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Case report

Secukinumab may be a valid treatment option in patients with CNS demyelination and concurrent ankylosing spondylitis: Report of two clinical cases

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ABSTRACT

The therapeutic approach to CNS demyelination associated to ankylosing spondylitis is a complex issue due to the contraindication of TNF inhibitors in demyelinating diseases. Secukinumab, a human IgG1κ monoclonal antibody that binds and inhibits IL-17A, was recently approved for the treatment of ankylosing spondylitis. We report the clinical cases of two patients affected by a CNS demyelinating disease and ankylosing spondylitis who were successfully treated with secukinumab, providing additional evidence of the feasibility of this therapeutic option when the use of TNF inhibitors is discouraged by challenging comorbidities.

1. Introduction

The therapeutic approach to central nervous system (CNS) demyelinating diseases, such as multiple sclerosis (MS), is a quite complex issue when it is associated to another immune-mediated disease, since the need to reduce the progression of the first without negatively affecting the course of the second is required. Currently, there are no approved drugs for MS that can also be used to treat a concomitant immune-mediated condition, and the choice of administering an add-on immunosuppressive therapy is challenging due to possible side effects.

Ankylosing spondylitis (AS) is one of the most frequent immune-mediated diseases associated to MS (Marrie et al., 2015). Indeed, the prevalence ranges from 0,12 to 1,98% (Barcellos et al., 2006; Henderson et al., 2000; Kang et al., 2010), which is about 3-fold higher than matched general population controls (Kang et al., 2010). AS is a rheumatological disease characterized by inflammatory back pain associated with radiographic sacroiliitis, asymmetrical peripheral oligoarthritis, enthesitis, and extra-articular manifestations, including anterior uveitis, psoriasis, and inflammatory bowel disease (Taurog et al., 2016). According to recent recommendations, biological agents should be preferred in AS patients with high disease activity despite conventional treatments. These agents neutralize TNF or IL-17 but, because of major experience, TNF inhibitors are recommended as the first biological treatment in clinical practice (van der Heijde et al., 2017). However, the use of TNF inhibitors is not advisable in MS, since these agents have been associated with central and peripheral nervous system demyelinating events (Kemanetzoglou and Andreadou, 2017).

Here, we report the clinical cases of 2 patients with CNS demyelination and AS who were successfully treated with secukinumab, the only antagonist of IL-17A currently available for the treatment of AS.

2. Clinical case 1

The first case pertains to a 37-year old female with no familiarity for neurological or rheumatological diseases. Since 2002, she assumed on-demand nonsteroidal anti-inflammatory drugs to treat low back pain. On January 2016, 3 months after childbirth, she developed right facial hemiparesis and lower limbs hypoesthesia. At that time, these symptoms were not investigated. In September 2016, she had a left optic neuritis, which has been treated with intravenous glucocorticoids. A brain and spinal cord MRI showed multiple periventricular, infratentorial and spinal T2-weighted hyperintense lesions with 2 gadolinium-enhancing brain lesions. CSF analysis disclosed type II oligoclonal bands. According to Polman criteria (Polman et al., 2011), she was diagnosed with relapsing-remitting MS. From the clinical perspective she had a severe residual ipovisus in her left eye and the EDSS was 3.5. In October 2016 the patient started treatment with subcutaneous IFNβ-1a 44 mcg t.i.w. The MRI performed in February 2017 showed no signs

