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PET-measurable reduction in innate immune cell activation in PPMS brain after rituximab treatment

Syventävien opintojen kirjallinen työ

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TURUN YLIOPISTO
Lääketieteellinen tiedekunta

ROOPE RAITANEN: **PET-measurable reduction in innate immune cell activation in PPMS brain after rituximab treatment**

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A 48-year-old woman with primary progressive multiple sclerosis (PPMS) was started on rituximab shortly after diagnosis. She underwent serial PET-imaging at an 18-month interval using [^{11}C]PK11195, a first generation 18-kDa translocator protein ligand targeting activated brain microglia and macrophages, before and after rituximab. I participated in the study as an assistant, and I handled the first processing of the MRI-images. The case report is meant to be published in Multiple sclerosis journal in 2021.

Rituximab is a monoclonal antibody, that identifies CD20-molecule on the surface of B-lymphocytes. Rituximab causes apoptosis in all the cells it binds to. B-cell activation is linked to MS pathogenesis and it has been shown in studies that decreased B-cell levels correlate with better outcome clinically and radiologically in RRMS- and young PPMS-patients. Rituximab does not have an official indication for treating MS, but later developed Ocrelizumab works very similarly to it and got an indication in 2018 in the European markets.

The patient remained clinically stable during a five-year follow-up, and a decrease in radioligand binding was noted in brain areas relevant to progressive MS pathology, such as perilesional white matter area and thalamus. The finding implicates that efficient and early B-cell therapy may lead to reduced microglial activation in PPMS, which may slow down later disease progression.

The case report opens new vistas for designing future therapeutic studies that use the evaluation of microglial activation as an imaging outcome measure in MS. The study is also in line with previous studies that have shown the predictive value of TSPO-PET imaging compared to conventional MRI.

Keywords: PET imaging; TSPO; rituximab; microglia; multiple sclerosis

PET-measurable reduction in innate immune cell activation in PPMS brain after rituximab treatment

A case report

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Keywords: PET imaging; TSPO; rituximab; microglia; multiple sclerosis

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Abstract:

A 48-year-old woman with primary progressive multiple sclerosis (PPMS) was started on rituximab shortly after diagnosis. She underwent serial PET-imaging at an 18-month interval using [^{11}C]PK11195, a first generation 18-kDa translocator protein ligand targeting activated brain microglia and macrophages, before and after rituximab. She remained clinically stable during a five-year follow-up, and a decrease in radioligand binding was noted in brain areas relevant to progressive MS pathology, such as perilesional white matter area and thalamus. The finding implicates that efficient and early B-cell therapy may lead to reduced microglial activation in PPMS, which may slow down later disease progression.

Introduction

Primary progressive multiple sclerosis (PPMS) has only limited treatment options and a relatively poor prognosis.[1] Unlike in relapsing-remitting MS (RRMS), where lymphocytes enter the CNS from the periphery to form focal inflammatory lesions, a process readily preventable by effective immune modulating treatments, the pathology in PPMS is mainly contained within the CNS.[2] Diffuse innate immune cell activation particularly in the normal appearing white matter (NAWM), in the thalamus and at the rim of chronic lesions is a characteristic pathological feature of PPMS, which is not detectable by conventional MRI.[3] The innate immune cell activation is co-localized with signs of neural damage and is thus considered to have a central role in promoting MS progression.[3]

The present DMTs have proven to be of limited value in treatment of progressive MS. Ocrelizumab is the first and currently the only approved therapy for PPMS, and previously another B-cell therapy, rituximab, demonstrated promising therapeutic effect in a Phase II PPMS study.[4] B-cells have well-known roles in antigen presentation and in cytokine and antibody production, but their precise role in MS immunopathology remains somewhat unclear. Particularly in progressive disease, where CNS-

contained diffuse inflammation and neurodegeneration have a presumably important pathophysiological role, the mechanism of action of anti-B-cell antibodies has remained elusive, as monoclonal antibodies generally have low blood-brain-barrier (BBB) penetration.[5]

Positron emission tomography (PET) using radioligands binding to the 18-kDa translocator protein (TSPO) molecule can be used to obtain information about the brain innate immune system activation *in vivo*.[6] Studies of secondary progressive MS (SPMS) have demonstrated an increase in TSPO-radioligand binding in brain areas relevant to progressive MS pathology, compared to RRMS patients and age-matched healthy controls.[7] In PPMS such studies are still lacking, but in this PPMS case report we describe a situation, where early initiation of rituximab let to reduction in TSPO-PET-measurable innate immune cell activation, and stabilization of the clinical disease progression.

