PDGFR inhibitor ARRY-768 prevents experimental dermal fibrosis and induces regression of pre-established dermal fibrosis

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Introduction

Systemic sclerosis (SSc) is a systemic, potentially lethal, chronic autoimmune disorder of unknown etiology. The disease is characterized by inappropriate wound healing leading to widespread fibrosis in the skin and other organs, accelerated collagen turnover, and systemic vascular and pulmonary hypertension. Mammalian target of rapamycin (mTOR) activation, profibrotic cytokines and myofibroblasts are key features of the disease. Moreover, PDGFRα and the downstream target AKT signaling are elevated in SSc skin. mTOR inhibitors are being tested in SSc. However, a targeted small molecule reduced systemic fibrosis in a rat model of SSc, and it was suggested that inhibition of PDGFR might be beneficial. Therefore, the aim of the present study was to determine the efficacy of the PDGFR inhibitor ARRY-768  in the prevention of dermal fibrosis and induction of regression of established dermal fibrosis in collagen-induced dermal fibrosis (CIDF)

Results

ARRY-768 shows potent inhibition of PDGFR induced phosphorylation in skin homogenates

Fig. ARRY-768 shows potent inhibition of PDGFR induced phosphorylation in skin homogenates of SSc patients and healthy subjects.

ARRY-768 selectively reduces the expression of activated (phosphorylated) PDGFR-β in the skin challenged with bleomycin

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Inhibition of PDGF via ARRY-768 prevents induction of dermal fibrosis by bleomycin

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Material and Methods

Knockout-induced dermal fibrosis

SSc patients were examined to detect the efficacy of ARRY-768 in the prevention of experimental fibrosis (Fig. A). A stable model of knockout-induced fibrosis was established and the effects of ARRY-768 were examined to define the mechanism of action of ARRY-768 in vivo. The skin was examined pharmacologically and histologically by immunohistochemistry and Western blotting.

In the experimental design of regression of pre-established bleomycin-induced dermal fibrosis, bleomycin concentration for ARRY-768 2 hours post final dose was 0.774 ± 0.022 µg/ml for the dose of 30 mg/kg and 0.035 ± 1.045 µg/ml for the dose of 150 mg/kg.

ARRY-768 Pharmacokinetics

The treatment with ARRY-768 was well tolerated for 3 weeks at all dosing regimens (20, 50 or 100 mg/kg) and no signs of toxicity such as weight loss, decreased activity or changes in the texture of the fur were observed.

Summary and Conclusion

- ARRY-768 is a highly potent, orally active PDGFR inhibitor
- ARRY-768 shows more potent inhibition of PDGFR compared to imatinib
- ARRY-768 shows significant selectivity over VEGFR-2, Kit and Abl which may give it a competitive advantage over other multikinase inhibitors that also target PDGFR and thus should not be dose limited in humans by off-target kinase toxicities.
- Treatment with ARRY-768 not only prevented induction of dermal fibrosis but also induced regression of pre-established dermal fibrosis induced by bleomycin to under-pre-treatment levels. ARRY-768 was well tolerated at all doses and showed no signs of toxicity.
- Control treatment with imatinib showed no superior anti-fibrotic effects than ARRY-768 suggesting that the effects of imatinib might be mediated primarily via inhibition of PDGFR, whereas inhibitory effects on c-abl, a downstream mediator of TGF-β, seem to be less relevant.

Acknowledgements

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References


Figures:

1. ARRY-768 shows potent inhibition of PDGFR induced phosphorylation in skin homogenates of SSc patients and healthy subjects.

2. ARRY-768 selectively reduces the expression of activated (phosphorylated) PDGFR-β in the skin challenged with bleomycin.

3. Inhibition of PDGF via ARRY-768 prevents induction of dermal fibrosis by bleomycin.