Effect of oral magnesium supplementation on the kinetics of magnesium wasting induced by EGFR targeted antibody therapy for colorectal carcinoma (MAGNET trial)


Abstract

Background
Hypomagnesemia will occur in most patients treated with anti-EGFR antibodies. This magnesium loss is due to inhibition of renal TRPM6 leading to increased renal magnesium wasting in patients with colorectal cancer treated with EGFR targeted antibody therapy. The aim of the study was to determine the impact of magnesium supplementation on the rate of magnesium wasting and QoL in patients with colorectal cancer treated with EGFR targeted antibody therapy.

Methods
A prospective randomized multi-centre trial in patients treated with anti-EGFR antibodies for CRC evaluating the efficacy and tolerability of oral Mg gluconate for prevention of and/or treatment of Mg wasting. Patients were randomized to two arms: Arm A Mg gluconate 3 g bid. or Arm B no Mg supplementation. After occurrence of hypomagnesaemia grade 1, Mg gluconate 3 g bid was initiated in arm A whereas the dosage was increased to 3 g 6 times daily in arm B. The primary outcome variables were the slope of the serum Mg levels since baseline and the mean number of bowel movements per day. An a priori statistical analysis plan estimated the need to screen 160 patients (β = 0.05) to demonstrate an effect on serum Mg levels.

Results
After excluding 7 patients during screening, 89 were randomized to arm A (n=45 intervention) and 84 to arm B (n=44 supplementation). In an ITT approach, the mean serum Mg slope was significantly higher in arm A compared to arm B. The mean serum Mg level change was 0.0021 mg/dl/day (SD: 0.0069) vs. 0.0045 mg/dl/day (SD: 0.0069) in arm A and B, respectively. This led to insufficient number of patients to draw conclusions for the second part of the trial. The mean number of bowel movements was not different across arms. Oral Mg supplementation was not associated to significant adverse events.

Conclusions
This prospective randomized trial demonstrated that oral Mg gluconate 3 g bid. significantly decreased Mg wasting during anti-EGFR treatment in colorectal cancer, thereby delaying the occurrence of hypomagnesaemia. This treatment was well tolerated.


Rationale
• Magnesium wasting is present in virtually all patients treated with anti-EGFR antibodies, but the slope of wasting varies.
• If treated for a sufficient period of time, hypomagnesaemia will occur in most patients.
• The magnesium loss is due to inhibition of renal TRPM6, leading to defective Mg reabsorption in the distal convoluted tubule. In congenital hereditary disorders with severe TRPM6 dysfunction, high dose oral/enteral intake can partially compensate for this loss and maintain acceptable serum Mg levels.

Hypothesis
Oral supplementation with magnesium salts may prevent and/or significantly improve the magnesium wasting induced by EGFR targeted antibody therapy in colorectal cancer.

Objectives
Primary objectives:
• To evaluate the efficacy and tolerability of magnesium gluconate 3 g bid. given orally to modulate magnesium wasting in patients with colorectal cancer treated with EGFR targeted antibody therapy.
• To evaluate the efficacy and tolerability of magnesium gluconate 3 g 6 times per day compared to 3 g bid. given orally to modulate magnesium wasting in patients with colorectal cancer with grade 1 hypomagnesaemia induced by EGFR targeted antibody therapy.

Secondary objectives:
• To measure compliance to magnesium supplementation regimen
• To measure the impact of magnesium supplementation on asthma and Quality-of-Life

Outcome variables
Primary
• The slope of the change in serum Mg levels
• The mean number of bowel movements per day.
Secondary
• Fatigue according to CTC version 3.0
• QoL score at two-weekly intervals
Sample size: 1-β=0.9; a=0.05: 34 patients per arm

Patients
• Arm A: Mg slope: -0.0045 mg/dl/day (SD: 0.0069)
• Arm B: Mg slope: -0.0021 mg/dl/day (SD: 0.0069)

Results
• Arm A: Mean number of stools: 2.0 /day (SD: 1.5)
• Arm B: Mean number of stools: 2.2/day (SD: 1.7)
NS: (P=0.312)

Conclusion
This adequately powered prospective randomized multi-centre trial demonstrated that:
• Oral Magnesium gluconate 3g bid. significantly decreased Magnesium wasting during anti-EGFR treatment for colorectal cancer
• There was no significant increase in the number of stools per day in the treatment arm.

The number of patients reaching hypomagnesemia grade 1 during the trial was insufficient to draw valid conclusions on the impact of low vs. high Mg dosages in rescue therapy.

There was no significant effect of the intervention on fatigue nor Quality of Life

The authors wish to thank:
• The patients for their participation
• Mrs Anna-Sophie Hints, Mrs Nathalie Verdon, Mrs Micheline Stampin, Mrs Lesley Debaeer and Mrs Greatje Vrenhout for data management.
• The investigators: