Vol.9 No.2 July-Sept 2013

Asthma Focus

ASTHMA MYTHS

Asthma can be cured?

Answer: FALSE!

Asthma is a treatable health condition. Despite great advances in treatments over the years, unfortunately we still don't have a cure.

Asthma is a chronic condition. That means it can be controlled but not cured. Asthma is usually caused by an underlying condition such as an allergy. In addition to your pulmonary specialist you should be under the care of an allergist or immunologist. These professionals can help you identify your triggers and develop a plan to control your exposures. Controlling the triggers is key to controlling the asthma. If you are female, there is more and more research that indicates that your hormone levels can have an affect on your asthma as well. You may want to discuss this with your pulmonologist.

However, with appropriate diagnosis and good management, just about everyone with asthma can lead normal, active lives.

SQUARE
PHARMACEUTICALS LTD.
BANGLADESH

Current and Future Therapies for Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF), a progressive disease with a dismal prognosis, is responsible for the deaths of up to 50,000 people in the United States each year. Despite considerable improvements over the last decade in understanding of the pathogenesis of IPF, it remains the case that, as yet, in the United States, there are no licensed therapies for the disease. This review will discuss what has been learned from recent and ongoing treatment trials in patients with IPF and will highlight possible future avenues for treatment development.

PATHOGENESIS OF IPF

Understanding of the molecular events that characterize the development of IPF has evolved dramatically over recent years. As little as a decade ago it was widely believed that IPF arose as the consequence of unopposed inflammation within the lung. Consequently, it was thought by some that the histologic lesion of desquamative interstitial pneumonitis was a precursor to IPF. This presumed primacy of inflammation in the pathogenesis of IPF is still reflected today in the widespread use of corticosteroids and other immunosuppressants for the treatment of IPF. The publication, in 2001, of the American Thoracic Society/European Respiratory Society consensus document on classification of the idiopathic interstitial pneumonias proved to be pivotal in catapulting forward understanding of the natural history of IPF. By confining a diagnosis of IPF to individuals with the histologic lesion of usual interstitial pneumonia, it rapidly became clear that IPF is an inexorably progressive disease that responds little, if at all, to high-dose immunomodulatory therapy (Fig. 1). These observations clarified a growing body of opinion that IPF is a disease of disordered wound healing occurring in response to repetitive alveolar injury.

At a molecular level, IPF is characterized by the apparently unopposed activation of multiple pathways, including inflammatory cascades, involved in wound healing (Fig. 2). The purpose of the normal wound healing process is to restore tissue integrity, structure, and function after injury. In the early stages of wound healing, there is tissue expansion with the laying down of granulation tissue; this is associated with migration to the site of injury of fibroblasts that then proliferate, transform into myofibroblasts, and rapidly synthesize extracellular matrix. Once structural integrity is restored to a tissue and reepithelialization of the basement membrane has occurred, the profibrotic phase of tissue repair switches off and resorbtion of the extracellular matrix, with fibroblast apoptosis and architectural remodeling of tissue occurs.

In IPF, by contrast, there is an imbalance between the profibrotic mediators that promote extracellular matrix expansion, fibroblast recruitment, proliferation and differentiation, and antifibrotic mediators that drive the process of tissue remodeling. Several strands of evidence point to repetitive alveolar epithelial injury being an important driver for the development of this imbalance. Damage and necrosis of alveolar epithelial cells with areas of

Asthma Focus

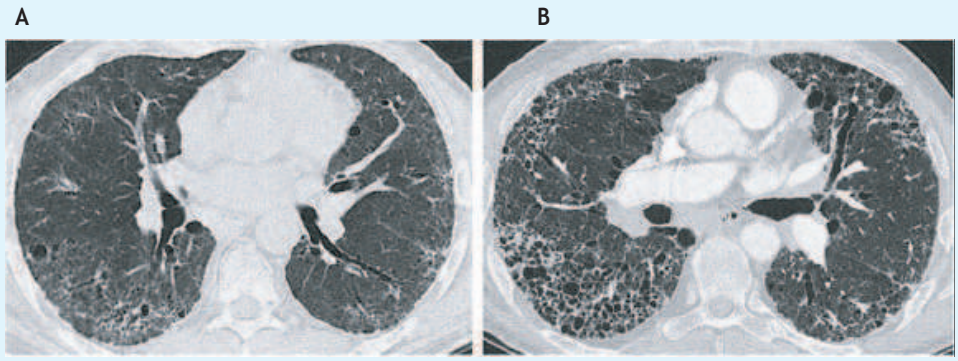

FIGURE 1. Serial high-resolution thoracic computed tomographic scans, 12 months apart, at a level just below the carina in a 63-yearold man with idiopathic pulmonary fibrosis (IPF). The scan at diagnosis (A) demonstrates subpleural reticular change with early honeycombing but an absence of ground-glass attenuation—an appearance typical of IPF. A scan 12 months later (B) discloses dramatic disease progression with the development of marked honeycomb change with associated traction bronchiectasis and architectural distortion.

basement membrane denudation are a consistent finding in IPF. These areas of epithelial damage correspond to sites of microscopic alveolar injury and invariably overlie fibroblastic foci. Areas of alveolar epithelial cell apoptotic activity in IPF are also found at sites adjacent to fibroblastic foci and to a lesser extent within histologically normal alveoli and in epithelium lining honeycomb spaces. In animal models, induction of widespread epithelial injury and apoptosis alone is sufficient to induce the development of fibrosis, whereas inhibition of epithelial cell death abrogates the development of bleomycin-induced fibrosis.

A wide range of factors may contribute to alveolar epithelial cell injury. The lung is continuously exposed to a multitude of noxious and potentially injurious stimuli. These range from cigarette smoke through to pollutants, dusts, infectious agents, and microaspiration of gastric contents. These and many other factors have the potential to cause lung epithelial cell injury and death. Epidemiological studies, across centers and countries, consistently show that cigarette smoking and exposure to wood dusts, metal dusts, and mineral dusts are all associated with an increased odds ratio for the subsequent development of IPF. Similarly, past viral infection with particular viral subtypes seems to be associated with the subsequent development of IPF. The sum of these observations is to suggest that IPF arises, in genetically susceptible individuals, as the consequence of an aberrant wound healing response that develops after repetitive, multifactorial, epithelial injury (Fig. 2). From a therapeutic perspective the involvement of these multiple mechanisms and pathways in the development of fibrosis in IPF provides an enormous range of potential drug targets that might attenuate the development of disease.

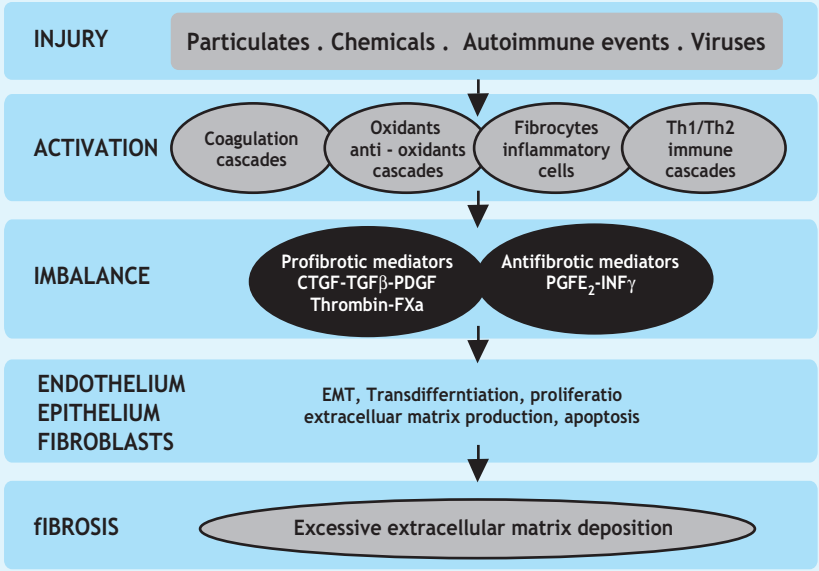

FIGURE 2. A schematic outlining of the proposed pathogenetic events involved in the development of idiopathic pulmonary fibrosis. Injury activates multiple inflammatory, cell signaling, and repair pathways. Activation of these cascades causes an imbalance in profibrotic and antifibrotic mediators. In turn, these mediators activate multiple cell types, causing changes in cellular functioning and cell-cell interactions that ultimately result in progressive fibrosis. CTGF indicates connective tissue growth factor; EMT, epithelialmesenchymal transition; FXa, factor Xa; IFNg, interferon-g; PDGF, platelet-derived growth factor; PGE2, prostaglandin E2; Th, T-helper; TGFb, transforming growth factor b. (Figure shown with permission from ERJ)

