

Phosphodiesterase inhibition in the treatment of autoimmune and inflammatory diseases: current status and potential

Mindi S Miller

University of Georgia College
of Pharmacy, Athens, GA, USA

Abstract: Cyclic nucleotide second messengers adenosine-3',5'-cyclic monophosphate (cAMP) and guanosine-3',5'-cyclic monophosphate (cGMP) influence numerous cellular functions, including inflammatory and immune responses. Intracellular levels of these nucleotides are regulated by a diverse group of phosphodiesterase enzymes. Inhibition of the various types of phosphodiesterase enzymes may offer a novel means to manage both inflammatory and autoimmune disorders. Recently, progress has been made in the development of phosphodiesterase inhibitors for a variety of conditions. This article reviews recent developments in the search for phosphodiesterase inhibitors as novel therapeutic agents for inflammatory and autoimmune conditions.

Keywords: phosphodiesterase (PDE) inhibitors, inflammatory disease, autoimmune disease

Introduction

The cyclic nucleotides adenosine-3',5'-cyclic monophosphate (cAMP) and guanosine-3',5'-cyclic monophosphate (cGMP) act as intercellular second messengers by facilitating the action of many hormones, neurotransmitters, and inflammatory mediators.^{1,2} These messengers play an integral role in numerous bodily processes, including inflammation, immune response, vascular resistance, cardiac output, gastrointestinal motility, neuroplasticity, reproduction, and vision.³ The phosphodiesterase (PDE) family of enzymes is responsible for the degradation of cAMP and cGMP, and therefore plays a key role in modulating intracellular levels of the second messengers and, in the process, also become regulators of cell function.⁴ The PDE enzymes have been described as a "super family", comprise at least 21 genes (over 40 isoforms), and are grouped into eleven subfamilies based on amino acid sequence, regulation, pharmacologic properties, and susceptibility to pharmacologic treatments.^{5,6} Because PDEs are located in every cell in the body, the enzymes are considered therapeutic targets for several disease states ranging from sexual dysfunction and congestive heart failure to asthma and chronic obstructive pulmonary disease (COPD) (Table 1).^{4,7,8}

Since the 1970s, PDE inhibitors have been investigated as potential and actual treatments for numerous medical conditions. These compounds include both non-specific PDE inhibitors such as theophylline as well as moieties that target a specific PDE family such as sildenafil and other PDE5 antagonists. Inflammatory cells seem to be especially sensitive to the effects of increased levels of cyclic nucleotides. In fact, PDE inhibitors demonstrate anti-inflammatory and immunosuppressive effects by suppressing immune cells such as T-cells, basophils, and mast cells.⁸ This review focuses on PDE inhibitors as treatment for inflammatory and autoimmune disease.

Correspondence: Mindi S Miller
University of Georgia College of
Pharmacy, 250 W Green Street,
Athens, GA 30602, USA
Tel +1 770 551 7021
Fax +1 770 558 1298
Email mmiller@rx.uga.edu

Table 1 Phosphodiesterase superfamily

PDE family	Substrate	Tissue distribution	Inhibitors	Clinical applications
PDE1	cGMP>cAMP	Brain, heart, smooth muscle, lung	Vinpocetine, nicardipine, nimodipine	Memory loss, dementia
PDE2	cGMP=cAMP	Adrenal gland, lung, heart, platelets, brain, liver, corpus cavernosum	EHNA	ARDS, sepsis, memory loss
PDE3	cAMP>cGMP	Heart, liver, lung, platelets, vascular smooth muscle, corpus cavernosum	Cilostamide, cilostazol, milrinone, enoxamone	CHF, pulmonary HTN, thrombosis, glomerulonephritis
PDE4	cAMP	Lung, mast cells, liver, kidney, brain	Rolipram cilomilast, roflumilast	Glomerulonephritis, asthma, COPD, bipolar disease
PDE5	cGMP	Corpus cavernosum, lung, vascular smooth muscle, platelets, brain, esophagus	Sildenafil, tadalafil, vardenafil, zaprinast, dipyridamole	Erectile dysfunction, BPH, pulmonary HTN, chronic renal failure
PDE6	cGMP>cAMP	Retina	Sildenafil, tadalafil, vardenafil, dipyridamole, zaprinast	No clinical applications
PDE7	cAMP>cGMP	Skeletal muscle, T-cells, heart, kidney, brain, pancreas	Dipyridamole	Immunologic disorders, lung disease
PDE8	cAMP	Testes, thyroid, eye, liver, kidney, heart, skeletal muscle, pancreas, T-cells	Dipyridamole	Immunologic disorders
PDE9	cGMP	Brain, kidney, liver, lung	Zaprinast	Possible hypoglycemic effects
PDE10	cGMP>cAMP	Brain, testes	Dipyridamole, papaverine	Schizophrenia and psychiatric disorders
PDE11	cAMP=cGMP	Prostate, skeletal muscle, kidney, liver, testes, pituitary, salivary glands	Tadalafil, zaprinast, dipyridamole	Possible improvement in testicular function

Notes: Adapted by permission from Macmillan Publishers Ltd: INTERNATIONAL JOURNAL OF IMPOTENCE RESEARCH, Bischoff E, Potency, selectivity, and consequences of nonselectivity of PDE inhibition, *Int J Impot Res.* 2004;16(Suppl 1):S11–S14, Copyright © 2004;⁶⁹ International Journal of PharmTech Research, Ghosh R, Sawant O, Ganpathy P, Pitre S, Kadam VJ, Phosphodiesterase inhibitors: their role and implications, *Int J Pharm Tech Res.* 2009;1(4):1148–1160;³ and Boswell-Smith V, Spina D, Page CP, Phosphodiesterase inhibitors, *British Journal of Pharmacology*, 2006;147(Suppl 1):S252–S257, published by John Wiley and Sons, Copyright © 2006 British Pharmacological Society.⁴

Abbreviations: ARDS, acute respiratory distress syndrome; BPH, benign prostatic hyperplasia; cAMP, adenosine-3',5'-cyclic monophosphate; cGMP, guanosine-3',5'-cyclic monophosphate; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; EHNA, erythro-9-(2-hydroxy-3-nonyl)adenine; HTN, hypertension; PDE, phosphodiesterase.

