Meeting report

New approaches to the modulation of inflammatory processes in airway disease models: ATS 2001, May 18–23, San Francisco

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Abstract

The 97th American Thoracic Society meeting proved to be an excellent meeting, providing a wealth of new information on inflammatory diseases of the airways. Once again there appeared to be an increased emphasis on chronic obstructive pulmonary disease (COPD) with most of the major drug companies concentrating a large part of their efforts in this field. An assessment of the new British Thoracic Society guidelines, which are designed to promote better management of COPD, was also presented at the meeting. Potential new treatments for inflammatory diseases of the airways including COPD were described, ranging from phase III trial data with GlaxoSmithKline's PDE4 inhibitor, Cilomilast (Ariflo®) to the development of AstraZeneca's novel dual dopamine D_2-receptor/β_2-adrenoreceptor agonist, Viozan™. Of particular interest was Byk Gulden's Ciclesonide, a new corticosteroid with equivalent efficacy to the market leaders but with an improved safety profile. The same company also presented data on their PDE4 inhibitor, Roflumilast, which is now in phase II/III. Bayer presented data on their PDE4 inhibitor, BAY 19-8004, in a smoking animal model and claimed greater anti-inflammatory efficacy than with a steroid. Asta Medica (now known as Elbion) also described a new potent PDE4 inhibitor, AWD 12-281, with anti-inflammatory activity. In the bronchodilator field, an analysis of data from a one-year trial with Boehringer Ingelheim's Tiotropium revealed a possible improvement in lung function in COPD patients; this needs to be confirmed in a specifically designed study. Inhibitors of p38 (c-Jun NH_2-terminal kinase and syk kinase) were also discussed as anti-inflammatory agents with potential in the treatment of COPD and asthma. GlaxoSmithKline's p38 kinase inhibitor, SB 239063, appeared to be the most advanced of these with clinical data expected in two to three years. Lyn kinase was also discussed as a novel target for inflammatory airway diseases.

Keywords: airway diseases, animal models, chronic obstructive pulmonary disease, new approaches, new treatments

Introduction

The American Thoracic Society meeting is the largest gathering of lung related specialists in the world. Approximately 16,000 people from 79 different countries attended the San Francisco meeting. The meeting was aimed at physicians, scientists and health care providers and offered up-to-date information on clinical practice and clinical and basic research. Among the topics covered were lung injury, asthma, allergy, chronic obstructive pulmonary disease (COPD), lung development, lung transplantation and gene expression in a programme containing more than 300 scientific and clinical symposia. Presenta-

COPD = chronic obstructive pulmonary disease; LPS = lipopolysaccharide; TNF-α = tumour necrosis factor-α.

tions of original research in all respiratory fields are always a highlight of the meeting.

Review

Dr D Halpin and Dr M Rudolf (The Royal Devon and Exeter Hospital, Exeter, Devon, UK) on behalf of the British Thoracic Society COPD consortium presented an assessment of the new British Thoracic Society guidelines, which are designed to promote better management of COPD. It showed that in terms of therapy, the use of long-acting β_2-adrenergic bronchodilators and anticholinergics is still increasing, whereas steroid use has not increased since 1997. The use of spirometry in diagnosis has increased but is still much underused and advice on smoking cessation or its therapy does not appear to be widely available to patients.

New approaches

MA Birrell (Imperial College, London, UK) described a murine model of lipopolysaccharide (LPS)-induced neutrophilic airway inflammation. He showed that the mouse has distinct advantages over the rat in that it provides the opportunity to dissect the mechanisms involved in inflammatory responses using the molecular (transgenic and gene knockout animals) and immunological (antibodies) tools, which are more readily available for the mouse than rat. To further explore the advantages conferred by using mice the same author also described the development and partial characterisation of a model of elastase-induced emphysema in the mouse. This model may be of great use to the many groups now seeking to study and develop drugs for the treatment of COPD.

Dr DC Underwood (GlaxoSmithKline, Philadelphia, USA) described a short-term murine model of smoke inhalation and outlined its use in the study of smoking-related inflammation. Mice were exposed to smoke for one to three days and the inflammatory response was studied. First he demonstrated the development of an inflammatory response and then showed that the resulting inflammation could be inhibited by pretreatment with the selective p38 MAP kinase inhibitor, SB 239063. The data support the use of this type of compound for the future treatment of inflammatory lung diseases such as COPD.