Asthma Focus

TREATMENT OF IPF—AIMS AND CHALLENGES

Histologically, IPF is characterized by expansion of the extracellular matrix together with architectural distortion, loss of alveolar structure, and subsequent remodeling in the form of honeycomb cysts lined by hyperplastic epithelial cells. Macroscopically, this phenomenon can be observed on computed tomographic scanning, with progressive loss of lung volume and honeycomb destruction (Fig. 1). In short, the fibrosis that characterizes IPF results in irreversible destruction of the delicate lace like structure of the normal lung parenchyma. Therefore, even if one developed a true antifibrotic therapy capable or resorbing collagen and extracellular matrix, it would be impossible to restore normal tissue structure and function. It is important to realize therefore, that the intention of treatment in patients with IPF is to prevent disease progression. Stability in serial lung function parameters in IPF should be considered a treatment success and not a therapeutic failure. By the same token there is no logic to short-term trials of high-dose corticosteroids or other immunomodulators in patients with confirmed IPF as it is not possible to gauge disease stability over a period of only a few weeks.

Treatment trials in IPF have been plagued by a number of difficulties. The relative rarity of the disease has meant that for large scale trials to be performed these have had to be multicenter and often multinational. Early trials were beset with difficulties in the selection of primary endpoints. Thinking in this area has evolved over the last decade as it has become clearer that serial change in forced vital capacity (FVC) is the most robust indicator, across multiple centers, of true progression in disease. Finally, for anybody hoping to understand the IPF literature, it is important to realize that before the 2001 American Thoracic Society/European Respiratory Society consensus statement, the term IPF was used to encompass a much broader category of diseases that are now categorized as subtypes of the idiopathic interstitial pneumonias. Some of the conditions once considered part of the IPF spectrum, such as desquamative interstitial pneumonitis, have subsequently been shown to carry a good prognosis and to be relatively responsive to treatments such as corticosteroids. For this reason all trials before 2001 need to be interpreted with some caution.

The last decade has seen a dramatic expansion in the number of therapeutic trials being performed in IPF (Table 1). The first large multicenter trial was published in 2004 and the size of trials has continued to grow since this time. Before 2004, however, most studies were single center, tended to contain fewer than 30 patients and were frequently open label. On account of these limitations it is difficult to be dogmatic about the true efficacy of many of the therapeutic interventions that have been trialed. For this reason, I have chosen to consider treatments under the headings of “what saeems to work,” “what might work,” and “what does not work.” *(Conituned on page 6)*

TABLE 1. Summary of Landmark Trials in IPF

Drug	Trial Acronym	Year	No. Patients	Sponsor	Primary Outcome	Result	Reference
Interferon-γ		2004	330	nterMune	Progression free survival	No effect	Raghu et al
Pirfenidone		2005	107	Shionogi	Change in lowest SpO2 during 6MW	Reduced acute exacerbations	Azuma et al
Warfarin		2005	56	Investigator	Survival	Improved survival	Kubo et al
N-Acetyl-Cysteine	IFGINIA	2005	182	Zambon group	Change in FVC	Reduced progression	Demedts et al
Bosentan	BUILD-1	2008	158	Actelion	Change in 6MWD	No effect	King et al
Etanercept		2008	88	Wyeth	Change in FVC, DLco, a-A gradient	No effect	Raghu et al
Interferon-γ	INSPIRE	2009	826	InterMune	Survival	No effect	King et al
Pirfenidone		2010	275	Shionogi	Change in FVC	Reduced progression	Taniguchi et al
Imatinib		2010	119	Novartis	Change in FVC, DLco, a-A gradient	No Effect	Daniels et al
Sildenafil	STEP-IPF	2010	180	Investigator	Twenty percent improvement in 6MWD	No effect	Zisman et al
Pirfenidone	CAPACITY 1+2	2010	779	InterMune	Change in FVC	Reduced progression	Noble et al
Bosentan	BUILD-3	2010	616	Actelion	Progression-free survival	No effect	King et al

6MWD indicates 6 minute walk distance; a-A gradient, alveolar arterial oxygen gradient; DLco, lung diffusion capacity for carbon monoxide; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis.

Simple Actions May Reduce Postop Pulmonary Complications

A postoperative care program focused on simple interventions and multidisciplinary care may reduce common pulmonary complications, according to a before-after trial.

The study compared pulmonary outcomes from the National Surgical Quality Improvement Program (NSQIP) before and after implementation of I COUGH. I COUGH is a multidisciplinary program consisting of *I*ncentive spirometry, *C*oughing and deep breathing, *O*ral care (brushing teeth and using mouthwash twice daily, *U*nderstanding (patient and family education), *G*etting out of bed frequently (at least 3 times daily), and Head-of-bed elevation.

The researchers compared outcomes for all patients who underwent vascular or general surgery at their institution before I COUGH implementation (January 1 to December 31, 2009) and after (July 1, 2010, to June 30, 2011).

According to a pre-I COUGH nursing practice audit, 80.4% of 250 patients were in bed during the visit, and 19.6% of patients were in a chair or walking. Post-I COUGH audits showed a significant difference, with 69.1% (P <.001) of 250 patients out of bed. Before implementation, most patients had the head of their bed elevated, and that remained the case after implementation (82.7% and 91.5%, respectively; P = .40).

The nursing audit also showed that just over half (52.8%) of patients had an incentive spirometer nearby before I COUGH. After I COUGH, 77.2% of patients had one nearby and used it with appropriate frequency (P < .001).

The incidence of postoperative pneumonia was 2.6% (1569 cases) during the year before implementation of I COUGH; this was similar to the period recorded previously. During the year after I COUGH implementation, the incidence of pneumonia decreased to 1.6% (1542 cases; P = .09).

Before I COUGH, the incidence of unplanned intubations was 2.0% (1569 cases), a rate similar to that in the previous period. This fell to 1.2% (1542 cases; P = .09) after I COUGH implementation. At similar hospitals, that figure ranged from 1.4% to 1.6%. According to risk-adjusted NSQIP data, the OE ratio of unplanned intubations decreased from 2.10 (95% CI, 1.42 - 2.98) before I COUGH to an odds ratio of 1.31 (95% CI, 0.87 - 1.97) after I COUGH implementation.

JAMA Surg. Published online June 5, 2013.

Avoid High-Dose Steroids in Elc

In a study of elderly Australians with chronic obstructive pulmonary dis
dose corticosteroids had an increased risk of being hospitalized for a dia

About 10% of patients in Australia who have diabetes also have COP
patients with moderate to severe COPD to reduce exacerbations, which
exacerbations, but the latter are not recommended chronically due to t

But the use of corticosteroids in patients with diabetes and COPD pos
part of guideline therapies for COPD but are associated with hyperglyce

In the 12 months after being diagnosed with diabetes, 67.2% of the pat
complication were similar among corticosteroid users and nonusers afte
.18). However, stratification by levels of corticosteroid use revealed a c
patients who took no corticosteroids. The median corticosteroid dose c
stratified into 3 levels of median daily corticosteroid dosage: more tha
greater. Compared with patients who did not take any corticosteroids o
dose/day had a 94% increased risk of being hospitalized for a diabetes-r

A dosage of 0.83 or greater defined daily dose/day over 12 months is co
- for example, 400 µg of budesonide twice daily for a year plus tre
prednisolone for 7 days. Or, it is equal to treating 9 COPD exacerbations

There was no difference in hospitalization in patients who had received

Diabetes Care. June 4, 2013

Vitamin C Kills Mycobacterium tuberculosis

Vitamin C kills drug-sensitive, multidrug-resistant (MDR), and extensively-drug resistant (XDR) strains of Mycobacterium tuberculosis in culture as a result of prooxidant effects.