PDE inhibitors in inflammatory disorders

Asthma

Asthma is defined as a chronic inflammatory disease of the airways. The disorder is characterized by infiltration of inflammatory cells, including mast cells, eosinophils, T-lymphocytes, and neutrophils.⁹ Patients with severe asthma show increased levels of neutrophils and eosinophils in sputum samples, and bronchial mucosa also shows elevated numbers of these cells.¹⁰ In addition, some research has shown that T-lymphocytes, particularly type 2 helper (Th2) differentiated cluster of differentiation (CD)4+ cells, are important in the inflammatory response. Cytokines, which play a role in the cellular response to asthma, are released from the CD4+ cells. These cytokines include interleukin (IL)-4 and IL-13.¹¹ The inflammatory response may cause bronchial hyper-responsiveness and airway obstruction that contribute to symptoms such as wheezing, dyspnea, coughing, and tightness in the chest.⁹

Theophylline, a nonselective PDE inhibitor, has been used in the treatment of asthma for almost a century. Theophylline (Figure 1A) is a methylxanthine that primarily inhibits PDE3 and PDE4 isoenzymes in airway smooth muscle, causing both

bronchodilation and anti-inflammatory effects. It is also a strong adenosine receptor antagonist and an activator of histone deacetylase 2.⁷ Theophylline exhibits an anti-inflammatory response and also may work synergistically with corticosteroids to reduce the inflammatory response seen in asthma.¹² Studies have shown that withdrawal of theophylline in asthmatic patients also taking corticosteroids causes a significant increase in symptoms of asthma. In addition, theophylline withdrawal in these patients results in an increase in T-lymphocytes in lung tissue.¹³ Use of theophylline is limited by side effects such as nausea, headache, diarrhea, tachycardia, and arrhythmias. It also has several drug interactions and a narrow therapeutic index.⁷

Most PDE isoenzymes are expressed in lung tissue, including PDE1, PDE2, PDE3, PDE4, PDE5, PDE7, PDE8, and PDE9; however, PDE3 and PDE4 have been the primary targets for drug therapy.^{4,14} The PDE4 isoenzyme is found in most inflammatory and immune cells, including T-cells, eosinophils, neutrophils, B-cells, monocytes, macrophages, and dendritic cells.⁷ In several preclinical studies, PDE4 inhibitors have been shown to suppress bronchial hyper-responsiveness, eosinophil infiltration, and production of histamine, leukotrienes, and cytokines.^{8,11,15}

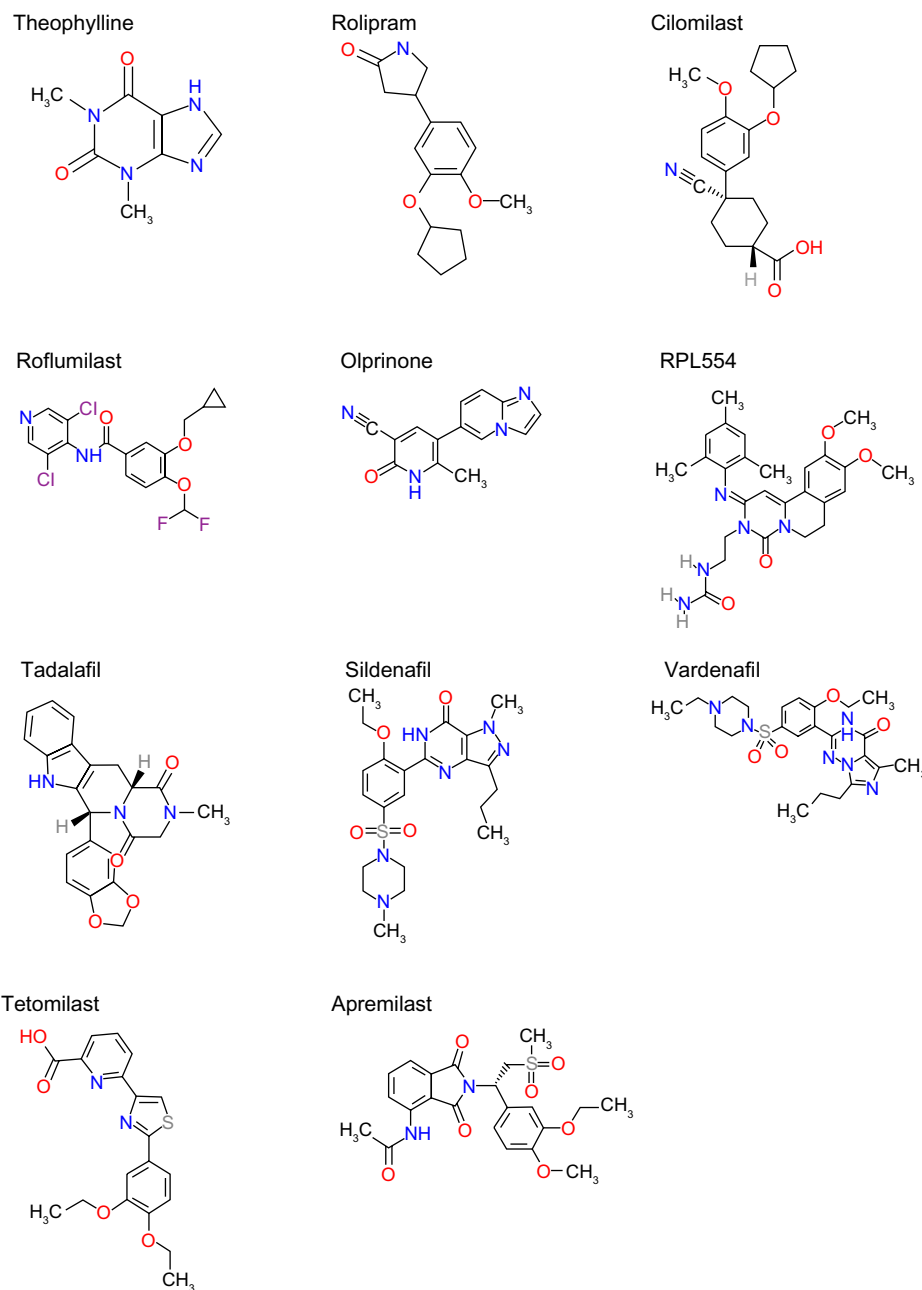


Figure 1 Structures of phosphodiesterase type 5 inhibitors.

