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Tiziana Life Sciences PLC (TLSA-NASDAQ)

KOL Discussion and SPMS 6-Month Results

Research Note

Introduction

Tiziana Life Sciences PLC (NASDAQ: TLSA) is investigating its lead candidate, foralumab, a fully human anti-CD3 monoclonal antibody, in an innovative, intranasal formulation in secondary progressive multiple sclerosis (SPMS). SPMS represents an advanced stage of multiple sclerosis with few treatment options and has a severe impact on a patient. Tiziana enrolled its first SPMS subject in May 2021 through the Individual Patient Expanded Access program. Three-month results released in January of this year provided sufficient evidence of safety and efficacy to justify the enrollment of a second SPMS subject. The second patient has been enrolled. On March 10, 2022, topline data for the full six months of evaluation was reported, and a key opinion leader (KOL) virtual event was held to further detail results and offer discussion with the study's principal investigators.

The trial is using biomarkers, specifically microglial activation as measured by Positron Emission Tomography (PET) to evaluate safety and efficacy of intranasal foralumab in SPMS. In this note we review the latest results shared in the recent March 10th press release and March 14th KOL virtual event. Subsequently, we reinforce these results with discussion of the scientific background of microglial activation in relation to the pathophysiology of SPMS.

Intranasal Foralumab's First SPMS Patient: 3- and 6-Month Data, KOL Discussion

On January 10, 2022, Tiziana announced a progress update for its first patient in the evaluation of intranasal foralumab in SPMS. The first patient enrolled had completed 3 out of 6 months of dosing and analysis of data found that intranasal foralumab was well-tolerated and demonstrated favorable clinical response. The brain imaging data, as analyzed by PET, showed reduction in microglial cell activation. Microglial activation has shown correlation with disease severity in multiple sclerosis and its reduction is hoped to remedy the disease. Based on the success of the first patient, Tiziana was allowed by the FDA to enroll a second patient under the Individual Access Program. On March 10th, Tiziana reported 6-month data for its first SPMS patient and subsequently, held a KOL virtual event on March 14th disclosing explicit results. Intranasal foralumab continued to be well tolerated, and data showed sustained inhibition of microglial activation as assessed by PET along with downregulation of pro-inflammatory cytokines. The disease was also stabilized as measured by clinical assessments.

As disclosed in the March 10th release, between the 3-month and 6-month timepoints, the patient demonstrated greater reduction in activated microglial cells versus baseline based on changes from baseline in Standardized Uptake Value Ratio (SUVR-1).[1] Pro-inflammatory cytokines that were observed to be downregulated included interferon-gamma, interleukin 18, IL-1beta and IL-6. Clinical measures of disease progression including Timed 25-Foot Walk Test, 9-Hole Peg Test, and Symbol Digit Modality Test showed improvement. The FDA authorized the patient to continue on intranasal foralumab for another 6 months, and Tiziana looks forward to efficacy and safety data over this extended timeframe. The March 14th KOL event provided further detail into these measures.

[1] SUVR-1 is calculated with reference to a pseudo reference region in white matter that showed minimal change in PET SUV across time points

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Exhibit I - 6-Month Data from First SPMS Patient[2]

	Whole Brain	Cerebral Cortex	Thalamus	White Matter	Cerebellum
3 Months	-23%	-23%	-20%	-25%	-22%
6 Months	-38%	-38%	-50%	-36%	-38%
Incremental Δ	-15%	-15%	-30%	-11%	-16%

