

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

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## Abstract

### Background

Progressive decrease of serum magnesium levels occurs in virtually all patients treated with anti-EGFR antibodies. This is supposedly linked to an inhibition of renal TRPM6 activity. This Mg loss may ultimately require stopping the anti-cancer treatment. In patients with congenital TRPM6 deficiency, high dose oral Mg supplementation allows to maintain acceptable serum Mg levels but may induce significant diarrhoea. We hypothesized that oral Mg gluconate substitution may prevent and/or treat Mg wasting due to anti-EGFR treatment in colorectal cancer (CRC).

### Methods

We performed 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 and/or treatment of Mg wasting. Upon initiation of anti-EGFR treatment, patients were randomized to no intervention (arm A) or Mg gluconate 3 g bid (arm B). After occurrence of hypomagnesaemia grade 1, Mg gluconate 3 g bid was initiated in arm A, whereas the dosage was increased to 3g 6 times daily in arm B. The co-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 180 patients ( $\beta = 0.90$ ) to demonstrate an effect on serum Mg slopes.

### Results

After excluding 7 patients during screening, 89 were randomized to arm A (no intervention) and 84 to arm B (Mg supplementation). In an ITT approach, the mean serum Mg slope was significantly ( $p = 0.015$ ) steeper in arm A:  $-0.0045$  (95%CI:  $-0.0062$  to  $-0.0034$ ) vs.  $-0.0021$  (95%CI:  $-0.0037$  to  $-0.0009$ ) mg/dl/day in arm B. Hypomagnesaemia occurred in 12 and 4 patients respectively ( $p = 0.05$ ). 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.

### References

1. Tejpar et al., Lancet Oncol 2007
2. Konrad et al., Am J Physiol Renal Physiol 2004

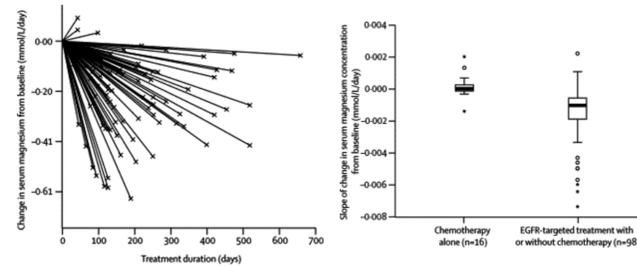
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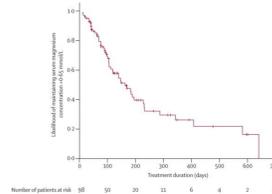
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## Rationale

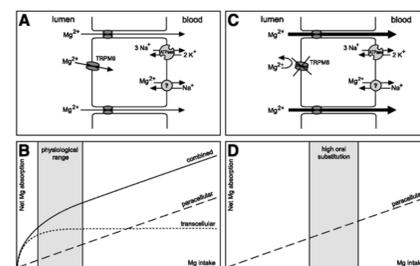
- Magnesium wasting is present in virtually all patients treated with anti-EGFR Ab, but the slope of wasting varies<sup>1</sup>.



- 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 similar TRPM6 dysfunction, high dose oral/enteral intake can partially compensate for this loss and maintain acceptable serum Mg levels<sup>2</sup>.



## 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

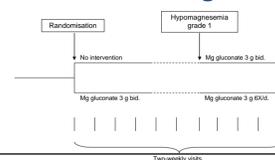
### Primary objectives:

- 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 six 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 regimens
- To measure the impact of magnesium supplementation on asthenia and Quality-of-Life

## Trial Design



## Outcome variables

### Primary

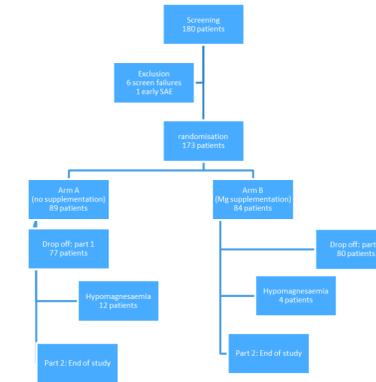
- The slope of the change in serum Mg levels
- The mean number of bowel movements per day.

### Secondary

- fatigue according to CTC version 3.0
- QoL score at two-weekly intervals

Sample size:  $1-\beta=0.9$ ;  $\alpha=0.05$ : 34 patients per arm

## Patients



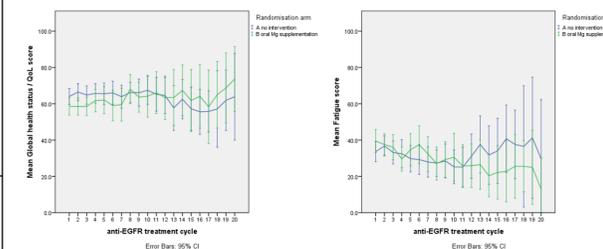
## Results

### Primary Outcome

- Arm A: Mg slope:  $-0.0045$  mg/dl/day (SD: 0.0069)
  - Arm B: Mg slope:  $-0.0021$  mg/dl/day (SD: 50)
- Normally distributed;  $P=0.015$  (t-test)

- 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: ( $P=0.312$ )

### Secondary Outcome



## Conclusion

This adequately powered prospective randomized multicentre 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 hypomagnesaemia grade 1 during the trial was insufficient to draw valid conclusions on the impact of low vs. high Mg dosage in rescue therapy.

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

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- The investigators:

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