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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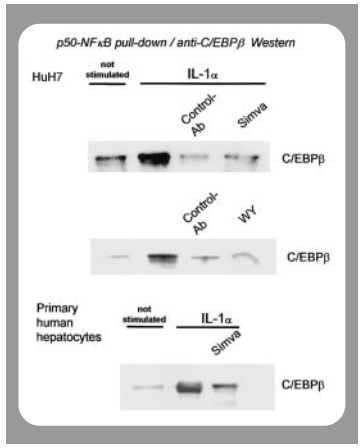
HEMOSTASIS, THROMBOSIS, AND VASCULAR BIOLOGY

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

anti-inflammatory effects; rosuvastatin specifically suppressed the expression of the inflammation parameters monocyte chemoattractant protein-1 (MCP-1) and tumor necrosis factor α (TNF-α) in the vessel wall.[4] It has been suggested that the pleiotropic effects of HMG-CoA reductase inhibitors and PPAR-α activators (eg, inhibition of tissue factor and plasminogen activator inhibitor 1 [PAI-1] expression and of endothelin-1 [ET-1] secretion) participate in the capacity of these molecules to reduce coronary heart disease.

Whether the huCRP-lowering capacity of statins and fibrates is secondary to reduced atherogenesis or a direct independent effect has been clarified by recent studies from the Gaubius Laboratory (Leiden, The Netherlands) on the mechanism of action of these agents. It was initially shown that fibrates reduce CRP levels by down-regulation of IL-1–stimulated CRP gene expression via reduction of nuclear p50-NFκB–C/EBPβ (CCAAT/enhancer binding protein β) complex formation.[5]

In this issue of *Blood*, Kleemann and colleagues (page 4188) have shown that atorvastatin and fenofibrate, at doses higher than those required for cholesterol lowering, decrease basal and IL-1β–induced plasma huCRP levels. Since these experiments were performed in nonatherosclerotic huCRP mice, the authors clearly demonstrate that these compounds exert a direct anti-inflammatory action independent of cholesterol lowering and atherogenesis. Furthermore, using human liver slices it was shown that these drugs suppressed the effect of IL-1β at the transcriptional level. The suppression of IL-1–induced huCRP gene transcription appears to involve both an up-regulation of IκBα, an inhibitor of the activity of NFκB, and a reduction of nuclear p50-NFκB-C/EBPβ complexes. It is of note that this direct anti-inflammatory effect was obtained with both the statins and fenofibrate.

Since huCRP may accelerate the progression of atherosclerosis in apolipoprotein E (ApoE)–deficient mice,[2] these results suggest that lowering huCRP with statins or fibrates will regulate the progression of atherosclerosis. However, the possibility that decreasing huCRP concentration may contribute to arrest plaque formation and decrease the likelihood of cardiovascular accidents, as do the cholesterol-lowering doses of statins in humans, remains to be demonstrated. A response will be obtained in this regard from the ongoing low-cholesterol/high-huCRP trial "Justification for the Use of Statins in Primary Prevention: an Interventional Trial Evaluating Rosuvastatin (JUPITER)."[6]

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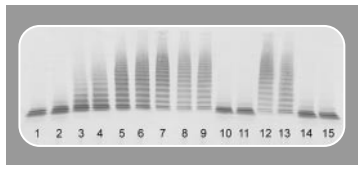
HEMOSTASIS, THROMBOSIS, AND VASCULAR BIOLOGY

ADAMTS13 and TTP: the clot thickens

Current beliefs are that familial thrombotic thrombocytopenic purpura (TTP) is caused by mutations of the *ADAMTS13* gene and that acquired TTP is caused by autoantibodies that inhibit ADAMTS13 activity. These concepts are consistent with observations on treatment: familial TTP can be effectively treated by plasma infusion to replace ADAMTS13, whereas plasma exchange, presumably performed to remove inhibitory autoantibodies in addition to replacement of ADAMTS13, is more effective treatment for acquired TTP. These observations provide a logical explanation for (1) how TTP occurs in relation to accumulation of unusually large multimers of von Willebrand factor (VWF), and (2) how the treatment works. This is a wonderful example of translational research. However, translation inevitably becomes less clear as more carefully designed clinical observations are reported. Nature speaks many languages with many nuances, subtleties, and surprises.

For example, our assumption about familial TTP is adjusted by the stunning case reports of identical twin sisters who developed TTP at ages 23 years and 24 years by Studt and colleagues (page 4195). Although both sisters had absent ADAMTS13 activity, the presence of immunoglobulin G (IgG) antibodies that inactivated ADAMTS13 and the eventual recovery of normal ADAMTS13 levels demonstrated that the TTP was acquired rather than due to an abnormality of the *ADAMTS13* gene. However, ADAMTS13 levels remained undetectable with persistent inhibitors 5 to 17



months after complete hematologic recovery, demonstrating that severe ADAMTS13 deficiency is not always sufficient to cause TTP.

Another report in this issue by Zheng and colleagues (page 4043) describes 37 consecutive patients with clinically diagnosed TTP. Of 20 patients who had idiopathic TTP, 16 (80%) had severe