

Immunopathogenesis, Immunomodulation and Management of Immune Thrombocytopenic Purpura in Children

a report by
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The bleeding disorder immune thrombocytopenic purpura (ITP) is a model for immunological research and new biological treatment modalities of chronic inflammatory and autoimmune disorders. In ITP, immunologically susceptible subjects are recognisable by disturbances of the immune response on various levels. Children have mostly a transient or persistent form (below 12 months' duration) and rarely have a chronic form of ITP. Children without bleedings may be observed without treatment or may need treatment according to a staging and management schedule (see *Table 1*).

Therapeutically, the immune cascade can be modulated on various levels by human immunoglobulins (Igs), anti-D Igs, corticosteroids, T-cell suppression, monoclonal anti-CD 20 or 52 antibodies or others. Agonists stimulating growth of thrombopoietin-dependent cell lines that increase platelet counts might soon be available, mainly for patients with severe persistent, refractory or chronic ITP. This article highlights and updates immunopathological findings and proposes a management procedure for children with short-term or refractory ITP.

Definition and Incidence

ITP is a bleeding disorder characterised by platelet destruction due to (auto-)antibody binding resulting in early platelet phagocytosis. ITP occurs in primary and secondary forms. The primary form is an isolated thrombocytopenia in an otherwise healthy individual. The secondary form includes all other ITP (e.g. lupus-, HIV- and drug-related ITP).

The severity of ITP depends on bleeding symptoms. In children, ITP is mostly a para- or a post-infectious transient event. A minority of children have a persistent or chronic form of ITP similar to the majority of adolescents and adults. An international expert group conducted by Francesco Rodeghiero and with the backing of the European Hematology Association (EHA) is working on recommendations and terminology.

The incidence in children with newly diagnosed ITP is estimated to be 5.3–5.7 patients per 100,000 children per year.^{1,2} At diagnosis, 55% of boys and 45% of girls were registered prospectively; in infancy the number of boys was dramatically higher.³ Incidence, duration and severity vary from continent to continent. A comparison between Vietnamese and European children with chronic ITP showed marked differences.⁴

Pathophysiology of Immune Thrombocytopenic Purpura

In patients with ITP the maintenance of self-tolerance and the effective immune response seems to be altered in the presence of an inflammatory or autoimmune process. In ITP, circulating antibodies and/or immunocomplexes adsorb to the platelet specifically via the fragment antigen binding (Fab) region of the antibody to glycoprotein-epitopes on platelets or unspecifically via the Fc part of

the IgG molecules, resulting in early opsonophagocytosis and destruction by macrophages.⁵ The quantity of early platelet destruction and platelet production correlate with the degree of thrombocytopenia and bleeding.

In ITP and many other inflammatory and autoimmune disorders, multiple possibilities of disturbances on the different levels of the immune cascade are documented, especially in connection with intravenous Ig (IVIg) treatment:^{6,7,8,9} on the level of antigen presentation, T-cell activation and signalling, B-cell regulation and antibodies/idiotypic antibodies production, activation/suppression of complement, opsonophagocytosis and apoptosis (see *Table 2*). These recognised alterations were used to develop new treatment modalities for many autoimmune disorders. A recent observation of ITP triggered by *Helicobacter pylori* illustrates the complexity of the immune response in susceptible patients, the host response and the country differences.^{10,11} The aetiology of ITP is still unknown, and why some children are susceptible and others not may be a question of molecular genetic alterations. First analyses support molecular genetic abnormalities of the immune response in ITP.^{12–14}

Significance of Immunological Aspects and of Growth Factors in Immune Thrombocytopenic Purpura

Three main developments made ITP a model of pathophysiology and treatment in inflammatory and autoimmune disorders within the last 60 years. In 1950, the causative platelet destructive factor was found by transfusion of blood/plasma from patients with chronic ITP to volunteers with normal platelet counts. The recipients developed transient thrombocytopenia.^{15,16} Later on, the causative factor was characterised as antibodies against epitopes, often against antigenic platelet glycoproteins. In 1980, a boy with long-term, severe ITP bleeding and secondary, iatrogenic hypogammaglobulinaemia due to immunosuppressive treatment showed a dramatic platelet increase after the substitution of antibody concentrate from healthy blood donors, the new IVIG. This was also the case in 12 consecutively IVIG treated normogammaglobulinaemic children with ITP.¹⁷ This observation was confirmed by a controlled multicentre study.¹⁸ This



