# Diagnosis and management of chronic ITP: comments from an ICIS expert group

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Ann Hematol (2010) 89 (Suppl 1):S11–S17
DOI 10.1007/s00277-010-0950-0

REVIEW ARTICLE

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Received: 10 March 2010 / Accepted: 22 March 2010 / Published online: 7 May 2010


**Abstract** Immune thrombocytopenia (ITP) is a common disorder in children and adults. In a patient with newly diagnosed ITP, the treatment strategy is relatively well defined. Second-line treatments are more controversial, and the management of chronic ITP is even more so. During the 3rd ICIS Expert Meeting on Consensus and Development of Strategies in ITP, held in Basel on September 3–5, 2009, a group of experts were tasked with reaching a consensus on some *frequently asked questions* relating to diagnosis and management of children and adults with chronic ITP. The content of this article is designed to provide a practical support to trained haematologists in their care of patients with chronic ITP.

**Keywords** Immune thrombocytopenia · ITP

## Introduction

Immune thrombocytopenia (ITP) is a common disorder in children and adults. In a patient with newly diagnosed ITP, the options and approaches to management are relatively well defined. Second-line treatments are more controversial, and management of chronic ITP (now defined as duration of more than 12 months) is even more so [1]. During the 3rd ICIS Expert Meeting on Consensus and Development of Strategies in ITP, held in Basel on September 3–5, 2009, a group of experts (see 'Acknowledgements') were tasked with reaching a consensus on some *frequently asked questions* relating to diagnosis and management of children and adults with chronic ITP. This article is designed to provide a practical support to trained haematologists in their care of patients with chronic ITP.

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## What is the role of the bone marrow examination in chronic ITP?

In patients with chronic ITP, bone marrow examination is usually unnecessary because of the past history including response to treatment if administered. However, refractoriness or poor response to first-line ITP therapy should always provoke review of the diagnosis, and therefore, bone marrow examination is highly recommended. In these situations, a bone marrow biopsy and cytogenetics should be routinely included with the smear in order to identify marrow failure syndromes or myelodysplasia [2, 3].

Bone marrow investigations in chronic ITP patients are also recommended when the clinical or haematological pattern of the disease changes: for instance, the development of major bleeding in a patient with formerly mild 'ITP', occurrence of constitutional symptoms and appearance of unexplained anaemia, macrocytosis, neutropenia and/or dysplastic changes in the peripheral blood.

The side effects of thrombopoietin (TPO) mimetics include development of marrow reticulin fibrosis. Considering the restricted knowledge on long-term risk, a routine bone marrow biopsy before (if not recently obtained) and during therapy as surveillance is recommended [4–6].

## Should we look for anti-platelet antibodies and how should we interpret them if obtained?

Increased levels of platelet-associated antibodies can be detected in most patients with ITP, but the results are neither sufficiently sensitive nor specific to justify use of these assays in patients with suspected ITP. The absence of anti-platelet antibodies does not eliminate the diagnosis and their presence does not affirm it.

The monoclonal antibody-specific immobilisation of platelet antigens assay [7] and the modified antigen capture enzyme-linked immunosorbent assay test [8] are able to detect antibodies against specific glycoproteins such as GPIIbIIIa and GPIbIX. These tests offer improved specificity but are less sensitive. Although they may possibly be useful in distinguishing between immune and non-immune thrombocytopenia in complex cases, their routine use in the diagnosis of ITP is not justified.

There is little published information regarding the impact of platelet auto-antibodies on the course of the disease or response to treatments. It has been suggested that chronic ITP accompanied by the presence of platelet antibodies could be more severe with higher risk of recurrence of the thrombocytopenia and more severe symptoms and bleeding. It has also been reported that the response to steroids could be better when platelet antibodies are present. However, conflicting results have been reported [9]. Finally, antibodies predominantly directed against GPIIbIIIa are speculated to portend good response to intravenous immunoglobulin (IVIg) and poor response to GPIbIX. Overall reliable conclusions as to the diagnostic or prognostic usefulness of measurement of auto-antibodies in chronic ITP are not possible at this time.