Case Report

This individual was diagnosed with PPMS in May 2016 when she was 48 years old. She had had some walking difficulties since the beginning of 2015, but new symptoms emerged, including numbness and loss of sensory function in the right lower trunk and leg in December 2015, in addition to dizziness and cognitive impairment, and these led to suspicion of MS. MRI examination demonstrated large demyelinating lesions in the entire brain and thoracic and cervical spine. Cerebrospinal fluid (CSF) examination revealed elevated immunoglobulin G (IgG) index and oligoclonal bands. At the time ocrelizumab had not yet been approved for PPMS and off-label use of rituximab was the chosen DMT. The first rituximab infusion (500mg) was given in June 2016, and the treatment was continued first every 6 months and later with 9-month interval with no adverse effects.

TSPO-PET imaging using the [^{11}C]PK11195 radioligand was performed before the administration of the first rituximab infusion and again after 18 months of treatment. Conventional MRI was performed at both time points. Microglial activation was evaluated as specific binding of [^{11}C]PK11195 using distribution volume ratio (DVR) in the NAWM, cortical grey matter, thalamus, T1 lesion, T2 lesion and in the T1 perilesional area extending 3 mm into the NAWM from the lesion edge. For the estimation of the [^{11}C]PK11195 DVR, the time–activity curve corresponding to a reference region devoid of specific TSPO-binding was acquired for both PET sessions using a supervised cluster algorithm with four predefined kinetic tissue classes (SuperPK software).[8] The reference tissue–input Logan method with a time interval from 20 to 60 min, was applied to the regional time–activity curves using the supervised cluster algorithm reference input. Imaging data from a group of 18 age-matched healthy individuals obtained in a similar way, was used for comparison.[9]

At baseline, our patient had higher DVR in the NAWM and thalamus compared to healthy control mean DVR in these areas (Table 1). After rituximab treatment, a decrease in [^{11}C]PK11195 binding was observed in T1 and T2 lesions, in thalamus and in the perilesional NAWM (Table 1). No noticeable change in MRI T1 or T2 lesion burden was observed during the 18-month follow-up (data not shown). The sensory loss improved during the 18-month follow-up, and this led to a decrease in the Expanded Disability Status Scale (EDSS) score from 3.5 to 3.0. The patient continued on rituximab treatment, and at her most recent annual appointment in February 2021, her EDSS score was 3.0 with no noticeable change in her MRI lesion burden.

Our case report demonstrates a decrease in TSPO-radioligand binding (reflecting reduced microglial activation) after initiation of rituximab in brain areas critical to MS pathology (Image 1 and Table 1).

Discussion

The treatment result described in this paper suggests that at least in certain PPMS patients, anti-B-cell therapy may be helpful in reducing microglial activation in brain areas most relevant for MS pathology. Importantly, in our patient, this phenomenon was associated with stabilization of the clinical worsening. Here, rituximab treatment was initiated within a month of PPMS diagnosis, and this might have been helpful in obtaining good control of the disease. The finding of reduced microglial activation after treatment with highly effective anti-inflammatory therapy is in line with previous studies, where other DMTs such as natalizumab and fingolimod have led to decreased microglial activity.[10-12]

Activated microglial cells are considered harmful, and have been shown to predict later disease progression independent of relapses.[9] Furthermore, increased iron uptake at lesion edge (reflecting microglial activity) was associated with more rapid clinical disease progression.[13] Despite the promising outcome presented in our patient case, the results cannot be directly extended to larger groups, where heterogenous underlying pathologies likely exist. Our case however gives a promising signal that anti-B-cell therapies might be effective in reducing the smoldering inflammation contained behind the BBB. It is unlikely that rituximab, being a large monoclonal antibody, would enter the CNS but rather, the positive treatment effect on the innate immune cell activation within the CNS likely comes as a secondary effect from the effective reduction of the inflammatory MS-related activity in the periphery. The key to success in treatment of PPMS, like RRMS, seems to be early initiation of effective therapy. In the future, treatments targeting directly the CNS innate immune cells can hopefully be combined to the present effective anti-inflammatory therapies for the maximal benefit of the patients.

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Conflict of Interest

The Authors declare that there is no conflict of interest.

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Table 1. Evaluation of innate immune cell activation in various brain regions of interest performed using PET imaging and the TSPO-binding [11C]PK11195 radioligand.

