# Traditional and New Approaches to the Management of Immune Thrombocytopenia: Issues of When and Who to Treat

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**KEYWORDS**

• ITP • Platelets • Autoimmunity • Bleeding • Thrombocytopenia

Chronic ITP is currently defined as immune thrombocytopenia (ITP) that has a minimum duration of 12 months, and often longer.[1] ITP, its diagnosis, and definition have been covered in other chapters in this issue and therefore general issues connected with ITP will not be discussed further here except where specific features are particularly relevant to the management of chronic ITP.

In the United States, in addition to steroids, either prednisone and/or dexamethasone, many patients with newly chronic ITP will already have received intravenous immunoglobulin (IVIG) or intravenous (IV) anti-D and rituximab as well before they have reached 12 months from diagnosis. Both high-dose dexamethasone (40 mg/m$^2$ $\times$ 4 days for 3 to 4 cycles 2 weeks apart), especially if used close to the time of diagnosis of ITP,[2,3] and rituximab may have curative-type effects with patients achieving stable normal platelet counts for at least 1 year or longer after treatment, if not indefinitely.[4] It would appear from several studies, including not only those with dexamethasone, but also with IV anti-D,[5,6] that at least 50% of patients improve within 1 to 2 years of diagnosis and no longer require platelet supportive therapy after

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that time. How much of this effect is the result of a specific treatment or a spontaneous remission in which a particular therapy ''buys time'' by maintaining a safe platelet count until spontaneous improvement takes place is uncertain. This distinction is complicated by the fact that many patients receive treatments with agents such as prednisone, IVIG, and IV anti-D that are not expected to have lasting effects, but may be used to maintain a safe platelet count. It is uncertain if there are many patients in whom repeated application of therapy such as anti-D or IVIG conveys a lasting benefit.[5,7,8]

Management of chronic ITP is different from that of acute ITP (**Fig. 1**). For acute ITP patients, treatment is initially aimed at rapidly increasing the platelet count and then at maintaining an adequate, safe count while hoping that, whatever therapy is administered, patients will improve and no longer require any treatment. For chronic ITP, the goals and needs are different. On the one hand there may still be further improvement so that short-term therapies may nonetheless be important. On the other hand, improvement and especially attaining remission becomes much less likely after more than 1 year from diagnosis and therefore short-term improvement in the platelet count is not a viable strategy on its own. However, short-term therapies may avoid severe thrombocytopenia while awaiting the response to a ''long-term therapy.'' Also, smaller changes in the count become more significant. A change in the platelet count from 5000 to 10,000/μL to 20,000 to 25,000/μL would likely provide an important impact on the risk and occurrence of bleeding.

Children with chronic ITP are different from adults with chronic ITP in several ''less-well-defined ways.'' There is an anticipation that they will be easier to manage. In fact, children with persistent severe chronic ITP past 1 year may be more difficult to manage than adults and often have subtle underlying immunologic problems. The approach to their care is discussed in the article by Drs Bennett and Tarantino and in the article by Kalpatthi and Bussel 2008.[9] The remainder of this text pertains to adults.

What are the advantages of doing no treatment at all (observation with ''emergency'' or ''rescue'' platelet support eg, steroid bolus, IVIG, or IV anti-D or even platelet transfusion) for a patient who has had ITP for more than 1 year without signs of improvement? The obvious advantage is that there is no toxicity of therapy. Virtually all treatments cause some problems. A subtler advantage, but one that is important to patients, is that they no longer have to make frequent appointments with their hematologists, ''face up to their condition,'' and continually decide on the best course of action. Instead typically they come in for follow-up when they feel like it, do not spend ''time worrying about their disease'' or its treatment, and generally act as if they had been ''cured.'' This frees up time, reduces medical bills, and may also relieve patient anxiety. Much of this depends on the patient however. If they have bruising or especially mouth sores and heavy menses, it may prove impossible to ''ignore'' their ITP and, even if this approach is tried, the patient may return to the hematologist for management. More serious bleeding may occur in the context of other illness or trauma; a very low platelet count may prevent use of medications to treat other conditions. For these reasons, periodic visits are optimal to maintain a dialog and to further develop the patient-physician relationship and prevent denial, which may have serious consequences.

