Autoimmunity Reviews xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Diagnosis and classification of immune-mediated thrombocytopenia

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ARTICLE INFO

Article history:
Accepted 13 November 2013
Available online xxxx

Keywords:
Immune thrombocytopenia
Idiopathic thrombocytopenic purpura
Immune thrombocytopenic purpura
Autoimmune thrombocytopenia
Eltrombopag
Romiplostim

ABSTRACT

Immune thrombocytopenia, or ITP, has been recognized as a clinical entity for centuries, and the importance of humoral mechanisms in the pathophysiology of ITP has been recognized for decades. Despite the long history of the syndrome, progress in understanding its epidemiology and management has been hindered by inconsistencies in nomenclature and classification schema together with the inherent heterogeneity in characteristics of global populations and ITP-associated disorders. In the past decade, great strides have been made in devising a common language for caregivers and investigators alike through standardization definitions and outcome measures, while new tools have become available for management of its clinical manifestations. In 2009, an International Working Group presented proposed standards for definitions, classification criteria, and outcome measures. The American Society of Hematology adopted these standards in 2011, including them in that body's guideline for immune thrombocytopenia. Despite the progress made so far, 20th century interventions such as corticosteroids and IVIg remain the mainstay of therapy. However, advances in treatment have led to the introduction of targeted therapies for select patients with chronic disease. In this paper, we review aspects of the epidemiology and pathophysiology of ITP and discuss the recent changes in guidelines for nomenclature, diagnosis, and treatment.

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Abbreviations: AIHA, autoimmune hemolytic anemia; ASH, American Society of Hematology; CLL, chronic lymphocytic leukemia; CMV, cytomegalovirus; CVID, common variable immunodeficiency; GPRD, General Practice Research Database; DIC, disseminated intravascular coagulation; HCV, hepatitis C virus; HELLP, hemolysis, elevated liver enzymes, low platelets; HIV, human immunodeficiency virus; HUS, hemolytic uremic syndrome; ITAM, immunoreceptor tyrosine activation motifs; ITIM, immunoreceptor tyrosine inhibitory motif; ITP, immune thrombocytopenia; IVIg, intravenous immunoglobulin; IWG, International Working Group; KIR, killer cell immunoglobulin receptor; NSAID, nonsteroidal anti-inflammatory drug; NK, natural killer; MMR, measles, mumps, and rubella vaccine; Parvo, parvovirus B19; RES, reticuloendothelial system; SR, sustained response; TPO, thrombopoietin; TTP, thrombotic thrombocytopenic purpura; VZV, varicella zoster virus.

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1568-9972/$ – see front matter. Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.autrev.2014.01.026

1. Introduction

Immune thrombocytopenia (ITP) has been recognized for centuries, although until recently nomenclature has been inconsistent [1]. ITP is often spoken of as a single disease state. In reality, it may be either an isolated phenomenon or a secondary complication of a wide range of primary diseases. In recent years, major strides have been made in diagnosis and treatment.

2. Definition

Immune thrombocytopenia has suffered from longstanding inconsistencies in nomenclature [2–5]. Unfortunately, the heterogeneity in classification of the disorder has created some obstacles to efforts to collate and synthesize historical data. In their review of literature published from 2000 to 2005, Ruggeri et al. demonstrated variability in the cutoffs for definitions of thrombocytopenia, criteria to start treatment, definitions of response, and definitions of refractory disease [6]. Nebulous definitions have historically affected even major guidelines; for example, the 1996 American Society of Hematology (ASH) guidelines defined ITP as "isolated thrombocytopenia with no clinically apparent associated conditions or other causes of thrombocytopenia…." and commented that "no specific criteria establish the diagnosis of ITP…" [7]. An evolution toward a more precise definition of ITP was evident in the later British Society of Haematology guidelines, which defined the syndrome as "an autoimmune disorder characterized by persistent thrombocytopenia (peripheral blood platelet count $<150 \times 10^9$/L) due to autoantibody binding to platelet antigens causing their premature destruction by the reticuloendothelial system (RES), and in particular the spleen"[8].

However, the platelet counts in various cohorts have been observed to vary widely, such that the recommended value for a "normal" peripheral blood platelet count of $<150 \times 10^9$/L has limited generalizability [9–12]. Furthermore, persons with incidentally discovered borderline thrombocytopenia may have a low incidence of progression to clinical disease. Stasi et al. followed patients with platelet values between 100×10^9/L and 150×10^9/L and found that only 6.9% of these patients developed more severe thrombocytopenia, and although 12% eventually developed some sort of autoimmune disease, the majority of the patients with borderline thrombocytopenia maintained stable numbers without developing evidence of associated disorders [13].

In 2009, an International Working Group (IWG) recommended standard terminology, definitions, and outcomes measures for ITP. The term "purpura" was removed, since many patients with immune thrombocytopenia do not develop cutaneous bleeding. Recognizing that the acronym "ITP" is entrenched in medicine, however, the IWG proposed redefining ITP as shorthand for immune thrombocytopenia.

