Treating COPD with PDE 4 inhibitors

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Abstract: While the pathogenesis of chronic obstructive pulmonary disease (COPD) is incompletely understood, chronic inflammation is a major factor. In fact, the inflammatory response is abnormal, with $CD8^+$ T-cells, $CD68^+$ macrophages, and neutrophils predominating in the conducting airways, lung parenchyma, and pulmonary vasculature. Elevated levels of the second messenger cAMP can inhibit some inflammatory processes. Theophylline has long been used in treating asthma; it causes bronchodilation by inhibiting cyclic nucleotide phosphodiesterase (PDE), which inactivates cAMP. By inhibiting PDE, theophylline increases cAMP, inhibiting inflammation and relaxing airway smooth muscle. Rather than one PDE, there are now known to be more than 50, with differing activities, substrate preferences, and tissue distributions. Thus, the possibility exists of selectively inhibiting only the enzyme(s) in the tissue(s) of interest. PDE 4 is the primary cAMP-hydrolyzing enzyme in inflammatory and immune cells (macrophages, eosinophils, neutrophils). Inhibiting PDE 4 in these cells leads to increased cAMP levels, down-regulating the inflammatory response. Because PDE 4 is also expressed in airway smooth muscle and, in vitro, PDE 4 inhibitors relax lung smooth muscle, selective PDE 4 inhibitors are being developed for treating COPD. Clinical studies have been conducted with PDE 4 inhibitors; this review concerns those reported to date.

Keywords: COPD, asthma, phosphodiesterase IV inhibitor

Introduction

Chronic obstructive pulmonary disease (COPD) is a serious and increasing global public health problem; physiologically, it is characterized by progressive, irreversible airflow obstruction and pathologically, by an abnormal airway inflammatory response to noxious particles or gases (MacNee 2005a). The COPD patient suffers a reduction in forced expiratory volume in 1 second (FEV_1), a reduction in the ratio of FEV_1 to forced vital capacity (FVC), compared with reference values, absolute reductions in expiratory airflow, and little improvement after treatment with an inhaled bronchodilator. Airflow limitation in COPD patients results from mucosal inflammation and edema, bronchoconstriction, increased secretions in the airways, and loss of elastic recoil. Patients with COPD can experience 'exacerbations,' involving rapid and prolonged worsening of symptoms (Seneff et al 1995; Connors et al 1996; Dewan et al 2000; Rodriguez-Roisin 2006; Mohan et al 2006). Many are idiopathic, though they often involve bacteria; airway inflammation in exacerbations can be caused or triggered by bacterial antigens (Murphy et al 2000; Blanchard 2002; Murphy 2006; Veeramachaneni and Sethi 2006). Increased IL-6, IL-1β, TNF-α, GRO-α, MCP-1, and IL-8 levels are found in COPD patient sputum; their levels increase further during exacerbations. COPD has many causes and significant differences in prognosis exist, depending on the cause (Barnes 1998; Madison and Irwin 1998).

COPD is already the fourth leading cause of death worldwide, according to the World Health Organization (WHO); the WHO estimates that by the year 2020, COPD will be the third-leading cause of death and the fifth-leading cause of disability worldwide (Murray and Lopez 1997). COPD is the fastest-growing cause of death

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in developed nations and is responsible for over 2.7 million deaths per year worldwide. In the US, there are currently estimated to be 16 million people with COPD. There are estimated to be up to 20 million sufferers in Japan, which has the world's highest per capita cigarette consumption and a further 8–12 million in Europe. In 2000, COPD accounted for over 20 million outpatient visits, 3.4 million emergency room visits, 6 million hospitalizations, and 116,500 deaths in the US (National Center for Health Statistics 2002). Factors associated with COPD, including immobility, often lead to secondary health consequences (Polkey and Moxham 2006).

Risk factors for the development of COPD include cigarette smoking, and occupational exposure to dust and chemicals (Senior and Anthonisen 1998; Anthonisen et al 2002; Fabbri and Hurd 2003; Zaher et al 2004). Smoking is the most common cause of COPD and the underlying inflammation typically persists in ex-smokers. Oxidative stress from cigarette smoke is also an issue in COPD (Domej et al 2006). Despite this, relatively few smokers ever develop COPD (Siafakas and Tzortzaki 2002).

While many details of the pathogenesis of COPD remain unclear, chronic inflammation is now recognized as a major factor, predominantly in small airways and lung parenchyma, characterized by increased numbers of macrophages, neutrophils, and T-cells (Barnes 2000; Stockley 2002). As recently as 1995, the American Thoracic Society issued a statement defining COPD without mentioning the underlying inflammation (American Thoracic Society 1995). Since then, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines have made it clear that chronic inflammation throughout the airways, parenchyma, and pulmonary vasculature plays a central role (Pauwels et al 2001; GOLD 2003). The comparatively recent realization of the role of airway inflammation in COPD has altered thinking with regard to potential therapies (Rogers and Giembycz 1998; Vignola 2004).

Most pharmacological therapies available for COPD, including bronchodilator and anti-inflammatory agents, were first developed for treating asthma. The mainstays of COPD treatment are inhaled corticosteroids (McEvoy and Niewoehner 1998; Borron and deBoisblanc 1998; Pauwels 2002; Gartlehner et al 2006; D'Souza 2006), supplemental oxygen (Petty 1998; Austin and Wood-Baker 2006), inhaled bronchodilators (Costello 1998; Doherty and Briggs 2004), and antibiotics (Taylor 1998), especially in severely affected patients (Anthonisen et al 1987; Saint et al 1995; Adams et al 2001; Miravitlles et al 2002; Donnelly and Rogers 2003; Sin et al 2003; Rabe 2006), though the use of antibiotics remains controversial (Ram et al 2006). Long-acting β_2-agonists (LABAs) improve the mucociliary component of COPD. Combination therapy with LABAs and anticholinergic bronchodilators resulted in modest benefits and improved health-related quality of life (Buhl and Farmer 2005; Appleton et al 2006). Treatment with mucolytics reduced exacerbations and the number of days of disability (Poole and Black 2006). The combined use of inhaled corticosteroids and LABAs has been demonstrated to produce sustained improvements in FEV_1 and positive effects on quality of life, number of hospitalizations, distance walked, and exacerbations (Mahler et al 2002; Szafranski et al 2003; Sin et al 2004; Miller-Larsson and Selroos 2006; van Schayck and Reid 2006). However, all of these treatments are essentially palliative and do not impact COPD progression (Hay 2000; Gamble et al 2003; Antoniu 2006a).