New treatments

Corticosteroids

Two posters, which generated a lot of interest, described preclinical studies with Ciclesonide, a new corticosteroid. Dr M Belvisi (Imperial College, London, UK) outlined *in vivo* data in the Brown Norway rat supporting the concept that Ciclesonide is a prodrug, which when delivered directly into the airways, can be transformed by esterase cleavage into the active metabolite (R-M1) producing high local anti-inflammatory activity. The anti-inflammatory efficacy of Ciclesonide in these studies was similar to that produced by Fluticasone but with an improved safety profile, thus demonstrating an improved therapeutic ratio over Fluticasone. These findings were supported by the findings of Dr D Bundschuh (Byk Gulden, Konstanz, Germany) who, in a range of *in vitro* and *in vivo* studies, demonstrated an improved safety margin with Ciclesonide when compared to Budesonide. He also demonstrated the prodrug anti-inflammatory activity of Ciclesonide at the target organ. Ciclesonide represents a corticosteroid with an improved safety profile when compared to other corticosteroids currently used in the treatment of inflammatory diseases of the airways. A compound with this profile has great potential and its future development will be watched with interest.

D_2-receptor and β_2-adrenoreceptor agonist

Viozan™ (AR-68397AA), a novel dual dopamine D_2-receptor/β_2-adrenoreceptor agonist, is being developed as a potential treatment for COPD. Dr A Young (AstraZeneca, Loughborough, UK) described work *in vitro* in guinea pig trachea and *in vivo* in the dog, demonstrating rapid onset and long duration of action of the compound at both the D_2 and β_2 receptors. Two other presentations examined the component properties of Viozan™. Dr I Oakley (AstraZeneca, Loughborough, UK), using the D_2-selective agonist AR-C65116AB and the β_2-adrenoceptor agonist salbutamol, demonstrated in ovalbumin-sensitised Brown Norway rats that the D_2 receptor agonist reduced tachypnoea, whereas the β_2-receptor agonist improved lung function without affecting respiratory rate. This suggests the combination of the two agonistic properties may provide greater benefit than either agonist in isolation.

Dr M Trevisiani (University of Ferrara, Italy) described studies using a guinea pig spinal cord preparation and capsaicin-induced plasma leakage in rat trachea. He showed that the D_2-receptor agonists ropinirole and AR-C65116AB inhibit both central and peripheral neuropeptide release, providing further evidence of the potential beneficial effects of these type of compounds in the treatment of inflammatory diseases of the airways.

Anticholinergics

In two poster presentations Dr A Anzueto (University of Texas, San Antonio, USA) and Dr DP Tashken (University of California, Los Angeles, USA) presented results of an analysis of two large one year clinical trials with the anticholinergic bronchodilator, Tiotropium, given by inhalation at 18 µg once daily to patients with COPD. One-year studies of Tiotropium demonstrated a sustained bronchodilator effect, reduction in exacerbation frequency and improvement in quality of life measures. The *post hoc* analyses suggest that the rate of lung function loss observed in placebo-treated patients might be mitigated in Tiotropium-treated patients, although such an effect of Tiotropium would require a specifically designed prospective trial.

PDE4 antagonists

Results from a six-month phase III trial with the novel selective PDE4 antagonist Cilomilast (Ariflo®) in stable COPD patients were reported at the meeting. Placebo or Cilomilast at 15 mg orally, twice daily, for 6 months was administered to a total of 2058 patients. Dr JD Edelson (GlaxoSmithKline, Philadelphia, USA) demonstrated a sustained improvement in lung function in COPD patients after treatment with Cilomilast, and a reduction in the risk of exacerbations. The same author using the St. Georges Respiratory Questionnaire (a questionnaire used to assess quality of life) also reported an improvement in health status in the Cilomilast treated group. Dr CH Compton (GlaxoSmithKline, Philadelphia, USA) demonstrated that the compound was safe and well tolerated in this large patient group. Gastrointestinal side effects in Cilomilast treated patients were generally self-limited and mild to moderate in intensity. In a separate study in the clinic, Dr J Kelly (GlaxoSmithKline, UK) looked at the possibility of interaction between Cilomilast and theophylline and found no evidence of pharmacokinetic or dynamic interaction and no cardiovascular interaction.

In a study using human bronchial epithelial and sputum cells, Dr G Chipappara (Institute of Respiratory Pathophysiology, Italina national Research Council, Palermo, Italy) demonstrated a reduction in the neutrophil chemoattractants tumour necrosis factor-α (TNF-α), interleukin-8 and granulocyte-macrophage colony stimulating factor in cells treated with Cilomilast. This suggests that at least part of the efficacy of Cilomilast in treating COPD patients may rest with its ability to reduce neutrophilic inflammation. Dr CA Owen (University of Utah, USA) demonstrated that Cilomilast inhibits the migration of activated neutrophils and reduces their capacity to mediate extracellular proteolysis. These effects also support the use of the compound in the treatment of COPD.