The platelet count threshold for the definition of ITP was set at 100×10^9/L, a change from previous guidelines. The group recommended sub-classification of ITP as a primary vs. secondary disorder, identifying the associated disease in secondary types. For example, ITP associated with common variable immunodeficiency (CVID) is termed "secondary ITP (CVID-associated)". The classification scheme included further division by disease phase: "newly diagnosed" ITP (0–3 months), "persistent" ITP (3–12 months), and "chronic" ITP (>12 months). "Severe" disease is defined not by platelet count, but by bleeding severity. "Refractory" disease requires relapse after or failure to respond to splenectomy, in patients who also meet classification criteria for "severe" disease or have a sufficiently high risk for bleeding to require therapy [14].

The IWG classification was largely adopted by the American Society of Hematology (ASH) guidelines in 2011. However, the ASH guidelines acknowledge that the IWG standards were unvalidated and may be imperfect with respect to secondary ITP. These caveats notwithstanding, the IWG standards were considered a useful scaffold for a common language in immune thrombocytopenia [15].

3. Epidemiology

A recent comprehensive review commented that a summary estimate of the incidence of ITP using the historical literature may not be possible due to variation in methodologies and definitions [16]. However, the authors commented that the best range of estimates for the incidence of acute ITP in children was 1.9 to 6.4 per 10^5 children per year; chronic ITP in children was estimated at 0.5 per 10^5 children per year based on a single study. Similarly, the authors felt that the most robust estimate for the incidence of ITP in adults came from a single study, at 3.3 per 10^5 persons per year [16]. Reports of the effect of gender on the epidemiology of ITP have varied; a large retrospective study using the General Practice Research Database (GPRD) in the United Kingdom demonstrated a female predominance in ITP with an incidence of 4.4 per 10^5 person-years in women and 3.4 per 10^5 person-years in men, whereas a prospective study from a similar population showed similar incidence rates by sex [17,18]. In contrast, a retrospective study of pediatric ITP using the GPRD database demonstrated a male predominance before age 5, whereas a retrospective study of the prevalence of ITP in North America suggested a female predominance before age 70 that reversed after age 70 [19,20].

4. Humoral mechanisms

The Harrington–Hollingsworth experiment convincingly demonstrated causality of a humoral factor in idiopathic thrombocytopenic purpura [21,22]. The importance of antibodies in the disease pathogenesis is now universally understood. Commercial antiplatelet antibody assays are available, but unfortunately have shown little utility in the diagnosis of ITP [15]. The specificity of the autoantibody repertoire may be heterogeneous in ITP, and commonly, autoantibodies directed at multiple platelet antigens can be identified [23].

In some cases, the immunology of autoantibodies in ITP deviates from classical models of B cell activation in a manner analogous to bacterial superantigens. Co-stimulation of B cells by helper T cells is central to the generation of the humoral immune response, and ITP is no exception to this rule [24]. However, platelets in some patients appear to express enough CD154 to stimulate B cells directly, rendering the platelet:B cell interaction alone sufficient to generate a self-sustaining antiplatelet antibody response and circumventing T cell mediated checks on loss of tolerance [25].

In contrast to the observed poly-specificity of the autoantibodies in ITP, the B cell populations involved have exhibited a constrained set of heavy and light chain pairings [26]. The suggested implication is loss of tolerance in a single B cell, followed by the generation of diverse antiplatelet specificity through somatic mutation. Interestingly, Roark et al. comment that the VH3-30 heavy chain region overrepresented in ITP has also been associated with CVID, systemic lupus erythematosus (SLE), autoimmune hemolytic anemia (AIHA), human immunodeficiency virus (HIV), and chronic lymphocytic leukemia (CLL), all of which have themselves been associated with ITP [26].

Once bound to circulating platelets, antibodies can serve as opsonins and mediate phagocytic clearance via surface Fc receptors. The spleen is central to this process, and splenectomy is pivotal in the management of patients with chronic disease [15,24,27]. Troublingly, the liver can in some cases compensate for the sequestration capacity lost after splenectomy, resulting in refractory disease [27]. Moreover, in some patients, antiplatelet antibodies may selectively impair function and result in bleeding disproportionate to the platelet count [28].

As with antibodies, genetic factors in Fc receptors may be associated with differential treatment outcomes [29]. Modulation of Fc receptor activity may be a mechanism of IVIG, through both competitive inhibition for Fc receptor binding sites and activation of FcγRIIb [30]. In contrast to the immunoreceptor tyrosine activation motifs (ITAMs) associated with the cytosolic domain of most other Fc receptor types, FcγRIIb is associated with a cytosolic immunoreceptor tyrosine inhibitory

Please cite this article as: Lo E, Deane S, Diagnosis and classification of immune-mediated thrombocytopenia, Autoimmun Rev (2014), http://dx.doi.org/10.1016/j.autrev.2014.01.026