PLASMA LEVELS OF POLYUNSATURATED OMEGA 3 EICOSAPENTAENOIC ACID ARE ASSOCIATED WITH ANTI-TNF RESPONSE IN RHEUMATOID ARTHRITIS, AND INHIBIT THE ETANERCEPT DRIVEN RISE IN TH17 CELL DIFFERENTIATION IN VITRO

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Background: Anti-TNF agents have revolutionized the management of RA, but a substantial proportion of patients fail to respond or do so only partially. Understanding the reasons for inadequate response may guide choice of alternative biological agents, or permit optimization of anti-TNF therapy. Long-chain omega-3-polyunsaturated fatty acids (PUFAs), including eicosapentaenoic acid (EPA), have immunomodulatory effects and supplementation is associated with modest efficacy in RA. Omega-3-PUFAs cannot be synthesized de novo in humans, and conversion into long-chain omega-3-PUFAs is poor. Levels of long-chain omega 3 PUFAs are therefore dependent upon dietary intake from marine sources, which is highly variable. We sought to determine whether plasma omega-3-PUFAs were associated with response to anti-TNF agents in RA.

Methods: Twenty-two patients with established RA, who had failed at least one DMARD and were on weekly MTX, were randomized to either infliximab (3 mg/kg at weeks 0, 2, 6 and 10), or etanercept (25 mg twice-weekly). Plasma was collected at baseline and at three months and its phosphatidylcholine fatty acid composition measured. The study was conducted in compliance with the Helsinki declaration and ethical approval was obtained from the West Glasgow Ethics Committee. All subjects gave written informed consent. To assess the effect of etanercept and EPA upon T helper 17 (Th17) differentiation, CD4+CD25− T cells and monocytes were purified from the blood of healthy donors by negative selection and co-cultured at a ratio of five T cells to one monocyte for 7 days in the presence of anti-CD3 (OKT3), with or without etanercept, EPA or the control fatty acid, linoleic acid. Expression of IL-17 and IFN-γ was measured by intracellular staining and flow cytometry.

Results: Time-averaged EPA levels and the EPA/arachidonic acid (AA) ratio correlated with change in DAS for 28 joints (DAS28) scores at 3 months (−0.51, P = 0.007 and −0.48, P = 0.01, respectively), indicating that higher plasma EPA was associated with a greater reduction in DAS28. EPA was also associated with EULAR response (P = 0.02), and the DAS28 components, ESR (P = 0.07) and tender joint count (P = 0.15) tended to be inversely associated with EPA tertile. An increase in Th17 cells post-therapy has been associated with non-response to anti-TNF, and may be driven by increased production of IL-23. Prostaglandins produced from AA also promote Th17 cell differentiation, and higher levels of EPA may impair AA-derived prostaglandin production. Thus, we examined the effect of etanercept and EPA upon Th17 generation. Etanercept increased Th17 frequencies in a dose-dependent manner (ANOVA P < 0.0001). Physiological doses of EPA, but not the control fatty acid, linoleic acid, prevented this etanercept-driven increase in Th17 frequency.

Conclusion: Dietary EPA supplementation might prove a simple method to improve anti-TNF outcomes in RA patients by suppressing accumulation of Th17 cells.

Disclosure statement: C.B. received a grant from Schering-Plough (now Merck) that supported this work. I.M. received a grant from Schering-Plough (now Merck) that supported this work. P.T. received a grant from Schering-Plough (now Merck) that supported this work. B.F. received a grant from Schering-Plough (now Merck) that supported this work. All other authors have declared no conflicts of interest.