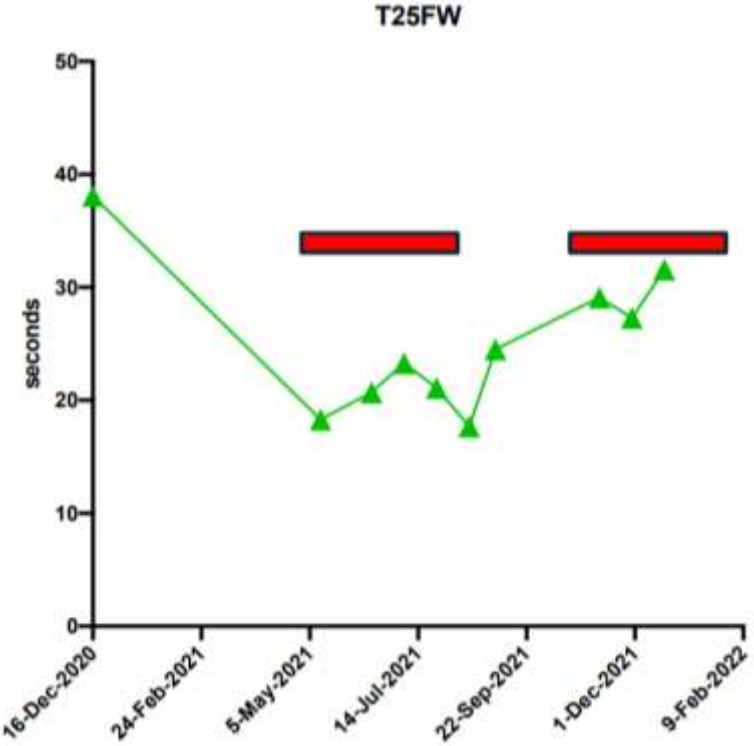
KOL Event

On March 14, 2022, Tiziana hosted a KOL event to share and discuss detailed results from the 6-months of treatment for the first SPMS patient. Participants included Drs. Kunwar Shailubhai (Tiziana CEO), Howard Weiner (Harvard), Tanuja Chitnis (Harvard), Tarun Singhal (Harvard), and Lawrence Steinman (Stanford).

The call began with a welcome and introduction from Tiziana's CEO, Dr. Kunwar Shailubhai. Dr. Weiner then provided an overview of the unmet need in SPMS, and background on anti-CD3 antibodies, citing multiple studies. Dr. Weiner reviewed *in vivo* studies of nasal anti-CD3 antibodies that evidenced protection against myelin loss and axonal injury, regulation of inflammatory phenotype of microglial cells, alteration of immune phenotype of astrocytes, and its general mechanism of action involving IL-10 Treg and TGF-β Tregs. Dr. Weiner ended with a review of the protocol for this first SPMS patient and handed over the call to Dr. Tanuja Chitnis.

Dr. Chitnis began by sharing the background on the first patient, namely that he had worsening disease progression over the past two years, had not experienced any interim relapses in the prior two years, and had no new lesions on brain or spine (as evidenced by MRI) in the prior two years. Also, the patient had been previously treated with rituximab, glatiramer acetate, teriflunomide, and ocrelizumab. She also detailed his exact treatment, including a 6-week intermission. The FDA approved continuation of this patient out to 12 months on foralumab and will begin the next six months treatment in two weeks. Observation of the patient's nasal-respiratory tract continues. Dr. Chitnis then reviewed the clinical measures of disease, which showed stability if not improvement. EDSS[3], 9-Hole Peg Test, and Symbol Digit Modality Test were largely stable, a win in advanced multiple sclerosis. Timed 25-foot walk (T25-FW) showed marked improvement with the first dose, improving from almost 40 seconds to under 20 seconds.

Exhibit II - Timed 25-Foot Walk Test[4]