Note: Data from www.chemspider.com.⁷⁰

Inhibitors of PDE4

Rolipram (Figure 1B) is the prototype selective PDE4 inhibitor. It was developed in the 1970s as a potential antidepressant, but was never marketed due to severe adverse effects such as nausea and vomiting.^{5,16} Although rolipram was unsuccessful as a drug therapy, it launched the search for an effective anti-inflammatory drug with a more favorable side effect profile.⁷ In the last 2 decades, many second-generation PDE4 inhibitors have been studied for use in asthma, but none have reached the asthma market. One of these compounds, CDP840, was developed in 1997 and

became the first oral PDE4 inhibitor to show efficacy in asthma without major side effects.⁴ Cilomilast (Figure 1C), an oral inhibitor of PDE4, has been studied for use in asthma. Cilomilast 10 mg twice daily was given to 27 patients for 1 week. A significant reduction (34%) in exercise-induced bronchoconstriction was seen.¹⁷ A randomized trial examined 303 asthma patients who were poorly controlled on low-dose corticosteroids. Participants received cilomilast 5 mg, 10 mg, 15 mg, or placebo along with continued inhaled corticosteroids. A greater improvement in forced expiratory volume in 1 second (FEV₁) was seen with cilomilast 15 mg

versus placebo, but the difference was not significant except at the 2-week time period. Of the patients receiving cilomilast, 69% reported great improvement in symptoms versus 41% of patients receiving placebo. Clinicians reported improvements in these patients of 59% and 29%, respectively.¹⁸

In a third trial, 211 patients received cilomilast 10 mg or 15 mg twice daily or placebo for 12 months. Non-significant improvements in FEV₁ were seen.¹⁹ Although cilomilast showed promise for the treatment of asthma, it was associated with significant rates of nausea and vomiting in the clinical trials. As a result, studies with cilomilast have been suspended.^{4,20}

Roflumilast (Figure 1D), the only PDE4 inhibitor to receive US Food and Drug Administration (FDA) approval, is indicated for use in COPD.²¹ The compound, which is more potent than cilomilast in vitro, has also shown efficacy for asthma in clinical trials.²⁰ A double-blind, randomized, placebo-controlled, crossover study examined 16 men with exercise-induced asthma. The patients received oral roflumilast 500 µg daily or placebo for 28 days. The mean FEV₁ fall after exercise was reduced by 41% with roflumilast versus placebo ($P=0.021$).²² In a randomized, double-blind, double-dummy, noninferiority study with 499 asthmatics, oral roflumilast 500 µg once daily was compared with inhaled beclomethasone 200 µg twice daily for 12 weeks. Both treatment groups showed similar significant improvement in lung function ($P\leq 0.001$) and reduced asthma symptom score and use of rescue treatments ($P\leq 0.001$).²³ In a randomized, double-blind, placebo-controlled, crossover trial, 23 patients with mild asthma received oral roflumilast 500 µg, 250 µg, or placebo for 7–10 days. Late asthmatic reactions to allergen challenge were reduced by 43% ($P=0.0009$) in patients taking roflumilast 500 µg and by 27% ($P=0.0110$) in patients taking roflumilast 250 µg versus placebo. Both doses also significantly reduced attenuated early reactions to allergen challenge versus placebo (28% [$P=0.0038$] and 25% [$P=0.0046$], respectively).²⁴ A larger study examined 693 subjects with mild to moderate asthma. Patients in this double-blind, parallel-group trial were randomized to receive 100 µg, 250 µg, or 500 µg of roflumilast daily for 12 weeks. All doses of roflumilast significantly increased lung function from baseline ($P<0.001$). As expected, roflumilast 500 µg daily produced the greatest improvements.²⁵ A more recent double-blind, crossover trial randomized 25 patients with mild allergic asthma to roflumilast 500 µg or placebo once daily for 14 days. On day 14, FEV₁ was measured after allergen challenge. Roflumilast significantly inhibited the maximum percentage

fall in FEV₁ compared with placebo ($P=0.02$). The drug also inhibited the allergen-induced increase in inflammatory cells in sputum samples.¹⁰ In trials that accessed adverse effects, roflumilast was well tolerated.^{23–25} Roflumilast seems to be efficacious for the treatment of asthma and is associated with fewer side effects than its PDE4 inhibitor predecessors.

Inhibitors of PDE3

PDE3 inhibitors have also been evaluated for use in asthma. A small placebo-controlled trial examined the effects of the PDE3 inhibitor MSK492 in 18 patients with atopic asthma. Patients inhaled an allergen 90 minutes after receiving one dose of oral MSK492 20 mg, 40 mg, or placebo. The 40 mg dose of MSK492 was associated with a significant decrease in both the early and the late response to inhaled allergen.²⁶ The second study examined the effect of an inhaled PDE3 inhibitor for the treatment of asthma. This double-blind study randomized nine asthmatic patients to receive olprinone (a PDE3 inhibitor, Figure 1E), salbutamol (a beta agonist), and placebo. Each patient received all study drugs on 3 separate days. Significant increases in FEV₁ from baseline were seen with both olprinone and salbutamol. Response seen with the two medications did not differ significantly ($P=0.28$).²⁷ Finally, eleven elderly patients with stable asthma were randomized to receive the oral PDE3 inhibitor cilostazol 100 mg twice daily or placebo. After 2 weeks of treatment with cilostazol, the patients' cough threshold after inhaled allergen (capsaicin) was significantly increased compared with placebo ($P<0.05$).²⁸

No significant adverse effects were seen in these studies with PDE3 inhibitors.^{26–28} Although studies with PDE3 inhibitors enrolled few patients, these agents may offer a viable treatment option for patients with asthma. The inhaled route may provide a benefit without systemic side effects commonly experienced with oral drugs.