## Is it relevant to distinguish primary from secondary forms of chronic ITP?

Twenty percent of adults with chronic ITP are estimated to have it secondary to another underlying disorder [10]. The approach to secondary ITP differs in a number of cases.

All adult patients with ITP should be screened for HIV and hepatitis C. In HIV, the incidence of thrombocytopenia increases with progressive immunosuppression. Effective antiretroviral therapy (HAART) improves platelet counts in the great majority of patients [11]. If counts do not increase with HAART, patients can be treated for short periods with corticosteroids but long-term use of steroids should be avoided because of the risk of secondary infections. IVIg, anti-D and splenectomy are safe and effective in refractory patients; anti-D is superior to IVIg in this patient group [12]. Rituximab carries the risk of progressive multifocal leucoencephalopathy and infectious complications [13]. TPO-R agonists have not yet been tried.

In hepatitis C patients, a platelet response to antiviral therapy is observed in approximately 50%, but initially, interferon treatment may create/worsen thrombocytopenia. Corticosteroids can be used if needed for short periods, but close monitoring of viral load and liver function is essential. IVIg and splenectomy may be effective. Possible co-infection with hepatitis B requires investigation and monitoring during therapy.

Up to 5–10% of chronic lymphocytic leukaemia or lymphoma (Hodgkin and non-Hodgkin) patients develop ITP. Occurrence and severity of ITP is not related to lymphoma stage. Therefore, treatment should primarily be directed to immune thrombocytopenia although with lymphoma, treatment of the lymphoma may often improve the ITP. Steroids and IVIg are preferred but thrombocytopenia usually recurs. Rituximab is also effective. Fludarabine and other purine analogues should be avoided. Consider splenectomy in refractory cases.

Autoimmune lymphoproliferative syndrome is an inherited disorder and usually seen in children. Genetic defects lead to impaired lymphocyte apoptosis, lymphoproliferation, immune cytopenia and malignancy. Thrombocytopenia is often persistent, and rituximab (which carries a special risk of hypogammaglobulinaemia) and mycophenalate mofetil appear to be effective.

Common variable immunodeficiency (CVID) patients develop ITP in 10% of cases. Their ITP respond to steroids

but prolonged treatment may cause infections. The same applies to splenectomy although 4-weekly IVIg may lessen this risk. Most patients need to receive IVIg, but if this is insufficient, consider addition of rituximab.

ITP and autoimmune haemolytic anaemia (Evans syndrome) may develop spontaneously or secondary to SLE, CLL, lymphoma, CVID or other immunodeficiency and following stem cell or solid organ transplantation. Ideally, a direct antiglobulin test and especially reticulocyte count should be part of every ITP work-up. Steroids and IVIg are the usual first-line therapy of the ITP; anti-D is contraindicated. Rituximab, cyclosporine, mycophenolate mofetil, splenectomy (not recommended in children) and combination chemotherapy have been used in second-line treatment [14].

Severe thrombocytopenia during periods of exacerbation of autoimmune disorders requires control of the underlying disease. In patients with no disease activity, treatment is similar to primary ITP.

Up to 10% of patients with ITP test positive for antiphospholipid antibodies and/or lupus anticoagulant. This does not change management of thrombocytopenia as long as these patients do not develop thrombosis [15]. Because of the risk of thrombosis associated with antiphospholipid antibodies/lupus anticoagulant, monitor patients closely for symptoms of thromboembolism when platelet counts rise during treatment and consider prophylaxis e.g. aspirin. Raise platelets only to levels, sufficient to prevent bleeding, not to the normal range.

