A novel autotaxin inhibitor, IOA-289, modulates tumor, immune and stromal cell function and has monotherapy activity in fibrotic cancer models

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Background

Autotaxin (ATX) is a secreted glycoprotein that hydrolyzes lysophosphatidylcholine (LPC) to lysophosphatic acid (LPA). The expression of both ATX and LPA is elevated in most solid tumors and plasma. LPA signaling directly modulates tumor cell function and contributes to the development of the fibrotic tumor microenvironment, which is a mechanism by which tumors evade host immunity and impair response to therapy. IOA-289 is a potent and orally available ATX inhibitor, being developed as a novel treatment of solid tumours burdened with a high degree of fibrosis. IOA-289 has completed a phase I clinical trial in healthy volunteers with an acceptable safety and PK profile supporting further clinical development.

Methods

PK/PD studies were performed following a single oral dose of IOA-289 in mice, and plasma LPA was used as a PD biomarker. Inhibition of ATX activity in human plasma was determined by measuring reduction in LPA species as quantified by LC-MS/MS. In vitro activity on biomarkers of fibrosis was assessed using the BioMAP® Fibrosis panel. Cell migration was measured using 48-well chemotaxis chambers. In vitro activity on fibrotic processes was characterized in the BioMAP® Fibrosis panel. In vivo efficacy was studied in two mouse models of breast cancer, 4T1 and E0771. An ELISA assay was used to analyse CA19-9 and ATX levels in human plasma samples. Bioinformatic analysis on gene expression used TCGA and GTEX publicly available datasets.

IOA-289 inhibits plasma LPA

Male CD1 mice dosed with 3, 10 or 30 mg/kg of IOA-289 p.o. showed dose-dependent reduction of circulating LPA C18:2 with an ED50 value at 1 h post-dose of around 3 mg/kg (Figure 1A and B).

Tumor-mediated inhibition of T-cell migration is reversed by ATXi

MDA-MB-435 cells secrete high levels of ATX and conditioned medium from MDA-MB-435 cultures inhibits CD8+ T cell migration. Inhibition of ATX by IOA-289 reverses the inhibitory effect of MDA-MB-435 conditioned media on CD8+ T cell migration. CCK110 is used as a positive control (Figure 2).

IOA-289 is a potent modulator of fibrotic processes in vitro

The BioMAP® Fibrosis panel consists of systems that models fibrotic tissues and disease by co-culturing stimulated human primary cells; lung epithelial cells and fibroblasts, lung fibroblasts only or renal epithelial cells with lung fibroblasts. IOA-289 was tested at concentrations of 6, 1.2 and 0.24 µM. At 6 µM IOA-289 decreased the activity of fibrosis relevant factors, including sIL-6, MCP-1, αSMA, collagen-III, and SV3GF (Figure 3).

IOA-289 inhibits metastasis in 4T1 model of breast cancer

Balb/c mice were orthotopically injected in the mammary fatpad with 4T1 tumor cells. One day before tumor inoculation, BID treatment with IOA-289 by oral gavage started. Fifteen days after tumor inoculation, the primary tumors were surgically removed and mice were taken off treatment. Primary tumor growth was assessed by weighing the excised tumor and did not show an effect (Figure 4A). In an independent experiment, histological analysis showed marked infiltration of CD8+ T cells (Figure 4B). Twenty days after removal of the primary tumor, lungs and bone marrow cultures inhibits CD8+ T cells (Figure 4C). Histological analysis of the lungs showed a marked reduction in metastatic burden for IOA-289 but not PF-8380 (Figure 4C). Colony formation assay from cultured bone marrow showed marked reduction in metastases by IOA-289 and PF-8380 (Figure 4D).

IOA-289 inhibits tumor outgrowth in E0771 model of breast cancer

C57BL/6 mice were orthotopically injected in the mammary fatpad with E0771 cells and treatment by oral BID started on day 3 and continued throughout the experiment. IOA-289 inhibited tumor outgrowth and induced two mice with complete tumor eradication (Figure 5A-C).

Conclusion

The ATX/LPA pathway represents a novel target for anti-cancer therapy with actions on the tumor and immune cells and on the stromal environment. IOA-289 is a high potency and selective inhibitor of ATX with demonstrated effects on T cell migration and fibrotic processes in vitro. IOA-289 has monotherapy activity in multiple fibrosis and cancer models, including breast and pancreatic cancer. Based on the mechanism of action we are investigating combinations of IOA-289 with chemotherapy, immunotherapy and novel agents in ongoing preclinical studies. IOA-289 has completed a phase I clinical trial in healthy volunteers with an acceptable safety and PK profile supporting further clinical development.

Conflict of interest statement:
MD, KNS, LvdV, ML and ZJ are employees and shareholders of iOnctura.