Inhibitors of PDE3 and PDE4

Research has suggested that PDE3 inhibitors have little effect on T-cell activation, but may potentiate the effect of PDE4 inhibitors on activation of T-cells. In addition, both PDE3 and PDE4 inhibitors must be inhibited to completely suppress macrophage release of tumor necrosis factor (TNF)- α and proliferation of T-cells.²⁹ Others have suggested that targeting the multiple PDE enzymes in the lung may be required for maximum anti-inflammatory effects. In addition, a combined PDE3/4 inhibitor may have the advantage of providing both a bronchodilator and an anti-inflammatory response.¹⁵

Previous clinical trials of dual PDE3/4 inhibitors such as benafentrine and zardaverine showed mixed results.¹⁴ Interest in these compounds has recently been renewed with the development of RPL554 (Figure 1F). Three studies in asthma patients (and one trial in COPD) showed that RPL554 is safe and effective. The first study examined 18 healthy men who received inhaled RPL554 (0.003 mg/kg or 0.009 mg/kg) or placebo. This study included an open-label phase in which six nonsmoking men with mild allergic asthma received single inhaled doses of RPL554 (three patients received 0.009 mg/kg and three patients received 0.018 mg/kg). In addition, ten men with mild allergic asthma were randomly assigned to receive RPL554 at 0.018 mg/kg or placebo to assess for safety, bronchodilation, and broncho-protection. Patients with asthma who received RPL554 had rapid bronchodilation, with a 14% increase in FEV₁ versus placebo ($P<0.0001$). Also, the dose of methacholine causing a 20% fall in FEV₁ was significantly increased in patients receiving RPL554 compared with placebo ($P=0.004$). In study 2, 12 men with clinically stable asthma received inhaled RPL554 at 0.018 mg/kg daily or placebo for 6 days. Results showed that RPL554 resulted in similar increases in FEV₁ 6 hours after dosing on days 1, 3, and 6 ($P<0.001$). Finally, in a randomized, double-blind, placebo-controlled crossover trial, 21 healthy men received RPL554 0.018 mg/kg and placebo. Sputum was induced in the subjects 6 hours after lipopolysaccharide challenge. The proportion of neutrophils in the sputum samples was similar in both groups ($P=0.15$). These results show that RPL554 has anti-inflammatory properties because it reduces neutrophils and total cells to a similar extent.³⁰ The drug was well tolerated, and adverse events were mild and similar in frequency to those experienced with placebo. Theoretically, a treatment with both anti-inflammatory and bronchodilator properties might be beneficial in patients with asthma. More studies are needed with the dual inhibitor RPL554 to determine its place in asthma therapy.

COPD

COPD is the fourth leading cause of death worldwide. The World Health Organization predicts that COPD prevalence will continue to rise and become the third leading cause of death by 2020. It is characterized by progressive, irreversible airflow restriction, and COPD is associated with pulmonary inflammation that is responsible for obstruction of small airways and destruction of lung tissue. Spirometry is utilized to determine severity of COPD based on FEV₁.³¹

Unlike the inflammatory process in asthma, cigarette smoke and other chemical irritants cause COPD. Symptoms include

dyspnea, cough, sputum production, wheezing, and chest tightness, and, in more severe cases, fatigue, weight loss, and anorexia.³¹ The inflammatory response in COPD is distinct from that seen in asthma and is characterized by infiltration of neutrophils, macrophages, and CD8+ T-lymphocytes. In addition, increased levels of pro-inflammatory mediators such as cytokines, chemokines, and growth factors are found in the lung tissue of patients with COPD.^{11,32,33} Because of the inflammatory nature of COPD, inhaled corticosteroids have been a mainstay of treatment. However, these medications have minimal effect on the inflammation associated with COPD and do not prevent disease progression. PDE inhibitors may provide more efficient anti-inflammatory effects because corticosteroids do not suppress neutrophil activation or production of cytokines and other mediators.³³ Potential therapies for COPD have focused on PDE4 inhibitors and dual PDE3/4 inhibitors.

PDE4 inhibitors

Roflumilast, the first (and currently only) PDE inhibitor to be FDA approved for use in COPD, has been evaluated in several phase III clinical trials involving over 4,000 patients. A multicenter, double-blind study randomized 1,411 patients with moderate to severe COPD to receive oral roflumilast (250 µg or 500 µg) or placebo daily for 24 weeks. Both doses of roflumilast significantly improved post-bronchodilator FEV₁ ($P<0.0001$) and reduced COPD exacerbations compared with placebo ($P=0.0029$). Roflumilast was generally well tolerated by patients.³³

A second randomized, placebo-controlled, double-blind trial examined 1,513 patients with severe COPD. Subjects received 500 µg oral roflumilast ($n=760$) or placebo ($n=753$) once daily for 1 year. Roflumilast improved post-bronchodilator FEV₁ from baseline ($P=0.001$); patients receiving placebo experienced a decrease in lung function. The exacerbation rate overall was comparable between treatments, but a retrospective analysis showed a 36% reduction in roflumilast-treated patients with the most severe stage of disease compared with placebo ($P=0.024$). Adverse events with roflumilast, such as diarrhea, nausea, and headache, usually subsided with continued treatment, but these patients had more withdrawals during the first 4 weeks of roflumilast therapy.³⁴

In two double-blind studies with identical design, COPD patients with severe airflow limitations were randomly assigned to receive oral roflumilast 500 µg ($n=1,537$) or placebo ($n=1,554$) for 52 weeks. In the pooled analysis, both pre-bronchodilator FEV₁ and post-bronchodilator FEV₁ significantly increased from baseline in patients taking

roflumilast compared with placebo ($P<0.0001$). In addition, the rate of moderate or severe COPD exacerbations was reduced with roflumilast ($P=0.0003$). Adverse events (diarrhea, nausea, and headache) were more common in the roflumilast group during the first 4–12 weeks of treatment.³⁵

