2012

216th Annual Oration

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ORATION: 50 Years of Medicine: Less Art, More Science

This year, 2012, marks my 50th year as a physician. During this time, changes in the delivery of medical care have been monumental, such as the introduction of Medicare, managed care and the electronic medical record. Equally impressive have been advances in the treatment of many chronic diseases which all too often resulted in significant long term morbidity and even increased mortality. Over the past 35 years, I have been fortunate to be involved in many clinical trials of novel agents to treat chronic systemic inflammatory diseases and will recount some of them here.

The destructive processes of all systemic inflammatory disease states are regulated by cytokines which are small glycoproteins whose primary function is to allow communication between cells of the immune system. These are the extracellular communicators which allow macrophages, lymphocytes and dendritic cells to relate to each other. Cytokines function by binding to specific receptors of the membranes of target cells which then initiate events within these cells ultimately leading to the production of new messenger RNA and protein.

Tumor necrosis factor-a (TNF) has for years been recognized as a key cytokine in the initiation and progression of the inflammatory process in diseases such as rheumatoid arthritis (RA), psoriasis and Crohn's disease. Inhibiting its function by binding monoclonal antibodies to its molecular structure stops or curtails the inflammatory process at a very basic level, allowing for symptom resolution and even, in some cases, complete remission.

In the case of RA, the propagating pathology can be very heterogeneous, so that the role of TNF in its pathogenesis may be variable. In such patients, inhibiting the contribution of cellular elements may be more efficacious than down regulating TNF. There are available 2 FDA approved medications which target lymphocytes and which are capable of inducing clinical improvement and even remission in RA. These are Orencia (abatacept) and Rituxan (rituximab), neither of which has currently demonstrated sufficient efficacy in diseases other than RA to gain FDA approval.

Recently, considerable research dollars are being invested to develop small molecules which, unlike monoclonal antibodies, can be taken orally. These drugs block intracellular signaling molecules called "kinases" so that the ability of these immune cells to secrete pro-inflammatory cytokines is blunted. Unlike monoclonal antibodies which are molecule specific, inhibiting these kinases results in the measured diminution of multiple mediators which contribute to the inflammatory response. The most advanced of these drugs is "tofacitinib" (Pfizer) which is likely to garner FDA approval for RA later in 2012.

Over the past 10-15 years, considerable progress has been made in the treatment of osteoporosis which is so prevalent in our aging population. While bisphosphonates such as alendronate, risidronate and ibandronate have had a major impact on reducing the incidence of fractures in people with increased bone fragility, there are well recognized limitations to the use of bisphosphonates over extended time periods. For this reason, alternatives to currently available medications could have broad clinical appeal. More recently, denosumab (Prolia) which is given subcutaneously every 6 months and which inhibits the formation and function of

osteoclasts has become available. Because this molecule does not embed itself in bone, it may well have some advantages with respect to resulting in fewer instances of osteonecrosis of the jaw and atypical femoral fractures which are being increasingly noted with prolonged bisphosphonate use. On the horizon and well into Phase 3 clinical trials, is a Merck compound which inhibits cathepsin K, an enzyme primarily found in osteoclasts and which functions to break down bone matrix. Multiple studies have demonstrated that inhibition of cathepsin K results in preventing loss of bone strength and decreasing fracture incidence in post menopausal women. This medication appears to have an acceptable safety profile making it likely that it will be commercially available within the next 2 years.

Psoriasis is a systemic inflammatory disease with an incidence of about 2% of the population. Though striking treatment advances have been made in the past 10 years with the use of TNF inhibitors and monoclonal antibodies directed to IL-12/23 (ustekinumab, Stelara), there is still a significant unmet need in that many patients either fail to respond or lose efficacy to these currently available medications. In a recent issue of the *New England Journal of Medicine* (March 29, 2012), clinical trials with monoclonal antibodies inhibiting the function of IL-17 have shown remarkable efficacy in resolution of psoriatic plaque lesions. Because very few adverse effects were noted in these short Phase 2 trials, further clinical trials are being initiated at this time. If the currently perceived efficacy and safety profile is maintained in these longer trials, I would expect that these agents will be another significant treatment option for patients who fail to respond to currently available agents. Clinical Pharmacology Study Group, my clinical trial group, is delighted to have been chosen to participate in the development program of both of these inhibitors of IL-17.

Considerable advances have also been made in the management of tophaceous gout with the recent FDA approval of Krystexxa, a recombinant uricase, which has demonstrated a dramatic ability to rapidly decrease serum uric acid and debulk tophi in a matter of weeks.

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