**11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases**

**References**

**Tominaga K, Kato M, Takeda H, et al. A randomized, placebo-controlled, double-blind clinical trial of rikkunshito for patients with non-erosive reflux disease refractory to proton-pump inhibitor: the G-PRIDE study. *Journal of Gastroenterology* 2014; 49: 1392-405. Pubmed ID: 24535455**

Sakata Y, Tominaga K, Kato M, et al. Clinical characteristics of elderly patients with proton pump inhibitor-refractory non-erosive reflux disease from the G-PRIDE study who responded to rikkunshito. *BMC Gastroenterology* 2014; 14: 116. Pubmed ID: 24990161

**1. Objectives**

To evaluate the efficacy and safety of rikkunshito (六君子湯) for proton pump inhibitor-refractory non-erosive reflux disease.

**2. Design**

Double-blind randomized controlled trial (DB-RCT).

**3. Setting**

One university hospital department of gastroenterology and 48 other medical institutions (including university hospitals, non-university hospitals, clinics), Japan.

**4. Participants**

Two hundred and forty-two patients with PPI-refractory (FSSG [Frequency Scale for the Symptoms of gastroesophageal reflux disease {GERD}] scores greater than 8 after treatment with regular use of rabeprazole (RPZ), omeprazole, and lansoprazole for 4 weeks or longer) for non-erosive reflux disease (NERD).

**5. Intervention**

Arm 1: Oral administration of RPZ 10mg/day + TSUMURA Rikkunshito (六君子湯) 7.5g/day in 3 divided doses (administration period: 8 weeks) (n=109).

Arm 2: Oral administration of RPZ 10mg/day + placebo (granules that have a taste and scent similar to rikkunshito and are packaged similarly to rikkunshito [六君子湯]) 7.5g/day in 3 divided doses (n=108).

**6. Main outcome measures**

FSSG, GSRS (Gastrointestinal Symptom Rating Scale), and SF-8 (Short-Form Health survey-8) scores. Each domain of the SF-8.

**7. Main results**

Sixteen patients in the rikkunshito-administered group and 9 patients in the placebo-administered group were excluded due to invalid results or drop out due to adverse events. Both groups showed no significant improvement in FSSG and GSRS scores at week 4 and week 8. Mental component Summary (MCS) scores improved significantly in the rikkunshito group at week 4 compared to the placebo group ($P<0.05$). In patients aged over 65, acid-related dysmotility symptoms (ARD) improved significantly in the rikkunshito group at week 8.

**8. Conclusions**

Administration of rikkunshito in addition to RPZ improved subjective symptoms of PPI-refractory NERD; however, the difference compared to placebo was not statistically significant.

**9. From Kampo medicine perspective**

None. However, the improvement in the SF-8 MCS score was prominent in patients with BMI below 22.

**10. Safety assessment in the article**

There were no differences in serious complications related to the treatment drugs.

**11. Abstractor's comments**

Conducting a multi-center placebo-controlled trial in patients with PPI-refractory NERD deserves praise. However, the improvement in subjective symptoms of PPI-refractory NERD due to administration of rikkunshito plus RPZ (when compared with placebo) was not statistically significant. A sub-analysis and supplementary paper demonstrated that rikkunshito is effective in improving MCS score and ARD (manifesting as abdominal distension, stomach feeling heavy, and indigestion after meals) in elderly patients. Future analysis of its intended use should be anticipated.

**12. Abstractor and date**

Kogure T, 31 March 2017