In two additional double-blind, multicenter trials, patients with moderate to severe COPD were randomly assigned to oral roflumilast 500 µg or placebo once daily for 24 weeks. Patients also received a long-acting bronchodilator: salmeterol (first study) or tiotropium (second study). The primary endpoint was change in pre-bronchodilator FEV₁. In the roflumilast and salmeterol trial, 466 patients received roflumilast and 467 patients received placebo; in the roflumilast and tiotropium trial, 371 patients received roflumilast and 372 patients received placebo. In both trials, significant improvements were seen in pre-bronchodilator FEV₁ in patients receiving roflumilast compared with placebo ($P<0.0001$). Improvements were also seen in post-bronchodilator FEV₁ for patients in both trials receiving roflumilast ($P<0.0001$).³⁶

Studies are ongoing for roflumilast in COPD. One such trial is investigating the use of roflumilast in addition to standard therapy for severe COPD. An additional study is examining strategies to improve adherence to roflumilast.

PDE4 inhibitors such as roflumilast and cilomilast have been shown to be effective in the treatment of asthma and COPD, but side effects have been problematic. As previously mentioned, cilomilast and other potential new oral anti-inflammatory drugs have been stopped in development due to patient acceptability. Inhaled PDE4 inhibitors may provide an alternative way to deliver these agents directly to the site of action in lung tissue. Studies are ongoing in this area to determine the efficacy of this novel delivery method.^{32,37}

Dual PDE3/4 inhibitors

At least five dual PDE3/4 inhibitors have been developed and studied in clinical trials. Unfortunately, four of these compounds have been discontinued. An inhaled drug, RPL554, shows promise for the treatment of asthma and COPD.³² Studies with RPL554 in asthma have been mentioned previously. The safety and efficacy of RPL554 (0.018 mg/kg) was assessed in an open-label, placebo-controlled crossover trial in 12 men with mild to moderate COPD. Safety was a primary endpoint for this study, and efficacy was a secondary endpoint. The study treatment was well tolerated, and side effect rates were similar between RPL554 and placebo. Inhaled RPL554 produced a mean maximum increase in FEV₁ of 17.2%.³⁰ Further studies are needed with this novel agent.

Benign prostatic hyperplasia

The exact mechanism of benign prostatic hyperplasia (BPH), or symptomatic enlargement of the prostate gland, is not known. However, recent evidence has strongly suggested that BPH is an inflammatory process involving activation of T-lymphocytes. These cells release cytokines and growth factors, which may induce cell proliferation in the prostate.^{38,39} PDE type 5 inhibitors, effective in erectile dysfunction, have also shown efficacy for use in BPH. In addition to proposed antiproliferative effects, PDE5 inhibitors have been shown to relax prostatic smooth muscle and may improve pelvic blood flow and affect sensory nerve signaling from the bladder and prostate.⁴⁰

Tadalafil (Figure 1G), the first PDE5 inhibitor with FDA approval for BPH, has been evaluated in several clinical studies. A double-blind placebo-controlled trial examined 281 patients who received tadalafil 5 mg daily for 6 weeks, increased to 20 mg daily for 6 weeks ($n=138$), or placebo ($n=143$) for 12 weeks. The patients who received tadalafil showed a significant improvement in lower urinary tract symptoms versus those who received placebo ($P=0.003$). Quality-of-life scores also improved with tadalafil.⁴⁰

A second double-blind study randomized 1,058 men to receive once-daily treatment with tadalafil 2.5 mg ($n=208$), 5 mg ($n=212$), 10 mg ($n=216$), or 20 mg ($n=209$), or placebo for 12 weeks. Again, significant improvements were seen in lower urinary tract symptoms in patients receiving tadalafil versus those receiving placebo.⁴¹ A third double-blind study randomized 200 men to treatment with tadalafil 20 mg or placebo daily for 12 weeks. Patients receiving tadalafil had improvements in lower urinary tract symptoms versus those receiving placebo ($P<0.001$).⁴² An additional trial with 325 participants randomized patients to receive tadalafil 5 mg once daily ($n=161$) or placebo ($n=164$) for 12 weeks. Subjects who received tadalafil had significant improvement in lower urinary tract symptoms versus placebo starting after 1 week of treatment ($P=0.004$).⁴³

Sildenafil (Figure 1H) has also been investigated for the treatment of BPH. After two open-label studies and one retrospective study showed efficacy in lower urinary tract symptoms, the PDE5 inhibitor was examined in a randomized double-blind, placebo-controlled trial. Men with erectile dysfunction and BPH received sildenafil 50 mg ($n=189$) or placebo ($n=180$) once daily for 12 weeks. The dose of sildenafil was increased to 100 mg daily after 2 weeks. Results showed a significant reduction in lower urinary tract symptoms in patients receiving sildenafil versus those receiving placebo ($P<0.0001$). Quality of life was also improved in these patients.⁴⁴

Vardenafil (Figure 1I) has been investigated for the treatment of BPH in several randomized, double-blind, placebo-controlled trials. A study examined 222 men who received vardenafil 10 mg twice daily ($n=109$) or placebo ($n=113$) for 8 weeks. Significant improvement in lower urinary tract symptoms and quality of life were seen in patients receiving vardenafil compared with placebo ($P=0.0013$).⁴⁵ A second clinical trial examined 80 men who were randomized to receive vardenafil 10 mg or placebo twice daily for 12 weeks. Again, patients receiving vardenafil reported significant improvements in lower urinary tract symptoms ($P=0.0014$) and quality of life.⁴⁶