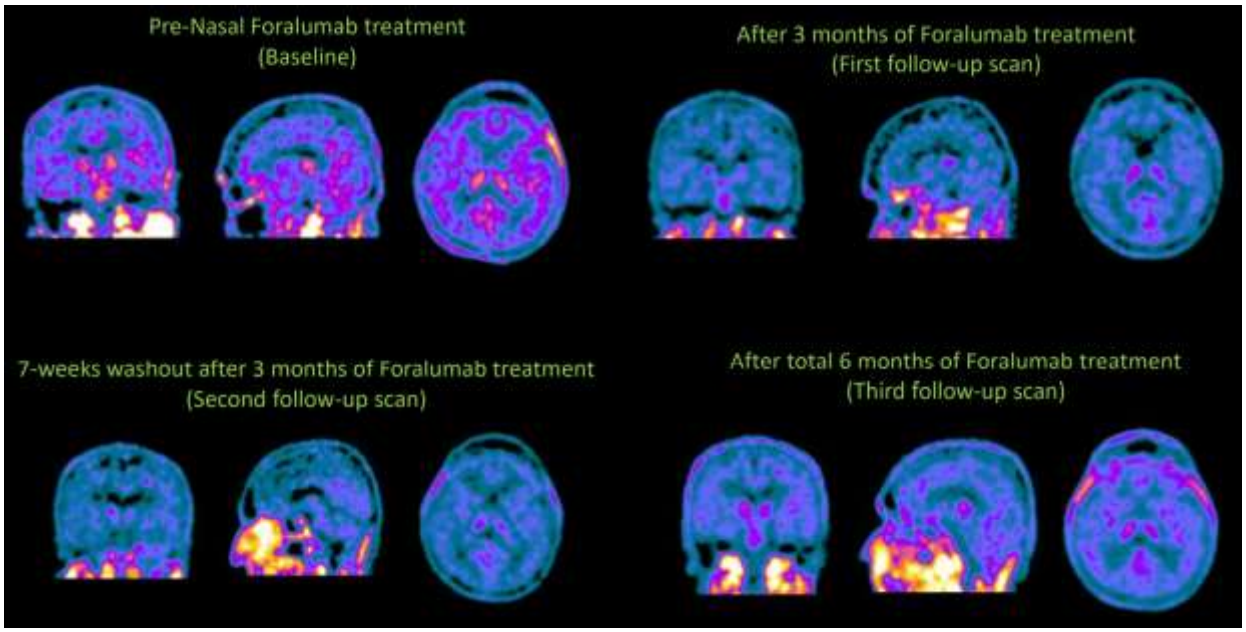


[2] Tiziana Life Sciences
[3] Expanded Disability Status Scale, a commonly used evaluation of MS disease
[4] Tiziana KOL Virtual Event, March 14, 2022

Likewise, there were significant drops in serum cytokines IL-6, IFN-γ, IL-18, and IL-1β, albeit at differing times during the 6-month observation period. There were no significant adverse events observed, and intranasal foralumab was generally well tolerated in this SPMS patient. Most importantly, his disease appeared stabilized by administration of intranasal foralumab. Dr. Chitnis then handed over the call to Dr. Tarun Singhal who presented and interpreted PET images from the patient.

Dr. Singhal briefly described PET imaging and the use of [11C]-(R)PK11195, [C-11]PBR28, and [F-18]PBR06 as radioligands indicating microglial activation, and the correlation between PET-imaged SUVR (thalamus) and EDSS, T25-FW and whole brain atrophy.

Exhibit III - Pre- and Post-Foralumab (Intranasal) PET, SPMS[5]



Of the observations by the investigators, most noteworthy was intranasal foralumab's effect on microglial activation as imaged by PET. No previous studies have shown PET signal reduction to this extent in multiple regions of the brain after other treatments, even in less advanced (RRMS) stages.

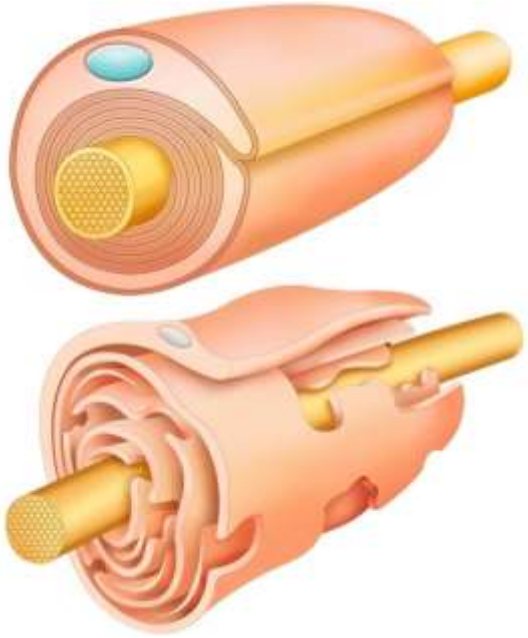
Finally, Dr. Steinman offered closing remarks, voicing his support for and the potential he sees in intranasal foralumab. The call then opened for Q&A. The Q&A session confirmed that the patient seemed to experience greater clinical benefit from his first phase of dosing (pre-vacation, within first three months) than his second, and that it may be due to the intermission where ground was lost. Secondly, though the patient exhibited clinical improvements to varying degrees across the duration of treatment and observation, the patient is still classically defined as a SPMS patient and did not share physiological similarities with other phases of MS, namely RRMS. The greater decrease in microglial activation as evidenced by PET and SUVR-1 was surprisingly in line with expectations, correlating with the two phases of dosing the patient received. Finally, while PET imaging of the brain and its regions with respect to microglial activation is common for the field, PET imaging of the spine will be considered as spinal cord lesions are a feature of SPMS. Early insights into the second patient's progress were revealed, citing clinical improvement.

SPMS and Microglia Background

What are Multiple Sclerosis (MS) and Secondary-Progressive MS (SPMS)?
Multiple sclerosis (MS) is an autoimmune disease affecting the central nervous system. The immune system attacks the myelin sheath that surrounds nerve fibers, damaging the underlying nerve resulting in lesions of the brain and spinal cord.