A further complication in drug development and therapy is that it can be difficult to determine the efficacy of therapy, because COPD has a long preclinical stage, is progressive, and patients generally do not present for treatment until their lung function is already seriously impaired. Moreover, because COPD involves irreversible loss of elasticity, destruction of the alveolar wall, and peribronchial fibrosis, there is often little room for clinical improvement.

Smoking cessation remains the most effective intervention for COPD. Indeed, to date, it is the only intervention shown to stop the decline in lung function, but it does not resolve the underlying inflammation, which persists even in ex-smokers. Smoking cessation is typically best achieved by a multifactor approach, including the use of bupropion, a nicotine replacement product, and behavior modification (Richmond and Zwar 2003).

In COPD, there is an abnormal inflammatory response, characterized by a predominance of $CD8^+$ T-cells, $CD68^+$ macrophages, and neutrophils in the conducting airways, lung parenchyma, and pulmonary vasculature (Soto and Hanania 2005; O'Donnell et al 2006; Wright and Churg 2006). Inflammatory mediators involved in COPD include lipids, inflammatory peptides, reactive oxygen and nitrogen species, chemokines, cytokines, and growth factors. COPD pathology also includes airway remodeling and mucociliary dysfunction (mucus hypersecretion and decreased mucus transport). Corticosteroids reduce the number of mast cells, but $CD8^+$ and $CD68^+$ cells, and neutrophils, are little affected (Jeffery 2005). Inflammation in COPD is not suppressed by corticosteroids, consistent with it

being neutrophil-, not eosinophil-mediated. Corticosteroids also do not inhibit the increased concentrations of IL-8 and TNF-α (both neutrophil chemoattractants) found in induced sputum from COPD patients. Neutrophil-derived proteases, including neutrophil elastase and matrix metalloproteinases (MMPs), are involved in the inflammatory process and are responsible for the destruction of elastin fibers in the lung parenchyma (Mercer et al 2005; Gueders et al 2006). MMPs play important roles in the proteolytic degradation of extracellular matrix (ECM), in physiological and pathological processes (Corbel, Belleguic et al 2002). PDE 4 inhibitors can reduce MMP activity and the production of MMPs in human lung fibroblasts stimulated with pro-inflammatory cytokines (Lagente et al 2005). In COPD, abnormal remodeling results in increased deposition of ECM and collagen in lungs, because of an imbalance of MMPs and TIMPs (Jeffery 2001). Fibroblast/myofibroblast proliferation and activation also occur, increasing production of ECM-degrading enzymes (Crouch 1990; Segura-Valdez et al 2000). Additionally, over-expression of cytokines and growth factors stimulates lung fibroblasts to synthesize increased amounts of collagen and MMPs, including MMP-1 (collagenase-1) and MMP-2 and MMP-9 (gelatinases A and B) (Sasaki et al 2000; Zhu et al 2001).

It is now generally accepted that bronchial asthma is also a chronic inflammatory disease (Barnes et al 1988; Barnes 1995). The central role of inflammation of the airways in asthma's pathogenesis is consistent with the efficacy of corticosteroids in controlling clinical symptoms. Eosinophils are important in initiating and continuing the inflammatory state (Holgate et al 1987; Bruijnzeel 1989; Underwood et al 1994; Teixeira et al 1997), while other inflammatory cells, including lymphocytes, also infiltrate the airways (Holgate et al 1987; Teixeira et al 1997). The familiar acute symptoms of asthma are the result of airway smooth muscle contraction. While recognition of the key role of inflammation has led to an emphasis on anti-inflammatory therapy in asthma, a significant minority of patients remains poorly controlled and some exhibit accelerated declines in lung function, consistent with airway remodeling (Martin and Reid 2006). Reversal or prevention of structural changes in remodeling may require additional therapy (Burgess et al 2006).

There is currently no cure for asthma; treatment depends primarily on inhaled glucocorticoids to reduce inflammation (Taylor 1998; Petty 1998), and inhaled bronchodilators to reduce symptoms (Torphy 1994; Costello 1998; Georgitis 1999; DeKorte 2003). Such treatments, however, do not address disease progression.

COPD and asthma are both characterized by airflow obstruction, but they are distinct in terms of risk factors and clinical presentation. While both involve chronic inflammation and cellular infiltration and activation, different cell types are implicated and there are differences in the inflammatory states (Giembycz 2000; Fabbri and Hurd 2003; Barnes 2006). In COPD, neutrophil infiltration into the airways and their activation appear to be key (Stockley 2002); in asthma, the inflammatory response involves airway infiltration by activated eosinophils and lymphocytes, and T-cell activation of the allergic response (Holgate et al 1987; Saetta et al 1998; Barnes 2006). While macrophages are present in both conditions, the major controller cells are $CD8^+$ T-cells in COPD (O'Shaughnessy et al 1997; Saetta et al 1998) and $CD4^+$ T-cells in asthma. IL-1, IL-8, and TNF-α are the key cytokines in COPD, while in asthma, IL-4, IL-5, and IL-13 are more important. There are differences in histopathological features of lung biopsies between COPD patients and asthmatics; COPD patients have many fewer eosinophils in lung tissue than asthmatics.

While the early phases of COPD and asthma are distinguishable, there are common features, including airway hyper-responsiveness and mucus hypersecretion. MUC5AC is a major mucin gene expressed in the airways; its expression is increased in COPD and asthmatic patients. At least in vitro, epidermal growth factor stimulates MUC5AC mRNA and protein expression; this can be reversed by PDE 4 inhibitors, which may contribute to their clinical efficacy in COPD and asthma (Mata et al 2005). Similar structural and fibrotic changes make COPD and asthma much less distinguishable in extreme cases; the chronic phases of both involve inflammatory responses, alveolar detachment, mucus hypersecretion, and subepithelial fibrosis. The two conditions have been linked epidemiologically; adults with asthma are up to 12 times more likely to develop COPD over time than those without (Guerra 2005).

Theophylline

Theophylline and related xanthine compounds have been used for decades to treat asthma (Weinberger 1988; Torphy and Undem 1991; Manganiello et al 1995; Dent and Giembycz 1996; Weinberger and Hendeles 1996; Torphy 1998; Ram et al 2002; Barnes 2003; Barr et al 2003). The use of these drugs has been limited, however, by their side effects and modest efficacy (Persson 1986; Rabe et al 1995). Additionally, theophylline is a difficult drug to use, requiring titration and plasma monitoring, because of the risk of cardiovascular and CNS side effects, even at therapeutic doses (Boswell-Smith, Cazzola et al 2006).