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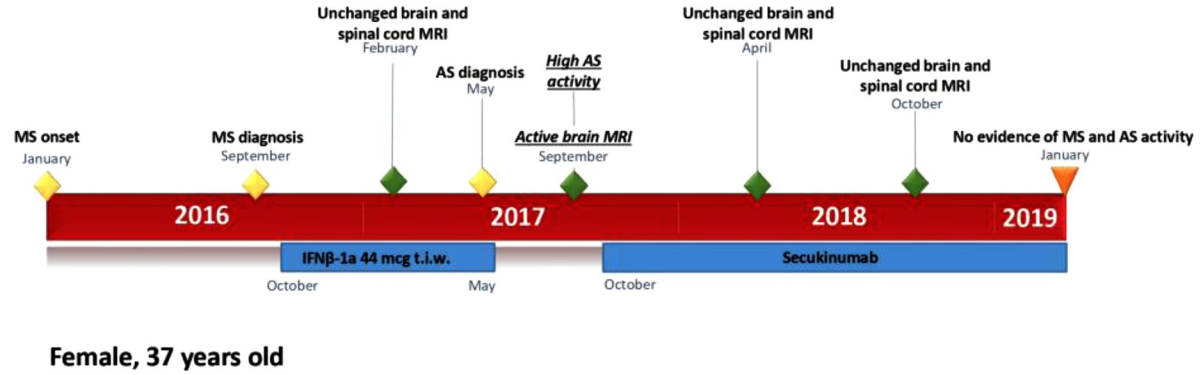

Fig. 1. Timeline of clinical case 1.

of disease activity. On May 2017, based on alternating buttock pain, enthesitis, HLA-B27 positivity, and bilateral radiographic sacroiliitis, she was diagnosed with AS in accordance with modified New York criteria (van der Linden et al., 1984) and treatment with IFNβ-1a was suspended. On September 2017, the brain MRI demonstrated MS activity with 2 new lesions, one of which was gadolinium-enhancing. Moreover, the patient presented high AS activity. Since anti-TNF treatment in patients with MS has been associated with clinical worsening and/or increased inflammatory activity markers (Kemanetzoglou and Andreadou, 2017), we decided to start secukinumab. The first injection was administered in October 2017 and the patient is still on treatment. At the last follow-up visit, in January 2019, the patient presented no new neurological relapses, EDSS was stable at 3,5 and the brain and spinal cord MRI performed after 6 and 12 months from the onset of treatment showed no MS activity. Not least, symptoms and signs of AS significantly improved, with achievement of remission after few weeks of secukinumab treatment, still persisting since then.

3. Clinical case 2

The second patient is a 27-year old female with a family history of psoriatic arthritis (her mother), rheumatoid arthritis (her blood maternal grandmother), and MS (her blood paternal aunt). In April 2012, she was diagnosed with AS in accordance with modified New York criteria (van der Linden et al., 1984) based on inflammatory back pain, radiographic sacroiliitis and right eye uveitis. Because of eye involvement, the patient was started on adalimumab (a TNF inhibitor) in December 2012, but after 3 months she was switched to golimumab (another TNF inhibitor) due to uveitis relapse. Golimumab was rapidly effective leading to remission of both musculoskeletal and eye manifestations. However, on April 2017, the patient experienced tactile hypoesthesia in the left soma. A brain and spinal cord MRI showed several periventricular, infratentorial and spinal T2-weighted hyperintense lesions with 6 gadolinium-enhancing lesions. CSF analysis highlighted type II oligoclonal bands. Back then, we considered the possibility that CNS demyelination had been triggered by TNF antagonist usage and MS diagnosis according to Polman criteria (Polman et al., 2011) could not be established due to the fact that the criterion of “no better explanation” could not been respected (Calabrese et al., 2019). Therefore, a cautious diagnosis of MS-like syndrome (Kemanetzoglou and Andreadou, 2017) was made and a decision of stopping golimumab and administering intravenous glucocorticoids was taken. However, remission was not achieved, as the residual EDSS was 2.0. In June 2017, the patient was started on dimethyl fumarate, which was suspended in less than 2 months for the reoccurrence of AS symptoms. Therefore, in the attempt to cover both the MS-like syndrome and AS manifestations, on September 2017 she started subcutaneous secukinumab. At that time, the brain MRI showed one new inactive lesion. To date, the patient is still on treatment and at the last follow-up visit, in January 2019, there was no evidence of MS-like activity (no new relapses, stable EDSS at 2,0 and stable MRI performed at 5, 10, and 16 month follow-up) and AS was still in remission.

