

THE ROLE OF GUT MICROBIOTA IN MIGRAINE SUBJECTS TREATED WITH ANTI-CGRP MONOCLONAL ANTIBODIES: RESULTS THE SPHERA PROJECT

F. Muscariello[1|2], G. Vaghi[1|2], R. Greco[2], V. Grillo[1|2], M. Corrado[2], F. Cammarota[1|2], B. Agostini[1|2], M. Giraudo[1|2], C. Angeli[1|2], M. Allena[2], E. Guaschino[2], N. Ghiotto[2], R. Ornello[3], S. Sacco[3], C. Demartini[2], M. Francavilla[1|2], S. Facchetti[1|2], V. Pazienza[4], D. Sproviero[2], G. Sances[2], C. Tassorelli[1|2], R. De Icco[1|2]

[1]Department of Brain and Behavioral Sciences, University of Pavia, Italy; [2]Headache Science and Neurorehabilitation Unit, IRCCS Mondino Foundation, Pavia, Italy; [3]Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, Italy; [4]Division of Gastroenterology, Fondazione IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy

Background. Gut microbiota plays an important role in the pathophysiology of different neurological disorders via the gut-brain axis. Approximately 40% of migraine subjects do not achieve a meaningful benefit with anti-CGRP monoclonal antibodies (mAbs). We hypothesized that gut microbiota composition may differ between Responders and Non-Responders to mAbs and serve as one of the determinants of therapeutic outcome.

Methods. We enrolled 93 individuals treated with mAbs (age 41.2 ± 13.3 years) 82.9% females, with 15.0 ± 6.8 monthly migraine days (MMDs) at baseline and a previous failure of 3.1±1.3 preventive medication classes. Responders were defined as subjects achieving at least 50% reduction in MMDs after a 3-moth treatment with mAbs. Fecal samples were collected before mAbs treatment and analyzed by means of 16S rRNA gene sequencing, followed by the evaluation of alpha and beta diversities and the application of the ANCOM-BC2 statistical approach.

Results. After a 3-month treatment period with mAbs, 48 participants qualified as Responders and 45 as Non-Responders. Regarding overall microbial diversity, no differences were observed between the two groups, with comparable alpha-diversity and beta-diversity profiles. However, the ANCOM-BC2 approach demonstrated specific alteration between Responders and Non-Responders in gut microbiota composition at both the genus and species levels. Specifically, at the species level, Responder subjects exhibited a significantly higher abundance of Coprococcus eutactus (LogFC 1.89, $p < 0.001$), Marseilla massiliensis (LogFC 2.15, $p < 0.001$), Paraprevotella xylaniphila (LogFC 2.08, $p < 0.001$), Parasutterella secunda (LogFC 1.95, $p < 0.001$), Clostridium carnis (LogFC 1.43, $p = 0.001$). Conversely, Responder subjects showed a lower abundance of Rikenellaceae (LogFC -3.45, $p < 0.001$), Megamonas rupellensis (LogFC -2.24, $p < 0.001$), Coriobacteriia (LogFC -1.41, $p < 0.001$), Megasphaera massiliensis (LogFC -2.08, $p < 0.001$).

Conclusions. Future mAbs Responders exhibited a distinct microbiota composition associated with an anti-inflammatory profile, featuring a significant enrichment of butyrate-producing bacteria; by contrast, Non-Responders were characterized by a predominantly pro-inflammatory intestinal microbiome. These differences suggest that gut microbiota may act as a biological regulator capable of modulating the therapeutic response. Targeted interventions aimed at restoring intestinal eubiosis may represent a strategy to enhance the clinical response to mAbs.