiting with frequent brain and cervical/thoracic spine MRI monitoring due to personal hesitation around immunosuppression. She restarted Combivir but had difficulty with compliance due to persistent nausea and nonspecific general malaise while on the drug. A few months later, a brain MRI demonstrated another new lesion. Although she was unwilling to start a DMT, she was agreeable to a short course of IV solumedrol, which was administered monthly. A few months later, a brain MRI demonstrated a third new lesion. At that time, the patient also experienced a recurrence of significant fatigue, but she had no clinical relapses during this time. Due to an aversion to immunosuppression, she refused all DMTs. The patient instead independently chose to start emtricitabine/tenofovir disoproxil fumarate (Truvada) with monitoring by her primary care provider and to continue close MRI follow-up. Six weeks after starting Truvada, she felt gradual relief from fatigue. A new brain and spine MRI was obtained a few months later, which was stable. Subsequent imaging has been stable over the last four years and there have been no new clinical relapses. She still reports occasional fatigue but has not had any disease progression and remains EDSS 0 in the absence of DMTs. She also reports better compliance with Truvada due to the lack of side effects compared to Combivir. We emphasize that significant efforts have been made to encourage starting a DMT, and the patient has been adequately counseled about MS treatments.

3. Discussion

Several cases in the literature report lower disease activity in MS after starting HIV treatment. (Torkildsen et al., 2020; Chalkley and Berger, 2014; Francesco and Myriam, 2015; Labella et al., 2021) The question of whether the treatment of HIV impacts the MS disease course in an HIV-dependent or independent manner is not possible to resolve without a placebo-controlled trial in HIV-negative individuals. The choice of medication(s) for such a trial is a complex task, as dozens of drugs exist for the treatment of HIV, and blind choice has already led to negative results. (Gold et al., 2018) The selection of rational endpoints for a trial is also unclear. Since this patient's new drug regimen consisted of only two drugs – tenofovir disoproxil fumarate and emtricitabine, it can be used to inform drug selection for future trials. Given that emtricitabine has no activity against EBV, we suggest that it is more logical to evaluate prodrugs of tenofovir. This case also strongly indicates that MRI disease activity should be used as the primary endpoint.

4. Conclusion

Given the established role of EBV as the primary cause of MS, (Bjornevik et al., 2022) the most pressing question is whether EBV is a trigger or a driver of the disease. We report this case to support the notion that EBV is more likely to be a driver of disease activity in MS. Prodrugs of tenofovir should be strongly considered when evaluating potential approaches to assess the role of EBV in MS. We acknowledge that this is not a trivial objective, but nevertheless must be undertaken. The answer is fundamental to the understanding of MS, with consequences for the concept of autoimmunity beyond MS.

https://doi.org/10.1016/j.msard.2023.105396
Received 16 December 2023; Accepted 21 December 2023
Available online 13 January 2024
2211-0348/© 2023 Published by Elsevier B.V.

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CRediT authorship contribution statement

Natalia Drosu: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Michael Levy:** Conceptualization, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Role of Funding Source

None.

References

Bjornevik, K., Cortese, M., Healy, B.C., et al., 2022. Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. Science 375 (6578), 296–301. https://doi.org/10.1126/science.abj8222.

Chalkley, J., Berger, J.R., 2014. Multiple sclerosis remission following antiretroviral therapy in an HIV-infected man. J Neurovirol 20 (6), 640–643. https://doi.org/10.1007/s13365-014-0288-9.

Drosu, N.C., Edelman, E.R., Housman, D.E., 2018. Could antiretrovirals be treating EBV in MS? A case report. Mult Scler Relat Disord 22, 19–21. https://doi.org/10.1016/j.msard.2018.02.029.

Drosu, N.C., Edelman, E.R., Housman, D.E., 2020. Tenofovir prodrugs potently inhibit Epstein-Barr virus lytic DNA replication by targeting the viral DNA polymerase. Proc Natl Acad Sci U A 117 (22), 12368–12374. https://doi.org/10.1073/pnas.2002392117.

Francesco, M., Myriam, S., 2015. Sustained Disease-Activity-Free Status in a Woman with Relapsing- Remitting Multiple Sclerosis Treated with Antiretroviral Therapy for Human Immunodeficiency Virus Type 1 Infection. J Mult Scler 02 (04). https://doi.org/10.4172/2376-0389.1000152.

Gold, J., Goldacre, R., Maruszak, H., Giovannoni, G., Yeates, D., Goldacre, M., 2015. HIV and lower risk of multiple sclerosis: beginning to unravel a mystery using a record-linked database study. J Neurol Neurosurg Psychiatry 86 (1), 9–12. https://doi.org/10.1136/jnnp-2014-307932.

Gold, J., Marta, M., Meier, U.C., et al., 2018. A phase II baseline versus treatment study to determine the efficacy of raltegravir (Isentress) in preventing progression of relapsing remitting multiple sclerosis as determined by gadolinium-enhanced MRI: the INSPIRE study. Mult Scler Relat Disord 24, 123–128. https://doi.org/10.1016/j.msard.2018.06.002.

Labella, F., Acebron, F., Blanco-Valero, M.D.C., Rodrigez-Martin, A., Monterde Ortega, A., Aguera Morales, E., 2021. HIV infection and multiple sclerosis: a case with unexpected "no evidence of disease activity" status. J Int Med Res 49 (3), 300060521999577. https://doi.org/10.1177/0300060521999577.

Lycke, J., 2017. Trials of antivirals in the treatment of multiple sclerosis. Acta Neurol Scand 136 (201), 45–48. https://doi.org/10.1111/ane.12839. Suppl.

Nexø, B.A., Pedersen, L., Sørensen, H.T., Koch-Henriksen, N., 2013. Treatment of HIV and Risk of Multiple Sclerosis. Epidemiology 24 (2), 331–332. https://doi.org/10.1097/EDE.0b013e318281e48a.

Torkildsen, O., Myhr, K.M., Skogen, V., Steffensen, L.H., Bjornevik, K., 2020. Tenofovir as a treatment option for multiple sclerosis. Mult Scler Relat Disord 46, 102569. https://doi.org/10.1016/j.msard.2020.102569.

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