C-2

Netazepide, a Gastrin/CCK$_2$ Receptor Antagonist, Can Eradicate Gastric Neuroendocrine Tumours in Patients with Autoimmune Chronic Atrophic Gastritis

Malcolm Boyce*[1]*; *Andrew R Moore[2]; Bryony Parsons[2]; Katie Lloyd[2]; Liv Sagatun[3]; Andrea Varro[2]; Reidar Fossmark[3]; Helge Waldum[3]; D Mark Pritchard[2]*

[1]Trio Medicines Limited; [2]University of Liverpool; [3]Norwegian University of Science and Technology

BACKGROUND: Type 1 gastric neuroendocrine tumours (g-NETs) arise from gastric mucosal ECL cells, which possess gastrin/CCK$_2$ receptors, and are found in patients with hypergastrinaemia secondary to achlorhydria caused by autoimmune chronic atrophic gastritis. ENETS guidelines estimate that 2–5% metastasise, and recommend annual gastroscopy/surveillance and endoscopic polypectomy or gastric antrectomy. NANETS guidelines for treatment are similar. However, recent surveys from centres in Europe and USA report metastasis rates of 8–19%.

Our aim was to find out if netazepide, a gastrin/CCK$_2$ receptor antagonist, can eradicate type 1 g-NETs, and to identify biomarkers to monitor efficacy.

METHODS: Sixteen patients with autoimmune chronic atrophic gastritis, hypergastrinaemia, multiple type 1 g-NETs, and raised blood CgA took netazepide, once daily for 12 weeks. After a mean 14 months off treatment, 13 took it for another 52 weeks. Assessments were gastroscopy, gene transcript expression in corpus biopsies, and blood CgA, miR-222 and gastrin.

RESULTS: Twelve weeks' treatment eradicated all tumours in one patient, reduced the number of tumours and size of the largest tumour in the others,

and normalised CgA. Gastrin was unaffected. While off treatment, the number and size of the tumours increased in all patients. 52 weeks' treatment eradicated tumours in 5 patients, left one patient with only one tumour, reduced further the number and size of tumours in the others, and normalised CgA ($p<0.01$). Again, gastrin was unaffected. Netazepide also reduced mRNA abundances of overexpressed CgA, histidine decarboxylase, pappalysin 2 (PAPPA2), glycoprotein hormones alpha polypeptide, and miR-222 in biopsies, and in blood ($p<0.05$). miR-222 targets the tumour suppressor and oncogene $p27^{kip^1}$. Netazepide was safe and well tolerated.

CONCLUSION: Netazepide is a potential medical and targeted treatment for type 1 g-NETs, and an alternative to endoscopic resection or surgery. Treatment can be monitored by biomarkers in blood or biopsies. The results justify a multicentre, placebo-controlled trial.