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Efficacy of combined treatment with S-carboxymethylcysteine (carbocisteine) and clarithromycin in chronic rhinosinusitis patients without nasal polyp or with small nasal polyp

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Abstract

Objective: In Japan, fourteen-membered ring macrolides, antibacterial agents, and S-carboxymethylcysteine (SCMC; carbocisteine), a mucolytic, are commonly used to treat chronic rhinosinusitis (CRS), and they are also used in combination. However, no large-scale randomized study has examined the effects of these pharmacotherapies. The aim of this study is to evaluate the effect of combined administration of clarithromycin (CAM), a fourteen-membered ring macrolide, and SCMC, compared with CAM single therapy.
Methods: Patients with CRS were centrally registered and randomly assigned to treatment with CAM (200 mg/day) alone (monotherapy group) or CAM (200 mg/day) in combination with SCMC (1500 mg/day; combination group) for 12 weeks. We assessed the clinical efficacy of the treatments using measures of subjective symptoms and objective findings, health-related quality of life (HRQOL) determined by the 20-Item Sino-Nasal Outcome Test (SNOT-20) score and computed tomography (CT) score.
Results: Four hundred twenty-five subjects were enrolled (combination group, 213; monotherapy group, 212). At week 12 of treatment, the rate of effectiveness was significantly higher in the combination group (64.2%) compared with the monotherapy group (45.6%; $P = 0.001$). In addition, objective findings, including characteristics of nasal discharge ($P = 0.008$) and post-nasal discharge ($P = 0.002$) were significantly improved in the combination group. In both groups, SNOT-20 and CT scores were significantly improved from week 0 ($P < 0.001$), and were not significantly different between groups.
Conclusion: The results indicated that long-term combination therapy with SCMC at a dose of 1500 mg/day and CAM at a dose of 200 mg/day is effective for improving subjective symptoms and objective findings in adult patients with CRS.

Keywords: Chronic rhinosinusitis; S-carboxymethylcysteine; Clarithromycin; Randomized

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1. Introduction

Chronic rhinosinusitis (CRS) is a common chronic inflammatory airway disease. Patients with CRS exhibit excess viscous nasal discharge, post-nasal discharge, nasal obstruction, headache, and fatigue, all of which can significantly reduce quality of life. Fourteen-membered ring macrolide antibiotics have been used for the treatment of CRS. For most of the long-term treatments available, low dose oral administration of macrolide is reported to be effective for the relief of these symptoms [1,2]. The effectiveness of macrolide on CRS largely depends on the drugs' immunomodulatory effects rather than their antibiotic effects [3]. S-carboxymethylcysteine (SCMC; carbocisteine) is a mucoactive agent with blocked thiol groups. A recent study reported that long-term administration of SCMC significantly reduced the rates of exacerbation in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD) [4]. The development and progression of COPD involves a process of oxidative stress and protease-antiprotease imbalance that often becomes self-perpetuating [5]. Neutrophils play an important role in oxidative stress [5]. Since neutrophils are a key mediator of CRS [3], we hypothesise that SCMC may have a therapeutic role in the treatment of CRS.

In Japan, fourteen-membered ring macrolides, antibacterial agents, clarithromycin (CAM) and SCMC are commonly used to treat CRS, and they are also used in combination. However, no large-scale randomized study has examined the effects of these pharmacotherapies.

We examined the efficacy of SCMC in combination with low dose administration of CAM in adult CRS patients, and compared the results with treatment with low-dose CAM administration.

2. Materials and methods

2.1. Patients

The subjects were adult outpatients with CRS aged 20 years or older who visited the 62 study sites from May 2008 to September 2009. Patients who met the following inclusion criteria were included in the study: (1) at least 12 weeks of nasal obstruction, rhinorrhoea, post-nasal discharge, cough; (2) a paranasal sinus shadow in CT or plain X-ray images obtained after the onset of any of the symptoms listed in (1); (3) at least one subjective symptom (nasal discharge, rhinorrhoea, post-nasal discharge, nasal obstruction, heaviness of head [i.e. headache], olfactory disorder) and at least one objective finding (nasal mucosal redness, nasal mucosal oedema, nasal discharge, post-nasal discharge) at the start of the study; (4) a nasal polyp score of 0 or 1 as defined by Tos et al. [6] (i.e. patients who had a nasal polyp score of 2 or 3 were excluded); (5) outpatient status, (6) 20 years or older at the time of informed consent; and (7) able to understand questions.

Patients who met any of the following exclusion criteria were excluded from the study: (1) unable to tolerate SCMC or CAM; (2) treated with drugs for the treatment of airway diseases (expectorants) and/or fourteen-membered ring macrolides within 2 weeks before the start of the study; (3) planned treatment with anti-inflammatory enzyme preparations, steroids (oral/inhalation/injection/nasal drip), antiallergic drugs, and/or traditional Chinese medicine at the start of the study; (4) participating in another study at the start of the study; (5) have undergone radical sinus surgery; (6) have undergone any sinus surgery within 12 weeks before the beginning of the study; (7) the presence of fungal rhinosinusitis or suspected fungal rhinosinusitis (paranasal sinus mycosis); (8) complicated with bronchial asthma; (9) complicated with serious hepatic disease, renal disorder, cardiac disease, and/or other diseases; (10) complicated with malignant tumour; (11) pregnant or possibly pregnant, or lactating; and (12) considered by the investigator to be ineligible for the study for other reasons.

Voluntary written informed consent to participate in the study was obtained from each patient prior to participation, after the objectives and methods of the study were fully explained.

2.2. Study design

The study used a prospective, randomized, open-label design. Subjects were centrally registered and randomly assigned to the SCMC plus CAM group (combination group) or the CAM monotherapy group (monotherapy group). Subjects in the combination group were treated with SCMC at a dose of 1500 mg/day t.i.d. and CAM at a dose of 200 mg/day q.d. for 12 weeks, and those in the monotherapy group were treated with CAM at a dose of 200 mg/day q.d. for 12 weeks. Assessments were conducted at weeks 4, 8, and 12 of treatment.

2.3. Endpoints

The endpoints of the present study were the clinical efficacy of the treatments using measures of subjective symptoms and objective assessments, health-related quality of life (HRQOL) determined by the 20-Item Sino-Nasal Outcome Test (SNOT-20) score and computed tomography (CT) score.

2.4. Clinical efficacy

The clinical efficacy was assessed at weeks 4, 8, and 12 according to the criteria for assessment of clinical efficacy in Table 1, based on subjective symptoms as assessed by an otorhinolaryngologist from the symptoms reported by each subject during an interview, as well as objective findings assessed by an otorhinolaryngologist from the nasal examination [7].

In brief, subjective symptoms and objective findings were assessed on a four-grade scale from 0 to 3 for seven symptoms (''frequency of nose blowing'', ''ease of nose