The new work builds on the long-standing observation that vitamin C is toxic to M tuberculosis, a Gram-positive bacterium. Experiments in the 1930s showed that only 6% of guinea pigs exposed to the bacteria and given tomato juice became infected compared with 70% of guinea pigs not given the vitamin C–rich juice. In vitro experiments conducted in 1950 confirmed the effect of the vitamin on bacterial cultures, and a study in 2011 correlated vitamin C content of various medicinal plants with antibacterial effects.

In the current study, Catherine Vilcheze, PhD, from the Department of Microbiology and Immunology, Howard Hughes Medical Institute, Albert Einstein College of Medicine, Bronx, New York, and colleagues conducted dose-response experiments, determining that 2 mM is the bactericidal level for drug-sensitive, MDR, and XDR bacteria. The effect was not seen when the bacteria were cultured in an anaerobic chamber. M tuberculosis is much more sensitive to the prooxidant effects of the vitamin than other Gram-positive and Gram-negative bacteria.

On the basis of these data, the researchers suggest that adding vitamin C to treatment regimens might shorten the time that chemotherapy is necessary, which is currently from 6 to 24 months. Noncompliance with chemotherapy fuels selection of drug-resistant bacterial strains. The findings also suggest that drug developers might look for the prooxidant effects of drug candidates.

Nature Communications. Published online May 21, 2013.

A SCOOP

Asthma Focus

derly With COPD and Diabetes

ease (COPD) and newly diagnosed diabetes, those who received high-abetes-related complication within a year.

PD. Treatment guidelines recommend the use of inhaled steroids in are frequent, and the use of oral steroids for short-term treatment of heir unfavorable risk/benefit profile.

ses a therapeutic conflict, since corticosteroids are recommended as mia and an increased risk of diabetes complications.

ients had used corticosteroids. Rates of hospitalization for a diabetic r 1 year (7.1% vs 6.3%, P = .37) and after 5 years (19.8% vs 16.2%, P = dramatic difference between patients who took the highest doses and luring 12 months was 0.34 of a defined daily dose/day. Patients were an 0 to less than 0.25; 0.25 or greater to less than 0.83; and 0.83 or ver 12 months, those who received 0.83 or greater of a defined daily elated complication.

mparable to receiving an inhaled maintenance dose of corticosteroids eatment of acute exacerbations 6 times in a year with 50-mg oral with oral prednisolone 50 mg per day for 7 days.

oral, inhaled, or both types of corticosteroids.

Pertussis Vaccines: Whole-Cell More Durable Than Acellular

Teenagers who received 4 diphtheria, tetanus toxoids, acellular pertussis (DTaP) vaccines in the first 2 years of life had nearly a 6-fold higher risk of contracting pertussis than teenagers who received 4 diphtheria, tetanus toxoids, whole-cell pertussis (DTwP) vaccines, according to a case-control study of 1037 teenagers.

The study was conducted after a pertussis outbreak in California in 2010 to 2011. The study population included teenagers born from 1994 to 1999 who were given 4 pertussis-containing vaccines during the first 2 years of life. Cases that were pertussis polymerase chain reaction (PCR)-positive (n = 138) were compared with PCR-negative cases (n = 899) and Kaiser Permanente Northern California matched controls (n = 54,339).

Among 1037 individuals who were PCR tested, 234 (22.6%) were given all whole-cell vaccines, 197 (19.0%) were given a mix of whole-cell and acellular vaccines, and 606 (58.4%) were given all acellular vaccines. Among those who received a mix, 157 (79.7%) received 3 DTwP and then 1 DTaP vaccine, 12 (6.1%) had 2 DTwP and then 2 DTaP vaccines, 17 (8.6%) had 1 DTwP and then 3 DTaP vaccines, and 11 (5.6%) received some other combination of vaccines.

As the number of DTaP doses increased from 0 to 4, the percentage of positive PCR tests for pertussis increased significantly (P < .001 for trend).

The acellular vaccines are effective at preventing pertussis; however, their duration of immunity is less than whole-cell pertussis vaccine.

The study won't change vaccination guidelines. It would not go back to using whole-cell vaccine era because thre were adverse reactions associated with it.

Am J Clin Nutr 2012.

Direct Nucleic Acid Amplification Testing Improves TB Diagnosis

Mycobacterium tuberculosis direct nucleic acid amplification testing improves diagnostic accuracy and timeliness and reduces unnecessary treatment, according to a retrospective cohort analysis.

The Mycobacterium tuberculosis Direct (MTD) NAAT is more accurate and timely in diagnosing TB disease than standard diagnostics using the AFB (acid-fast bacilli) smear.

While AFB smear is cheap and simple, it has poor sensitivity, especially in patients infected with HIV. The gold standard culture takes two to eight weeks for results, whereas NAAT for M. tuberculosis can yield results within 24-48 hours.

Dr. Marks and colleagues evaluated the use, effectiveness, health-system benefits, and cost-effectiveness of MTD in an analysis of 2,140 patients.

Forty percent of patients had at least one smear-positive specimen, and 60% had all smear-negative specimens, . More than one-third (37%) of the cultures were positive.

Overall, 59% of hospitalized patients received MTD, compared with 25% of those not hospitalized. The turn-around time from specimen collection to reported MTD result averaged 2.6 days for hospital specimens and 4.0 days for clinic specimens.

In all subpopulations examined MTD showed higher positive predictive value, sensitivity, and negative predictive value than no-MTD.

In multivariable analysis, MTD-positive results significantly shortened the time to TB determination, but MTD did not significantly decrease the time to TB exclusion for culture-negative patients.

The 2013 updated 'Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents' also recommend NAAT for patients with advanced immunodeficiency who are at risk of rapid clinical progression of TB.

Clin Infect Dis 2013.

Asthma Focus

Current and Future Therapies for Idiopathic Pulmonary Fibrosis (Cont.)

TREATMENT OF IPF—WHAT SEEMS TO WORK?

The first therapeutic trial in IPF to achieve a positive primary outcome was a comparison of the antioxidant N-acetyl cysteine (NAC) administered with prednisolone and azathioprine compared with prednisolone and azathioprine alone. After 12 months of treatment, there was a slower rate of loss of FVC in the NAC-treated group. Similarly, there was a slowing in the deterioration of lung diffusion capacity for carbon monoxide (DLco), by 24%. In the placebo group, there was a significant excess of myelotoxicity. NAC has been widely adopted as a treatment for IPF. It is unclear if NAC alone is effective as a treatment for IPF or whether it needs to be given in combination with prednisolone and azathioprine.

Pirfenidone was first reported as a potential therapy for IPF in an open label study of 54 patients published by Raghu et al 1999. A Japanese study of 275 patients with IPF, pirfenidone was successful in reducing disease progression, as measured by change in FVC, compared with placebo. These studies paved the way for 2 large, double-blind, international studies of pirfenidone against placebo, CAPACITY 1 and CAPACITY. CAPACITY 2, a study of 435 patients, demonstrated a significant reduction in progression of IPF (as measured by decline in FVC) in the pirfenidone-treated individuals compared with placebo at 72 weeks. By contrast, there was no significant treatment effect seen at the same time point in CAPACITY 1 (a study of 344 IPF patients).

