Dalazatide modulates CD4⁺ effector memory T cell activity of patients with Granulomatosis with polyangiitis

L.L. Lintermans¹, E.J. Muñoz-Elias², M.G. Huitema³, A. Rutgers³, C.A. Stegeman³, P. Heeringa³, W.H. Abdulahad¹

Departments of ¹Rheumatology & Clinical Immunology, ²Nephrology and ³Pathology and Medical Biology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands ⁴Kineta Inc., Seattle, United States

BACKGROUND

CD4⁺ effector memory T cells (T_{EM}) play a key role in the pathogenesis of Granulomatosis with polyangiitis (GPA). The activation of CD4⁺ T_{EM} cells is uniquely dependent on the voltage-gate potassium channel Kv1.3. These Kv1.3 channels are highly expressed on chronically activated CD4⁺ T_{EM} cells and represent a novel target for therapeutic intervention. Dalazatide (formerly ShK-186) is a highly specific and potent peptide inhibitor of Kv1.3 channels. Blocking Kv1.3 channels has been shown to ameliorate autoimmune diseases in animal models of multiple sclerosis and rheumatoid arthritis. Therefore, selective targeting of pathogenic CD4⁺ T_{EM} cells by blocking Kv1.3 channels may be of benefit in the treatment of GPA patients.

OBJECTIVE

Does dalazatide suppress the pro-inflammatory cytokine production of CD4⁺ T_{EM} cells from GPA patients in vitro?

METHODS

Peripheral blood of remission GPA patients (R-GPA, n=23) and age-matched healthy controls (HCs; n=12) was stimulated in vitro with PMA/Ca-ionophore in the presence or absence of dalazatide. After stimulation cells were stained for surface markers and intracellular cytokines. Relative frequencies of cytokine expression were assessed within total CD4⁺ T cells and CD4⁺ T cell subsets using flow cytometry, and cytokine expression profiles of R-GPA patients were compared with HCs.

RESULTS

Dalazatide normalizes the pro-inflammatory cytokine production in CD4⁺ T cells from R-GPA patients in a dose dependent manner

Figure 1: Flow cytometry dot plots of cytokine production during different conditions

Figure 2: Dalazatide suppression of cytokine production by CD4⁺ T cells from R-GPA patients

Dalazatide inhibits cytokine production in CD4⁺ T_{EM} cells with minor effects in naive- and central memory CD4⁺ T cells

Figure 3: Flow cytometry dot plots of sorted CD4⁺ T cell subsets

Figure 4: Dalazatide inhibits cytokine production in CD4⁺ T_{EM} cells

CONCLUSION

- Dalazatide suppresses cytokine production in CD4⁺ T cells of R-GPA patients in vitro
- Dalazatide predominantly affects cytokine production by CD4⁺ T_{EM} cells
- Dalazatide may be of benefit in the treatment of GPA patients

Correspondence: L.L.lintermans@umcg.nl