[5] Tiziana KOL Virtual Event, March 14, 2022

Exhibit IV - Myelinated and Demyelinated Axon[6]



Signs and symptoms of MS vary widely depending on the extent of nerve damage and which nerves are affected. Advanced MS can result in the loss of the ability to walk, although some MS patients experience periods of remission lasting months or longer with no new symptoms and even recovery. The exact cause of MS is unknown, although a combination of genetics and environmental factors are thought to be responsible. There is no cure for MS. Several treatment options for MS attacks exist and include the use of corticosteroids to reduce inflammation and plasmapheresis. Treatments intended to modify the progression of MS are varied and depend on the type of MS: primary-progressive MS, relapsing-remitting MS, or secondary-progressive MS. For primary-progressive MS, only ocrelizumab (Ocrevus) is approved. For relapse-remitting MS, several treatments, including injectable; oral; and infusion-related treatments are available including interferon-β, glatiramer acetate, fingolimod and natalizumab among numerous others. Secondary-progressive MS (SPMS) is a stage of MS subsequent to relapsing-remitting MS (RRMS) characterized by progressive worsening of the disease and an absence of remission.

Through the use of disease-modifying therapies, time to SPMS extends now beyond 20 years from first diagnosis and fewer people are likely to develop SPMS.[7] Approved treatments for SPMS include interferon beta (Extavia) and siponimod (Mayzent). However, these therapies act by modulating or suppressing the peripheral immune response and have limited effect on progressive forms of multiple sclerosis. La Mantia *et al.* reviewed multiple clinical trials which included over 3,000 patients. The paper concluded that recombinant interferon β did not prevent the development of permanent physical disability in SPMS and that, overall, interferon's anti-inflammatory effect is unable to slow established progression.[8] Thus, there is an unmet need in the treatment of progressive MS, especially SPMS.

What are Microglia?

Microglia are glial cells that function as macrophages in the central nervous system (CNS) and are key players in CNS inflammatory response. Microglia and CNS-infiltrating inflammatory monocytes (Ly6ChighCCR2+) are major components of the immune response in the CNS with profound effects on neurodegeneration, and pro-inflammatory microglia and monocytes are thought to contribute to the pathogenesis of MS and other CNS disorders.[9] Microglia have been implicated not only in the pathology of MS, but in other inflammatory and neurodegenerative diseases such as Alzheimer's disease, frontotemporal dementia and Parkinson's disease.[10] Microglial cells are responsible for synaptic organization, trophic neuronal support during development, phagocytosis of apoptotic cells in the

[6] Source: Shutterstock
[7] Secondary progressive MS | Multiple Sclerosis Society UK (mssociety.org.uk)
[8] La Mantia L, Vacchi L, Di Pietrantonj C, Ebers G, Rovaris M, Fredrikson S, Filippini G. Interferon beta for secondary progressive multiple sclerosis. Cochrane Database Syst Rev. 2012 Jan 18;1:CD005181. doi: 10.1002/14651858.CD005181.pub3. PMID: 22258960.
[9] Mayo L, Cunha AP, Madi A, Beynon V, Yang Z, Alvarez JI, Prat A, Sobel RA, Kobzik L, Lassmann H, Quintana FJ, Weiner HL. IL-10-dependent Tr1 cells attenuate astrocyte activation and ameliorate chronic central nervous system inflammation. Brain. 2016 Jul;139(Pt 7):1939-57. doi: 10.1093/brain/aww113. Epub 2016 May 31. PMID: 27246324; PMCID: PMC4939696.
[10] Bachiller, S. *et al.* Microglia in Neurological Diseases: A Road Map to Brain-Disease Dependent-Inflammatory Response. Front. Cell. Neurosci., 18 December 2018 | https://doi.org/10.3389/fncel.2018.00488

developing brain, myelin turnover, control of neuronal excitability, phagocytic debris removal as well as brain protection and repair.