A new addition to the PDE4 inhibitor field is Roflumilast, a potent and selective compound from Byk Gulden. Dr D Bundschuh (Byk Gulden, Konstanz, Germany) presented data in antigen-driven or LPS-driven rat airway inflammation models. These studies showed that Roflumilast is much more potent than Cilomilast at reducing cell infiltration, total protein and TNF-α concentration in bronchoalveolar fluid after antigen challenge, and some 310-fold more potent than Cilomilast in inhibiting LPS-induced circulating TNF-α. These data were supported by studies conducted by Dr L Wollin (Byk Gulden, Konstanz, Germany) and Dr HG Hoymann (Fraunhofer Institute of Toxicology and Aerosol Research, Hanover, Germany) who demonstrated a reduction in airway hyperresponsiveness after pretreatment with Roflumilast in an antigen-induced airway hyperresponsiveness model in the rat. These data suggest that Roflumilast may provide a potential new candidate for the treatment of chronic inflammatory disorders of the airways such as asthma and COPD.

Dr MF Fitzgerald (Bayer, Stoke Poges, UK) described work with a PDE4 inhibitor, BAY 19-8004, currently in phase II for asthma and COPD treatment. In an acute cigarette smoke exposure model in the guinea pig, BAY 19-8004 showed greater efficacy in reducing the resulting inflammation than the steroid, betamethasone. These data suggest the model may be useful for the evaluation of alternative inflammatory concepts for the treatment of COPD.

Dr H Poppe (Elbion, Dresden, Germany) described one further PDE4 antagonist, AWD 12-281, employing a different angle of attack by looking at the effect of the compound on mucus secretion in the mouse and LPS-induced neutrophilia in the rat and domestic pig. In COPD in man, bronchioles are filled with viscous mucus produced by goblet cells. Secretion of serous mucus containing lysozyme is beneficial in dissolving mucus plugs. AWD 12-281 increased the secretion of serous mucus in mouse trachea as well as reducing LPS-induced neutrophilia in rats and pigs.

Kinase inhibitors

In a session on the role of protein kinases in airway inflammatory diseases several speakers discussed target identification, validation and the profiling of novel small molecule inhibitors in animal models. Dr DW Hay (GlaxoSmithKline, USA) outlined work with the p38 kinase inhibitor, SB 239063, in models that represent different pathological aspects of COPD. This compound reduced neutrophil infiltration, reduced inflammatory cytokine production (such as interleukin-6) and reduced matrix metalloproteinase-9 activity thus supporting the therapeutic potential of SB 239063 in the treatment of COPD. Dr Hay stated that the compound should be in the clinic within two to three years.

Dr GP Anderson (University of Melbourne, Australia) discussed lyn tyrosine kinase as a possible target for intervention in the treatment of asthma. lyn kinase has been shown to be a signal transduction intermediate involved in the production of various cytokines and although not present in T cells it has been shown to regulate the inflammatory response and the influx of T cells. Also, animals deficient in lyn kinase as a result of homozygous knockout have been shown to have an enhanced response to antigen challenge. This evidence supports lyn kinase as a possible target in the treatment of asthma.

Dr AJ Lewis (Signal, San Diego, USA) presented data with the c-Jun NH_2-terminal kinase antagonist, SP 600125. This compound is selective for c-Jun NH_2-terminal kinase 1, 2 and 3 but is not orally available and is being tested as a proof of concept molecule. It showed good anti-inflammatory activity in a range of *in vitro* and *in vivo* screens and is being followed up with a new lead compound, SPC

105, which has a good pharmacokinetic profile, is selective and orally active and may be useful in the treatment of inflammatory diseases of the airways. Dr C Walker (Novartis, UK) rounded off the session with a talk on two undisclosed syk kinase inhibitors, again with a good anti-inflammatory profile aimed more at asthma than COPD.

Conclusion

It was evident from this meeting that a great deal of effort is going into research on the inflammatory aspects of diseases of the airways and that the greater part of that effort may now be directed towards potential treatments for COPD. New animal models, which may be of great benefit to study the mechanisms involved in the development of COPD, were described. Many of the major drug companies are looking for compounds that will modulate the inflammatory response. The new developments showing some promise are the steroid with an improved safety profile (Ciclesonide), the PDE4 inhibitors (such as Cilomilast and Roflumilast), compounds that modify cytokine signal transduction via a specific kinase inhibitor and Viozan™, which provides a novel approach by combining β_2-adrenoreceptor agonist activity with dopamine D_2-receptor agonist activity to produce a long acting drug which is a bronchodilator and inhibits neuroinflammatory peptide release. One other approach showing some promise is the use of the long acting anticholinergic, Tiotropium, which may slow the progressive decline in lung function that occurs with COPD. This observation, however, needs to be confirmed in a specifically designed study. In conclusion the American Thoracic Society meeting was again very successful, providing plenty of food for thought for both scientists and clinicians.