EDITORIALS

Management of Immune Thrombocytopenia — Something Old, Something New

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For most of my career, the management of immune thrombocytopenia has evolved from clinical experience rather than clinical evidence. When I was a medical student at Ohio State University in 1960, my mentors were shifting their initial treatment for immune thrombocytopenia from splenectomy to the recently available glucocorticoids.[1] Over the next 40 years, although multiple other treatments were reported in case series of selected patients, glucocorticoids and splenectomy remained the most common first and second treatments, respectively, for immune thrombocytopenia. When a guideline for immune thrombocytopenia was developed by the American Society of Hematology in 1996,[2] there was little clinical-trial evidence on which to base recommendations.

During the past 10 years, the management of immune thrombocytopenia and the quality of clinical evidence have changed dramatically. Rituximab has become a common second treatment, although the frequency and durability of a complete response may be less with rituximab as compared with splenectomy.[3,4] The development of thrombopoietin-mimetic agents, which can increase platelet counts by increasing platelet production, began a new era in the management of immune thrombocytopenia. Two agents, romiplostim and eltrombopag, have been approved by the Food and Drug Administration and the European Medicines Agency for use in treating immune thrombocytopenia. Multiple randomized clinical trials have shown the benefit of these agents for patients in whom previous treatments have failed; recent publications include the study by Kuter and colleagues in this issue of the *Journal*[5] and a study by Cheng and colleagues.[6]

The study by Kuter and colleagues is an example of the enormous enterprise required to study an uncommon disorder such as immune thrombocytopenia.[5] In this randomized study, 85 investigational sites in 14 countries enrolled 234 patients to compare romiplostim with standard care in patients who had not undergone splenectomy and in whom at least one previous treatment for immune thrombocytopenia had failed. The conclusions are clear. The outcomes were better in patients receiving romiplostim than in patients receiving standard care (short of splenectomy): romiplostim was associated with a greater incidence of a sustained platelet response, less bleeding and fewer transfusions, a decreased requirement for other treatments (including splenectomy), and greater improvement in quality of life. The side effects of romiplostim therapy were minimal, but understanding the potential harms of a new treatment is more difficult than documenting its benefit; confidence about the safety of the drug requires that more patients be observed for a longer time. Because patients treated with romiplostim had better outcomes, does the work of Kuter and colleagues establish romiplostim as the new standard of care? This may have been one of the goals of the sponsor of this study (for which I consulted on romiplostim and served as an investigator in clinical trials), and this may be how it is interpreted.

The standard first treatment for immune thrombocytopenia continues to be glucocorticoids[2,7]; they are familiar, inexpensive, and usually effective. However, durable remission is uncommon, and glucocorticoids quickly become intolerable in many patients[8]; therefore, a second treatment is commonly required. Romiplostim may increase platelet counts with possibly few

side effects, but it is an expensive maintenance treatment, required indefinitely. Splenectomy and rituximab can induce remission, and perhaps even cure immune thrombocytopenia, but carry the respective risks of surgery and immunosuppression. Which of these options (romiplostim vs. splenectomy or rituximab) is more appropriate for second-line treatment?

Let's go back to the beginning and consider splenectomy. Splenectomy was the first, and is still the most effective, treatment for immune thrombocytopenia. It is a clear contrast to romiplostim: the oldest treatment, versus the newest; treatment that induces a remission, versus maintenance treatment; and therapy with potential surgical risks, versus the uncertain risks of a new treatment. In a systematic review of 130 articles describing studies of 15 or more consecutive patients undergoing splenectomy for immune thrombocytopenia across 58 years, splenectomy consistently resulted in complete remission (defined as a normal platelet count requiring no further treatment) in two thirds of patients and a partial response in another 20% of patients; recurrence was uncommon.[4] Surgical complications are unusual in current practice. The long-term risks of infection and thrombosis have been described but may be rare. Among patients who had undergone splenectomy for immune thrombocytopenia more than 1 year previously, the relative risk of severe infection was 1.4 (95% confidence interval [CI], 1.0 to 2.0) as compared with patients who had not undergone the surgery,[9] and the relative risk of venous thrombosis was 2.6 (95% CI, 0.9 to 7.1) as compared with patients who had undergone appendectomy rather than splenectomy.[10] Randomized clinical trials of splenectomy have not yet been done, and although they are not needed to document effectiveness, they are important for comparing splenectomy with treatments such as rituximab and thrombopoietin-mimetic agents with respect to the benefits, risks, effects on quality of life, cost, and long-term outcomes.

