

Protocol for a prospective, randomised, double-blind, placebo-controlled study to assess the clinical efficacy of crenotherapy with sulfurous thermal waters in patients with chronic rhinitis / rhinosinusitis

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Background Chronic rhinitis / rhinosinusitis (CRS) is associated with inflammation of the nasal and perinasal mucosa, with subsequent clinical symptoms. Sulfurous (natural mineral) thermal waters (STW) have been used as complementary therapeutic approach to CRS, with studies demonstrating clinical efficacy. However, few prospective, randomised, double-blind, placebocontrolled studies have been developed in order to assess clinical efficacy and none has been implemented in Portugal. Furthermore, worldwide, there is scant information of the modulatory effects STW crenotherapy may have on immune-inflammatory aspects underlying CRS.

Purpose The main purpose is to perform the first prospective, randomised, placebo-controlled, double-blind study of the clinical efficacy of crenotherapy with STW in patients with CRS treated in Portugal. Secondly, we also aim to assess the relationship between clinical efficacy and underlying immunopathological changes.

Methods In this two arm, parallel design study, 200 adult patients with confirmed CRS are being recruited and randomized to an active (STW crenotherapy) or a control (saline crenotherapy) arm. This study was approved by the Ethics Com-

mittee of UBI, and the National Agency for Data Protection. All patients will sign a written, informed consent. Recruitment is taking place at three natural mineral water Spas in Central Portugal, with predominantly STW (São Pedro do Sul, Caldas da Felgueira, and Unhais da Serra). At these places specifically designed equipment was set up in order to allow application of crenotherapy treatments with saline, in a fashion that is similar to that involving active STW. Patient inclusion criteria include moderate or severe CRS, with frequent exacerbations, insufficiently controlled with pharmacological treatment. The primary clinical outcome will be changes in the 22-item Sino-Nasal Outcomes Test (SNOT-22). Secondary outcomes will be: nasal symptom score, medication score, number of medical visits due to exacerbations, nasal symptom control (CARAT), quality of life (Rhino-AQLQ), medication costs, inspiratory nasal peak flow and Lund-Kennedy anterior rhinoscopy score. Secondary laboratory outcomes will be: changes in cytokine levels (IL-2, IL-4, IL-5, IL-6, IL-10, TNF, IFN γ , IL-17), in cisteinyl-leucotriene levels, and in differential cell counts, both in nasal fluid and in peripheral blood. Statistical analysis will involve Mann-Whitney U test, ANCOVA and Spearman rank correlation test. Clinical data analysis will follow an Intention-to-Treat model.

Conclusions This prospective, randomized, double-blind, placebo-controlled study will allow, for the first time, an adequate analysis of the clinical efficacy of STW crenotherapy in CRS in Portugal, as well as the study of its effects on underlying pathophysiological aspects.