A Novel Signature of Lipoxin A_4 and Prostaglandin E_2 in Plasma Associated With Disease Severity in Patients With Relapsing-Remitting and Secondary Progressive Multiple Sclerosis

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Introduction

- Multiple Sclerosis (MS) is a demyelinating and neuro-inflammatory disease characterised by an initially relapsing course (relapsing-remitting multiple sclerosis; RRMS) which later progresses to a chronic progressive form of MS (secondary progressive multiple sclerosis; SPMS)
- The factors which mediate the progression from RRMS to SPMS are of key interest in terms of both treatment strategy and innovation, and biomarker identification
- Chronic neuroinflammation may be due to dysregulation of resolution of inflammation. The chronic inflammatory phase sees the presence of pro-inflammatory immune cells and widespread glial activation within the central nervous system[1,2]
- Specialized pro-resolving lipid mediators play an important role in the resolution of chronic inflammation[1]
- There is an emerging hypothesis that failed resolution might be caused by a lack of pro-resolving lipid mediators, such as lipoxin A_4 (LXA_4), while pro-inflammatory lipids, such as prostaglandins (PG) like prostaglandin E_2 (PGE_2) may exacerbate or prolong inflammation[1,3]

Objective

- To explore whether pro-resolving lipids mediators (including LXA_4) and pro-inflammatory lipids (including PGE_2) can be used as candidate of disease activity in patients with SPMS

Pro-resolving Lipids

Lipoxin A_4 (LXA_4)
Resolvin D_1 (RvD_1)
13-HO-TrE
17-HDHA

Lipid Mediators

Pro-inflammatory Lipids

Prostaglandin E_2 (PGE_2)
Prostaglandin D_2 (PGD_2)
Leukotriene B_4 (LTB_4)
6-trans-LTB_4
6-trans-12-epi-LTB_4
Thromboxan B_2 (TxB_2)

Methods

- In this post hoc analysis, baseline (BL) samples from the Phase 3 (EXPAND; N=55 randomly selected patients with SPMS) and the Phase 4 (LONGTERMS; N=28 who converted from RRMS to SPMS) studies were included
- Lipids levels were quantified in plasma samples using high performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) for lipidomics
- Both lipid mediators were categorised as LXA_4 (low)+PGE_2 (high), LXA_4 (low)+PGE_2 (low), LXA_4 (high)+PGE_2 (high), or LXA_4 (high)+PGE_2 (low); [Low=0 pg/mL; High>0 pg/mL]
- Baseline (BL) characteristics, including disease duration since first symptom (DD), Expanded Disability Status Scale (EDSS), normalised brain volume (NBV), T2 lesion volume (LV), 9-Hole Peg Test (9-HPT), Paced Auditory Serial Addition Test (PASAT) and serum neurofilament light chain (sNfL), were summarized by lipid category or lipid signature
- Due to the limited sample size and exploratory nature of this analysis, only summary statistics were provided

Results

EXPAND patient population

- In SPMS, plasma samples were PGE_2 (high) and LXA_4 (high) in 13/55 and 6/55 of the patients, respectively
- SPMS patients with PGE_2 (high) versus PGE_2 (low) showed longer disease duration (20.6 vs 17.6 years), higher EDSS (5.7 vs 5.5), lower NBV (1384 vs 1425 cm^3), higher LV (20.5 vs 17.1 cm^3), higher sNfL (58.0 vs 47.9 pg/mL) and weaker performance in the 9-HPT (42.5 vs 32.4 seconds) and PASAT score (35.6 vs 40.2)

Table 1. EXPAND: Lipid Biosignatures

	LXA_4		PGE_2		LXA_4+PGE_2		
Baseline Characteristics	0 pg/mL	>0 pg/mL	0 pg/mL	>0 pg/mL	LXA_4 (low)+ PGE_2 (high)	LXA_4 (low)+PGE_2 (low) or LXA_4 (high)+PGE_2 (high)	LXA_4 (high)+ PGE_2 (low)
	N=49	N=6	N=42	N=13	N=12	N=38	N=5
Years since first MS symptom (mean)	18.0	18.0	17.6	20.6	20.7	17.7	17.7
EDSS (mean)	5.5	5.6	5.5	5.7	5.8	5.5	5.6
NBV (mean; cm^3)	1414	1439	1425	1384	1383	1423	1438
T2 Lesion Volume (mean; mm^3)	18129	16430	17140	20539	20986	17149	16681
sNfL (mean; pg/mL)	64.4	63.1	47.9	58.0	63.5	64.7	62.5
GFAP (median; pg/mL)	162.1	179.7	126.7	138.8	-	-	-
9-HPT (sec)	35.2	31.6	32.4	42.5	43.3	32.6	31.3
PASAT score	38.8	42.0	40.2	35.6	37.2	38.8	48.0