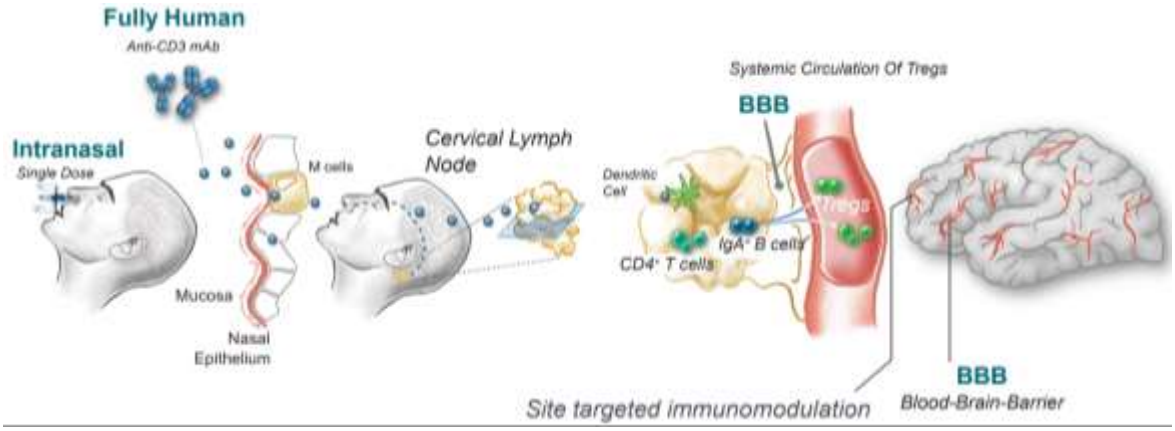
Microglia and PET
To study microglia and their activation in neurodegenerative disease, positron emission tomography (PET) and radioligands have been used. Radioligands are molecules that bind selectively to targets, and because the molecules are radioactive, they are able to be imaged using PET. Most of the PET studies on MS have focused on imaging the activated microglia by using a radioligand that binds 18-kDa translocator protein (TSPO). TSPO is a protein expressed on the exterior of mitochondria in activated microglia, making it an ideal target for imaging.

How do Microglial Activation and SPMS Relate?
Microglia activation is present in early and late MS stages and studies have shown that lesions in MS are associated with microglia activation.[11] Using TSPO radioligands, investigators have demonstrated that microglial activation is increased in focal inflammatory lesions, in the normal-appearing white matter (NAWM), and at the perimeter of chronic active lesions in patients with SPMS.[12] In progressive MS, lesions are most apparent in brain gray matter and gray matter loss in the spinal cord is highly correlated with disability. Increased TSPO expression has been observed in the cortex and cortical lesions, thalamus, and hippocampus in MS, and cortical lesions in SPMS are characterized by a dominant presence of activated microglia. Microglial activation correlates with clinical disability and its expression is linked to neuroinflammation and neuronal injury.

In addition to microglial activation, other pathologic processes investigated for their role in MS include iron accumulation, [13] mitochondrial dysfunction,[14] and oxidative stress.[15] SPMS is characterized by immune reactions within the CNS (compartmentalized), in contrast to RRMS that appears to be driven by peripheral immune response.[16] CNS inflammation is present in both RRMS and SPMS. The compartmentalization in SPMS drives interest in the blood-brain barrier, which has been shown to have varying permeability, especially during relapse,[17] and that the resulting leakage of fibrinogen contributed to axonal damage and neurodegeneration.

Microglial activation is a feature of progressive MS. In MS, microglia can become dysfunctional and contribute to the disease. While these cells normally clean up unwanted debris in the brain, they can also cause damage. Microglia and their immune partners, astrocytes, can cause inflammation when homeostatic microglia are lost and disease-promoting microglia proliferate. The latter form of microglia secretes chemicals that bring about the inflammatory state of astrocytes.

Exhibit V - Foralumab in Neurodegenerative Diseases[18]



[11] Barnett, M., Prineas, J. Relapsing and remitting multiple sclerosis: Pathology of the newly forming lesion. Annals of Neurology, March 21, 2004
[12] Högel, H., Rissanen, E., Vuorimaa, A., & Airas, L. (2018). Positron emission tomography imaging in evaluation of MS pathology in vivo. Multiple Sclerosis Journal, 24(11), 1399–1412. https://doi.org/10.1177/1352458518791680
[13] Haider L, Simeonidou C, Steinberger G, et al. Multiple sclerosis deep grey matter: the relation between demyelination, neurodegeneration, inflammation and iron. J Neurol Neurosurg Psychiatry. 2014;85(12):1386-1395.
[14] Witte ME, Mahad DJ, Lassmann H, van Horssen J. Mitochondrial dysfunction contributes to neurodegeneration in multiple sclerosis. Trends Mol Med. 2014;20(3):179-187.
[15] Azevedo CJ, Cen SY, Khadka S, et al. Thalamic atrophy in multiple sclerosis: a magnetic resonance imaging marker of neurodegeneration throughout disease. Ann Neurol. 2018;83(2):223-234.
[16] Correale J, Gaitan MI, Ysrraelit MC, Fiol MP. Progressive multiple sclerosis: from pathogenic mechanisms to treatment. Brain. 2017;140(3):527-546.
[17] Correale J, Gaitan MI, Ysrraelit MC, Fiol MP. Progressive multiple sclerosis: from pathogenic mechanisms to treatment. Brain. 2017;140(3):527-546.
[18] Tiziana Corporate Presentation January 2022

What Effect Could Foralumab Have on Microglia and SPMS?