The second messenger cyclic 3′,5′-adenosine monophosphate (cAMP) controls many cellular functions and it is well established that an elevated cAMP level can inhibit some inflammatory processes. Thus, inhibitors of enzymes that catalyze cAMP hydrolysis would seem to be good candidates to treat inflammatory conditions.

Phosphodiesterase (PDE)

Theophylline is believed to cause bronchodilation by inhibiting cyclic nucleotide phosphodiesterase (PDE), an enzyme that catalyzes the hydrolysis of cAMP and cyclic 3′,5′-guanosine monophosphate (cGMP) to inactive 5'-nucleotide products (Muller et al 1996), cAMP and cGMP exhibit many intracellular effects, mediated largely through their stimulatory effect on multisubstrate protein kinases (Torphy and Undem 1991; Montminy 1997; Daniel et al 1998; Spina 2003). By inhibiting PDE, theophylline increases the level of cAMP and cGMP, resulting in relaxation of airway smooth muscle and inhibition of inflammatory cell activation (Holgate et al 1987; Bryson and Rodger 1987; Schramm and Grunstein 1992; Cortijo et al 1993; Kotlikoff and Kamm 1996; Spina 2003).

Theophylline is now known to have many properties in addition to that of a bronchodilator (Persson 1986; Sullivan et al 1994; Rabe et al 1995; D'Alonzo 1996; Weinberger and Hendeles 1996; Vassallo and Lipsky 1998). Theophylline also causes pulmonary arterial vasodilatation, enhances diaphragmatic contractility, and increases CNS respiratory drive. Theophylline is a cardiac ionotrope and chromotrope. It is also a weak diuretic and increases mucociliary sweep. Theophylline has anti-inflammatory effects in COPD, reducing neutrophil counts, IL-8, and the total number inflammatory cells in sputum. Theophylline is also subject to many drug interactions and has adenosine receptor antagonist activity (Barnes 2003).

Far from there being a single PDE, it is now clear that there are many with differing activities, substrate preferences, and tissue distributions (Nicholson et al 1991; Thompson 1991; Lowe and Cheng 1992; Beavo et al 1994; Manganiello et al 1995; Torphy 1998; Silver et al 1988; Matsumoto et al 2003); theophylline is actually a non-specific PDE inhibitor (Persson 1986; Rabe et al 1995; D'Alonzo 1996; Weinberger and Hendeles 1996; Vassallo and Lipsky 1998). Some of its various properties and side-effects have been attributed to non-selective inhibition of PDEs (Barnes 2003).

Indeed, there are believed to be at least 11 gene families of PDE enzymes in mammals, encoding more than 50 enzymes, because of alternative splicing and alternative transcriptional start sites (Bolger 1994; Lobban et al 1994; Horton et al 1995; Bushnik and Conti 1996; Jin et al 1998; Houslay et al 1998; Conti and Jin 1999; Giembycz 2000; Giembycz 2001; Scapin et al 2004; Giembycz 2005a; Bender and Beavo 2006). PDE enzymes share approximately 25% sequence identity over the conserved catalytic domain of about 300 amino acids (Ke 2004). While all PDEs catalyze the hydrolysis of cAMP and/or cGMP, the enzymes differ in their biochemical and pharmacological properties and exhibit different affinities for various inhibitors (Silver et al 1988; Torphy and Undem 1991; Manganiello et al 1995; Muller et al 1996; Torphy 1998). PDE 4, PDE 7, and PDE 8 are specific for cAMP (Conti and Yin 1999; Soderling and Beavo 2000). This diversity of enzyme type and tissue-specific expression raises the possibility of selectively inhibiting only the enzyme(s) in the tissue(s) of interest, if sufficiently specific inhibitors can be found (Giembycz and Dent 1992; Card et al 2004).

PDE 4 in COPD

With regard to COPD, PDE 4 is the primary cAMP-hydrolyzing enzyme in inflammatory and immune cells, especially macrophages, eosinophils, and neutrophils, all of which are found in the lungs of COPD and asthma patients (Torphy et al 1992; Karlsson and Aldous 1997; De Brito et al 1997; Wang et al 1999; Torphy and Page 2000). Inhibition of PDE 4 leads to elevated cAMP levels in these cells, down-regulating the inflammatory response (Dyke and Montana 2002).

PDE 4 has also attracted much attention because it is expressed in airway smooth muscle (Ashton et al 1994; Undem et al 1994; Nicholson et al 1995; Kerstjens and Timens 2003; Mehats et al 2003; Lipworth 2005; Fan Chung 2006). In vitro, PDE 4 inhibitors relax lung smooth muscle (Undem et al 1994; Dent and Giembycz 1995). In COPD and asthma, a selective PDE 4 inhibitor with combined bronchodilatory and anti-inflammatory properties would seem desirable (Nicholson and Shahid 1994; Lombardo 1995; Palfreyman 1995; Cavalia and Frith 1995; Palfreyman and Souness 1996; Karlsson and Aldous 1997; Compton et al 2001; Giembycz 2002; Jacob et al 2002; Soto and Hanania 2005).

PDE 4 inhibitors in COPD

So, because PDE 4 inhibitors suppress inflammatory functions in several cell types involved in COPD and asthma (Huang and Mancini 2006) and because, at least in vitro, PDE 4 inhibitors relax lung smooth muscle, selective PDE 4 inhibitors, originally intended for use in treating depression (Renau 2004), have been developed for the treatment of

COPD and asthma (Torphy et al 1999; Spina 2000; Huang et al 2001; Spina 2004; Giembycz 2005a, 2005b; Lagente et al 2005; Boswell-Smith, Spina et al 2006). PDE 4 enzymes are strongly inhibited by the antidepressant drug rolipram (Pinto et al 1993), which decreases the influx of inflammatory cells at sites of inflammation (Lagente et al 1994; Lagente et al 1995; Alves et al 1996). PDE 4 inhibitors down-regulate cytokine production in inflammatory cells, *in vivo* and *in vitro* (Undem et al 1994; Dent and Giembycz 1995). TNF-α is an important inflammatory cytokine in COPD; its release is reduced by PDE 4 inhibitors (Souness et al 1996; Chambers et al 1997; Griswold et al 1998; Gonçalves de Moraes et al 1998; Corbel, Belleguic et al 2002). Some PDE 4 inhibitors, including cilomilast and AWD 12-281, can inhibit neutrophil degranulation, a property not shared by theophylline (Ezeamuzie 2001; Jones et al 2005). PDE 4 inhibitors reduce overproduction of other pro-inflammatory mediators, including arachidonic acid and leukotrienes (Torphy 1998). PDE 4 inhibitors also inhibit cellular trafficking and microvascular leakage, production of reactive oxygen species, and cell adhesion molecule expression in vitro and in vivo (Sanz et al 2005). PDE 4 inhibitors, including cilomilast and CI-1044, inhibit LPS-stimulated TNF-α production in whole blood from COPD patients (Burnouf et al 2000; Ouagued et al 2005).

