DCE-MRI Provides Evidence for Vascular Effects of AMG 386, a First-in-Class Anti-angiogenic Peptibody that Specifically Inhibits Interaction of Angiopoietins-1 and -2 with Tie-2

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Introduction

AMG 386 is a peptide-fc fusion protein (peptibody) that specifically inhibits the interaction of angiopoietins-1 and -2 (Ang1/2) with Tie-2 receptor (1). In a preclinical setting, angiopoietin inhibitors have been shown to suppress Colo205 tumor xenograft growth (with an associated increase in necrotic tumor fraction) and VEGF-induced corneal angiogenesis (1). We performed DCE-MRI in Colo205 xenografts and in the first in human (FIH) clinical trial (2) to study the effect of AMG 386 on tumor vasculature.

Materials & Methods

Preclinical: An MRI study was performed on anesthetized Colo205 xenograft - CD 1 nu/nu mice using a 4.7 T Bruker BioSpec. DCE-MRI with gadopentetate dimeglumine (GD, 0.2 mmol/kg i.v.) was used to assess tumor vascularity (3) and retention of a novel biodegradable polyglutamic acid Gd-DTPA polymer (PG, 0.3 mmol/kg i.v.) was used to assess tumor necrosis (4) [only DCE-MRI data are reported here]. DCE-MRI (8 slices, TE=1.4 ms, TR=40 ms, α=35°, 5 sec per acquisition) was performed at baseline and 7 days after treatment in six vehicle control animals and six treatment animals, at each of four dose levels (0.56, 2.8, 14, and 350 µg AMG 386 s.c. twice weekly). GD was administered 5 min following injection of PG, which saturated the blood pool signal. In order to more closely mimic the clinical setting, a second study was performed using GD only to acquire DCE-MRI without prior injection of PG at baseline and 7 days after treatment in six vehicle control animals and six 350 µg AMG 386 treated animals. DCE-MRI data were analyzed as previously described (3) to determine the muscle normalized initial area under the curve (IAUC). T-tests were used to test whether a mean differed from zero (paired) or differed between two groups.

FIH clinical: Four-six subjects in 5 sequential dose escalation cohorts received weekly IV doses of AMG 386 at 0.3, 1, 3, 10, and 30 mg/kg and ten subjects in a dose expansion cohort received weekly IV doses of 30 mg/kg AMG 386. Three-dimensional oblique coronal gradient echo image DCE-MRI (12 slices (8 used), TE=1.1 ms, TR=5.3 ms, α=30°, 11 sec per acquisition) was performed at 1.5 T at baseline, day 2, and week 4 (escalation cohorts) or week 8 (expansion cohort) for 17 of the 32 subjects entered into the study. DCE-MRI data were analyzed as previously described (5) to determine the blood normalized IAUC and K^{trans}. Since multiple tumors were assessed in some subjects, a mixed model with subject as a random effect was used to estimate the mean percent change in median IAUC and the standard error (SE) from baseline to both day 2 and week 8.

Results & Discussion

Preclinical: Figure 1 shows the percent changes in tumor IAUC (normalized to the same measure in muscle) at Day 7 compared to baseline. The mean (±SE) change in IAUC was -2.2% ± 11.5% for control mice (N=12; P=0.85) and -25.1% ± 3.8% for treated mice (N=28; P<0.001), no dose-response relationship was evident. For mice treated with 350 µg AMG 386, there is no difference between the change in IAUC when both contrast agents were used and when only GD was used (P=0.45). This indicates that clinically-available low MW contrast agent should be able to assess the vascular effect of angiopoietin-targeted agents in clinical trials. It should be noted that the treatment effect is substantially less than that previously reported for VEGF-targeted agents.

FIH clinical: A ≥ 20% reduction from baseline in median IAUC (normalized to the same measure in blood) was observed in 8 of 15 evaluable lesions (6 of 12 subjects) 48 hours after the first dose of AMG 386, in 2 of 5 lesions (2 of 5 subjects) at week 4, and in 5 of 8 evaluable lesions (4 of 7 subjects) at week 8 (Figure 2). No exposure response relationship was evident; 13 of 17 subjects studied by DCE-MRI (including 10 of 12 subjects with analyzable DCE-MRI data) received the highest dose of AMG 386 (30 mg/kg). The mean (±SE) change in median IAUC for subjects treated with 30 mg/kg AMG 386 was -19.4% ± 7.1% two days after the start of treatment (N=10; P=0.023) and -28.9% ± 10.5% eight weeks after the start of treatment (N=6; P=0.040). The changes in K^{trans} data are similar to those in IAUC, which are consistent with the changes observed in the preclinical study.

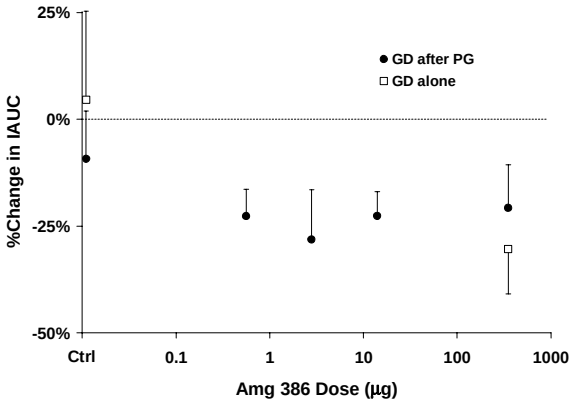

Figure 1 Mean %change in IAUC in Colo205 tumors at Day 7 following treatment with AMG 386. Solid circles represent the study using both contrast agents; open squares represent the GD only group. (Error bars = SE)

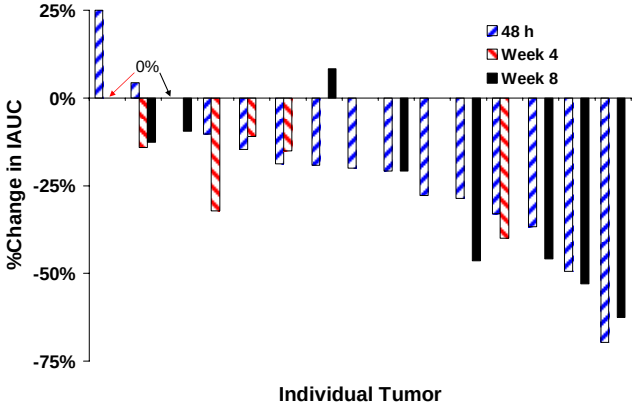

Figure 2 'Waterfall' bar graph showing %change in median IAUC at 48 h (blue), week 4 (red) and week 8 (black) after AMG 386 treatment in the FIH study. The change was 0% for the first tumor at Week 4 and for the third tumor at 48 h.

Conclusion

Even though the vascular effects are not as dramatic as for VEGF-targeted molecules, both pre-clinical and clinical DCE-MRI results demonstrate a significant vascular effect of this first-in-class anti-angiogenic investigational drug that provides highly potent and selective inhibition of angiopoietins (1).

References

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