For patients with end stage IPF, lung transplantation is an important therapeutic option. Despite significant limitations including donor organ shortage, complications of immunosuppression, infection, and acute and chronic rejection, lung transplantation remains the 1 treatment capable of improving life expectancy for patients with IPF.

TREATMENT OF IPF—WHAT MIGHT WORK?

Until very recently, corticosteroids, often in combination with the immunosuppressant azathioprine, have been considered standard therapy for IPF. The rationale for the use of immunomodulatory therapy harkens back to the notion that inflammation is the primary driver of fibroproliferation in IPF. Despite their widespread use, there is little evidence to either support, or refute, the efficacy of either corticosteroids or azathioprine for IPF.

There have been no randomized placebo-controlled trials of corticosteroids in IPF. A 2003 systematic review by Richeldi et al of corticosteroids in IPF found no evidence to support their efficacy. Similarly, the only study of the use of azathioprine was conducted by Raghu et al and was published in 1991. Patients were treated for 9 years and most received concomitant corticosteroids. There was a survival advantage observed in the group receiving azathioprine; however, this only became apparent after 5 years of treatment. Despite this lack of evidence to support the use of the combination of prednisolone and azathioprine, it is worth remembering that the patients in the IFIGENIA study, who were shown to benefit from the addition of NAC, were also receiving prednisolone and azathioprine.

There is increasing evidence that coagulation pathways also play a pivotal role in the pathogenesis of IPF. These observations led Kubo et al to study the use of anticoagulant therapy for patients with IPF in a 5-center Japanese study. Anticoagulation was achieved using low-molecular heparin for hospitalized patients and warfarin in the domiciliary setting. At 1 year, there was a striking, and statistically significant survival advantage in the anticoagulated patients (87% 1 year survival vs. 54%, P = 0.049). The small size of the study, together with the fact that the enrollment criteria are not applicable to the majority of patients with IPF have meant that it has not been possible for warfarin therapy to be recommended for IPF.

Patients with IPF frequently report an infective type prodrome before the development and diagnosis of their IPF. Infection seems to be a likely trigger for acute exacerbations of IPF. This observation led Varney et al to test the role of septrin in patients with a range of fibrosing idiopathic interstitial pneumonias. This pilot study subsequently led on to a UK based multicenter study of trimethoprim/sulfamethoxazole versus placebo (treating interstitial pneumonia with the addition of cotrimoxazole study) in 140 patients with idiopathic fibrosing lung disease.

TREATMENT OF IPF—WHAT DOES NOT WORK?

The trials with interferon g-1b showed no survival advantage

over placebo. Another treatment to show initial promise in the treatment of IPF was the endothelin receptor antagonist Bosentan. However, bosentan failed to meet the primary endpoint of reducing time to disease worsening or death. Same is true about anti-TNF-a monoclonal antibody etanercept.

TREATING COMPLICATIONS AND SYMPTOMS OF IPF

Although the principal focus in clinical IPF trials has been treatment of the disease process with the aim of arresting disease progression, it is important to recognize that there are a number of disease complications that may be amenable to therapy. The most frequently occurring complications of IPF are acute exacerbations, pulmonary hypertension, and respiratory failure. Acute exacerbations, as their name suggests, are episodes characterized by rapid worsening in symptoms of breathlessness, often accompanied by new infiltrates on thoracic imaging and, in severe cases, acute respiratory failure. When biopsied, acute exacerbations are characterized by the histologic lesion of diffuse alveolar damage. This is the same lesion as that seen in acute respiratory distress syndrome. For this reason, and by analogy to acute respiratory distress syndrome, many physicians treat these episodes with high-dose corticosteroids and supportive care. When invasive ventilation becomes necessary most clinicians advocate a protective ventilator strategy with low tidal volumes and permissive hypercapnia. There is, however, no evidence base to support any specific therapeutic maneuver in acute exacerbations of IPF.

Pulmonary hypertension is a frequent finding in patients with end-stage IPF. In IPF patients undergoing right heart catheterization as part of lung transplant assessment, more than 60%, in some series, have demonstrable pulmonary hypertension. Although in the majority of patients pulmonary hypertension develops in the context of end-stage hypoxic respiratory failure, there are a subset of patients with IPF who develop disproportionate pulmonary hypertension early in the evolution of their disease. The treatment of pulmonary hypertension has changed dramatically in the last decade with the development of a number of novel and highly effective therapies; these include prostacyclin analogues, endothelin receptor antagonists, and phosphodiesterase inhibitors. Given that IPF is a progressive disease lacking effective therapies, treatment of IPF-related pulmonary hypertension potentially affords the opportunity of improving symptoms of dyspnea if not actually increasing longevity. In an open label study of sildenafil in 14 patients with IPF and documented pulmonary hypertension, Collard et al were able to demonstrate a mean improvement in 6-minute walk distance of 49m after 3 months.

IPF is almost invariably a terminal disease. It is important therefore that consideration is given to therapeutic strategies aimed at reducing symptoms and improving quality of life. Pulmonary rehabilitation has been shown to be safe and highly effective in patients with chronic obstructive pulmonary disease. In small studies of patients with IPF, pulmonary rehabilitation seems to confer improvements in functional exercise capacity, dyspnea, and quality of life immediately after training. Oxygen is widely used for patients with respiratory failure due to IPF. Most clinicians prescribe oxygen for this patient group on the basis of symptoms and severity of hypoxia. For individuals in the final stages of their disease the palliative use of anxiolytics including benzodiazapines and opiates can be very effective in alleviating the distressing symptoms of dyspnea and the frequently associated feelings of panic. Cough is another frequently debilitating and difficult to treat symptom of IPF. There is little evidence to support the use of any specific antitussive in IPF. In a small study of 11 patients, Horton et al reported that thalidomide had a dramatic effect in alleviating intractable cough in IPF.

TREATMENT OF IPF—THE FUTURE ?

As is suggested by Figure 2, it is plausible to postulate a number of different approaches to the treatment of IPF. The first is to ameliorate or prevent epithelial injury. This could be achieved by directly preventing injury, for example, through prevention of microaspiration or prophylactic dosing with antimicrobials or antivirals, or by protecting against injury through augmentation of host defense mechanisms. Alternatively, it might be possible to prevent injury-induced epithelial cell death and basement membrane denudation; this could be achieved either by using inhibitors of apoptosis or through promotion of epithelial cell proliferation with agents such as hepatocyte growth factor or kerationcte growth factor.

After epithelial injury, the next apparent step in the pathogenesis of IPF is the persistent activation of pathways involved in normal wound healing. As noted earlier, blocking the coagulation cascade may be effective in improving survival in IPF and this is currently being studied in a multicenter placebo-controlled trial of warfarin (NCT00957242). Similarly, immunomodulatory therapy may be effective in preventing the recruitment of inflammatory cells to the sites of fibroproliferation.

It is possible to envisage therefore, a treatment approach that either inhibits the actions of profibrotic mediators or augments the action of antifibrotic mediators. It was this rationale that underpinned the trials of interferon g-1b as a potential treatment for IPF.

The rapid growth in clinical trials in IPF over the last 10 years makes it possible to be optimistic that effective therapeutic regimens for IPF will begin to emerge in the relatively near future.

Ref: Current and Future Therapies for Idiopathic Pulmonary Fibrosis. Maher. Clinical Pulmonary Medicine Volume 18, Number 6, November 2011

Vol.9 No.2 July-Sept 2013

Asthma Focus

ASTHMA MYTHS

Asthma can be cured?

Answer: FALSE!

Asthma is a treatable health condition. Despite great advances in treatments over the years, unfortunately we still don't have a cure.

Asthma is a chronic condition. That means it can be controlled but not cured. Asthma is usually caused by an underlying condition such as an allergy. In addition to your pulmonary specialist you should be under the care of an allergist or immunologist. These professionals can help you identify your triggers and develop a plan to control your exposures. Controlling the triggers is key to controlling the asthma. If you are female, there is more and more research that indicates that your hormone levels can have an affect on your asthma as well. You may want to discuss this with your pulmonologist.