There are now thought to be at least four PDE 4s, A, B, C, and D, derived from four genes (Lobbam et al 1994; Muller et al 1996; Torphy 1998; Conti and Jin 1999; Matsumoto et al 2003). Alternative splicing and alternative promoters add further complexity (Manganiello et al 1995; Horton et al 1995; Torphy 1998). Indeed, the four genes encode more than 16 PDE 4 isoforms, which can be divided into short (~65–75 kDa) and long forms (~80–130 kDa); the difference between the short and long forms lies in the N-terminal region (Bolger et al 1997; Huston et al 2006). PDE 4 isoforms are regulated by extracellular signal-related protein kinase (ERK), which can phosphorylate PDE 4 (Houslay and Adams 2003).

The four PDE 4 genes are differentially expressed in various tissues (Silver et al 1988; Lobbam et al 1994; Manganiello et al 1995; Horton et al 1995; Muller et al 1996; Torphy 1998). PDE 4A is expressed in many tissues, but not in neutrophils (Wang et al 1999). PDE 4B is also widely expressed and is the predominant PDE 4 subtype in monocytes and neutrophils (Wang et al 1999), but is not found in cortex or epithelial cells (Jin et al 1998). Upregulation of the PDE 4B enzyme in response to pro-inflammatory agents suggest that it has a role in inflammatory processes (Manning et al 1999). PDE 4C is expressed in lung and testis, but not in circulating inflammatory cells, cortex, or hippocampus (Obernolte et al 1997; Manning et al 1999; Martin-Chouly et al 2004). PDE 4D is highly expressed in lung, cortex, cerebellum, and T-cells (Erdogan and Houslay 1997; Jin et al 1998). PDE 4D also plays an important role in airway smooth muscle contraction (Mehats et al 2003).

A major issue with early PDE 4 inhibitors was their side effect profile; the signature side effects are largely gastrointestinal (nausea, vomiting, increased gastric acid secretion) and limited the therapeutic use of PDE 4 inhibitors (Dyke and Montana 2002). The second generation of more selective inhibitors, such as cilomilast and roflumilast, have improved side effect profiles and have shown clinical efficacy in COPD and asthma (Barnette 1999; Spina 2000; Lagente et al 2005). However, even cilomilast and roflumilast, the most advanced clinical candidates, discussed below, cause some degree of emesis (Spina 2003).

It is now thought that the desirable anti-inflammatory properties and unwanted side effects of nausea and emesis are associated with distinct biochemical activities (Torphy et al 1992; Jacobitz et al 1996; Barnette et al 1996; Souness et al 1997; Souness and Rao 1997). Specifically, the side effects are believed to be associated with the so-called 'high-affinity rolipram binding site' (HARBS) (Barnette et al 1995; Muller et al 1996; Jacobitz et al 1996; Kelly et al 1996; Torphy 1998) and/or inhibition of the form of PDE 4 found in the CNS (Barnette et al 1996). The exact nature of HARBS remains unclear, although it has been described as a conformer of PDE 4 (Souness and Rao 1997; Barnette et al 1998). Using mice deficient in PDE 4B or PDE 4D, it appears that emesis is the result of selective inhibition of PDE 4D (Robichaud et al 2002; Lipworth 2005), which is unfortunate, because the most clinically advanced PDE 4 inhibitors are selective for PDE 4D. Also, from animal studies, it appears that the nausea and vomiting are produced via the CNS, though there may also be direct effects on the gastrointestinal system (Barnette 1999).

While beyond the scope of this review, it has been proposed that PDE 4 inhibitors may be useful in treating inflammatory bowel disease (Banner and Trevethick 2004), cystic fibrosis (Liu et al 2005), pulmonary arterial hypertension (Growcott et al 2006), myeloid and lymphoid malignancies (Lerner and Epstein 2006), Alzheimer's disease (Ghavami et al 2006), rheumatoid arthritis and multiple sclerosis (Dyke and Montana 2002), infection-induced preterm labor (Oger et al 2004), depression (Wong et al 2006), and allergic disease (Crocker and Townley 1999). Varying degrees of in vitro, in vivo, and clinical data exist to support these claims.

So, after that theoretical buildup, we reach the proof of the pudding; clinical studies have been conducted with PDE 4 inhibitors. A potent, but not-very-selective, PDE 4 inhibitor is approved in Japan and is used clinically, including for treating asthma. Another is awaiting approval in the US. One is in advanced clinical development and others are at earlier stages.

Ibudilast

The drug ibudilast (3-isobutyryl-2-isopropylpyrazolo[1,5-a] pyridine) is a nonselective PDE inhibitor. It is approved in Japan and has been widely used to treat bronchial asthma and ischemic stroke. Ibudilast preferentially inhibits PDE 3A, PDE 4, PDE 10, and PDE 11. Ibudilast potently inhibits purified human PDE 4A, 4B, 4C and 4D with IC_{50} values of 54, 65, 239 and 166 nM, respectively (Huang et al 2006). It may be useful in treating a range of neurological conditions, linked to its ability to elevate cellular cyclic nucleotide concentrations (Gibson et al 2006).

Cilomilast

Cilomilast is a second-generation PDE 4 inhibitor that was developed to separate activity at the HARBS and PDE 4 (Christensen et al 1998; Barnette et al 1998; Griswold et al 1998; Underwood et al 1998; Torphy et al 1999). Cilomilast is as strong an anti-inflammatory as rolipram, but causes much less nausea and gastric acid secretion. Cilomilast is also negatively charged at physiological pH, limiting its penetration into the CNS.

Cilomilast is being developed as a treatment for COPD; the drug has been assessed in phase III trials (Norman 1999; Norman 2000; Barnette and Underwood 2000; Torphy and Page 2000; Martina et al 2006). The compound had previously been in development for asthma, and phase II trials were conducted in the US and Japan in 2001; however, development for asthma was apparently discontinued.

