KINASE SELECTIVITY PROFILES OF NINTEDANIB AND IMATINIB.

Methods In this cross-sectional study, demographics, medication and spirometry were prospectively recorded from patients attending a secondary care asthma clinic who were also genotyped and completed the Asthma Control Questionnaire (ACQ-6).

Results A total of 223 patients prescribed ICS were included in the analysis. Overall mean age was 46 years, FEV1 86%, median ICS dose 800 μg/day and 73% were prescribed LABA. There were no differences in terms of spirometry and ACQ-6 between the three genotypes (Table 1). In patients who were prescribed LABA there was no difference in ACQ-6 comparing patients with no Arg copies (n = 80, ACQ-6 1.82) versus those with one or two Arg copies (n = 83, ACQ-6 1.70). Moreover salbutamol reliever use was no different.

Conclusion Gly16Arg polymorphism was not associated with impaired asthma control in ICS treated adult asthmatics irrespective of LABA exposure.

REFERENCES

Basic mechanisms of IPF

Introduction Tyrosine kinase inhibition has shown inconsistent success in the treatment of idiopathic pulmonary fibrosis (IPF). While a study of imatinib showed no impact on survival or lung function in a placebo-controlled study, two recently announced placebo-controlled phase 3 trials of nintedanib demonstrated statistically significant impact on forced vital capacity. Comparing the kinase target profiles could inform future target selection for drugs in IPF.

Methods In vitro kinase selectivity data of nintedanib and imatinib were collected using the kinomescan platform (DiscoveRx Inc). Binding data (% binding) for 451 human kinases (~80% of the human kinome) were initially collected at a single concentration (10 μM). For kinases that displayed significant binding, potencies (Kd) were measured in dose-response format.

Results At a common concentration of 100 nM, imatinib and nintedanib bound to 12 and 50 kinases, respectively. Maximal drug concentrations (Cmax) observed in patients were used to project therapeutically relevant kinase inhibition for both drugs. Using these criteria, nintedanib binds 44 kinases at drug levels seen in patients (Kd < Cmax of 64 nM). Imatinib binds 34 kinases at drug levels seen in patients (Kd < Cmax of 7500 nM). 14 kinases were bound by both compounds, including PDGFRα, PDGFRβ and VEGFR2.

Conclusions Our results suggest that nintedanib and imatinib have partially overlapping inhibition profiles; the kinases that are targeted by both agents are unlikely to be responsible for efficacy differences. Further work is required to identify which of the remaining kinase target (s) are responsible for efficacy in IPF and could therefore represent targets for follow-up compounds.