

THE development of selective PAF receptor antagonists may provide a novel approach to the treatment of human bronchial asthma. In preclinical animal models of human asthma, PAF receptor antagonists have been found to be efficacious in blocking antigen-induced changes in lung function. However, the majority of these models involve acute inflammatory events and transient changes in lung function and, therefore, their relevance to human asthma is questionable. In a recent study with a primate model of chronic airway inflammation and hyperresponsiveness, we have shown that treatment with a PAF receptor antagonist had no effect on reducing chronic inflammation and hyperresponsiveness. Similarly, recent studies in human asthmatics with PAF receptor antagonists have failed to show efficacy in blocking allergen-induced airway responses or to have any steroid sparing effects in patients with ongoing asthma. Thus, it seems that PAF may not be a key mediator which can be blocked and thereby provide therapy for bronchial asthma.

Key words: PAF, Asthma, PAF receptor antagonists.

Is platelet activating factor (PAF) an important mediator in bronchial asthma?

R. H. Gundel,^{CA} H. O. Heuer and L. G. Letts

Department of Pharmacology, Boehringer
Ingelheim Pharmaceuticals, Inc., Ridgefield,
CT 06877, USA

^{CA} Corresponding Author

Bronchial asthma is a disease that affects approximately 5–8% of the population and despite the availability of more potent, selective therapies, the incidence of asthma morbidity and mortality is increasing. Asthma is a complex disease that is characterized, in part, by a reversible, episodic bronchoconstriction and wheeze. The airways of asthmatics are inflamed and hyperresponsive making them respond (constrict) to a variety of stimuli.

Over the past few years it has become increasingly apparent that asthma has a strong inflammatory component. This realization has prompted an intense effort within academia and industry to define the role of inflammatory cells and mediators in asthma. The hypothesis that PAF is an important mediator in the pathophysiology of asthma was initially derived from studies demonstrating its ability to constrict airway smooth muscle at very low doses¹ as well as its pro-inflammatory properties.² While the bronchoconstrictive and oedema-inducing effects of PAF are shared by other putative mediators of inflammation such as histamine, thromboxane and leukotrienes, PAF is the only mediator which simultaneously increases mucus secretion³ and recruits platelets and eosinophils⁴ from the extravascular space into the lungs. Since eosinophils are thought to play an important role in the pathogenesis of asthma, it is of interest therefore, that PAF is among the most potent chemotactic factors for eosinophils.⁵ Furthermore, similar to antigen inhalation, inhaled PAF induces an acute and late-phase response in

dual responder animals⁶ and, in addition, has been shown to induce bronchial hyperreactivity in different species including man.⁷ Thus, in light of the biology of PAF, the development of selective PAF-receptor antagonists seemed most promising in terms of a novel approach to the treatment of bronchial asthma.

PAF antagonists in preclinical animal models: Studies of PAF antagonists in preclinical models of asthma have produced encouraging results demonstrating potent inhibition of allergen induced bronchoconstriction, infiltration of eosinophils into the airways, lung oedema formation, late phase reactions and the development of nonspecific bronchial hyperresponsiveness. In addition, the formation and release of inflammatory mediators (including leukotrienes, prostaglandins, thromboxanes and histamine) have been shown to be inhibited by selective PAF receptor antagonists *in vivo*, although a direct interaction of the PAF antagonists with these mediators has been excluded. The role of PAF in a sequence of pathophysiological events involving other mediators, and the possibility of interactive synergism, strengthens the view that antagonists of PAF may have effects extending beyond those assumed for a single mediator. In models of *in vivo* anaphylaxis the divergent results obtained with PAF antagonists may be due to differing experimental conditions (e.g. testing in the absence of a small dose of an antihistamine, antigen load during challenge, booster sensitization etc.) and the different potency and bioavailability of PAF

antagonists *in vivo*. PAF antagonists seem to work more consistently in passive anaphylaxis and during challenge with the antigen by the inhaled route.⁸ In active anaphylaxis PAF antagonists are more effective when animals are once sensitized compared to a booster sensitization regimen,^{9,10} however, PAF antagonists can still block anaphylaxis in boosted animals.¹⁰ With respect to microvascular permeability, in one set of experiments a PAF antagonist failed to block leakage at a dose which inhibited PAF induced microvascular leakage.¹¹ Other results are in favour of a PAF antagonist blocking antigen induced microvascular leakage.¹²