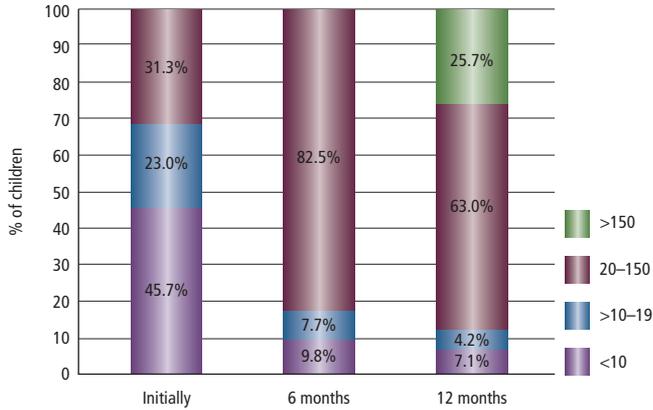
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Table 1: Staging and Management of Patients with Immune Thrombocytopenic Purpura

| Stages/Bleeding | Platelet (x10 ⁹ /l) | Management |
|---|--------------------------------|--|
| 1. Minor/mild bleeding, normal lifestyle | >10–20 | Consent for observation |
| 2. Moderate bleeding, troublesome lifestyle | <10–20 | Punctual intervention to reach stage 1 |
| 3. Severe, life-threatening bleeding | Mostly <10 | Intervention |

Figure 1: ICIS Registry 1 – Follow-up of 308/2,031 Children with Ongoing Immune Thrombocytopenic Purpura Six to 12 Months After Diagnosis – Platelet Count (x10⁹/l)



Source: *Pediatr Blood Cancer, 2006;46:351.*

was the first targeted immunomodulation, which today is used in a broad field of chronic inflammatory and autoimmune diseases.^{6–9} In 1980, 300kg of IVIG was produced worldwide, which increased to over 60 tons until 2007 (personal communication by CSL Behring).

In 1994, thrombopoietic growth factor has been developed and its administration increased platelet counts in volunteers.¹⁹ This first generation of thrombopoietic growth factor as recombinant human thrombopoietin (rhTPO) and as pegylated human recombinant megakaryocyte growth and development factor PEG rHu MGDF had to be stopped in clinical trials when autoantibodies against the administered factor (PEG rHu MGDF) were detected in healthy human subjects. A second generation of thrombopoietin-receptor agonists (AMG 531 for subcutaneous use, eltrombopag and AKR 501 for oral use and others) stimulate growth of thrombopoietin-dependent cell lines and increase platelet counts. Within the last five years these second-generation thrombopoietic factors have demonstrated safety, tolerability and efficacy in patients with ITP.¹⁹ Further studies (long-term application, activation of platelet function etc.) have to be concluded before approval for clinical use of these agent will be released.

Although the serum level of thrombopoietin of patients with ITP is normal or slightly increased, recent *in vitro* studies showed reduced megakaryocyte production and impaired maturation in the presence of ITP plasma-containing autoantibodies against platelets²⁰ – apparently a reason for efficacy in patients with ITP.

Clinical Manifestation of Immune Thrombocytopenic Purpura

The clinical manifestation, severity of bleeding and platelet count and the natural history of ITP are heterogenous. Child patients and their parents are

Table 2: Summary of Immunomodulation

| Immunomodulation | Examples | References |
|------------------------------------|---------------------------------------|------------------------|
| Antigen suppression | Fcr on Antibiotics, virostatics, IVIG | 11, 56, 57, 58, |
| dendritic cells activation | | 59, 60, 61, 62 |
| Toll like receptor | | |
| Inhibition of T cells | Cyclosporin A, tacrolimus, IVIG | 63, 64, 65, 66, 67, 68 |
| Regulation of autoreactive B cells | Anti-CD20/-CD52 | 42, 44, 45, 69, |
| and anti-idiotypic network | Antiidiotypic antibodies, IVIG | 70, 71, 72, 73 |
| Modulation of: | Anti-D IgG, IVIG | 9, 34, 74, 75, |
| • phagocytosis | | 76, 77, 78 |
| • complement | | |
| • apoptosis | | |

Figure 2: Cascade of Immune Response

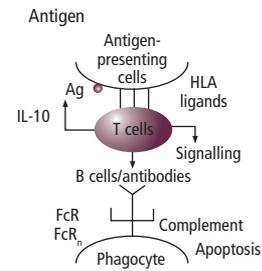


Table 3: Routine Testing in Addition to Initial Laboratory Analysis in Children with Persistent Immune Thrombocytopenic Purpura of Three to Six Months' Duration

| |
|--|
| Bone marrow analysis, endocrine function, urine analysis, abdominal ultrasound |
| Antinuclear antibody, direct antiglobin, lupus anticoagulant, platelet antigen-specific antibodies, serum immunoglobulins with IgG subclasses, platelet function test, coagulation studies |
| Viral serology (HIV, CMV, EBV, VZV, rubeola, parvovirus B19 and others) |

fearful of bleeding and tyrannised by low platelet counts. The outcome of the individual patient cannot be predicted, although most children and some adults show spontaneous resolution or improvement of ITP.

In two prospective Intercontinental Childhood ITP (ICIS) registries with newly diagnosed children (n=2,031 and 1,015, respectively) two-thirds of patients initially had platelet counts below 20x10⁹/l.² In Registry II 20 of 629 patients (3.2%) had severe bleeding, 150 (23.6%) showed moderate bleeding and 459 (73%) showed mild or no bleeding initially.²¹ This is in accordance with the British assessment²² and a single-centre analysis in the US.²³ Intracranial bleeding occurs in about 1:500–700 children, and is fatal in one-third.²⁴ The initial management (mean platelet counts) in ICIS registry I was as follows: about one-third of children received IVIG (8.1x10⁹/l) and one-third corticosteroids (13.3x10⁹/l), and the remaining one-third were observed (28.6x10⁹/l).² In children with persistent ITP of three to six months in duration, additional laboratory tests are recommended (see *Table 1*).