## Can we define a profile of patients with chronic ITP with a lower risk of bleeding complications?

ITP is a relatively benign disorder, and theoretically, many of the chronic ITP patients rarely require treatment. In clinical practice, certain patients may be over treated because the treatment decisions are based primarily on low platelet counts, independent of clinical manifestations. To predict the risk of bleeding in patients with chronic ITP, the recognition of an individualised adequate platelet levels can be helpful.

The course of ITP may be more serious in adults than in children. Major bleeding, including spontaneous intracerebral haemorrhage, occurs predominantly in patients with platelet counts $<20\times10^9$/L, generally $<10\times10^9$/L [16, 17]. Haemorrhagic complications may be more common in patients older than 60 years of age and those with co-morbidities. A number of bleeding assessment tools have been developed for adult ITP patients [18, 19].

To define a low-risk patient, any physical activity in professional and social life that may be linked to an increased risk of traumatic injury should be taken into account. Cardiovascular aerobic exercises (fast walking, jogging, or swimming) or muscle strengthening has a lower risk for bleeding. Therefore, ITP patients can and should be encouraged to participate in this type of exercise. The practice of an activity with higher risk of trauma, such as contact sports, should not be considered low risk. In patients with unexpected bleeding, additional laboratory tests should be performed to identify platelet dysfunction [20] or an additional haemostatic abnormality e.g. underlying von Willebrand disease [21, 22].

In conclusion, in chronic ITP, a low-risk profile for bleeding could be defined as: patients younger than 40 years, without co-morbidities, absence of any major bleedings during the course of ITP, no increased risk of injury in professional or social activity, previous brisk response to therapy and no requirement of anticoagulation or anti-aggregation therapy. In these cases, even when platelet counts are lower than $30\times10^9$/L, a 'watch and wait' strategy is a reasonable option.

## What to consider for decision making in treatment of childhood chronic ITP

The approach to chronic ITP in children is not well defined mainly because of the low incidence of chronic ITP in children. This section will provide pros and cons of newer treatments and includes a consideration of splenectomy (Table 1).

Despite the long experience of splenectomy for ITP, studies specific to children are limited. One large review of cases primarily in adults identified thousands of cases, but the children are generally not distinguished and the long-term effects, beyond sepsis, are not well delineated in any population [23]. Conversely, there are relatively few late relapses of splenectomy in children reported, but again there are little data.

Studies of patients with hereditary spherocytosis and splenectomy have raised concern that pulmonary hypertension may develop, and there is recognition of a long-lasting increased risk of arterial and venous thromboembolism [24].

Rituximab has been infused in approximately one million people including over 500 adults and 100 children with ITP. The obvious advantage of rituximab therapy is that it may provide a long-term 'remission', but the exact length of this remission and the frequency of it remain poorly defined. Serum sickness may be more common, 5–10%, in paediatric ITP [25]. Infections, including progressive multifocal leucoencephalopathy (PML), occurring after rituximab in children have not been reported [26] nor has there been hepatitis B activation in children with chronic ITP. Limited studies have suggested that upon their return, B-cell subpopulations may be changed by rituximab.

