knockout mice are likely to reveal new therapeutic targets that regulate platelet numbers and function.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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IMMUNOBIOLOGY

Comment on Ward et al, page 680

Unraveling the immune response during AIHA

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In this issue of *Blood*, Ward and colleagues make some novel fundamental observations on the nature of the immune response during autoimmune hemolytic anemia (AIHA). They show a key role for T regulatory cells (Tregs) in the pathogenesis of this autoimmune disease.

Tregs in individuals with AIHA were shown to recognize a peptide epitope derived from the Rh proteins, correlating with the known anti-Rh specificity of red cell autoantibodies in this disease. Their work has, for the first time, enabled the cloning (based on the propensity of Tregs to secrete IL-10) and subsequent characterization of Tregs that are primarily responsible for this autoimmune condition, which is of significant clinical importance in hematology. It is generally accepted that Tregs (which represent roughly 5% of the $CD4^+$ T cell population) play a fundamental role in the development of tolerance to self antigens and also in the pathology of autoimmune disease.[1]

The management of autoimmune diseases represents a major challenge to medicine in the 21st century. These diseases constitute a major cause of long-term dehabilitation, and the only effective treatment is often global immunosuppression, which has considerable, sometimes disastrous, side effects. AIHA is a classical example of such conditions, and front-line treatment almost invariably requires immunosuppression involving administration of corticosteroids and sometimes even splenectomy.[2,3] In extreme cases, AIHA can cause significant problems during transfusion, as panagglutinating or red cell–bound autoantibodies interfere with crossmatching and may reduce the effectiveness of transfusion due to the production of alloantibodies.[4] A better understanding of the pathogenesis of the aberrant immune response to autoantigens is a long-term goal in the treatment of AIHA and other autoimmune diseases.

AIHA is the first disease in which Tregs have been identified to respond to autoantigen—a peptide epitope derived from the human red cell Rh proteins. Ward et al confirm that one hallmark of Tregs involved in the pathology of AIHA is that they express IL-10 and the transcription factor FoxP3. However, more importantly, the authors confirm that autoreactive Tregs show discrete phenotypic differences that indicate they derive from a Th1 effector T-cell population specific for the Rh proteins, a result that warrants further investigation. Ward et al also demonstrate that CTLA-4 ligation costimulates (along with interaction with the TCR) the isolated Tregs to express cytokines (IL-10 and IFN-γ) involved in their further proliferation. Now that the individual cells and their surface markers involved in the pathogenesis of AIHA have been defined, further studies may reveal precisely how effector cells that promote inflammation switch to tolerance-inducing Tregs during the course of disease. This will ultimately lead to better regimes for the clinical management of autoimmunity, which currently lacks specific therapies.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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CLINICAL OBSERVATIONS

Comment on Cohen et al, page 583

Oral iron chelation: new drug, old rules

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The dose and schedule of an iron chelator, whether given parenterally or orally, is variable and depends on the rate of iron loading.

An important new therapeutic has entered the ranks in the fight to mitigate transfusion-induced iron overload. Deferasirox, a new and effective oral iron chelator, has released afflicted patients from the discomfort of subcutaneous deferoxamine. Though not free of problems, the new drug is a far better option than its predecessor. In this issue of *Blood*, Cohen and his colleagues remind us, however, that the physician must still obey the old rules of chelation even when using the novel oral agent.

A cardinal rule of iron chelation therapy was established by Modell and her colleagues in the 1970s and reiterated in the 1990s.[1,2] The dose and the schedule of deferoxamine *must* be adjusted to the rate of iron loading. If the rate of iron loading is increased by, let us say, an increased rate of hemolysis induced by the treatment of hepatitis C, the dose and frequency of

the chelator must be increased pari passu. Cohen et al have shown this to be the case with respect to deferasirox.

There might have been reason to hope that deferasirox would permit the physician and insurer to avoid the rule and save money. After all, deferasirox has a very long plasma half-life,[3] whereas deferoxamine rapidly disappears from the circulation. Deferasirox is a member of a class of drugs that removes iron almost exclusively through the liver and gastrointestinal (GI) tract. A single dose can induce increased iron excretion for days, as the excreted unbound drug is repeatedly reabsorbed and travels through the enterohepatic circulation. In contrast, although deferoxamine removes iron through the stools and the urine, the effect of a single dose is very time-limited because it is not absorbed or, better, reabsorbed from the GI tract. One might also have hoped that the long half-life of deferasirox would protect the patient from the toxic effects of accelerating iron overload, because the circulating drug snaps up nontransferring bound iron and presumably protects the heart even though the hepatic iron load is increasing.[3,4]

Despite the above aspirations, clinical experience and the results of the studies of Cohen et al have already shown that the Modell rule has not been nullified. Iron load must be regularly monitored during treatment of chronic transfusion-dependent anemia, and chelator dose adjusted accordingly. Fortunately, new technology has made iron-load assessment much more practical. The so-called gold standard, the liver biopsy, is a bit tarnished because its accuracy is weakened by hepatic fibrosis. The superconducting quantum interference device (SQUID) is largely unavailable, terribly unwieldy, and poorly reproducible from machine to machine. But magnetic resonance imaging (MRI) methods have markedly improved, and are reproducible if each patient serves as his or her own control.[5]

Although the old rules have not changed, the advent of an oral iron chelator has made a huge difference for patients who require chronic transfusions. This is surely a boon for patients and for physicians, nurses, and parents who have struggled to achieve compliance with an unpleasant subcutaneous treatment regimen.

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