Treating COPD — The TORCH Trial, P Values, and the Dodo
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In the United States, the overall, age-standardized death rate decreased from 1242 deaths per 100,000 population in 1970 to 845 deaths per 100,000 in 2002. This good news must be viewed against the doubling during the same interval of the age-standardized death rate among persons with chronic obstructive pulmonary disease (COPD), which makes COPD a major cause of death (Fig. 1).

COPD is the diagnostic term for a group of disorders that are characterized by respiratory symptoms — dyspnea, cough, and sputum production; airflow limitation; and chronic inflammation of the lung. Risk factors include exposure to a wide variety of inhaled particles and gases, but in the Western world, inhaled cigarette smoke is the most important known causative factor. COPD is more than a pulmonary disorder with a known effect on cardiovascular function and on the risks of lung cancer, the metabolic syndrome, osteoporosis, cachexia, and depression. (Information for health care professionals and patients with COPD is available on the Web site of the National Heart, Lung, and Blood Institute, at www.nhlbi.nih.gov/health/public/lung/copd.)

Patients with COPD die mainly from extrapulmonary diseases, and COPD-related mortality is probably underestimated because identifying the precise cause of death is difficult in elderly patients with this disease, in whom cardiac arrhythmias, ischemia and chronic pulmonary heart disease (cor pulmonale) or pulmonary embolism, or both could be suspected. For example, 25% of patients with COPD who were hospitalized for severe exacerbations were shown to have pulmonary embolisms.

Treatment of COPD has been focused on improving lung function and relieving symptoms with the use of inhaled anticholinergic agents and beta-adrenergic–receptor agonists. These drugs, in principle, also reduce exacerbations, but there is no convincing evidence so far to suggest that this therapy substantially changes the course of the disease or affects mortality.

Although the mechanism linking COPD and coexisting diseases is uncertain, recent data suggest that it might be chronic inflammation, in the lung and systemically. Inhaled corticosteroids have been reported to affect the frequency of exacerbations, and, in retrospective analyses, to reduce COPD-related mortality, although both claims have been challenged in other statistical analyses. Furthermore, database studies suggest a beneficial effect of inhaled corticosteroids on deaths from cardiovascular disease and lung cancer. In this issue of the Journal, Calverley and colleagues report the results of the Towards a Revolution in COPD Health (TORCH) trial, a large randomized, prospective study involving patients with COPD in which mortality was the primary end point and the intervention consisted of therapy with long-acting beta-agonists and inhaled corticosteroids, alone or in combination. Deaths from any cause were analyzed with the use of a Cox proportional-hazards model, and all efficacy analyses were performed in the intention-to-treat population — probably the most rigorous approach that could have been taken. The study was powered on the assumption of a mortality rate in the placebo group equal to or greater than 17% and a 25% reduction in mortality in the group receiving study treatments containing inhaled corticosteroids, as compared with placebo. During the trial, the number of patients to be enrolled had to be increased because the overall death rate was lower than expected.
How are the findings of this trial to be interpreted? The truly strong part of the trial is the meticulous recording of the causes of deaths. However, there are weaknesses in the study design, namely the risk of skewed results due to differential withdrawal from the assigned treatment. This risk turned into reality: 40% or more of the subjects enrolled in the study dropped out. Since all patients in the study clearly had an indication for therapy, clinically, it is conceivable that some patients found that their COPD symptoms became intolerable (as might be expected in the placebo group, for example) and left the study to obtain some relief. This weakness in the study design probably could have been avoided if the primary comparison had been between patients receiving the combination therapy and those receiving long-acting beta-agonists alone. The placebo-controlled design could also have affected enrollment: recruiting patients who would take the chance of receiving placebo for 3 years might have excluded those with more severe disease —

**Figure 1. Causes of Death in Patients with COPD.**
Among patients with COPD, death can result from causes in a number of disease categories, in part, because of the strong association between COPD and exposure to cigarette smoke. In the Towards a Revolution in COPD Health (TORCH) trial, 35% of deaths were adjudicated as due to pulmonary causes, 27% to cardiovascular disease, and 21% to cancer. Ten percent were attributed to other causes, whereas the primary cause of death could not be determined by the clinical end point committee in 7% of cases.
that is, patients known to have frequent exacerbations, which are associated with a higher mortality rate.

These factors may have led to the failure of the trial to demonstrate the expected mortality in the placebo group. Setting total mortality as the end point was an ambitious target, and it raises the question of what the minimally clinically important difference for this end point would be. One can only speculate that those designing the study were (too) convinced of the effects of inhaled corticosteroids on the basis of their own retrospective data. These data might have pertained to a different group of patients, such as those who may not have wanted either to enroll or to stay in the trial. In the end, the trial failed to meet its goal: the P value for death from any cause was 0.052, which was higher than the prespecified value of 0.50. All clinical trials are a gamble, and the TORCH investigators came close to winning but did not win. Thus, the results of this trial are difficult to interpret.