Unlike ITP in adults, persistent thrombocytopenia is observed in 20–30% of children and the rate of severe ITP is decreasing with duration of ITP (see *Figure 1*). In the above-mentioned registry I, follow-up data 12 months after diagnosis was evaluable for 308 children with persistent ITP at six months.²⁵ Between six and 12 months from diagnosis, 79 of the 308 children (25.6%) recovered with platelet counts above 150x10⁹/l, while 229 (74.4%) still had persistent ITP. The distribution of platelet counts at diagnosis at six and 12 months showed that the number of children with platelet counts below 10 and 20x10⁹/l markedly decreased within the first 12 months of diagnosis.

Thus, a reduction of severity of ITP over time was observed. In retrospective analyses, even after one year children recovered from their ITP.^{26–29} These observations raise the question whether the term ‘chronic’ ITP – now defined as persisting for six months after diagnosis – should be postponed to 12 months or longer. On the other hand, at 12 months after diagnosis in registry I, 11.3% of children still had platelet counts below $20 \times 10^9/l$ despite treatment. These children have refractory ITP.

Management

Since 1980, the therapeutic intervention of ITP has been challenged by the rapid effect of IVIG administration (see above). Today therapeutic approaches are targeted to the disturbed immune response (see *Table 1*): antigens are eliminated by antibiotics or antiviral drugs; lymphocyte functions are downmodulated by cyclosporine A or tacrolimus; B cells and antibody generation are modified by monoclonal antibodies (e.g. anti-CD-20, anti-CD 52); phagocytosis is competitively decreased by anti-D Igs; and IVIG alters the immune response on various levels (see *Table 2* and *Figure 2*).

While the infusion of IVIG or anti-D have rapid immunomodulatory effects (platelet increase within one to three days), the platelet stimulatory effect occurs five to 14 days after starting thrombopoietin agonist. In the near future, the stimulation of thrombopoiesis will eventually be an additional approach. For practical patient care a simple categorisation of the clinical severity of ITP is necessary and should be validated. A proposal is ‘staging and management’ based on bleedings²² and quality of life³⁰ rather than on platelet counts (see *Table 1*). In stages 2 and 3, consensus between the individual patients and physicians should be reached. For interventional management the following procedures may be used.³¹ Standard treatment includes:³²

- IVIG 0.4–0.8g/kg bodyweight (bw) once;
- anti-D Ig 50–75µg/kg bw once;^{33,34}
- corticosteroids 4mg/kg bw daily for two to four days, then tapering for three days; and
- (thrombopoietin-receptor agonist):^{35–40} available in the US.

Where emergency treatment is needed in cases of severe life-threatening bleeding, treatment should:

- begin with corticosteroids 30mg/kg bw or dexamethason 1–2mg/kg bw;⁴¹
- progress to IVIG 0.8–1.0g/kg bw per dose; and⁴¹
- include a platelet transfusion after the above measures.

In cases of refractory ITP, treatment should include:

- (thrombopoietin agonist):^{35–40} available in the US;
- anti-CD 20-, anti-CD 52-monoclonal antibody for the suppression of B-cells;^{42–45}
- cyclosporine A 2–5mg/kg bw per day tacrolimus for the suppression of T-cells;
- vincristin IV 1.5mg (2mg maximum)/m² four to six times weekly plus 2mg corticosteroid/kg/bw/day three times per week;
- interferon, mycophenolate mofetil,⁴⁶ high-dose corticosteroids or dexamethasone should also be considered;⁴⁷
- splenectomy; and⁴⁸
- classic options (individual indications) such as azathioprine and cyclophosphamide.

Clinical Research

There is a considerable amount of convincing evidence-based data available on incidence, demographics, natural history and managements of ITP. Retrospective case series, surveys,^{49,50} guidelines,^{51,52} assessment and²² reports from expert meetings^{53,54} are the sources of information for patient management. As a result of the heterogeneity of ITP and various controversies, current practice does not always follow the recommendations. Prospective evidence-based studies are needed.

Since 1997, the ICIS group has established an international network of physicians and scientists collaborating in prospective databases and studies (see www.unibas.ch/itpbasel) that will define less heterogeneous patient subgroups for controlled treatment/management efficacy trials. The first results are promising.^{2,3,25,55} The ongoing Paediatric and Adult Registry of Chronic (PARC) ITP database has the objective of defining subgroups within ITP on the basis of natural history, genetics, demographics, quality of life and other criteria.

One of the studies will focus on genetic differences. In these studies, polymorphisms and variations of genes^{12–14} in patients with ITP that may be involved in the loss of tolerance and unbalanced immune responses have shown variants in interleukin (IL)-1 haplotypes and an association with autoimmune disease. ■

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