Cilomilast is a potent (K_i = 92 nM), selective PDE 4 inhibitor (Christensen et al 1998; Barnette et al 1998; Griswold et al 1998; Underwood et al 1998). Cilomilast is considerably more selective for PDE 4D (IC_{50} = 12 nM) than 4A (IC_{50} = 115 nM), 4B (IC_{50} = 86 nM), or 4C (IC_{50} = 308 nM). The drug is essentially inactive against PDEs 1, 2, 3, 5, and 7 (Christensen et al 1998). Cilomilast inhibited human TNF-α production and PDE 4, and increased intracellular cAMP levels in both neutrophils and PBMCs (Chambers et al 1997). Cilomilast (10 μM) inhibited the degradation of three-dimensional collagen gel by fibroblasts (Kohyama et al 2002).

The anti-inflammatory effects of cilomilast have been assessed in bronchial epithelial cells and sputum cells from smokers, COPD patients, and normal controls (Profita et al 2003). TNF-α and IL-8 were released at a significantly higher level in bronchial epithelial and sputum cells from patients with COPD than in controls or smokers. Cilomilast significantly reduced TNF-α release by bronchial epithelial and sputum cells, and GM-CSF release by sputum cells; IL-8 release was not significantly changed. Thus, cilomilast inhibited the production of some neutrophil chemoattractants by airway cells (Profita et al 2003). In bronchial biopsies from COPD patients, cilomilast treatment was associated with reductions in $CD8^+$ and $CD68^+$ cells; both cell types are increased in COPD and correlate with disease severity (Gamble et al 2003).

The cilomilast COPD clinical program included over 4000 patients in phase II and III trials. Evidence of safety and efficacy was based on four pivotal trials, involving 2883 patients. In addition, two phase-III open-label extension studies followed 1069 cilomilast patients for as long as three years. Inclusion criteria for the pivotal studies were patients between the ages of 40 and 80-years, with a diagnosis of COPD. Two primary endpoints were used: FEV_1 and total score on the St George's respiratory questionnaire (SGRQ), a self-administered questionnaire intended to determine the impact of chronic respiratory disease on health-related quality of life and well-being.

To date, four clinical trials have evaluated the efficacy of cilomilast and demonstrated improvement in lung function (FEV_1) and quality of life and reduction in the occurrence of COPD exacerbations, compared with placebo. Cilomilast was generally well tolerated, with adverse effects being overall mild and self-limiting.

The phase I and phase II studies demonstrated that cilomilast significantly improved lung function and quality of life to a clinically meaningful extent. A phase III program followed, to evaluate efficacy, safety, and mechanism of action.

By late 2003, GSK had performed four pivotal studies of cilomilast in a total of 2883 patients (n = 647 (study 039), 700 (study 042), 711 (study 091) and 825 (study 156)), comparing cilomilast (15 mg bid) with placebo over 24-weeks. Data from these trials, relating to various combinations of patients, have now been reported in several publications.

Phase III results in 2058 stable COPD patients were reported comparing cilomilast (15 mg bid for 6-months) with placebo. Cilomilast caused a sustained improvement in lung function and a reduction in the risk of exacerbation. Using

the SGRQ to assess quality of life, there was an improvement in health status in the cilomilast-treated group.

In a 6-month study, involving 647 patients with stable COPD (431 received 15 mg cilomilast bid and 216 received placebo), the cilomilast-treated patients exhibited an improved health status (assessed by SGRQ). These patients also demonstrated improved lung function (FEV_1: 40 mL improvement over placebo), reduced healthcare resources utilization (physician visits, emergency room visits, hospitalization), and a lower rate of COPD exacerbation (39% lower than placebo).

After a 4-week, single-blind, run-in phase, 1411 patients with stable COPD received placebo or cilomilast (15 mg bid) for 24-weeks. FEV_1 was maintained in patients receiving cilomilast versus placebo, with a treatment difference of 300 mL. Cilomilast achieved a clinically significant reduction (26%) in the risk of moderate-to-severe COPD exacerbations, compared with placebo.

Thus, two of the four pivotal studies (studies 039 and 156) reached clinical significance and two (042 and 091) did not. There was a mean change in FEV_1 of 10 mL from baseline following cilomilast treatment in the two positive trials, compared with 20 and 30 mL reductions, for placebo in these trials (for studies 156 and 039, respectively).

Side effects and contraindications

GI-related side effects, including nausea, diarrhea, dyspepsia, vomiting, and abdominal pain, have been observed; they are believed to be dose-related and were monitored specifically because of preclinical studies finding vasculitis in cilomilast-treated mice and rats. Ischemic colitis (a consequence of mesenteric arteritis) was a monitored adverse event in the clinical program; it was observed in three patients receiving cilomilast and in two receiving placebo, a low rate consistent with the normal incidence in the general population. The frequency of GI symptoms that concerned the patients or interfered with daily activities was 3-fold higher in patients receiving cilomilast than placebo.

Roflumilast

Roflumilast (3-cyclopropylmethoxy-4-difluoromethoxy-N-[3,5-dichloropyrid-4-yl]-benzamide) is a potent and selective PDE 4 inhibitor. It is being developed as an oral therapy for COPD and asthma (Reid 2002; Christie 2005; Cowan 2005; Antoniu 2006b; Boswell-Smith and Page 2006). It is an effective anti-inflammatory agent in COPD and asthma. Animal data and clinical trials to date have demonstrated favorable efficacy and safety, and no documented drug interactions (Hatzelmann and Schudt 2001).

Roflumilast inhibits PDE 4 activity in human neutrophils (IC_{50} = 0.8 nM), without affecting PDE 1, 2, 3, or 5, even at 10,000-fold higher concentrations. Roflumilast has good bioavailability following oral administration, a long half-life (~10 h), and an active metabolite (roflumilast-N-oxide, with a half-life of ~20 h). Roflumilast is approximately equipotent with its major in vivo metabolite (roflumilast-N-oxide).

It can be given once a day; it has been studied as an oral tablet at doses of 250 or 500 μg/day. Roflumilast is thus convenient to administer and has a favorable side effect profile in clinical studies reported to date (Karish and Gagnon 2006).

Roflumilast has a range of anti-inflammatory properties and has potential for treating inflammatory diseases. Roflumilast increases levels of cellular cAMP and inhibits microvascular leakage, trafficking, and the release of cytokines and chemokines from inflammatory cells (Christie et al 2005). Roflumilast apparently mediates some of its anti-inflammatory effects by inducing heme oxygenase-1 expression in macrophages (Kwak et al 2005). The anti-inflammatory and immunomodulatory potential of roflumilast has been assessed in human leukocytes. Regardless of cell type and the response investigated, the IC_{50} values were in a narrow range (2–21 nM), similar to that of roflumilast N-oxide (3–40 nM) (Hatzelmann and Schudt 2001).