9HPT, 9-Hole Peg Test; EDSS, Expanded Disability Status Scale; GFAP, glial fibrillary acidic protein; LXA_4, lipoxin A_4; MS, multiple sclerosis; NBV, normalised brain volume; PASAT, Paced Auditory Serial Addition Test; PGE_2, prostaglandin E_2; sNfL, serum neurofilament light chain

- In contrast, SPMS patients with LXA_4 (high) versus LXA_4 (low) showed higher NBV (1439 vs 1414 cm^3), lower LV (16.4 vs 18.1 cm^3), similar EDSS (5.6 vs 5.5) and a better performance in the 9-HPT (31.6 vs 35.2 seconds) and PASAT score (42.0 vs 38.8), respectively
- SPMS patients with the signature LXA_4 (low)+PGE_2 (high) showed advanced disease severity compared to patients with LXA_4 (high)+PGE_2 (low), based on EDSS (5.8 vs 5.6), NBV (1383 vs 1438 cm^3), LV (21.0 vs 16.7 cm^3), sNfL (63.5 vs 62.5 pg/mL) and 9-HPT (43.3 vs 31.3 seconds) and PASAT score (37.2 vs 48.0) (**Table 1**)

LONGTERMS patient population

- In RRMS converted SPMS patients, plasma samples were PGE_2 (high) and LXA_4 (high) in 14/28 and 4/28 of the patients, respectively (**Table 2**)
- The signature LXA_4 (low)+PGE_2 (high) showed similar results as of SPMS towards association with higher EDSS, advanced brain atrophy and low performance in the 9-HPT and PASAT

Table 2. LONGTERMS: Lipid Biosignatures

	LXA_4		PGE_2		LXA_4+PGE_2		
Baseline Characteristics	0 pg/mL	>0 pg/mL	0 pg/mL	>0 pg/mL	LXA_4 (low)+ PGE_2 (high)	LXA_4 (low)+PGE_2 (low) or LXA_4 (high)+ PGE_2 (high)	LXA_4 (high)+ PGE_2 (low)
	N=24	N=4	N=14	N=14	N=10	N=18	N=0
Years since first MS symptom (mean)	9.1	4.5	7.6	9.3	11.2	6.9	-
EDSS (mean)	3.7	4.1	3.4	4.1	4.1	3.6	-
NBV (mean; cm^3)	1505	1541	1522	1500	1482	1526	-
T2 Lesion Volume (mean; mm^3)	7814	5696	6138	8885	10160	6040	-
sNfL (mean; pg/mL)	39.2	38.8	34.0	44.2	46.4	35.1	-
9-HPT (sec)	26.6	29.7	47.9	45.8	31.8	24.4	-
PASAT score	46.1	51.3	22.8	31.2	43.6	48.7	-

9HPT, 9-Hole Peg Test; EDSS, Expanded Disability Status Scale; LXA_4, lipoxin A_4; MS, multiple sclerosis; NBV, normalised brain volume; PASAT, Paced Auditory Serial Addition Test; PGE_2, prostaglandin E_2; sNfL, serum neurofilament light chain

Conclusions

- A total of 14/28 (50%) patients who later progressed to SPMS had high PGE_2 while the pro-resolving lipid LXA_4 was high in 4/28 patients
- SPMS patients with PGE_2 (high) at baseline, had longer disease duration, higher EDSS, lower brain volume, higher T2 lesion volume and weaker performance in 9-HPT and PASAT than patients without detectable prostaglandins
- SPMS patients with the signature LXA_4 (low)+PGE_2 (high) shared an advanced disease phenotype compared to LXA_4 (high)+PGE_2 (low), based on MRI activity, EDSS and 9-HPT
- SPMS patients with vs without pro-resolving lipid LXA_4 showed higher brain volume, lower T2 lesion volume and a better performance in 9-HPT and PASAT
- The initial findings from the study are promising and further longitudinal analyses are in progress to better understand how these lipid signatures are related to disease progression and the switch from RRMS to SPMS

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Acknowledgments

The authors acknowledge the following Novartis employees: **Neha Kulkarni** and **Rohit Bhandari** for medical writing assistance and coordinating author reviews, and **Saketh Vellanki** for creative design assistance. The final responsibility for the content lies with the authors.

Disclosures

Jelle Y. Broos, Helga de Vries and **Martin Giera** have nothing to disclose. **Gijs Kooij** is partly supported by a grant from Novartis. **Jeff Maca** and **Goeril Karlsson** are employees of Novartis. **Harald Kropshofer†** was an employee of Novartis at the time of abstract submission, but sadly passed away in May 2022, the authors wish to acknowledge his significant contribution to this work via this posthumous authorship

This study was funded by Novartis Pharma AG, Switzerland.

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Poster presented at the 38th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, 26–28 October 2022.

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