However, with appropriate diagnosis and good management, just about everyone with asthma can lead normal, active lives.

SQUARE
PHARMACEUTICALS LTD.
BANGLADESH

Current and Future Therapies for Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF), a progressive disease with a dismal prognosis, is responsible for the deaths of up to 50,000 people in the United States each year. Despite considerable improvements over the last decade in understanding of the pathogenesis of IPF, it remains the case that, as yet, in the United States, there are no licensed therapies for the disease. This review will discuss what has been learned from recent and ongoing treatment trials in patients with IPF and will highlight possible future avenues for treatment development.

PATHOGENESIS OF IPF

Understanding of the molecular events that characterize the development of IPF has evolved dramatically over recent years. As little as a decade ago it was widely believed that IPF arose as the consequence of unopposed inflammation within the lung. Consequently, it was thought by some that the histologic lesion of desquamative interstitial pneumonitis was a precursor to IPF. This presumed primacy of inflammation in the pathogenesis of IPF is still reflected today in the widespread use of corticosteroids and other immunosuppressants for the treatment of IPF. The publication, in 2001, of the American Thoracic Society/European Respiratory Society consensus document on classification of the idiopathic interstitial pneumonias proved to be pivotal in catapulting forward understanding of the natural history of IPF. By confining a diagnosis of IPF to individuals with the histologic lesion of usual interstitial pneumonia, it rapidly became clear that IPF is an inexorably progressive disease that responds little, if at all, to high-dose immunomodulatory therapy (Fig. 1). These observations clarified a growing body of opinion that IPF is a disease of disordered wound healing occurring in response to repetitive alveolar injury.

At a molecular level, IPF is characterized by the apparently unopposed activation of multiple pathways, including inflammatory cascades, involved in wound healing (Fig. 2). The purpose of the normal wound healing process is to restore tissue integrity, structure, and function after injury. In the early stages of wound healing, there is tissue expansion with the laying down of granulation tissue; this is associated with migration to the site of injury of fibroblasts that then proliferate, transform into myofibroblasts, and rapidly synthesize extracellular matrix. Once structural integrity is restored to a tissue and reepithelialization of the basement membrane has occurred, the profibrotic phase of tissue repair switches off and resorbtion of the extracellular matrix, with fibroblast apoptosis and architectural remodeling of tissue occurs.

In IPF, by contrast, there is an imbalance between the profibrotic mediators that promote extracellular matrix expansion, fibroblast recruitment, proliferation and differentiation, and antifibrotic mediators that drive the process of tissue remodeling. Several strands of evidence point to repetitive alveolar epithelial injury being an important driver for the development of this imbalance. Damage and necrosis of alveolar epithelial cells with areas of

Asthma Focus

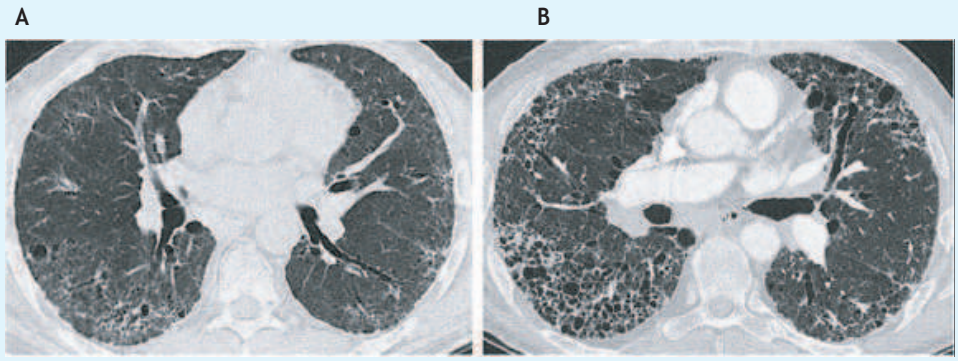

FIGURE 1. Serial high-resolution thoracic computed tomographic scans, 12 months apart, at a level just below the carina in a 63-yearold man with idiopathic pulmonary fibrosis (IPF). The scan at diagnosis (A) demonstrates subpleural reticular change with early honeycombing but an absence of ground-glass attenuation—an appearance typical of IPF. A scan 12 months later (B) discloses dramatic disease progression with the development of marked honeycomb change with associated traction bronchiectasis and architectural distortion.

basement membrane denudation are a consistent finding in IPF. These areas of epithelial damage correspond to sites of microscopic alveolar injury and invariably overlie fibroblastic foci. Areas of alveolar epithelial cell apoptotic activity in IPF are also found at sites adjacent to fibroblastic foci and to a lesser extent within histologically normal alveoli and in epithelium lining honeycomb spaces. In animal models, induction of widespread epithelial injury and apoptosis alone is sufficient to induce the development of fibrosis, whereas inhibition of epithelial cell death abrogates the development of bleomycin-induced fibrosis.

A wide range of factors may contribute to alveolar epithelial cell injury. The lung is continuously exposed to a multitude of noxious and potentially injurious stimuli. These range from cigarette smoke through to pollutants, dusts, infectious agents, and microaspiration of gastric contents. These and many other factors have the potential to cause lung epithelial cell injury and death. Epidemiological studies, across centers and countries, consistently show that cigarette smoking and exposure to wood dusts, metal dusts, and mineral dusts are all associated with an increased odds ratio for the subsequent development of IPF. Similarly, past viral infection with particular viral subtypes seems to be associated with the subsequent development of IPF. The sum of these observations is to suggest that IPF arises, in genetically susceptible individuals, as the consequence of an aberrant wound healing response that develops after repetitive, multifactorial, epithelial injury (Fig. 2). From a therapeutic perspective the involvement of these multiple mechanisms and pathways in the development of fibrosis in IPF provides an enormous range of potential drug targets that might attenuate the development of disease.

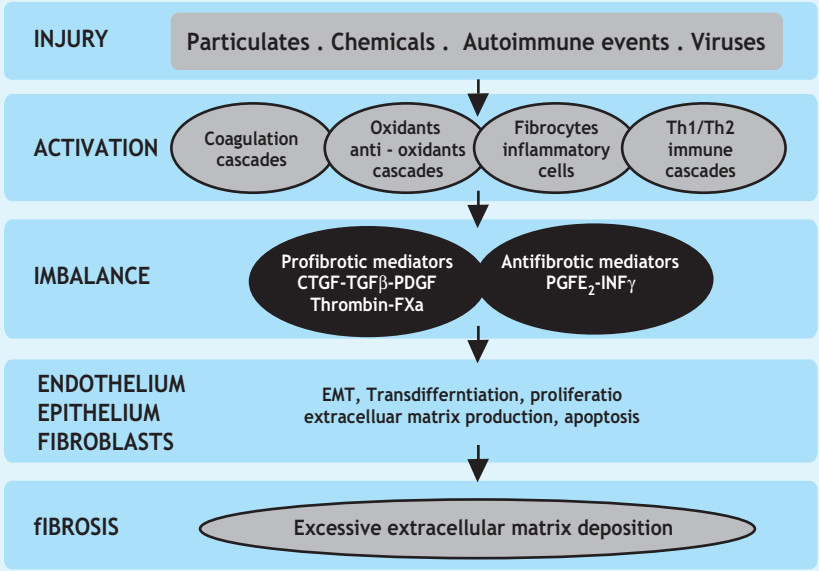

FIGURE 2. A schematic outlining of the proposed pathogenetic events involved in the development of idiopathic pulmonary fibrosis. Injury activates multiple inflammatory, cell signaling, and repair pathways. Activation of these cascades causes an imbalance in profibrotic and antifibrotic mediators. In turn, these mediators activate multiple cell types, causing changes in cellular functioning and cell-cell interactions that ultimately result in progressive fibrosis. CTGF indicates connective tissue growth factor; EMT, epithelialmesenchymal transition; FXa, factor Xa; IFNg, interferon-g; PDGF, platelet-derived growth factor; PGE2, prostaglandin E2; Th, T-helper; TGFb, transforming growth factor b. (Figure shown with permission from ERJ)

