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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: In multiple sclerosis (MS), chronic neuroinflammation may be due to deregulation of resolution of inflammation. This protective process is normally orchestrated by specialised pro-resolving lipid mediators derived from omega-3/-6 fatty acids. Failed resolution might be caused by a lack of pro-resolving lipid mediators, such as lipoxin A_4 (LXA_4), while pro-inflammatory lipid mediators, such as prostaglandin E_2 (PGE_2), may persist.
Objective: To explore whether LXA_4 and PGE_2 can be used as candidate biomarkers of disease activity in patients with relapsing-remitting MS (RRMS) and secondary progressive MS (SPMS).
Methods: In this post hoc analysis, involving baseline (BL) samples from the Phase 4 study LONGTERMS (N=28 RRMS-SPMS converters) and the Phase 3 study EXPAND (N=55 randomly selected patients with SPMS), LXA_4 and PGE_2 levels were quantified by quantitative liquid chromatography with tandem mass spectrometry. Lipids were categorised as lo (not detectable) or hi (detectable) or as signatures LXA_4(lo)+PGE_2(hi) vs LXA_4(hi)+PGE_2(lo). Mean BL characteristics – such as disease duration (DD), Expanded Disability Status Scale (EDSS) score, normalised brain volume (NBV), T2 lesion volume (LV) & 9-Hole Peg Test (9-HPT) were analysed by lipid category.
Results: In RRMS, 14/28 patients were PGE_2-positive at BL, while LXA_4 was only detectable in 4/28 patients. In SPMS, samples were PGE_2(hi) and LXA_4(hi) in 13/55 and 6/55 of the patients, respectively. SPMS patients with PGE_2(hi) vs PGE_2(lo) showed a trend towards a longer DD (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), and weaker performance in the 9-HPT (42.5 vs 32.4 seconds). In contrast, SPMS patients with LXA_4(hi) vs LXA_4(lo) trended towards higher NBV (1439 vs 1414 cm^3), lower LV (16.4 vs 18.1 cm^3), and a better performance in the 9-HPT (31.6 vs 35.2 seconds). SPMS patients with the signature LXA_4(lo)+PGE_2(hi) shared a trend of advanced disease severity compared to patients with LXA_4(hi)+PGE_2(lo), based on EDSS (5.8 vs 5.6), NBV (1383 vs 1438 cm^3), LV (21.0 vs 16.7 cm^3), and 9-HPT (43.3 vs 31.3 seconds). In RRMS patients, the signature LXA_4(lo)+PGE_2(hi) showed a similar trend towards association with higher EDSS, advanced brain atrophy, and low performance in the 9-HPT.
Conclusion: Circulating levels of LXA_4 and PGE_2 appear to be a candidate lipid biosignature of disease severity in RRMS and SPMS. Validation in larger studies is underway.
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