	DVR at baseline	**DVR at 18 months**	**DVR of HC* (mean±SD)**
Thalamus	1,49	1,42	1,28 (± 0,06)
NAWM	1,26	1,26	1,19 (± 0,04)
Cortical GM	1,15	1,19	1,23 (± 0,04)
T1 lesion rim 0-3mm	1,29	1,25	N/A
T1 lesion	1,24	1,23	N/A
T2 lesion	1,26	1,23	N/A

*n=18. Abbreviations: DVR = distribution volume ratio; HC = healthy control; NAWM = normal appearing white matter; GM = grey matter, SD= standard deviation, N/A= not applicable

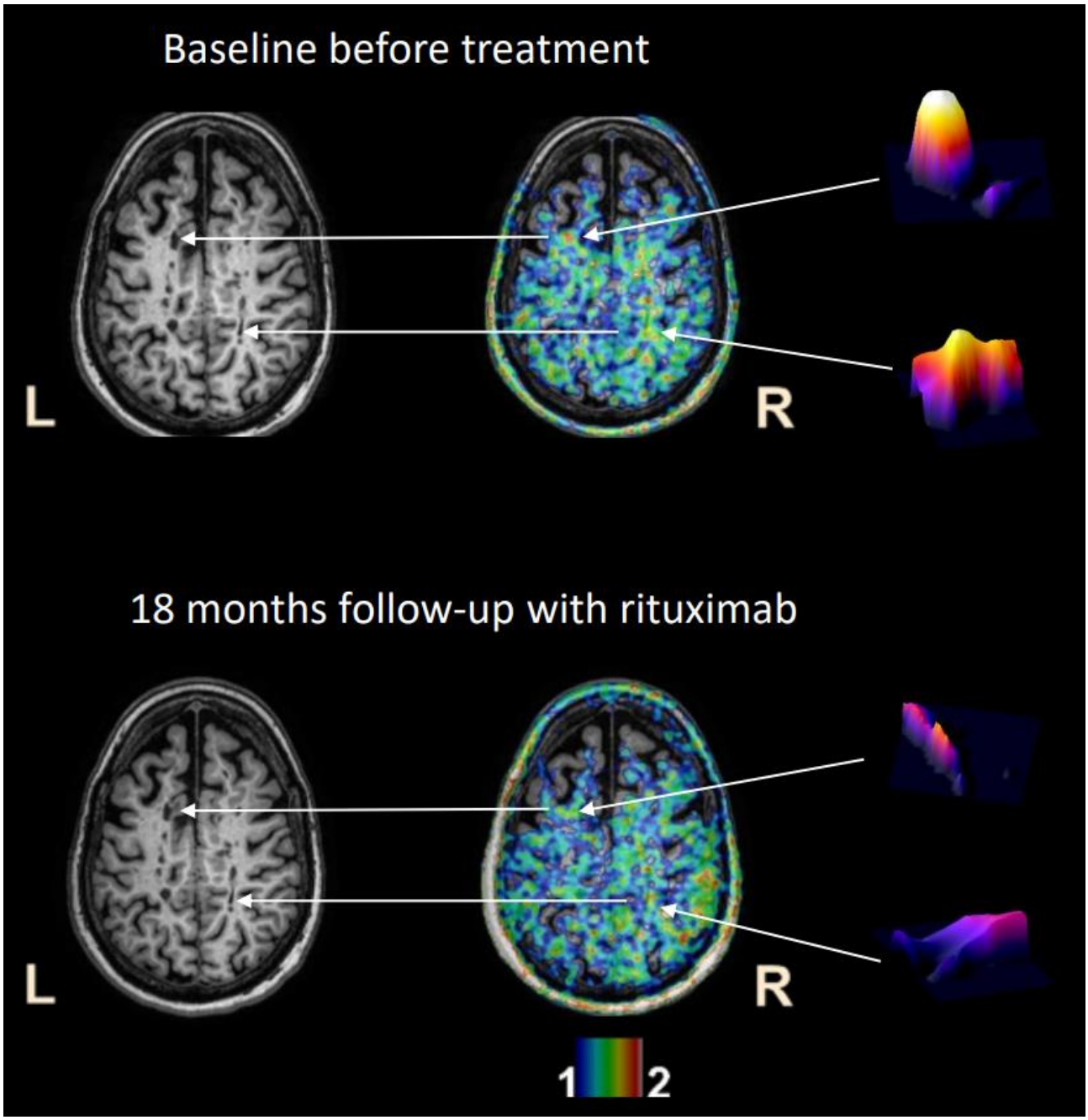

Image 1. Visual demonstration of innate immune cell activation in PPMS brain. Axial view of 3DT1 MRIs (left) and respective DVR images (right) at baseline (top row) and after 18 months of rituximab-treatment (bottom row). White arrows point at two representative individual lesions, whose high innate immune cell activation (high DVR) are visualized as 3D surface plots in the top PET image. Post-treatment image demonstrates a decrease in [11C]PK11195 -radioligand binding in these lesions after treatment. The colour bar of the PET images shows the dynamic range of DVR in the images. PPMS = primary progressive MS, DVR = distribution volume ratio