Asthma Focus

TREATMENT OF IPF—AIMS AND CHALLENGES

Histologically, IPF is characterized by expansion of the extracellular matrix together with architectural distortion, loss of alveolar structure, and subsequent remodeling in the form of honeycomb cysts lined by hyperplastic epithelial cells. Macroscopically, this phenomenon can be observed on computed tomographic scanning, with progressive loss of lung volume and honeycomb destruction (Fig. 1). In short, the fibrosis that characterizes IPF results in irreversible destruction of the delicate lace like structure of the normal lung parenchyma. Therefore, even if one developed a true antifibrotic therapy capable or resorbing collagen and extracellular matrix, it would be impossible to restore normal tissue structure and function. It is important to realize therefore, that the intention of treatment in patients with IPF is to prevent disease progression. Stability in serial lung function parameters in IPF should be considered a treatment success and not a therapeutic failure. By the same token there is no logic to short-term trials of high-dose corticosteroids or other immunomodulators in patients with confirmed IPF as it is not possible to gauge disease stability over a period of only a few weeks.

Treatment trials in IPF have been plagued by a number of difficulties. The relative rarity of the disease has meant that for large scale trials to be performed these have had to be multicenter and often multinational. Early trials were beset with difficulties in the selection of primary endpoints. Thinking in this area has evolved over the last decade as it has become clearer that serial change in forced vital capacity (FVC) is the most robust indicator, across multiple centers, of true progression in disease. Finally, for anybody hoping to understand the IPF literature, it is important to realize that before the 2001 American Thoracic Society/European Respiratory Society consensus statement, the term IPF was used to encompass a much broader category of diseases that are now categorized as subtypes of the idiopathic interstitial pneumonias. Some of the conditions once considered part of the IPF spectrum, such as desquamative interstitial pneumonitis, have subsequently been shown to carry a good prognosis and to be relatively responsive to treatments such as corticosteroids. For this reason all trials before 2001 need to be interpreted with some caution.

The last decade has seen a dramatic expansion in the number of therapeutic trials being performed in IPF (Table 1). The first large multicenter trial was published in 2004 and the size of trials has continued to grow since this time. Before 2004, however, most studies were single center, tended to contain fewer than 30 patients and were frequently open label. On account of these limitations it is difficult to be dogmatic about the true efficacy of many of the therapeutic interventions that have been trialed. For this reason, I have chosen to consider treatments under the headings of “what saeems to work,” “what might work,” and “what does not work.” *(Conituned on page 6)*

TABLE 1. Summary of Landmark Trials in IPF

Drug	Trial Acronym	Year	No. Patients	Sponsor	Primary Outcome	Result	Reference
Interferon-γ		2004	330	nterMune	Progression free survival	No effect	Raghu et al
Pirfenidone		2005	107	Shionogi	Change in lowest SpO2 during 6MW	Reduced acute exacerbations	Azuma et al
Warfarin		2005	56	Investigator	Survival	Improved survival	Kubo et al
N-Acetyl-Cysteine	IFGINIA	2005	182	Zambon group	Change in FVC	Reduced progression	Demedts et al
Bosentan	BUILD-1	2008	158	Actelion	Change in 6MWD	No effect	King et al
Etanercept		2008	88	Wyeth	Change in FVC, DLco, a-A gradient	No effect	Raghu et al
Interferon-γ	INSPIRE	2009	826	InterMune	Survival	No effect	King et al
Pirfenidone		2010	275	Shionogi	Change in FVC	Reduced progression	Taniguchi et al
Imatinib		2010	119	Novartis	Change in FVC, DLco, a-A gradient	No Effect	Daniels et al
Sildenafil	STEP-IPF	2010	180	Investigator	Twenty percent improvement in 6MWD	No effect	Zisman et al
Pirfenidone	CAPACITY 1+2	2010	779	InterMune	Change in FVC	Reduced progression	Noble et al
Bosentan	BUILD-3	2010	616	Actelion	Progression-free survival	No effect	King et al

6MWD indicates 6 minute walk distance; a-A gradient, alveolar arterial oxygen gradient; DLco, lung diffusion capacity for carbon monoxide; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis.

Simple Actions May Reduce Postop Pulmonary Complications

A postoperative care program focused on simple interventions and multidisciplinary care may reduce common pulmonary complications, according to a before-after trial.

The study compared pulmonary outcomes from the National Surgical Quality Improvement Program (NSQIP) before and after implementation of I COUGH. I COUGH is a multidisciplinary program consisting of *I*ncentive spirometry, *C*oughing and deep breathing, *O*ral care (brushing teeth and using mouthwash twice daily, *U*nderstanding (patient and family education), *G*etting out of bed frequently (at least 3 times daily), and Head-of-bed elevation.

The researchers compared outcomes for all patients who underwent vascular or general surgery at their institution before I COUGH implementation (January 1 to December 31, 2009) and after (July 1, 2010, to June 30, 2011).

According to a pre-I COUGH nursing practice audit, 80.4% of 250 patients were in bed during the visit, and 19.6% of patients were in a chair or walking. Post-I COUGH audits showed a significant difference, with 69.1% (P <.001) of 250 patients out of bed. Before implementation, most patients had the head of their bed elevated, and that remained the case after implementation (82.7% and 91.5%, respectively; P = .40).

The nursing audit also showed that just over half (52.8%) of patients had an incentive spirometer nearby before I COUGH. After I COUGH, 77.2% of patients had one nearby and used it with appropriate frequency (P < .001).

The incidence of postoperative pneumonia was 2.6% (1569 cases) during the year before implementation of I COUGH; this was similar to the period recorded previously. During the year after I COUGH implementation, the incidence of pneumonia decreased to 1.6% (1542 cases; P = .09).

Before I COUGH, the incidence of unplanned intubations was 2.0% (1569 cases), a rate similar to that in the previous period. This fell to 1.2% (1542 cases; P = .09) after I COUGH implementation. At similar hospitals, that figure ranged from 1.4% to 1.6%. According to risk-adjusted NSQIP data, the OE ratio of unplanned intubations decreased from 2.10 (95% CI, 1.42 - 2.98) before I COUGH to an odds ratio of 1.31 (95% CI, 0.87 - 1.97) after I COUGH implementation.

JAMA Surg. Published online June 5, 2013.

Avoid High-Dose Steroids in Elc

In a study of elderly Australians with chronic obstructive pulmonary dis
dose corticosteroids had an increased risk of being hospitalized for a dia

About 10% of patients in Australia who have diabetes also have COP
patients with moderate to severe COPD to reduce exacerbations, which
exacerbations, but the latter are not recommended chronically due to t

But the use of corticosteroids in patients with diabetes and COPD pos
part of guideline therapies for COPD but are associated with hyperglyce

In the 12 months after being diagnosed with diabetes, 67.2% of the pat
complication were similar among corticosteroid users and nonusers afte
.18). However, stratification by levels of corticosteroid use revealed a c
patients who took no corticosteroids. The median corticosteroid dose c
stratified into 3 levels of median daily corticosteroid dosage: more tha
greater. Compared with patients who did not take any corticosteroids o
dose/day had a 94% increased risk of being hospitalized for a diabetes-r

A dosage of 0.83 or greater defined daily dose/day over 12 months is co
- for example, 400 µg of budesonide twice daily for a year plus tre
prednisolone for 7 days. Or, it is equal to treating 9 COPD exacerbations

There was no difference in hospitalization in patients who had received

Diabetes Care. June 4, 2013

Vitamin C Kills Mycobacterium tuberculosis

Vitamin C kills drug-sensitive, multidrug-resistant (MDR), and extensively-drug resistant (XDR) strains of Mycobacterium tuberculosis in culture as a result of prooxidant effects.