4. Discussion

The management of CNS demyelinating diseases, e.g. MS, in patients with coexisting AS is complicated by the limited therapeutic options. TNF inhibitors are indeed the first recommended biological choice in patients with active AS who have failed standard treatment, overtaking the use of anti-IL-17 because of major clinical experience (van der Heijde et al., 2017). However, demyelination of the central and peripheral nervous system has been associated with TNF inhibitor treatment (Kemanetzoglou and Andreadou, 2017). Albeit it remains uncertain whether these events are coincidental or causally linked, possible mechanisms underlying the impact of TNF inhibitors on demyelinating disorders have been advanced (Robinson et al., 2001). Therefore, it seems prudent to avoid use of TNF antagonists in patients with demyelinating diseases. Recently, secukinumab was approved for the treatment of AS. Secukinumab is a human IgG1κ monoclonal antibody that binds and inhibits IL-17A, a cytokine playing a key role in MS pathogenesis (Kolbinger et al., 2016) apart from AS. The primary source of IL-17A are the cells involved in adaptive immune responses, such as Th17 and cytotoxic T cells but also innate immune cells, such as mucosal-associated invariant T cells, γδ T lymphocytes, and glial cells might contribute to the local production of IL-17A.

IL-17A, through the activation of NF-κB and the stabilization of inflammatory mediators’ mRNA, induces different cell types, e.g. fibroblasts, endothelial and epithelial cells, to secrete proinflammatory mediators leading to neutrophil and macrophage recruitment, tissue inflammation and blood-brain barrier disruption (Kolbinger et al., 2016).

Evidence that IL-17A may have an important role in MS pathogenesis is based on *in vitro* studies and preclinical animal models (Kolbinger et al., 2016). Microarray analysis of MS plaques showed an increase of IL-17A mRNA. Memory T cells producing IL-17A were identified in brain lesions, but not in normal appearing white matter or in non-inflamed specimens. Increased numbers of mononuclear cells expressing IL-17A were found in CSF and blood from MS patients. Myelin basic protein-specific IL-17A-producing PBMCs are higher in individuals with relapsing remitting MS and secondary progressive MS compared to healthy controls. In addition, increased IL-17A production by peripheral blood CD3+ T cells from MS patients was observed, and elevated frequencies of circulating IL-23 receptor-positive CD4+ T cells have been reported. Finally, experimental autoimmune encephalomyelitis (EAE) could not be induced by adoptive transfer of encephalitogenic CD4+ T cells after depletion of Th17 cells, and treatment with a monoclonal antibody against IL-17A reduced EAE severity.

Recently, a proof-of-concept randomized trial showed encouraging results on the use of secukinumab in relapsing-remitting MS (Havrdová et al., 2016 Jul). Although limited by a small sample size and short

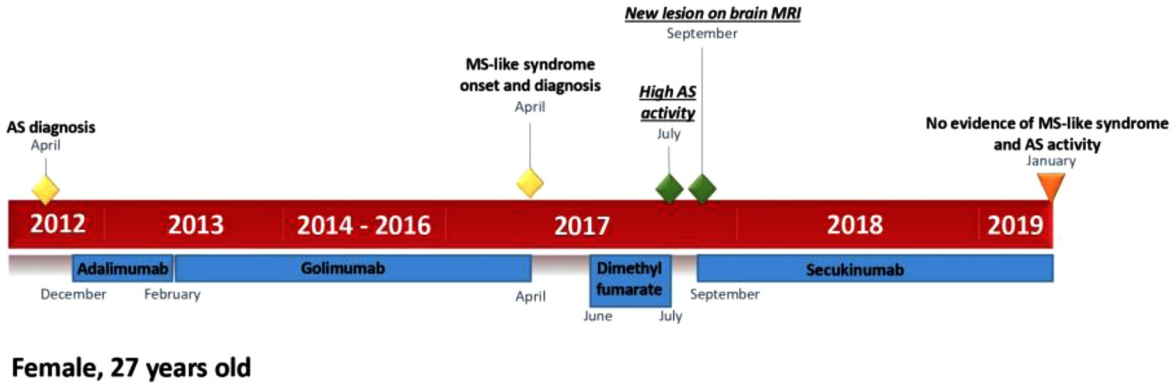

Fig. 2. Timeline of clinical case 2.

duration, secukinumab reduced the number of combined unique active lesions by 49% and significantly reduced the number of cumulative new gadolinium-enhancing T1 lesions by 67%, thus fostering further studies in patients with MS.