The real challenge, however, is what to make of the trial for clinical practice. Lewis Carroll, in Alice in Wonderland, offers a wonderful conclusion that may be applicable here:

However, when they had been running half an hour or so, and were quite dry again, the Dodo suddenly called out “The race is over!” and they all crowded round it, panting, and asking “But who has won?” This question the Dodo could not answer without a great deal of thought, and it stood for a long time with one finger pressed upon its forehead . . . while the rest waited in silence. At last the Dodo said “Everyone has won, and all must have prizes.”

In the case of the TORCH trial, I am afraid this conclusion is not an option. The interpretation of the data for the primary outcome as published is conservative — and, in principle, it is correct: the reduction in mortality in the combined-therapy group did not reach the predetermined level of statistical significance. On further weighing these results, however, I think the treatment with long-acting beta agonists was a winner and that with inhaled corticosteroids was a clear loser. The clinical guidance is obvious: monotherapy with corticosteroids should not be advocated for patients with COPD, monotherapy with a long-acting bronchodilator appears to be safe, and the combination therapy offers no statistically significant additional survival benefit. In this context, the results of the Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) trial investigating the effect of an anticholinergic drug over 4 years in patients with COPD, which should be available in 2008, will be of interest.56

Combination therapy, as compared with monotherapy with long-acting beta-agonists or inhaled corticosteroids, offers statistically significant advantages for health status, frequency of exacerbations, use of oral steroids, and — probably most important clinically — protection against a decline in lung function. This finding confirms the position of combination therapy in current guidelines for the treatment of patients with COPD that recommend its use for those with severe COPD with frequent exacerbations but not for patients with milder disease or without frequent exacerbations. Caution in the use of combination therapy is urged because of the finding in the TORCH trial of an increased rate of pneumonia among all patients receiving treatment containing inhaled corticosteroids. This finding urgently requires further investigation, and I urge the sponsor of this study to undertake a large trial to determine its importance.

The TORCH trial is important, not only because it provides data on the natural history of COPD but also because it clarifies, in part, the role (and the shortcomings) of pharmacotherapy for COPD in the overall mortality resulting from this disease and highlights some of the inherent problems of retrospective analyses of treatment trials. Believe it or not, we still need more data, from even larger trials.

Dr. Rabe is member of the Global Initiative for Obstructive Lung Disease and chair of the science committee. He reports receiving consulting or lecture fees from GlaxoSmithKline, AstraZeneca, Boehringer Ingelheim, Chiesi, Pfizer, Novartis, Altana Pharma, Merck, and Almirall and grants from Altana Pharma, AstraZeneca, Boehringer Ingelheim, and Pfizer. No other potential conflict of interest relevant to this article was reported.

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Synergistic Copathogens — HIV-1 and HSV-2

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The variability in both the clinical progression and transmission of human immunodeficiency virus (HIV) infection has prompted a search for cofactors influencing replication of the virus. Although it is clear that host immune and genetic factors, as well as the replication kinetics of particular viral strains, influence the progression of HIV disease, a variety of exogenously acquired infectious agents also appear to influence the pace of HIV replication, the destruction of CD4+ T cells, and HIV transmission to infants and sexual partners. Transient bursts of HIV replication occur after vaccination and during episodes of acute systemic infection. More persistent elevations in plasma HIV levels have been seen in patients with chronic infections (such as those with Mycobacterium tuberculosis and herpes and hepatitis viruses), and such coinfected patients have a more rapid loss of CD4+ T cells and an increased rate of progression to AIDS and death.1

HIV replication is compartmentalized in anatomic sites of the body, and the interactions between HIV type 1 (HIV-1) and microbes occupying these anatomic sites influence the amount and strain of HIV-1 in these regions. Interactions between the gut flora with HIV in gut lymphoid tissue and between sexually acquired pathogens and HIV-1 in the genital tract are perhaps the two areas of greatest importance in influencing the progression of disease and viral transmission. Localized infections of the genital tract with sexually acquired bacterial infections such as Neisseria gonorrhoeae and, to a lesser extent, Chlamydia trachomatis are associated with higher amounts of HIV in genital secretions; treatment of these infections with antimicrobial agents is associated with a lowering of the HIV load in these secretions.2 Thus, the identification and treatment of such infections have been important parts of the medical care of patients with HIV infection.

The clinical management of herpes simplex virus type 2 (HSV-2) in patients with HIV infection has lagged seriously behind the large body of medical literature on the importance of the interaction between these two pathogens.3 Persistent HSV-2 infection was one of the original opportunistic infections that resulted in the identification of HIV. Since the initial reports in 1988 studying men who have sex with men, many additional studies have shown the association between prevalent and incident HSV-2 infection and the risk of HIV acquisition.4,5 In this issue of the Journal, a study by Nagot et al.6 underlines the association of HSV-2 with significantly higher amounts of HIV-1 in plasma and in genital secretions. This finding has direct clinical implications, suggesting that HIV-1 replication can be reduced with antiviral therapy directed solely at HSV-2, since acyclovir has no direct antiviral activity against HIV.7

The conceptual importance of this observation is high. HSV-2 is acquired rapidly after the onset