The new work builds on the long-standing observation that vitamin C is toxic to M tuberculosis, a Gram-positive bacterium. Experiments in the 1930s showed that only 6% of guinea pigs exposed to the bacteria and given tomato juice became infected compared with 70% of guinea pigs not given the vitamin C–rich juice. In vitro experiments conducted in 1950 confirmed the effect of the vitamin on bacterial cultures, and a study in 2011 correlated vitamin C content of various medicinal plants with antibacterial effects.

In the current study, Catherine Vilcheze, PhD, from the Department of Microbiology and Immunology, Howard Hughes Medical Institute, Albert Einstein College of Medicine, Bronx, New York, and colleagues conducted dose-response experiments, determining that 2 mM is the bactericidal level for drug-sensitive, MDR, and XDR bacteria. The effect was not seen when the bacteria were cultured in an anaerobic chamber. M tuberculosis is much more sensitive to the prooxidant effects of the vitamin than other Gram-positive and Gram-negative bacteria.

On the basis of these data, the researchers suggest that adding vitamin C to treatment regimens might shorten the time that chemotherapy is necessary, which is currently from 6 to 24 months. Noncompliance with chemotherapy fuels selection of drug-resistant bacterial strains. The findings also suggest that drug developers might look for the prooxidant effects of drug candidates.

Nature Communications. Published online May 21, 2013.

A SCOOP

Asthma Focus

derly With COPD and Diabetes

ease (COPD) and newly diagnosed diabetes, those who received high-abetes-related complication within a year.

PD. Treatment guidelines recommend the use of inhaled steroids in are frequent, and the use of oral steroids for short-term treatment of heir unfavorable risk/benefit profile.

ses a therapeutic conflict, since corticosteroids are recommended as mia and an increased risk of diabetes complications.

ients had used corticosteroids. Rates of hospitalization for a diabetic r 1 year (7.1% vs 6.3%, P = .37) and after 5 years (19.8% vs 16.2%, P = dramatic difference between patients who took the highest doses and luring 12 months was 0.34 of a defined daily dose/day. Patients were an 0 to less than 0.25; 0.25 or greater to less than 0.83; and 0.83 or ver 12 months, those who received 0.83 or greater of a defined daily elated complication.

mparable to receiving an inhaled maintenance dose of corticosteroids eatment of acute exacerbations 6 times in a year with 50-mg oral with oral prednisolone 50 mg per day for 7 days.

oral, inhaled, or both types of corticosteroids.

Pertussis Vaccines: Whole-Cell More Durable Than Acellular

Teenagers who received 4 diphtheria, tetanus toxoids, acellular pertussis (DTaP) vaccines in the first 2 years of life had nearly a 6-fold higher risk of contracting pertussis than teenagers who received 4 diphtheria, tetanus toxoids, whole-cell pertussis (DTwP) vaccines, according to a case-control study of 1037 teenagers.

The study was conducted after a pertussis outbreak in California in 2010 to 2011. The study population included teenagers born from 1994 to 1999 who were given 4 pertussis-containing vaccines during the first 2 years of life. Cases that were pertussis polymerase chain reaction (PCR)-positive (n = 138) were compared with PCR-negative cases (n = 899) and Kaiser Permanente Northern California matched controls (n = 54,339).

Among 1037 individuals who were PCR tested, 234 (22.6%) were given all whole-cell vaccines, 197 (19.0%) were given a mix of whole-cell and acellular vaccines, and 606 (58.4%) were given all acellular vaccines. Among those who received a mix, 157 (79.7%) received 3 DTwP and then 1 DTaP vaccine, 12 (6.1%) had 2 DTwP and then 2 DTaP vaccines, 17 (8.6%) had 1 DTwP and then 3 DTaP vaccines, and 11 (5.6%) received some other combination of vaccines.

As the number of DTaP doses increased from 0 to 4, the percentage of positive PCR tests for pertussis increased significantly (P < .001 for trend).

The acellular vaccines are effective at preventing pertussis; however, their duration of immunity is less than whole-cell pertussis vaccine.

The study won't change vaccination guidelines. It would not go back to using whole-cell vaccine era because thre were adverse reactions associated with it.

Am J Clin Nutr 2012.

Direct Nucleic Acid Amplification Testing Improves TB Diagnosis

Mycobacterium tuberculosis direct nucleic acid amplification testing improves diagnostic accuracy and timeliness and reduces unnecessary treatment, according to a retrospective cohort analysis.

The Mycobacterium tuberculosis Direct (MTD) NAAT is more accurate and timely in diagnosing TB disease than standard diagnostics using the AFB (acid-fast bacilli) smear.

While AFB smear is cheap and simple, it has poor sensitivity, especially in patients infected with HIV. The gold standard culture takes two to eight weeks for results, whereas NAAT for M. tuberculosis can yield results within 24-48 hours.

Dr. Marks and colleagues evaluated the use, effectiveness, health-system benefits, and cost-effectiveness of MTD in an analysis of 2,140 patients.

Forty percent of patients had at least one smear-positive specimen, and 60% had all smear-negative specimens, . More than one-third (37%) of the cultures were positive.

Overall, 59% of hospitalized patients received MTD, compared with 25% of those not hospitalized. The turn-around time from specimen collection to reported MTD result averaged 2.6 days for hospital specimens and 4.0 days for clinic specimens.

In all subpopulations examined MTD showed higher positive predictive value, sensitivity, and negative predictive value than no-MTD.

In multivariable analysis, MTD-positive results significantly shortened the time to TB determination, but MTD did not significantly decrease the time to TB exclusion for culture-negative patients.

The 2013 updated 'Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents' also recommend NAAT for patients with advanced immunodeficiency who are at risk of rapid clinical progression of TB.

Clin Infect Dis 2013.

Asthma Focus

Current and Future Therapies for Idiopathic Pulmonary Fibrosis (Cont.)

TREATMENT OF IPF—WHAT SEEMS TO WORK?

The first therapeutic trial in IPF to achieve a positive primary outcome was a comparison of the antioxidant N-acetyl cysteine (NAC) administered with prednisolone and azathioprine compared with prednisolone and azathioprine alone. After 12 months of treatment, there was a slower rate of loss of FVC in the NAC-treated group. Similarly, there was a slowing in the deterioration of lung diffusion capacity for carbon monoxide (DLco), by 24%. In the placebo group, there was a significant excess of myelotoxicity. NAC has been widely adopted as a treatment for IPF. It is unclear if NAC alone is effective as a treatment for IPF or whether it needs to be given in combination with prednisolone and azathioprine.

Pirfenidone was first reported as a potential therapy for IPF in an open label study of 54 patients published by Raghu et al 1999. A Japanese study of 275 patients with IPF, pirfenidone was successful in reducing disease progression, as measured by change in FVC, compared with placebo. These studies paved the way for 2 large, double-blind, international studies of pirfenidone against placebo, CAPACITY 1 and CAPACITY. CAPACITY 2, a study of 435 patients, demonstrated a significant reduction in progression of IPF (as measured by decline in FVC) in the pirfenidone-treated individuals compared with placebo at 72 weeks. By contrast, there was no significant treatment effect seen at the same time point in CAPACITY 1 (a study of 344 IPF patients).

For patients with end stage IPF, lung transplantation is an important therapeutic option. Despite significant limitations including donor organ shortage, complications of immunosuppression, infection, and acute and chronic rejection, lung transplantation remains the 1 treatment capable of improving life expectancy for patients with IPF.

TREATMENT OF IPF—WHAT MIGHT WORK?

Until very recently, corticosteroids, often in combination with the immunosuppressant azathioprine, have been considered standard therapy for IPF. The rationale for the use of immunomodulatory therapy harkens back to the notion that inflammation is the primary driver of fibroproliferation in IPF. Despite their widespread use, there is little evidence to either support, or refute, the efficacy of either corticosteroids or azathioprine for IPF.