Roflumilast has shown encouraging efficacy in patients with COPD, with significant improvements observed in FEV_1 and PEFR versus baseline (Cowan 2005). COPD patients receiving roflumilast experienced fewer exacerbations. The most common adverse effects reported in clinical trials were diarrhea, nausea, headache, and abdominal pain (Cowan 2005). In a biopsy study of COPD patients, roflumilast significantly reduced the numbers of $CD8^+$ T-cells and caused lesser reductions in the numbers of $CD4^+$ T-cells and neutrophils, and no changes in the expression of IL-8 or TNF-α.

A 6-month dose ranging study of roflumilast in COPD patients has been reported. Patients receiving roflumilast exhibited a significant, although modest, improvement in FEV_1. Patients in the roflumilast group had a 48% reduction in the number of exacerbations, as compared with an 8% reduction in the placebo group.

In a phase III, multicenter, double-blind, randomized, placebo-controlled study undertaken in an outpatient setting, 1411 patients with moderate-to-severe COPD were randomly assigned to receive roflumilast 250 μg (n = 576), roflumilast

500 μg (n = 555), or placebo (n = 280) given orally once daily for 24-weeks. Primary outcomes were post-bronchodilator FEV_1 and health-related quality of life. Secondary outcomes included exacerbations. 1157 (82%) patients completed the study. Post-bronchodilator FEV_1 at the end of treatment significantly improved with roflumilast 250 μg and 500 μg, compared with placebo. Most adverse events were mild-to-moderate in intensity and resolved during the study. Roflumilast improved lung function and reduced exacerbations compared with placebo (Rabe et al 2005).

Roflumilast has also been assessed in several clinical studies of asthma. In a double-blind, randomized study, roflumilast was compared with inhaled beclomethasone dipropionate. 499 patients (FEV_1 = 50%–85% predicted) received roflumilast 500 μg once daily or beclomethasone dipropionate 200 μg twice daily for 12 weeks. Roflumilast and beclomethasone dipropionate significantly improved FEV_1 and FVC. Once daily roflumilast (500 μg oral) was comparable with inhaled twice-daily beclomethasone dipropionate (400 μg/d) in improving pulmonary function and asthma symptoms and reducing rescue medication use (Bousquet et al 2006). In a dose-ranging study of roflumilast in patients with mild-to-moderate asthma, patients (n = 693) were randomized in a double-blind, parallel-group manner. After a 1–3-week placebo run-in period, patients (mean FEV_1 73% of predicted) were randomized to receive roflumilast 100, 250, or 500 μg once daily for 12-week. The primary end point was change in FEV_1 from baseline. Secondary end points included change in morning and evening peak expiratory flow from baseline. Roflumilast significantly increased FEV_1 (improvements from baseline at the last visit were 260, 320, and 400 mL for the 100, 250, and 500 μg doses, respectively). Roflumilast was well tolerated at all doses tested; most adverse events were mild to moderate in intensity and transient (Bateman et al 2006). Roflumilast was assessed in a placebo-controlled, randomized, double-blind, crossover study in 16 patients with exercise-induced asthma. Patients received placebo or roflumilast (500 μg/d) for 28 d. Exercise challenge was performed 1 h after dosing on days 1, 14, and 28. FEV_1 was measured before exercise challenge, immediately after the end of exercise, and then 1, 3, 5, 7, 9, and 12 min later. The mean percentage fall in FEV_1 after exercise was reduced by 41%, compared with placebo. The median TNF-α level decreased by 21% during roflumilast treatment, but remained constant with the placebo. Roflumilast was effective in treating exercise-induced asthma and there was a significant reduction of TNF-α levels ex vivo (Timmer et al 2002).

Roflumilast's anti-allergy properties have been assessed in several clinical studies. The efficacy of oral roflumilast (500 μg/day) has been investigated in allergic rhinitis, in a randomized, placebo-controlled, double-blind, crossover study. Twenty five people (16 male, 9 female; median age, 28 years) with histories of allergic rhinitis, but who were asymptomatic at screening, received roflumilast (500 μg once daily) and placebo for 9 d each with a washout period of at least 14 d between treatments. Controlled intranasal allergen provocation with pollen extracts was performed daily beginning on the third day of treatment, ~2 h after drug administration. After allergen provocation, rhinal airflow was measured and subjective symptoms (obstruction, itching, rhinorrhea) were assessed. Rhinal airflow improved during roflumilast treatment and was significantly higher at study day 9 than with placebo. Thus, roflumilast, effectively controlled symptoms of allergic rhinitis (Schmidt et al 2001).

The effects of repeated doses of roflumilast (250 or 500 μg oral) on asthmatic airway responses to allergen were examined in a randomized, double-blind, placebo-controlled, crossover study. Patients (n = 23) with mild asthma ($FEV_1 \geq 70\%$ of predicted value) participated in 3 treatment periods (7–10 d), separated by washout periods (2–5-week). Patients received roflumilast (250 μg or 500 μg oral) or placebo once daily. Allergen challenge was performed at the end of each treatment period, followed by FEV_1 measurements over the next 24 h. Once-daily oral roflumilast attenuated late asthmatic reactions and, to a lesser degree, early asthmatic reactions to allergen in patients with mild allergic asthma (van Schalkwyk et al 2005).

Several studies on roflumilast's pharmacokinetic properties and metabolism have been reported. In an open, randomized, single-dose crossover study, the effects of a high-fat meal on the pharmacokinetics of roflumilast and its N-oxide metabolite were investigated. Twelve healthy subjects received roflumilast (2 × 250 μg orally) after an overnight fast and after breakfast. Blood was sampled up to 54 h for pharmacokinetic profiling of roflumilast and its N-oxide. After the meal, roflumilast C_{max} was modestly reduced and the N-oxide C_{max} was unchanged. Roflumilast t_{max} was delayed in the fed (2 h) versus the fasted state (1 h), while the N-oxide t_{max} was unchanged. No significant food effect was seen on roflumilast or the N-oxide AUC_{0-last} or AUC_{0-8}. Thus, roflumilast can be taken with or without food (Hauns et al 2006).

Roflumilast is partly metabolized by cytochrome P450 (CYP) 3A4, and may inhibit its activity. Therapeutic steady-state concentrations of roflumilast and its active

metabolite roflumilast N-oxide did not alter the metabolism of the CYP3A substrate midazolam in healthy adult male subjects, suggesting that roflumilast is not likely to affect the clearance of drugs that are metabolized by CYP3A4 (Nassr et al 2006).