**Table 1** Recognised treatment options for chronic ITP

| | Pros | Cons |
|---|---|---|
| Watch and wait | Spontaneous remissions or 'cure' in up to 10% of children per year | May lead to restricted HRQoL |
| | The majority of children and adults remain free of severe bleeding | Ongoing risk of severe or life-threatening haemorrhage |
| | Inexpensive | Adverse effects of drugs used for break-through bleeds |
| Splenectomy | 'Cure' in 2/3–3/4 of patients | 'Only' works in 2/3–3/4 of patients |
| | Side effects of procedure low | Risk that accessory splenectomy may be needed |
| | Apparent low rate of late complications of splenectomy especially following laparoscopic procedure | Undetermined optimal means of prophylaxis against sepsis |
| | Low rate of post-splenectomy sepsis | High cost |
| | | Risk of peri-operative bleeding |
| | | Potential removal of healing monocytes stored in spleen |
| | | Anti-D ineffective after splenectomy |
| | | Irreversible |
| | | Potential long-term adverse outcomes: pulmonary hypertension, thrombotic events, sepsis and effects on immunity beyond decreasing filtration of organisms in blood |
| Rituximab | Effective in at least 33% of cases with normalisation of platelet count lasting at least 6–12 months | Long-term toxicity not well defined in any population and especially not in paediatrics |
| | Tolerable in that no overt major toxicity of infusions with slow initial rate and premedication | Risk of long-lasting immunosuppression, development of PML and of activation of hepatitis B |
| | Dosing weekly for 4 weeks and then finished | High cost |
| | Effective both pre- and post-splenectomy | Rate of durable responses to rituximab does not exceed 40% |
| | Ability to retreat responders who relapse | No recognised predictive factor for response to rituximab |
| | No blocking effects on other ITP treatments | Serum sickness in an unclear percent of patients |
| | | No randomised trials and unlicensed for ITP |
| TPO-mimetic agents | Multiple placebo-controlled trials | Non-curative treatment |
| | Greater percentage of response than other second-line treatments | Rebound of thrombocytopenia after cessation |
| | Effective both pre- and post-splenectomy | Long-term safety unknown including issues of marrow fibrosis |
| | Response almost always maintained while the drugs continue to be administered | High cost |
| | Evidence of improved quality of life | Potential for thrombosis |
| | Well tolerated | Potential rarely for malignancy |
| | Licensed for treatment of adults refractory to splenectomy (in the USA, Europe and Australia) | Concern regarding liver toxicity with one agent |

There are two ongoing TPO-R agonist studies which include children. Efficacy and dosing in the children may not be very different from that of adults. Safety assessment is precluded by the small numbers of children treated although no drug-related serious adverse events have been seen. In adults, the rate of efficacy with these agents is 70% or higher [27, 28]. Toxicity issues include thrombosis and fibrotic changes in the marrow which remains of undetermined significance [29]. A separate issue that remains to be defined is that once these agents are started, how long should treatment be continued and how should they be stopped?

With any therapy of chronic ITP, considerations of toxicity need to be weighed against perpetual low platelet counts in children. The 'watch and wait' approach for acute childhood ITP is based on the likelihood that children have a lower risk of severe bleeding and are likely to improve with time. However, children with chronic ITP have a far lower likelihood of immediate spontaneous improvement than adult patients. Restrictions in activity, concern of bleeding and diminished health-related quality of life become important and need to be factored into management decisions.

## When should we use supportive therapy in chronic ITP?

Supportive therapy in ITP is an essential adjunct to therapy that increases the platelet count, whether in the setting of episodic severe bleeding or in mild persistent bleeding. It

may be sufficient to promote haemostasis without additional systemic therapy or lessen the degree of systemic therapy required. The use of antifibrinolytic agents is established in dental treatment and mucosal bleeding [30]. Antifibrinolytic drugs should be avoided in treating massive urogenital haemorrhages because of possible obstructive clot formation in the urinary tract but may be particularly effective in minor urinary bleeding by neutralising urokinase.

Some patients may also benefit from desmopressin which has been shown to promote haemostasis in congenital or acquired platelet disorders [31]. The administration of desmopressin by intranasal spray has been shown to be effective in women with menorrhagia and platelet dysfunction disorders. Secondary iron deficiency is not unusual in patients with ITP and may contribute to further bleeding. Correction of co-existent iron deficiency is therefore recommended [32].

Recurrent epistaxis and gingival bleeding are some of the most common symptoms of patients with ITP. Many of these bleeding episodes can be treated conservatively using local application of adrenaline-soaked nosepads, collagen-coated fleece and fibrin sealant. Nasal cautery may prove useful if an active bleeding vessel can be identified; however, the use of recurrent nasal cautery can promote mucosal damage and stimulate further bleeding.