Inflammatory bowel disease

PDE inhibitors have been investigated for treatment of inflammatory bowel disease (IBD), which includes Crohn's disease and ulcerative colitis. The pathogenesis of IBD involves activated T-cells, which release various cytokines. These cytokines, in turn, facilitate the release of free radicals and destructive enzymes, causing tissue injury in the gastrointestinal tract.⁴⁷ PDE type 4 inhibitors have shown efficacy for IBD in animal studies. In addition, tetomilast (Figure 1J) has also been evaluated for use in IBD in one phase II and two phase III trials. In the phase II study, 186 patients with mild to moderate ulcerative colitis were randomized to receive tetomilast 25 mg ($n=62$), tetomilast 50 mg ($n=62$), or placebo ($n=62$) by mouth once daily for 8 weeks. A significant improvement in disease activity index (DAI) was seen at 8 weeks in the patients receiving tetomilast 25 mg versus placebo ($P=0.041$). The most common adverse effects seen with tetomilast were nausea, vomiting, dizziness, fatigue, and headache.⁴⁸ Tetomilast was also examined in two phase III clinical trials. In these randomized, controlled, multicenter studies, 750 patients received tetomilast 25 mg, tetomilast 50 mg, or placebo by mouth daily for 8 weeks with or without 5-aminosalicylic acid (5-ASA). Improvements in symptoms were seen with tetomilast versus placebo, but they were not statistically significant.⁴⁷

PDE5 and PDE7 inhibitors may also be investigated in the future as potential treatments for IBD.⁴⁹ In summary, various PDE inhibitors have been investigated for inflammatory conditions such as asthma, COPD, BPH, and IBD. Table 2 provides a summary of the clinical data discussed.

PDE inhibitors in autoimmune disease

Systemic sclerosis (scleroderma)

Systemic sclerosis, also known as scleroderma, is a rare autoimmune connective tissue disease characterized by

microvascular injury and fibrosis in the skin and internal organs.⁵⁰ Manifestations of systemic sclerosis include Raynaud's phenomenon, lung fibrosis, and pulmonary artery hypertension (PAH).⁵¹ An immune response is generated by antigens in these patients. T-cells are activated early in the disease process, and these, along with other inflammatory cells such as macrophages, monocytes, mast cells, and eosinophils, infiltrate tissues. Cytokines, growth factors, and autoantibodies cause the development of fibrosis.^{52,53} Raynaud's phenomenon can cause periods of ischemia in the extremities in response to emotions or cold temperatures. Patients suffer from pain and functional impairment and may develop digital ulceration or gangrene as a result of the ischemic episodes.^{50,54}

PDE5 inhibitors have shown efficacy in the treatment of Raynaud's phenomenon associated with systemic sclerosis. A recent meta-analysis examined the use of PDE5 inhibitors for treatment of Raynaud's disease caused by systemic sclerosis. Six randomized, double-blind, placebo-controlled trials were included in the meta-analysis. Three studies examined tadalafil, two studies examined sildenafil, and one study examined vardenafil. The review of PDE5 inhibitors for Raynaud's phenomenon showed that these drugs significantly decreased symptoms (Raynaud's phenomenon condition score), frequency, and duration of attacks. The authors conclude that PDE5 inhibitors are effective for treating secondary Raynaud's disease, but more research is needed.⁵⁴

PDE5 inhibitors have also been studied for PAH secondary to systemic sclerosis and other connective tissue disease. Sildenafil has shown efficacy for PAH in numerous clinical trials and was FDA approved for this indication in June 2005. A recent meta-analysis of sildenafil for PAH reviewed four trials involving over 500 patients. The authors conclude that sildenafil therapy lasting at least 12 weeks improves clinical and hemodynamic outcomes in these patients but does not improve serious adverse events or mortality.⁵⁵ Tadalafil received FDA approval for PAH in May 2009. Several clinical trials have shown efficacy of tadalafil for PAH. In the PHIRST (Pulmonary Arterial Hypertension and Response to Tadalafil Study), 405 patients with PAH were randomized to receive placebo or tadalafil 2.5 mg, 10 mg, 20 mg, or 40 mg once daily for 16 weeks. Tadalafil 40 mg significantly improved exercise capacity ($P<0.01$) and quality of life and reduced clinical worsening ($P=0.041$) versus placebo.⁵⁶ In PHIRST-2, a total of 357 patients who completed PHIRST were randomized to receive tadalafil 20 mg or 40 mg once daily for 52 weeks. Improvements seen in the original study were continued for the duration of the trial.⁵⁷ Vardenafil

Table 2 Summary of trials with selective phosphodiesterase inhibitors for inflammatory disorders