BAY 19-8004

The effects of a 1-week treatment with BAY 19-8004 (5 mg once per day) have been examined on trough FEV_1 and markers of inflammation in induced sputum in patients with COPD or asthma. Eleven patients with COPD (FEV_1 ~60% predicted, all smokers) and 7 patients with asthma (FEV_1 ~70% predicted, all non-smokers) took part in a randomized, double-blind, placebo-controlled trial. FEV_1 was measured before and after 1 week of treatment; sputum was induced by 4.5% saline inhalation on the last day of treatment. FEV_1 did not improve during either treatment in either patient group. Sputum cell counts were not different following placebo and BAY 19-8004 treatment in COPD and asthma patients. In patients with COPD, small but significant reductions in sputum levels of albumin and eosinophil cationic protein were observed. Thus, a 1-week treatment with BAY 19-8004 did not affect FEV_1 or sputum cell numbers in patients with COPD or asthma. However, such treatment did reduce levels of albumin and eosinophil cationic protein in sputum samples obtained from patients with COPD (Grootendorst, Gauw, Benschop et al 2003).

Other PDE 4 inhibitors for COPD in development

CC3

CC3 is another PDE 4 inhibitor with low affinity for the HARBS. Its airway-relaxing properties were analyzed using rat precision-cut lung slices (PCLS) in which airways were contracted by methacholine or in passively sensitized PCLS exposed to ovalbumin. The anti-inflammatory properties were investigated by measuring the release of TNF from endotoxin-treated human monocytes. CC3 in combination with motapizone, attenuated methacholine-induced bronchoconstriction in a concentration-dependent manner. CC3 has bronchospasmolytic and anti-inflammatory properties (Martin et al 2002).

AWD 12-281

AWD 12-281 (N-(3,5-dichloro-4-pyridinyl)-2-[1-(4-fluorobenzyl)-5-hydroxy-1H-indol-3-yl]-2-oxoacetamide), is a potent (IC_{50} = 9.7 nM) and selective inhibitor of PDE 4, with a low affinity for the HARBS (Kuss et al 2003; Gutke et al 2005). The compound was optimized for topical treatment of COPD, asthma, and allergic rhinitis. The compound has a low oral bioavailability and a low solubility. It exerts long-lasting pharmacological effects after intratracheal administration, indicating persistence in lung tissue in various animal models. It has high plasma-protein binding and hepatic metabolism (primarily glucuronidation); both contribute to low systemic exposure after intratracheal dosing. The drug has a large difference between emetic and anti-inflammatory dose levels (a factor of more than 100 in ferrets) (Kuss et al 2003).

SCH 351591

SCH 351591 (N-(3,5-dichloro-1-oxido-4-pyridinyl)-8-methoxy-2-(trifluoromethyl)-5-quinoline carboxamide) has been identified as a potent (IC_{50} = 58 nM) and highly selective PDE 4 inhibitor with oral bioactivity in several animal models of lung inflammation and is being investigated as a potential therapeutic for COPD and asthma.

Ciclamilast

Ciclamilast is a piclamilast (RP 73-401) analog, though is a more potent inhibitor of PDE 4 and airway inflammation and has a more favorable side-effect profile than piclamilast (Deng et al 2006). In a murine model, oral administration of ciclamilast dose-dependently inhibited changes in lung resistance and lung dynamic compliance, up-regulated cAMP-PDE activity, and increased PDE 4D, but not PDE 4B, mRNA expression in lung tissue. Ciclamilast also dose-dependently reduced mRNA expression of eotaxin, TNF-α and IL-4, but increased mRNA expression of IFN-γ in lung tissue. There was a correlation between increases in PDE 4D mRNA expression and airway hyper-responsiveness (Deng et al 2006).

Piclamilast

Piclamilast (RP 73-401) reduced antigen challenge induced-cell recruitment in airways of sensitized mice, and reduced gelatinase B (MMP-9) (Belleguic et al 2000). Piclamilast also reduced MMP-9 activity and TGF-β1 release during acute lung injury in mice, suggesting that PDE 4 inhibitors might modulate tissue remodeling in lung injury (Corbel, Germain et al 2002). Fibroblasts cultured with PMA or TNF-α released increased amounts of pro-MMP-1, whereas TGF-β1 had no effect (Martin-Chouly et al 2004). Incubation with CI-1044 or cilomilast significantly prevented the TNF-α increase in pro-MMP-1. These results suggest that PDE 4 inhibitors are effective in inhibiting the pro-MMP-2 and pro-MMP-1 secretion induced by TNF-α and might

indicate the potential therapeutic benefit of selective PDE 4 inhibitors in lung diseases associated with abnormal tissue remodeling (Martin-Chouly et al 2004).

CGH2466

CGH2466 resulted from a study to identify a theophylline-like compound with improved effectiveness. CGH2466 antagonized the adenosine A1, A2b and A3 receptors and inhibited the p38 mitogen-activated protein (MAP) kinases α and β and PDE 4D. CGH2466 inhibited the production of cytokines and oxygen radicals by human peripheral blood leucocytes in vitro. When given orally or locally into the lungs, CGH2466 potently inhibited the ovalbumin- or LPS-induced airway inflammation in mice (Trifilieff et al 2005).

The in vitro activity of CI-1044 has been compared with that of rolipram and cilomilast and to the glucocorticoid dexamethasone in reducing LPS-induced TNF-α release in whole blood from COPD patients. In whole blood from COPD patients, pre-incubation with PDE 4 inhibitors or dexamethasone resulted in a dose-dependent inhibition of LPS-induced TNF-α release. There was a similar inhibition using whole blood from healthy volunteers, however, at higher IC_{50} values. Thus, CI-1044 inhibited in vitro LPS-induced TNF-α release in whole blood from COPD patients (Ouagued et al 2005).

Other treatments for COPD in development

Many other treatments for COPD and asthma are in various stages of development (Donnelly and Rogers 2003; Buhl and Farmer 2004; Buhl and Farmer 2005; Malhotra et al 2006). They include aids to smoking cessation (Richmond and Zwar 2003), antiproteases, including inhibitors of neutrophil elastase (Ohbayashi 2002), matrix metalloprotease inhibitors (Owen 2005; Gueders et al 2006), cathepsin inhibitors (de Garavilla et al 2005), selectin antagonists (Romano 2005), inhibitors of TNF-α (Spond et al 2003), adenosine A2a receptor agonists (Bonneau et al 2005), ω-3 polyunsaturated fatty acids (Matsuyama et al 2005), inhibitors of mucus hypersecretion (Knight 2004; Rogers and Barnes 2006), purinoceptor $P2Y_2$ receptor agonists to increase mucus clearance (Kellerman 2002), inhibitors of p38 mitogen-activated protein (MAP) kinase (Adcock et al 2006), inhibitors of NF-κB kinase-2 (IKK2) (Caramori et al 2004), leukotriene (LT) blockers (Riccioni et al 2004), anti-chemokine therapy (Panina et al 2006; Hardaker et al 2004), anti-cytokine therapy (Chung 2006), statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers (Mancini et al 2006), antioxidant therapy (Bowler et al 2004; Owen 2005; MacNee 2005b; Rahman and Kilty 2006; Hanta et al 2006; Sadowska et al 2006; Rahman and Adcock 2006), and activators of histone deacetylase (Adcock et al 2005; Antoniu 2006; Kirkham and Rahman 2006; Barnes 2006; Ito et al 2006).