PAF antagonists block eosinophil and leukocyte infiltration in the bronchial tissue and appearance of the cells in bronchoalveolar fluid of sensitized guinea pigs,⁴ rabbits¹³ and monkeys.¹⁴ A few studies have, however, failed to show this effect. Inhibition of the late phase response to antigen with selective PAF antagonists has been demonstrated in several animal models including allergic guinea-pigs,¹⁵ rabbits,¹⁶ sheep⁶ and monkeys.¹⁴ Inhibition of antigen increased bronchial responsiveness by selective PAF antagonists has been reported by several groups in guinea-pigs,¹¹ rabbits¹³ and other species.¹⁷ The experimental conditions in the studies cited above involve a single antigen challenge to sensitized animals with normal (uninflamed) lungs and the relevance of these preclinical models to human bronchial asthma remains unclear.

PAF antagonists in clinical studies: In contrast to supportive results from preclinical models of asthma, the clinical data obtained so far are not in favour of a major role of PAF in human bronchial asthma.¹⁸⁻²⁰ Despite the fact that several clinical studies have documented that PAF antagonists block exogenous PAF induced effects in man,^{21,22} oral or inhaled PAF antagonists have failed to block antigen induced early or late phase responses or increases in bronchial responsiveness. In addition, there is also no support for clinical efficacy from a recent phase II steroid sparing study in ongoing human bronchial asthma (S. Holgate, personal communication). One may speculate on the possible reasons for the discrepancy between supportive preclinical results and failure of PAF antagonists in clinical human asthma. The first and most obvious conclusion that can be drawn from the clinical data is that, in contrast to different animal species (including monkeys), PAF is not an important mediator in human asthma. Secondly, although there is no convincing evidence that different subtypes of PAF receptors exist in lung tissue and inflammatory cells present in lung tissue, there may be subtypes of PAF receptors including intracellular receptors with varying affinities for PAF and PAF antagonists. This question deserves further investi-

gation. Third, due to priming and synergism of PAF with other mediators of inflammation produced during chronic asthma, the doses of PAF antagonists needed may be far higher than those needed to antagonize exogenous PAF.²³ However, it is also conceivable that a high dose therapy of PAF antagonists may result in an up-regulation of PAF receptors or expression of other ligands involved in the inflammatory process. This latter point emphasizes the importance of the dosing regimen and the possibility of a rebound phenomenon. Finally, the question remains open whether only subtypes of asthma (severe, mild, intrinsic, extrinsic) are sensitive to PAF antagonists and whether the appropriate clinical target parameter has been addressed in recent clinical studies. This complexity of disease diagnosis further illustrates and exposes the limitations of preclinical models.

In conclusion, based on available clinical studies so far, it seems that platelet activating factor is not a key mediator which can be blocked and thereby provide therapy in human bronchial asthma. However, several critical questions of its physiological function remain unanswered. In preclinical settings PAF antagonists have only been shown to be effective in single challenge, acute disease related models when the action of other mediators could be inhibited indirectly via their release being subsequent to a synergism with PAF. These data could be interpreted that an obvious limitation of all preclinical models is the lack of a baseline chronic airway inflammatory setting. It may well reflect that there is a basic, underlying abnormality in lung function which influences, in part, the release and actions of inflammatory mediators. It needs to be demonstrated that in humans, the antagonism of PAF goes beyond the antagonism of this single mediator to have implications for any disease including bronchial asthma. It seems unlikely that the transient release of a single mediator or transient cell infiltrate may account for the complex pathophysiology of bronchial asthma. Bronchial asthma is a chronic disease and the results of a study from our laboratory with a PAF antagonist reported in this issue illustrates the possible limitations of preclinical models and the potential dangers of too little information.

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