Disease	PDEI	Drug	Reference	Patients (n)	Design	Result
Asthma	PDE4i	Cilomilast	Nieman et al ¹⁷	27	Randomized, DB, PC, 1 week	34% reduction in exercise-induced asthma
		Cilomilast	Compton et al ¹⁸	303	Randomized, DB, PC, 6 weeks	NS increase in FEV ₁
		Cilomilast	Compton et al ¹⁹	211	Randomized, DB, PC, 12 months	NS increase in FEV ₁
		Roflumilast	Timmer et al ²²	16	Randomized, DB, PC, 28 days	41% reduction in FEV ₁ (<i>P</i> =0.021)
		Roflumilast, beclomethasone	Bousquet et al ²³	499	Randomized, DB, 12 weeks	Similar improvements in lung function (<i>P</i> ≤0.001)
		Roflumilast	van Schalkwyk et al ²⁴	23	Randomized, DB, PC, 7–10 days	Reduced early and late reactions to allergen
		Roflumilast	Bateman et al ²⁵	693	Randomized, DB, PC, 12 weeks	Increase in lung function (<i>P</i> <0.001)
		Roflumilast	Gauvreau et al ¹⁰	25	Randomized, DB, PC, 14 days (<i>P</i> =0.02)	Inhibited the maximum fall in FEV ₁ after allergen challenge
	PDE3i	MSK492	Bardin et al ²⁶	18	Randomized, DB, PC	Decrease in early and late response to allergen
		Olprinone	Myou et al ²⁷	9	Randomized, DB, PC	Increase in FEV ₁ with active treatments vs placebo
		Cilostazol	Ishiura et al ²⁸	11	Randomized, DB, PC	Cough threshold increased (<i>P</i> <0.05)
	PDE3/4i	RPL554	Franciosi et al ³⁰	18	Open-label, PC	14% increase in FEV ₁ (<i>P</i> <0.0001)
				12	Single-blind, PC, 6 days	Increases in FEV ₁ (<i>P</i> <0.001)
COPD	PDE4i	Roflumilast	Rabe et al ³³	21	Randomized, PC	Anti-inflammatory properties are seen
				1,411	Randomized, DB, PC, 24 weeks	Improved FEV ₁ (<i>P</i> <0.0001)
				1,513	Randomized, DB, PC, 1 year	Improved FEV ₁ (<i>P</i> =0.001)
				3,091	Randomized, DB, PC, 52 weeks (two studies)	Improved FEV ₁ (<i>P</i> <0.001)
				933	Randomized, DB, PC, 24 weeks	Improved FEV ₁ (<i>P</i> <0.001)
				743	Randomized, DB, PC, 24 weeks	Improved FEV ₁ (<i>P</i> <0.001)
BPH	PDE3/4i	RPL554	Franciosi et al ³⁰	12	Open-label, PC	Improved FEV ₁
	PDE5i	Tadalafil	McVary et al ⁴⁰	281	Randomized, DB, PC, 12 weeks	Improved IPSS (<i>P</i> =0.003)
				1,058	Randomized, DB, PC, 12 weeks	Improved IPSS
				200	Randomized, DB, PC, 12 weeks	Improved IPSS (<i>P</i> <0.001)
				325	Randomized, DB, PC, 12 weeks	Improved IPSS (<i>P</i> =0.004)
				369	Randomized, DB, PC, 12 weeks	Improved IPSS (<i>P</i> <0.0001)
				222	Randomized, DB, PC, 8 weeks	Improved IPSS (<i>P</i> =0.0013)
				80	Randomized, DB, PC, 12 weeks	Improved IPSS (<i>P</i> =0.0014)
IBD	PDE4i	Tetomilast	Schreiber et al ⁴⁸	168	Randomized, DB, PC, 8 weeks	Improved DAI (<i>P</i> =0.041)
		Tetomilast ±5-ASA	Salari-Sharif and Abdollahi ⁴⁷	750	Randomized, DB, PC, 8 weeks	Improved DAI (not statistically significant)
					Outcomes DB, PC	

Abbreviations: BPH, benign prostatic hyperplasia; COPD, chronic obstructive pulmonary disease; DAI, Disease Activity Index; DB, double-blind; FEV₁, forced expiratory volume in 1 second; IBD, inflammatory bowel disease; IPSS, International Prostate Symptom Score (measure of lower urinary tract symptoms); MA, meta-analysis; NS, not significant; PC, placebo-controlled; PDE, phosphodiesterase; PDEI, phosphodiesterase inhibitor; QOL, quality of life; 5-ASA, 5-aminosalicylic acid.

was studied for use in PAH in a double-blind trial with 66 patients. Subjects were randomized to receive vardenafil 5 mg once daily for 4 weeks, followed by vardenafil 5 mg twice daily or placebo for 12 weeks. Patients completing the first 12 weeks of treatment were given open-label vardenafil for an additional 12 weeks. Vardenafil was shown to significantly improve exercise capacity and hemodynamics.⁵⁸ In summary, PDE5 inhibitors may benefit patients with systemic sclerosis by reducing symptoms, frequency and duration of Raynaud's attacks, and by improving clinical outcomes in those who suffer from PAH.

Psoriasis and psoriatic arthritis

Psoriasis is a chronic autoimmune disease characterized by inflammation and development of raised plaques with silvery scales.⁵⁹ In addition, up to 40% of patients with psoriasis have a systemic component with involvement of joints and other tissues (psoriatic arthritis).⁶⁰ Skin manifestations of psoriasis are caused by premature maturation of keratinocytes and inflammatory infiltrates containing dendritic cells, T-cells, and macrophages.⁵⁹ Apremilast (Figure 1K) is an oral selective PDE4 inhibitor that suppresses several inflammatory cytokines, including TNF, IL-2, IL-12, and IL-23. Apremilast has also been shown to reduce epidermal thickness.⁶¹ Several clinical trials have assessed the efficacy of apremilast for the treatment of psoriasis. An open-label trial evaluated apremilast in patients with severe plaque psoriasis. A total of 19 patients received apremilast 20 mg orally for 29 days. Epidermal thickness was reduced from baseline, T-cells were reduced in the dermis and epidermis, and 74% of patients demonstrated improvement in Psoriasis Area and Severity Index (PASI) score.⁶² In a phase II open-label study, apremilast 20 mg twice daily was assessed in 30 patients with recalcitrant plaque psoriasis. After 12 weeks, epidermal cell thickness ($P=0.083$) and PASI score were significantly improved.⁶³ A phase IIb multicenter trial randomized patients with moderate to severe psoriasis to receive oral placebo ($n=88$) or apremilast 10mg ($n=89$), 20mg ($n=87$), or 30mg ($n=88$) twice daily for 16 weeks. Significant improvements in PASI score were seen in patients who received apremilast 20 mg and 30 mg versus placebo ($P<0.001$).⁶⁴ In a phase II, multicenter, double-blind trial, 259 patients with moderate to severe plaque psoriasis were randomized to receive placebo, apremilast 20 mg once daily, or apremilast 20 mg twice daily for 12 weeks. Significant improvements in PASI score and mean body surface area involvement were seen with apremilast 20 mg twice daily versus placebo ($P<0.001$).⁶⁵ A phase II trial randomized 352 patients with moderate to severe psoriasis to receive placebo or apremilast 10 mg, 20 mg, or 30 mg

twice daily for 16 weeks. Significant improvements were seen in quality of life and pruritus scores with apremilast 20 mg and 30 mg versus placebo ($P\leq 0.005$).⁶⁶ Two phase III clinical trials (ESTEEM 1 and 2) examined a total of 1,250 patients with psoriasis duration of at least 12 months. Subjects were randomized to apremilast 30 mg twice daily or placebo for 16 weeks. Significant improvements in PASI score were seen with apremilast versus placebo.⁶⁷