Here, we share our experience on the efficacy of secukinumab for more than one year in 2 patients with a concurrence of AS and CNS demyelination, herein specifically the first being affected by relapsing-remitting MS and the second by a MS-like syndrome possibly triggered by TNF antagonist usage. This evidence agrees with that related to a MS patient affected by psoriatic arthritis, effectively treated with secukinumab after unsatisfactory response to ustekinumab (Assefa et al., 2018).

We thus suggest that using secukinumab for treatment of CNS demyelination in patients with AS comorbidity may be efficacious for both conditions, and we recommend further studies on this topic (Figs. 1 and 2).

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Declaration of Competing Interest

None.

References

Assefa, G.T., Kaneko, S., Oguro, H., Morita, E., 2018. Treatment of psoriasis and psoriatic arthritis with secukinumab after unsatisfactory response to ustekinumab in multiple sclerosis patient. J Dermatol.

Barcellos, L.F., Kamdar, B.B., Ramsay, P.P., et al., 2006. Clustering of autoimmune diseases in families with a high-risk for multiple sclerosis: a descriptive study. Lancet Neurol. 5, 924–931.

Calabrese, M., Gasperini, C., Tortorella, C., 2019. "Better explanations" in multiple sclerosis diagnostic workup: a 3-year longitudinal study. Neurology 92 (22), e2527–e2537.

Havrdová, E., Belova, A., Goloborodko, A., et al., 2016 Jul. Activity of secukinumab, an anti-IL-17A antibody, on brain lesions in RRMS: results from a randomized, proof-of-concept study. J. Neurol. 263 (7), 1287–1295.

Henderson, R.D., Bain, C.J., Pender, M.P., 2000. The occurrence of autoimmune diseases in patients with multiple sclerosis and their families. J. Clin. Neurosci. 7, 434–437.

Kang, J.-H., Chen, Y.-H., Lin, H.-C., 2010. Comorbidities amongst patients with multiple sclerosis: a population-based controlled study. Eur. J. Neurol. 17, 1215–1219.

Kemanetzoglou, E., Andreadou, E., 2017. CNS Demyelination with TNF-α blockers. Curr. Neurol. Neurosci. Rep. 17, 36.

Kolbinger, F., Huppertz, C., Mir, A., Padova, F.D., 2016. IL-17A and multiple sclerosis: signaling pathways, producing cells and target cells in the central nervous system. Curr. Drug Targets 17 (16), 1882–1893.

Marrie, R.A., Reider, N., Cohen, J., et al., 2015. A systematic review of the incidence and prevalence of autoimmune disease in multiple sclerosis. Mult. Scler. 21 (3), 282–293.

Polman, C.H., Reingold, S.C., Banwell, B., et al., 2011. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann. Neurol. 69 (2), 292–302.

Robinson, W.H., Genovese, M.C., Moreland, L.W., 2001. Demyelinating and neurologic events reported in association with tumor necrosis factor alpha antagonism: by what mechanisms could tumor necrosis factor alpha antagonists improve rheumatoid arthritis but exacerbate multiple sclerosis? Arthritis Rheum. 44 (9), 1977–1983.

Taurog, J.D., Chhabra, A., Colbert, R.A., 2016. Ankylosing spondylitis and axial spondyloarthritis. N. Engl. J. Med. 374 (26), 2563–2574.

van der Heijde, D., Ramiro, S., Landewé, R., et al., 2017. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann. Rheum. Dis. 76 (6), 978–991.

van der Linden, S., Valkenburg, H.A., Cats, A., 1984. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum. 27 (4), 361–368.