Menorrhagia can be a major problem in female patients with chronic ITP. Progesterone-containing intrauterine contraceptive device and oral contraceptives can decrease the frequency and amount of menstrual bleeding [33]. Since progesterone can increase the platelet count in ITP, it is appropriate to use it orally or intramuscularly to control vaginal bleeding.

## How to handle anticoagulation and/or anti-aggregation in patients with chronic ITP?

There are an increasing number of chronic ITP patients who require anticoagulation for cardiovascular co-morbidities. In ITP, thrombocytopenia of any degree does not appear to protect against thromboembolic events. At the same time, anticoagulant therapy may cause severe bleeding. Except for a small number of case reports [34–36], there are minimal data to guide therapy in ITP patients who need anticoagulation.

For each individual patient, the risk of thromboembolic complications, e.g. stent thrombosis and stroke from atrial fibrillation, has to be weighed against the risk of bleeding based upon prior bleeding history, severity of thromboembolic risk, co-morbidities, age and access to emergency medical treatment.

In patients with ITP and coronary artery disease, the risk of myocardial infarction usually outweighs the risk of mild bleeding. Aspirin and thienopyridines (clopidogrel, prasugrel, etc.) should be given as in non-thrombocytopenic patients if the platelet count is above $30\times10^9$/L. If severe bleeding develops, anticoagulant treatment has to be held or reduced. During the initial treatment period, the patient needs close monitoring. Coated coronary stents should not be used because they require more intensive anticoagulation.

In patients with ITP and atrial fibrillation, initial anticoagulation with low-molecular-weight heparins (LMWH) is preferred and subsequent continuation of anticoagulation only if no bleeding develops. Initial target international normalised ratio (INR) should be in the lower range (e.g. 1.5–2) and increased to the regular level (INR 2–2.5) only if this has been shown to be safe. Warfarin should be preferred to phenprocoumon because of the shorter half life.

*Thromboprophylaxis in ITP patients with high-risk surgery (e.g. orthopaedic or cancer surgery)* In these patients, platelet counts are usually raised to sufficient levels before intervention. As long as platelet counts stay above $30\times10^9$/L, administer prophylactic dose LMWH as usual. If platelet counts drop below $30\times10^9$/L, one may consider early mobilisation, compression stockings or pneumatic devices, or increasing the platelet count.

*Treatment of thrombosis in ITP patients* With low platelet counts and thrombosis, start continuous unfractionated heparin (UFH) at half-therapeutic dose while increasing the platelet count. UFH has a short half life, and in the case of bleeding, the anticoagulant effect disappears quickly. If the patient tolerates half-therapeutic UFH for a few days, increase to therapeutic levels and later switch to LMWH or warfarin. With counts $>30\times10^9$/L, start with half-therapeutic dose LMWH, $>50\times10^9$/L with full dose LMWH. Consider giving LMWH for the duration instead of switching to vitamin K antagonists. There are no experiences with the new oral inhibitors (dabigatran, rivaroxaban) for prophylaxis or treatment of thromboembolism in ITP patients.

## Summary

In summary, many of the questions raised above have at best partial answers derived from data and the answers are based on “expert opinion”. Several of these questions would make good starting points for the design of ITP studies in the future.

**Acknowledgements** We would like to thank all participants in the chronic ITP expert group who participated in the discussion at ICIS, namely: Bessho, Fumio—Moroyama, Japan; Diesch, Tamara—Basel, Switzerland; Erduran, Erol—Trabzon, Turkey; Fouda, Ashraf—Al-Mansoura, Egypt; Hainmann, Ina—Freiburg, Germany; Kaplinsky, Chaim—Tel Hashomer, Israel; Konja, Josip—Zagreb, Croatia; Kreuzbauer, Georg—Zug, Switzerland; Kroiss, Sabine—Zürich, Switzerland; Strauss, Gabriele—Berlin, Germany; Tamminga, Rienk—Groningen, Germany; and Veronese, Luisa—London, UK.

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