

AMAP102: an orally available small molecular drug with beneficial effects on arthritis and inflammatory pain

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Background

AMAP102 is a novel small molecular drug under development for oral treatment of rheumatoid arthritis (RA), a disease associated with severe joint inflammation and chronic pain. Previous studies (EULAR 2006, Poster SAT0185) have shown that AMAP102 reduces the *in vitro* release of TNF- α and IL-6 by human macrophages and rat synovial fibroblasts, respectively. Furthermore, oral administration of AMAP102 twice daily reduces arthritis severity in two animal models, i.e. collagen-induced arthritis (CIA) in mouse and antigen-induced arthritis (AIA) in rat. After being evaluated in an extensive pre-clinical toxicology and safety programme, AMAP102 is now ready for tolerability and safety studies in healthy human subjects.

Objectives

The current study had three objectives: (1) to further investigate the therapeutic potential of AMAP102 in rat AIA, (2) to test AMAP102 in a third animal model of RA, glucose-6-phosphate isomerase (GPI)-induced arthritis in mouse, and (3) to investigate whether AMAP102 affects inflammatory pain.

Methods

In AIA, Dark Agouti rats were immunized with antigen and thereafter challenged intra-articularly 11 days later. AMAP102 (10 mg/kg or 30 mg/kg) was administered orally either once or twice daily, starting either 4 h before or 24 h after challenge. Knee joint swelling was assessed by caliper measurements. In GPI-induced arthritis, DBA/1 mice were immunized with rabbit GPI. Starting on day 7, the mice were scored for arthritis and orally treated with AMAP102 (10 and 30 mg/kg) once daily. To investigate the effect of the compound on inflammatory pain, AMAP102 (1, 10 and 30 mg/kg) was orally administered to Sprague Dawley rats 60 min before injection of 50 μ l of 5 % formalin into the dorsum of the right hind paws. Nociceptive responses to the formalin injection were measured as the cumulative time of lifting, licking, shaking and flinching of the injected paws. The nociceptive response occurs in two phases (0-15 min and 15-60 min), of which the second (phase 2) represents the pain response to the inflammatory reaction, whereas the first (phase 1) is caused by the direct stimulation of nerve ends by formalin.

Results

Once daily oral administration of AMAP102 (10 mg/kg) was shown to reduce AIA with similar effectiveness as administration of the compound twice daily, when treatment was initiated at challenge. Also, AMAP102 (30 mg/kg, twice daily) reduced joint swelling in established AIA ($p < 0.01$). In addition, AMAP102 was shown to reduce the severity of GPI-induced arthritis at both dose levels (day 14: $p < 0.001$ and $p < 0.05$ for 10 and 30 mg/kg, respectively). Importantly, oral administration of AMAP102 at 30 mg/kg significantly ($p < 0.01$) reduced the inflammatory pain response (phase 2), without influencing the first phase of the nociceptive response. The level of pain reduction was similar to that obtained with 30 mg/kg ketoprofen, an NSAID. **Conclusions:** These results expand the previous knowledge regarding the therapeutic potential of orally administered AMAP102. In addition

to its anti-arthritic effects, AMAP102 also diminishes inflammatory pain responses. In conclusion, the study strongly supports the clinical development of AMAP102 for RA treatment.