Apremilast has also been evaluated for the treatment of psoriatic arthritis. A phase II, double-blind study randomized 204 patients to receive placebo ($n=68$), apremilast 20 mg twice daily ($n=69$), or apremilast 40 mg once daily ($n=67$) for 12 weeks. The primary endpoint was the proportion of patients achieving the American College of Rheumatology criteria for 20% improvement (ACR20). At the end of 12 weeks, 43.5% of patients receiving apremilast 20 mg twice daily ($P<0.001$) and 35.8% of patients receiving apremilast 40 mg once daily ($P=0.002$) achieved an ACR20 response compared with 11.8% of those receiving placebo.⁶⁸

Apremilast was also evaluated in three randomized, double-blind, phase III studies. PALACE-1, PALACE-2, and PALACE-3 included 1,493 patients with active psoriatic arthritis despite treatment with disease-modifying antirheumatic drugs and/or biologics. PALACE-4 included 527 patients with no prior treatment with disease-modifying antirheumatic drugs. Patients in all four trials were randomized to receive placebo, apremilast 20 mg twice daily, or apremilast 30 mg twice daily for 16 weeks. In the first three trials, patients receiving apremilast had significantly higher ACR20 achievement rates than those receiving placebo (19.4%, 31.3%, and 39.8%, respectively). Apremilast was also associated with significant improvement in symptoms and PASI scores. In PALACE-4, apremilast was also associated with significantly improved ACR20 achievement rates (16.9% for placebo, 29.2% for apremilast 20 mg twice daily, and 32.3% for apremilast 30 mg twice daily). Most adverse effects seen in trials with apremilast were mild to moderate in intensity. The most frequent side effects included diarrhea, upper respiratory tract infection, nausea, nasopharyngitis, and headache.⁶⁷ Although studies are ongoing, apremilast appears to offer benefit in patients with psoriasis and psoriatic arthritis. Apremilast received FDA approval on 21 March 2014 for the treatment of psoriatic arthritis in adults.

Clinical trials assessing the efficacy of PDE inhibitors have shown benefit in patients with several autoimmune diseases, including systemic sclerosis, psoriasis, and psoriatic arthritis (Table 3). Future research may investigate these drugs in patients suffering from other autoimmune disorders such as ankylosing

Table 3 Summary of trials with selective phosphodiesterase inhibitors for autoimmune disorders

Disease	PDEI	Drug	Reference	Patients (n)	Design	Result
Systemic sclerosis						
Raynaud's phenomenon	PDE5i	Tadalafil, vardenafil, sildenafil (MA)	Roustit et al ⁵⁴	244	Randomized, DB, PC	Decreased symptoms, frequency, duration of attacks
Pulmonary arterial hypertension	PDE5i	Sildenafil (MA)	Wang et al ⁵⁵	545	Randomized, DB, PC	Improved outcomes
		Tadalafil (MA)	Galie et al ⁵⁶	405	Randomized, DB, PC, 16 weeks	Improved exercise capacity and QOL (40 mg)
		Tadalafil	Oudiz et al ⁵⁷	357	Randomized, DB, PC, 1 year	Improved exercise capacity and QOL (40 mg)
		Vardenafil	Jing et al ⁵⁸	66	Randomized, DB, PC, 12 weeks	Improved exercise capacity ($P<0.001$) and hemodynamics
Psoriasis	PDE4i	Apremilast	Gottlieb et al ⁶²	19	Open-label, 29 days	Reduced epidermal thickness, T-cells, and improved PASI
		Apremilast	Gottlieb et al ⁶³	30	Open-label, 12 weeks	Improved epidermal thickness ($P=0.083$) and PASI
		Apremilast	Papp et al ⁶⁴	89	Randomized, DB, PC, 16 weeks	Improved PASI for 20 mg and 30 mg ($P<0.0001$ for both)
		Apremilast	Papp et al ⁶⁵	259	Randomized, DB, PC, 12 weeks	Improved PASI and mean body surface involvement with 20 mg bid ($P<0.001$)
		Apremilast	Strand et al ⁶⁶	352	Randomized, DB, PC, 16 weeks	Improved QOL ($P\leq 0.005$) and pruritus scores ($P\leq 0.005$) with 20 mg and 30 mg
Psoriatic arthritis	PDE4i	Apremilast	Chaplin ⁶¹	1,250 (two trials)	Randomized, DB, PC, 16 weeks	Improved PASI
		Apremilast	Schett et al ⁶⁸	204	Randomized, DB, PC, 12 weeks	Improved ARC20 with 20 mg bid ($P<0.001$) and 40 mg qd ($P=0.002$)
		Apremilast	Poole and Ballantyne ⁶⁷	1,493 (four trials)	Randomized, DB, PC, 16 weeks	Improved ACR 20, symptoms, and PASI scores

Abbreviations: ACR20, American College of Rheumatology criteria for 20% improvement; bid, twice daily; DB, double-blind; MA, meta-analysis; qd, once daily; PASI, Psoriasis Area and Severity Index; PC, placebo-controlled; PDE, phosphodiesterase; PDEI, phosphodiesterase inhibitor; QOL, quality of life.

spondylitis, rheumatoid arthritis, systemic lupus erythematosus, sarcoidosis, Alzheimer's disease, and multiple sclerosis.²¹

Conclusion

PDE inhibitors increase levels of second messengers cAMP and cGMP in many cells in the body. As a result, these compounds are able to inhibit inflammatory and immune processes that cause or contribute to numerous diseases and conditions. In the last 2 decades, selective PDE inhibitors have shown promise for the treatment of inflammatory lung and bowel diseases, BPH, systemic sclerosis, psoriasis, and psoriatic arthritis. In addition, PDE inhibitors are under investigation in the treatment of other inflammatory conditions such as rheumatoid arthritis, systemic lupus erythematosus, atopic dermatitis, multiple sclerosis, and Alzheimer's disease. As additional therapies are discovered, the quality of life improves for patients with inflammatory and autoimmune disorders.

Disclosure

The author reports no conflicts of interest in this work.

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