Conclusion

The concept of PDE 4 inhibitors as treatments for COPD, asthma, and other inflammatory airway conditions has been widely discussed in the literature in recent years and may soon come to fruition. Taking one step back, PDE inhibitors have proven to be successful drugs. Today, the first-line oral pharmacotherapy for most patients with erectile dysfunction is a PDE 5 inhibitor: sildenafil (Viagra), tadalafil (Cialis), or vardenafil (Levitra) (Briganti et al 2005; Boswell-Smith, Spina, et al 2006). Furthermore, ibudilast, a drug that does inhibit PDE 4, is marketed in Japan and is used to treat asthma.

There is much preclinical data supporting the use of PDE 4 inhibitors in treating COPD. In vitro, PDE 4 inhibitors relax lung smooth muscle and decrease the production of cytokines from inflammatory cells (Torphy and Undem 1991; Undem et al 1994; Dent and Giembycz 1995; Teixeira et al 1997). PDE 4 inhibitors also reduce TNF-α release (Profita et al 2003). Furthermore, some PDE 4 inhibitors inhibit neutrophil degranulation (Jones et al 2005). These inhibitors also suppress the activity of many pro-inflammatory and immune cells (Lipworth 2005).

To date, only limited clinical data is available to assess PDE 4 inhibitors. Results from large, phase III COPD studies of cilomilast have been reported; cilomilast was well-tolerated, improved health status, and lung function, and reduced the utilization of healthcare resources and incidence of COPD exacerbations. However, the results of these phase III trials were somewhat unremarkable and disappointing (Giembycz 2006).

Questions remain about both the efficacy and safety of cilomilast, the one PDE 4 inhibitor to have undergone a full clinical program to date. Its efficacy has been somewhat limited and, furthermore, somewhat inconsistent results have been reported; indeed, the FDA has yet to approve the drug, apparently because of its limited efficacy. In two of the four pivotal phase III trials, cilomilast did not reach statistical significance over the placebo. In a 6-week phase II study in 424 patients with moderate COPD, significant improvements in lung function were seen in patients receiving cilomilast. Administered at 15 mg bid, it resulted in

significant improvements in FEV_1 compared with placebo (130 mL versus –30 mL at week 6); FVC and peak expiratory flow rate also improved. However, no improvement in quality of life (SGRQ) was found. The observed difference in FEV_1 compared with placebo after 12-weeks was 70 mL (10 mL versus -60 mL at week 12; statistically insignificant). This was compared with 160 mL (130 mL versus –30 mL at week 6) in the larger study, despite patients having similar levels of baseline function (Compton et al 1991). In a smaller (59-patient) phase II study, no significant change in FEV_1 was found (Gamble et al 2003).

The FDA expressed concern about cilomilast's toxicity and side effects. Vasculitis was seen in rats at doses lower than those used in the phase III studies and GI-related side effects were seen in patients receiving cilomilast at three times the frequency seen in those taking placebo.

It remains unclear whether the effects of cilomilast on lung function are the result of bronchodilator activity or of an anti-inflammatory effect; the relatively slow improvement in FEV_1 suggests an anti-inflammatory action, not bronchodilation. The acute bronchodilating effects of a single dose of cilomilast have been assessed in COPD patients. FEV_1 was measured before and at up to 8 h intervals after patients received placebo, cilomilast, or cilomilast and inhaled salbutamol (400 μg) and/or ipratropium bromide (80 μg). A single dose of cilomilast did not cause acute bronchodilation in COPD patients who were responsive to inhaled bronchodilators (Grootendorst, Gauw, Baan et al 2003). Anti-inflammatory properties of cilomilast have been assessed in several studies. In one, patients with COPD received cilomilast (15 mg bid) or placebo for 12-weeks. In bronchial biopsies, cilomilast treatment was associated with reductions in $CD8^+$ and $CD68^+$ cells; this was the first report of a reduction in airway tissue inflammatory cells characteristic of COPD by any agent (Gamble et al 2003).

While the FDA issued an 'approvable' letter for cilomilast to treat CODP, significant safety and efficacy issues remain. In two of four pivotal phase III studies, the drug failed to reach statistical significance in FEV_1 change, the co-primary endpoint. Indeed, in the two studies that did, this was largely the result of decreases in FEV_1 in the placebo group, not increases in those receiving cilomilast (FEV_1 remained close to baseline, even after 6-months of treatment, in all four studies). The FEV_1 changes seen were small and there is a question as to whether even statistically significant results would be of much clinical significance. For comparison, the changes were smaller than those reported in a meta-analysis of theophylline studies (Ram et al 2002). Three of the four phase III studies failed to reach statistical significance in SGRQ, the other primary endpoint. However, cilomilast did reduce the incidence of exacerbations.

In rat studies, cilomilast was associated with vasculitis and death at doses lower than the human dose, although there is some reason to believe that rats may be more sensitive to PDE inhibitor toxicity (Bian et al 2004). Vasculitis has been seen with other PDE inhibitors (Larson et al 1996; Slim et al 2003). The FDA was apparently not satisfied with the investigation by GSK of patients with GI-related side effects.

Cilomilast seems unlikely to be a replacement for existing COPD therapies (supplemental oxygen, inhaled bronchodilators, corticosteroids and antibiotics (Sin et al 2003)). Cilomilast, however, may be a useful additional drug (for example, in combination with corticosteroids), especially if it can be shown in longer-term studies that the increases in FEV_1 are more substantial. Cilomilast has other anti-inflammatory properties, which may also be of clinical significance (Gamble et al 2003).

The concept of using PDE 4 inhibitors to treat COPD may well be sound, but the first drug in the class may be roflumilast (Antoniu 2006b), not cilomilast. The completion and publication of its clinical development is awaited with interest.

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