inside blood

CLINICAL OBSERVATIONS, INTERVENTIONS, AND THERAPEUTIC TRIALS

Returns on long-term investments in sickle cell disease

For many years sickle cell disease served as the classic example of the disheartening gap between scientific knowledge and clinical application. On the one hand, remarkable achievements in the laboratory led to the characterization of the structure and function of hemoglobin, an understanding of the distinctive characteristics of sickle hemoglobin (Hb S), and the identification of the molecular basis of sickle cell disease. On the other hand, patients continued to experience repeated painful crises, frequent hospitalizations, organ failure, and early death.

With the initiation of the Cooperative Study of Sickle Cell Disease in 1979 and the implementation of newborn screening programs, clinical research and clinical care began to catch up with basic science. The detailed characterization of the clinical course of sickle cell disease was followed by important interventional trials, such as penicillin prophylaxis for the prevention of bacterial sepsis and hydroxyurea for enhancement of fetal hemoglobin. An improvement in the critical outcome of life expectancy as a result of these studies would be as dramatic as the advances in science that had occurred 50 years earlier.

In this issue of *Blood*, Quinn and colleagues (page 4023) show that the life expectancy of children with sickle cell disease has indeed improved. In their careful study of a large cohort, identified by newborn screening and treated in a single comprehensive sickle cell center, the authors found the predicted overall survival of patients with sickle cell anemia (Hb SS) and sickle-β°-thalassemia (Hb Sβ°) at 18 years of age to be 86%. Although differences in methodology confound precise comparisons with other cohorts,[1,2] the data in the present study suggest that a substantial reduction in mortality has occurred during the past 30 years. A large portion of this reduction is almost certainly attributable to newborn screening programs, the early introduction of prophylactic antibiotics, and the availability of effective vaccines for the prevention of life-threatening bacterial infection. Indeed, 10 years ago Platt et al[1] predicted with remarkable accuracy that these measures would achieve a survival rate at age 20 years of 85%, virtually identical to the results in the current study.

Like most landmark studies, this paper identifies new challenges. First, the prophetic words of Platt et al[1] regarding improved life expectancy were accompanied by the important caution that prevention of the later complications of sickle cell disease would be particularly challenging. Deaths from acute chest syndrome and multiorgan failure, accounting for one third of the total in this study, are a grim reminder of the need for better understanding and management of these complications in children and adults. Second, mortality unrelated to sickle cell disease in the current study, such as the 5 deaths from motor vehicle accidents, drowning, and head injuries, emphasizes that comprehensive care cannot be limited to hematologic issues alone. Finally, the improved outcomes in this comprehensive sickle cell center raise the provocative question of whether the care of patients with sickle cell disease should be entrusted solely to such programs, or, on the other hand, whether detailed and closely followed clinical pathways would allow successful management at least partially outside of such centers. As further studies address these issues, the paper by Quinn et al will provide a new benchmark to assess their impact on the quality and length of life for patients with sickle cell disease.

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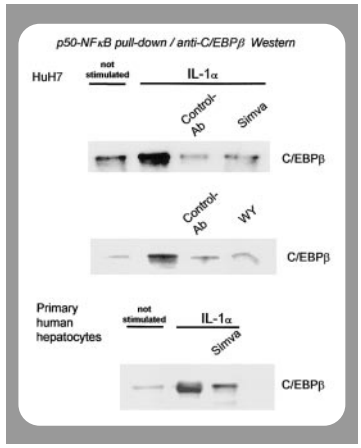
1. Platt OS, Brambilla DJ, Rosse WF, et al. Mortality in sickle cell disease: life expectancy and risk factors for early death. N Engl J Med. 1994;350:1639-1644.
2. Lee A, Thomas P, Cupidore L, Serjeant B, Serjeant G. Improved survival in homozygous sickle cell disease: lessons from a cohort study. BMJ. 1995;311:1600-1602.

HEMOSTASIS, THROMBOSIS, AND VASCULAR BIOLOGY

How statins and fibrates lower CRP

Human C-reactive protein (huCRP) is a major acute-phase protein synthesized in the liver under interleukin-1 (IL-1) and IL-6 control. An elevated concentration of huCRP is currently considered as both a marker and an independent predictor of cardiovascular disease.[1] HuCRP is indeed present in atheromatous plaques, and a recent in vivo study indicates that huCRP may have a direct proatherogenic role via the up-regulation of angiotensin type 1 receptors.[2] Lowering huCRP levels could therefore be of benefit in modulating the evolution of atherosclerosis.

Statins and fibrates are cholesterol-lowering agents that also decrease plasma levels of huCRP.[3] The hypolipidemic effect of fibrates is obtained via the nuclear receptor peroxisome proliferator–activated receptor-alpha (PPAR-α). In addition,



PPAR-α activation by fibrates has been shown to act as a negative regulator of inflammatory processes by antagonizing the activity of the transcription factor pathways (eg, nuclear factor κ B [NFκB]).

The statins block cholesterol synthesis by interrupting the conversion of 3-hydroxymethylglutaryl coenzyme A (HMG-CoA) to mevalonate. In addition, they may also have