AZD1402/PRS-060, an inhaled Anticalin® IL-4Rα antagonist, potently inhibits IL-4 induced functional effects in human whole blood, which can be employed translationally in clinical studies.


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Abstract

Introduction: AZD1402 is an Anticalin® protein in clinical development that has the potential to offer an inhaled treatment for asthma patients suffering from T2-driven disease through selective blockade of IL-4Rα.

Aims and objectives: To characterise the effect of AZD1402 on IL-4Rα signalling in human whole blood (WB) and establish a method to evaluate the functional impact of systemic exposure to AZD1402 following inhaled dosing.

Methods: WB from healthy subjects was stimulated with IL-4 in the presence or absence of AZD1402. Phosphorylation of signaling components and released soluble biomarkers were quantified using FACS and multiplex ELISA, respectively.

Results: Stimulation of human WB with IL-4 resulted in increased levels of phosphorylated STAT6 (pSTAT6) and in the release of eotaxin-3, TARC, and MDC. AZD1402, when added to WB samples (n=12), inhibited pSTAT6 in a concentration-dependent manner and with similar potency to the anti-IL-4Rα monoclonal antibody dupilumab (IC50 values 1.3 and 0.8 nM, respectively). Inhibition of the release of the soluble cytokines eotaxin-3, TARC, and MDC by AZD1402, at equivalent potency to dupilumab, was observed (IC50 values 2.1 nM, 1.3 nM, and 2.0 nM, respectively). The low level of variation observed renders this method suitable for detecting the presence of systemic (pharmacologically active) levels of AZD1402 following inhaled dosing.

Conclusions: AZD1402, potently inhibits IL-4Rα signalling in human WB with IC50 values comparable to those of dupilumab. pSTAT6 responses in WB are used in the NCT03384290 Phase I trial to assess systemic exposure.

Introduction

- AZD1402 is an Anticalin® antagonist of IL-4Rα, intended as an inhaled treatment for moderate to severe asthma through selective receptor blockade in T2-driven disease.
- AZD1402 is currently in Phase 1 studies; a single ascending dose study in healthy volunteers and multiple ascending dose study in mild asthmatics.
- IL-4 signals via IL-4Rα and results in phosphorylation of STAT6, downstream gene transcription and cytokine release of mediators such as Eotaxin-3, TARC, and MDC (Fig. 1).
- Assessing AZD1402 functional effects in whole blood with robust assays allows us to determine systemic target engagement and potentially to help dissect local from systemic effects of the inhaled drug.

Figure 1: IL-4Rα is the common receptor subunit for signalling of IL-4 and IL-13

Results

- AZD1402 inhibits IL-4 signaling in whole blood as assessed by STAT6 phosphorylation and MDC production induced by IL-4 stimulation. It had a similar potency to dupilumab in these functional assays.
- Measurement of ex vivo IL-4-stimulated pSTAT6 responses in whole blood as well as downstream cytokine release can be used to assess systemic target engagement following inhaled dosing of AZD1402. Furthermore, these assays will contribute to a more complete understanding of the site of action of this drug.

Conclusions

- AZD1402 inhibits IL-4 signaling in whole blood as assessed by STAT6 phosphorylation as well as Eotaxin-3, TARC and MDC production induced by IL-4 stimulation. It had a similar potency to dupilumab in these functional assays.
- Measurement of ex vivo IL-4-stimulated pSTAT6 responses in whole blood as well as downstream cytokine release can be used to assess systemic target engagement following inhaled dosing of AZD1402.

References


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