Faced with these distinct management choices, how do we physicians and our patients know what to do? Information will come from many sources. Advertising and advocacy for the thrombopoietin-mimetic agents are apparent; splenectomy has no organized advocacy. Clinical trials published in high-profile journals[5,6] will promote consideration of the thrombopoietin-mimetic agents.

A third source of information is systematic reviews of published data with interpretation aimed at providing recommendations for practice. An example is the recent international consensus report on the investigation and management of immune thrombocytopenia.[7] In this report, thrombopoietin-mimetic agents are the only treatments that received the highest (grade A) recommendation, on the basis of evidence from randomized, controlled trials. The level of recommendation for splenectomy is unclear; the text suggests a grade B recommendation, while the "Recommendations Box" in the supplemental documents suggests a grade C recommendation, the weakest. Interpretation of these recommendations should take into account that this report was supported by the companies that produce romiplostim and eltrombopag.[7] Conflict-of-interest issues have arisen in relation to clinical-practice guidelines. Therefore, it will be important to compare these recommendations for immune thrombocytopenia[7] with the revised guideline of the American Society of Hematology (currently in preparation), which was drafted with neither commercial support nor participation by anyone with a commercial conflict of interest.

At this time, two things are certain. First, the availability of the thrombopoietin-mimetic agents has been a great advance for patients with immune thrombocytopenia. Thrombopoietin-mimetic agents can be effective in inducing safe platelet counts when all other treatments, including splenectomy and rituximab, have failed, providing hope for patients with the most severe thrombocytopenia. Second, active discussion of the proper place for thrombopoietin-mimetic agents in the sequence of immune thrombocytopenia treatments will continue. For patients with immune thrombocytopenia, an orphan disease, this attention is both new and welcome. Patients with immune thrombocytopenia will feel less isolated, and their care will be better.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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Infant Formula, Autoimmune Triggers, and Type 1 Diabetes

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Families are devastated when a child receives a diagnosis of type 1 diabetes. Although tremendous strides in insulin-based treatments — made feasible by technical advances such as continuous glucose monitors, modern "designer" insulin formulations, and novel insulin-delivery devices — have contributed to remarkable improvements in the prognosis of the disease, the proper management of type 1 diabetes is expensive and time-consuming. In addition, not all families and patients marshal the diligence and skills required to control glycemia with sufficient rigor to prevent complications. Moreover, the benefits of tight control of diabetes must be balanced with the detrimental consequences of hypoglycemia, particularly in young children. Thus, one of modern medicine's "holy grails" since insulin was first used as a therapy in 1922 has been that an understanding of the pathogenic mechanisms underlying type 1 diabetes would lead to a cure or prevention.

For more than 30 years, the center stage of the story of the pathogenesis of type 1 diabetes has been occupied by compelling data on T-cell–mediated autoimmunity. For instance, recent genomewide association studies have identified unambiguous genetic linkages associated with an increased risk for type 1 diabetes, and nearly all identified genes have known roles in cellular immunity.[1-3] In addition, clinical trials have shown that interventions aimed at modifying the cellular immune response (e.g., cyclosporine, antithymocyte globulin, and anti-CD3) can delay the inexorable decline in beta-cell function that follows the onset of the disease. Although anti–beta-cell–specific autoantibodies are predictive of an increased risk for type 1 diabetes, those antibodies themselves are not considered to be pathogenic. Currently, there is no consensus regarding the factors that initiate the autoimmune response.

Although genetics is a strong determinant of risk, concordance for type 1 diabetes is only about 50% among identical twins.[4] The increasing incidence of type 1 diabetes, particularly among younger persons and persons not traditionally considered to be at the highest risk, fuels efforts to identify environmental autoimmune triggers. Leading most lists are diet and microorganisms (in particular, viruses). Indeed, diet and microbiota may be intimately intertwined. For instance, transmission of maternal antibodies to the newborn through breast-feeding has long been known to decrease the infant's susceptibility to certain infections, and early introduction of enteral feedings in premature infants is known to alter their susceptibility to disease.

In this issue of the *Journal*, Knip and colleagues report the results of a study[5] that may shed some light on dietary triggers and type 1