Title

Can TRPA1-Antagonists Solve The Unmet Medical Need For Chemotherapy-Induced Peripheral Neuropathy?

Introduction

Ever since the first phase-I clinical trials indicated a favourable safety profile, the clinical development of Transient Receptor Potential Ankyrin 1 (TRPA1) antagonists took further shape as novel, first-in-class analgesics (1). Unfortunately, only limited analgesia was observed in a small subgroup of patients with peripheral diabetic neuropathy, despite vast preclinical evidence for TPRA1 dysfunctionality in this context (2). To support their clinical development, we identified a novel target population via TRPA1 functionality assessments in vivo in patients with chemotherapy-induced peripheral neuropathy (CIPN).

Method and Materials

Patients with a grade ≥1 neuropathy (total neuropathy score [TNSc]) up to 12 months after oxaliplatin treatment were included, together with a sex- and age-matched healthy control group. Quantitative Sensory Testing (QST) was performed to assess thermal and mechanical pain thresholds, using a thermode and von Frey filaments, respectively. TRPA1 and, to control for any general TRPA1-unspecific effect, TRP Vanilloid 1 (TRPV1) functionality was evaluated by measuring the dermal blood flow (DBF) response to topical application of their agonists, 10% (v/v) cinnamaldehyde and 1000µg capsaicin, respectively. The DBF was quantified in Perfusion Units (PUs), using laser speckle contrast imaging during 60 minutes. Pain thresholds and maximal DBF changes were compared between both groups using an unpaired t-test or Mann-Whitney U test, $\alpha=0.05$, in GraphPad Prism. Data are presented as mean ± SEM.

Results

A total of 36 patients (50% male, aged 59±1 years) and 33 controls (52% male, aged 59±2 years) were included. Respectively 19 and 17 patients had a grade 1 (TNSc ≤ 7) and grade 2 (8 ≤ TNSc ≤ 14) neuropathy. Mechanical pain thresholds were lower in patients compared to controls, whereas cold and heat pain thresholds were similar in both groups (Figure 1). The maximal DBF upon application of cinnamaldehyde was significantly increased in patients compared to controls (Figure 2A), whereas capsaicin induced similar DBF changes (Figure 2B).

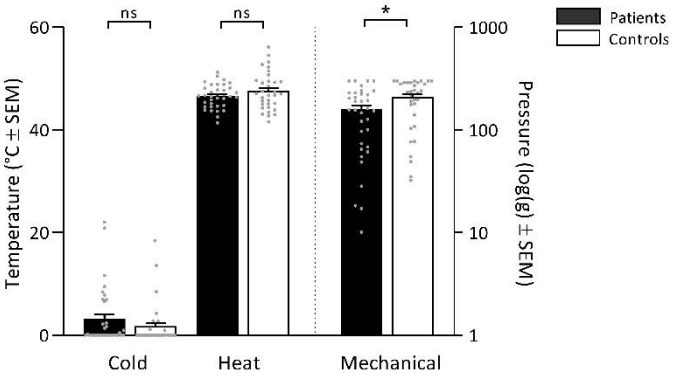

Figure 1. Pain thresholds for cold, heat and mechanical pressure in patients with chemotherapy-induced peripheral neuropathy compared to matched healthy controls. Statistical analysis using an unpaired t-test (heat) or Mann-Whitney U test (cold, mechanical), *p<0.05 is considered statistically significant.

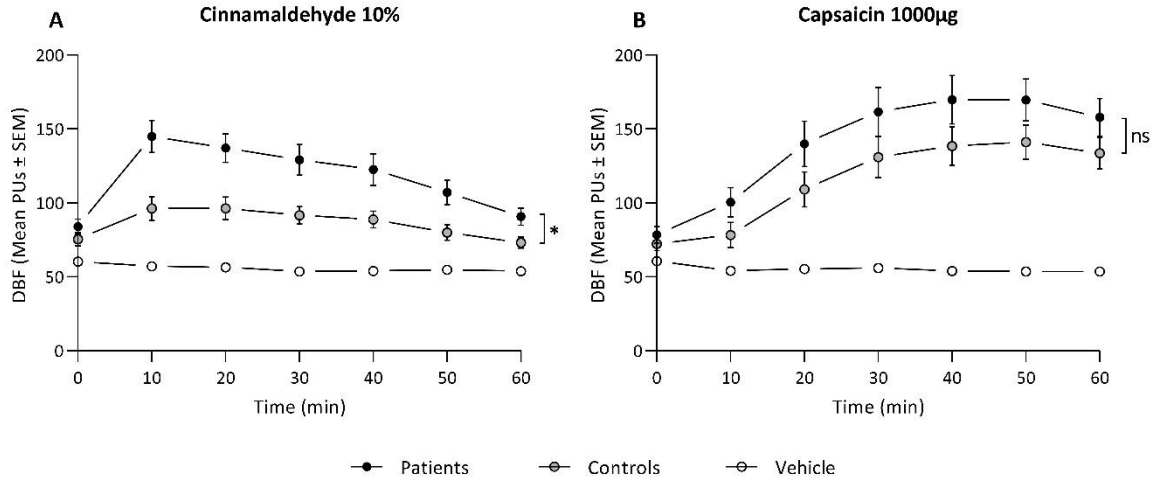

Figure 2. TRP-mediated dermal blood flow (DBF) upon topical cinnamaldehyde 10% (A), capsaicin 1000µg (B) and vehicle application in patients with chemotherapy-induced peripheral neuropathy, and matched healthy controls. Statistical analysis of the maximal DBF change using an unpaired t-test, *p<0.05 is considered statistically significant.

Conclusion

Patients suffering from chronic CIPN after oxaliplatin treatment displayed an increased TRPA1 functionality, identifying a promising novel indication for TRPA1 antagonists.

References

(1) Bamps D., et al. Annu Rev Pharmacol Toxicol;61:655-677 (2021)

(2) Jain SM., et al. Pain;163(6):e738-e747 (2022)

Authors

Heleen Marynissen, Jeroen Dekervel, Eric van Cutsem, Jan de Hoon; Leuven