Foralumab is Tiziana's lead candidate, a fully-human anti-CD3 monoclonal antibody. SPMS is one of the indications that Tiziana is pursuing using an intranasal formulation. SPMS disease progression and severity has been observed to correlate with microglial activation, which are associated with gray matter lesions characteristic of SPMS. Mayo *et al.* conducted an *in vivo* study in a murine model of progressive MS, where it was found that nasal administration of a CD3-specific antibody ameliorated disease progression.[19] The CD3 antibodies induced T regs that secrete IL-10, which in turn attenuates microglial activation. Conversely, decreased IL-10 levels have been associated with patient MS severity and progression.[20,21,22] Furthermore, the transition from RRMS to SPMS has been linked to a change in the nature of CNS inflammation and is thought to be mainly driven by the local innate immune response, which may in turn be associated with abnormalities in the Tr1 cells and changes in the levels of IL-10.[23] Astrocytes play a role in chronic CNS inflammation, presenting a therapeutic target in SPMS. Mayo *et al.* also found that nasal anti-CD3 mAb attenuated pro-inflammatory astrocytes that resulted in downregulation of demyelination, blood-brain barrier degradation, monocyte recruitment, and microglial regulation. The nasal anti-CD3 mAb skews the microglial and monocyte phenotype towards an anti-inflammatory orientation. Recruitment of inflammatory monocytes to the CNS was also attenuated. These results suggest similar outcomes in humans, potentially driven by the same mechanisms.

[19] Mayo, L., Cunha, A. P., Madi, A., Beynon, V., Yang, Z., Alvarez, J. I., Prat, A., Sobel, R. A., Kobzik, L., Lassmann, H., Quintana, F. J., & Weiner, H. L. (2016). IL-10-dependent Tr1 cells attenuate astrocyte activation and ameliorate chronic central nervous system inflammation. *Brain: a journal of neurology*, *139*(Pt 7), 1939–1957. https://doi.org/10.1093/brain/aww113

[20] van Boxel-Dezaire AH, Hoff SC, van Oosten BW, Verweij CL, Dräger AM, Adèr HJ, van Houwelingen JC, Barkhof F, Polman CH, Nagelkerken L. Decreased interleukin-10 and increased interleukin-12p40 mRNA are associated with disease activity and characterize different disease stages in multiple sclerosis. Ann Neurol. 1999 Jun;45(6):695-703. doi: 10.1002/1531-8249(199906)45:6<695::aid-ana3>3.0.co;2-r. PMID: 10360761.

[21] Petereit HF, Pukrop R, Fazekas F, Bamborschke SU, Röpele S, Kölmel HW, Merkelbach S, Japp G, Jongen PJ, Hartung HP, Hommes OR. Low interleukin-10 production is associated with higher disability and MRI lesion load in secondary progressive multiple sclerosis. J Neurol Sci. 2003 Feb 15;206(2):209-14. doi: 10.1016/s0022-510x(02)00420-3. PMID: 12559513.

[22] Soldan SS, Alvarez Retuerto AI, Sicotte NL, Voskuhl RR. Dysregulation of IL-10 and IL-12p40 in secondary progressive multiple sclerosis. J Neuroimmunol. 2004 Jan;146(1-2):209-15. doi: 10.1016/j.jneuroim.2003.10.033. PMID: 14698865.

[23] Mayo L, Cunha AP, Madi A, Beynon V, Yang Z, Alvarez JI, Prat A, Sobel RA, Kobzik L, Lassmann H, Quintana FJ, Weiner HL. IL-10-dependent Tr1 cells attenuate astrocyte activation and ameliorate chronic central nervous system inflammation. Brain. 2016 Jul;139(Pt 7):1939-57. doi: 10.1093/brain/aww113. Epub 2016 May 31. PMID: 27246324; PMCID: PMC4939696.

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