There have been no randomized placebo-controlled trials of corticosteroids in IPF. A 2003 systematic review by Richeldi et al of corticosteroids in IPF found no evidence to support their efficacy. Similarly, the only study of the use of azathioprine was conducted by Raghu et al and was published in 1991. Patients were treated for 9 years and most received concomitant corticosteroids. There was a survival advantage observed in the group receiving azathioprine; however, this only became apparent after 5 years of treatment. Despite this lack of evidence to support the use of the combination of prednisolone and azathioprine, it is worth remembering that the patients in the IFIGENIA study, who were shown to benefit from the addition of NAC, were also receiving prednisolone and azathioprine.

There is increasing evidence that coagulation pathways also play a pivotal role in the pathogenesis of IPF. These observations led Kubo et al to study the use of anticoagulant therapy for patients with IPF in a 5-center Japanese study. Anticoagulation was achieved using low-molecular heparin for hospitalized patients and warfarin in the domiciliary setting. At 1 year, there was a striking, and statistically significant survival advantage in the anticoagulated patients (87% 1 year survival vs. 54%, P = 0.049). The small size of the study, together with the fact that the enrollment criteria are not applicable to the majority of patients with IPF have meant that it has not been possible for warfarin therapy to be recommended for IPF.

Patients with IPF frequently report an infective type prodrome before the development and diagnosis of their IPF. Infection seems to be a likely trigger for acute exacerbations of IPF. This observation led Varney et al to test the role of septrin in patients with a range of fibrosing idiopathic interstitial pneumonias. This pilot study subsequently led on to a UK based multicenter study of trimethoprim/sulfamethoxazole versus placebo (treating interstitial pneumonia with the addition of cotrimoxazole study) in 140 patients with idiopathic fibrosing lung disease.

TREATMENT OF IPF—WHAT DOES NOT WORK?

The trials with interferon g-1b showed no survival advantage

over placebo. Another treatment to show initial promise in the treatment of IPF was the endothelin receptor antagonist Bosentan. However, bosentan failed to meet the primary endpoint of reducing time to disease worsening or death. Same is true about anti-TNF-a monoclonal antibody etanercept.

TREATING COMPLICATIONS AND SYMPTOMS OF IPF

Although the principal focus in clinical IPF trials has been treatment of the disease process with the aim of arresting disease progression, it is important to recognize that there are a number of disease complications that may be amenable to therapy. The most frequently occurring complications of IPF are acute exacerbations, pulmonary hypertension, and respiratory failure. Acute exacerbations, as their name suggests, are episodes characterized by rapid worsening in symptoms of breathlessness, often accompanied by new infiltrates on thoracic imaging and, in severe cases, acute respiratory failure. When biopsied, acute exacerbations are characterized by the histologic lesion of diffuse alveolar damage. This is the same lesion as that seen in acute respiratory distress syndrome. For this reason, and by analogy to acute respiratory distress syndrome, many physicians treat these episodes with high-dose corticosteroids and supportive care. When invasive ventilation becomes necessary most clinicians advocate a protective ventilator strategy with low tidal volumes and permissive hypercapnia. There is, however, no evidence base to support any specific therapeutic maneuver in acute exacerbations of IPF.

Pulmonary hypertension is a frequent finding in patients with end-stage IPF. In IPF patients undergoing right heart catheterization as part of lung transplant assessment, more than 60%, in some series, have demonstrable pulmonary hypertension. Although in the majority of patients pulmonary hypertension develops in the context of end-stage hypoxic respiratory failure, there are a subset of patients with IPF who develop disproportionate pulmonary hypertension early in the evolution of their disease. The treatment of pulmonary hypertension has changed dramatically in the last decade with the development of a number of novel and highly effective therapies; these include prostacyclin analogues, endothelin receptor antagonists, and phosphodiesterase inhibitors. Given that IPF is a progressive disease lacking effective therapies, treatment of IPF-related pulmonary hypertension potentially affords the opportunity of improving symptoms of dyspnea if not actually increasing longevity. In an open label study of sildenafil in 14 patients with IPF and documented pulmonary hypertension, Collard et al were able to demonstrate a mean improvement in 6-minute walk distance of 49m after 3 months.

IPF is almost invariably a terminal disease. It is important therefore that consideration is given to therapeutic strategies aimed at reducing symptoms and improving quality of life. Pulmonary rehabilitation has been shown to be safe and highly effective in patients with chronic obstructive pulmonary disease. In small studies of patients with IPF, pulmonary rehabilitation seems to confer improvements in functional exercise capacity, dyspnea, and quality of life immediately after training. Oxygen is widely used for patients with respiratory failure due to IPF. Most clinicians prescribe oxygen for this patient group on the basis of symptoms and severity of hypoxia. For individuals in the final stages of their disease the palliative use of anxiolytics including benzodiazapines and opiates can be very effective in alleviating the distressing symptoms of dyspnea and the frequently associated feelings of panic. Cough is another frequently debilitating and difficult to treat symptom of IPF. There is little evidence to support the use of any specific antitussive in IPF. In a small study of 11 patients, Horton et al reported that thalidomide had a dramatic effect in alleviating intractable cough in IPF.

TREATMENT OF IPF—THE FUTURE ?

As is suggested by Figure 2, it is plausible to postulate a number of different approaches to the treatment of IPF. The first is to ameliorate or prevent epithelial injury. This could be achieved by directly preventing injury, for example, through prevention of microaspiration or prophylactic dosing with antimicrobials or antivirals, or by protecting against injury through augmentation of host defense mechanisms. Alternatively, it might be possible to prevent injury-induced epithelial cell death and basement membrane denudation; this could be achieved either by using inhibitors of apoptosis or through promotion of epithelial cell proliferation with agents such as hepatocyte growth factor or kerationcte growth factor.

After epithelial injury, the next apparent step in the pathogenesis of IPF is the persistent activation of pathways involved in normal wound healing. As noted earlier, blocking the coagulation cascade may be effective in improving survival in IPF and this is currently being studied in a multicenter placebo-controlled trial of warfarin (NCT00957242). Similarly, immunomodulatory therapy may be effective in preventing the recruitment of inflammatory cells to the sites of fibroproliferation.

It is possible to envisage therefore, a treatment approach that either inhibits the actions of profibrotic mediators or augments the action of antifibrotic mediators. It was this rationale that underpinned the trials of interferon g-1b as a potential treatment for IPF.

The rapid growth in clinical trials in IPF over the last 10 years makes it possible to be optimistic that effective therapeutic regimens for IPF will begin to emerge in the relatively near future.

Ref: Current and Future Therapies for Idiopathic Pulmonary Fibrosis. Maher. Clinical Pulmonary Medicine Volume 18, Number 6, November 2011

Vol.9 No.2 July-Sept 2013

Asthma Focus

Congratulations!!!

The Winners of Asthma Focus Quiz Competition
Vol. 9 No. 1

Dr. Md. Mazibar Rahman
MBBS, DTCD, MD (Cardiology)
SZMCH, Bogra.

Dr. Imam Uddin Ahmed
MBBS, DTCD
CDC-Comilla.

Dr. Muhammad Asaduzzaman Biswas
MBBS, DTCD
Jr. Consultant, Feni Diagnostic Hospital.

Dr. Poritosh Chowdhury
MBBS, DTCD
Babulkhan Road, Khulna.

Dr. Khalilur Rahman
MBBS, DTCD
Jr. Consultant, CDC, Pabna.

Editorial Note

Dear Doctor,
We are happy to present you the 2nd issue of "Asthma Focus" Newsletter, 2013. In this issue we have concentrated on Idiopathic PulmonaryFibrosis. We hope you will enjoy reading the publication!
We appreciate your comments and queries.
Please participate in Quiz competition & win prizes.

For further information : **Product Management Department**, Square Centre, 48 Mohakhali C/A, Dhaka-1212, ***web*** : www.squarepharma.com.bd
Production by: **dhaka*health*** Cell # 01715 219 808, e-mail: dtp@dhakahealth.org web: **www.dhakahealth.org**