There are no data on this particular point but one would expect that this would be a time when patients would be most likely to try alternative therapies. Many, possibly most, patients believe that if a substance is ''natural'' that guarantees that there will be no toxicity and therefore trying anything natural is good, even if realistic expectations of benefit may be very small. This has clearly been proven wrong on a number of

Diagnosis of ITP
Failure to respond to 1st line therapies: glucocorticoids, IVIG, IV Anti-D
Investigations for alternative/exacerbating causes of thrombocytopenia
Therapeutic options for persistent thrombocytopenia requiring treatment
Drugs:
Heparin
Quinidine
Valproic acid
Oestrogen
Infections:
Hepatitis C
HIV
H pylori
CMV
Immuno-logical disorders:
SLE
Evans Syndrome
ALPS
CVID
Other alternative diagnoses to consider
Inherited thrombocytopenias e.g. MYH9-RD
MDS
CLL
PNH
TTP
Conventional therapies
Splenectomy / accessory splenectomy
Repeated IVIG or IV anti-D infusions
Chronic low-dose corticosteriods
Danazol
Immunosuppressive therapy (azathioprine, mycophenalate mofetil, vinca alkaloids, cyclosporin A, dapsone)
Cytotoxic chemotherapy (cyclophosphamide)
Emerging therapies
Multi-agent therapy*
Rituximab
TPO-receptor agonists

occasions; eg, fatal hepatic failure with herbal teas. Many patients also think that a ''Naturopath'' saying ''this works for my patients with ITP'' means that there are sufficient data that a given remedy should reasonably be tried with a reasonable expectation of success. These may be the same patients who would not try an allopathic treatment because they feel the data of a randomized trial were insufficient. In particular, careful reporting in a clinical trial of unrelated adverse events may bias patients who ignore the possibility that adverse events occur with ''natural'' substances and without treatment.

Therefore ''observation and no treatment'' may only be no ''allopathic'' treatment. Patients may decide that certain agents improved their bleeding without changing their platelet counts, which can be very difficult to decide objectively. Nonetheless, it is clear that if the count is low enough (certainly if it is <20,000/μL) and if there is bleeding, then the risk of serious hemorrhage is appreciable. Certain issues need to be considered at this juncture before discussing available treatments. First what if any other reasons exist to treat patients even if they do not appear to be at immediate risk of life-threatening hemorrhage (ICH). Second, what investigations are required to distinguish a case of ''refractory'' ITP from that of another etiology such as myelodysplasia. Third, where should the balance be between treatment to prevent bleeding, improve health-related quality of life, and a policy of reasonable observation.

The *first* consideration involves Health-Related Quality of Life (HRQoL). Studies of HRQoL in patients have clearly demonstrated that many patients have substantial deficits in this area.[10,11] A discussion of which methods are optimal to define impaired HRQoL, either in general or in ITP, are beyond the scope of this article. However areas in which at least a substantial fraction of patients have reported deficits include libido, cognitive function, time, money required to be used for care of their ITP, and the most universal finding: chronic fatigue. Recent studies with the thrombopoietic agents have suggested that treatment that improves the platelet count may improve complaints in this area across a wide variety of complaints.[12,13] Therefore, this becomes an important impetus to improve HRQoL for the patient, even if one believes that their risk of death or serious impairment from bleeding appears to be small. This approach requires that there be treatments that are sufficiently efficacious, tolerable, and easy to administer that they do not themselves create a substantial impairment in HRQoL. The only ones that have been well demonstrated thus far to fit this category (high response rate, good tolerability, low toxicity) are the thrombopoietic agents. Splenectomy probably would qualify as well, but it and other chronic treatments are largely unstudied and thus more specific comments cannot be made.

**Fig.1.** An investigation and treatment algorithm for patients with a diagnosis of ITP who are poorly responsive to first-line therapies. The available therapies are not listed in any suggested order of preference, as there is no consensus on this at present and the choice of agents should be chosen according to the individual patients' clinical needs and preferences. TPO-R agonists are highlighted in red as they still available only in clinical trials. *Multi-agent therapy: IVIG and methylprednisolone plus IV anti-D and/or vincristine for induction and danazol plus azathioprine for oral maintenance therapy.[46] ALPS autoimmune lymphoproliferative syndrome; CLL, chronic lymphocytic leukemia; CMV, cytomegalovirus; CVID, common variable immune deficiency; H pylori, *Helicobacter pylori*; HIV, human immunodeficiency virus; ITP, immune thrombocytopenic purpura; IVIG, intravenous immunoglobulin; MDS, myelodysplastic syndrome; MYH9-RD, May Hegglin anomaly related disorders; PNH, paroxysmal nocturnal hemoglobinuria; SLE, systemic lupus erythematosis; TTP, thrombotic thrombocytopenic purpura; TPO, thrombopoietin. (*From* Psaila B, Bussel JB. Refractory immune thrombocytopenic purpura: current strategies for investigation and management. Br J Haematol 2008;143(1):16–26; with permission.)

*Second*, if a physician sees a patient with chronic ITP for the first time (or has not ''reevaluated'' the patient since diagnosis), it is worthwhile to review the items in **Box 1** in deciding how to approach the patient to ensure that this patient really has chronic ITP. The primary considerations are whether this might be a case that resembles ITP, but is not or is a case of secondary ITP in which resolution of the primary, underlying disease would impact on the management of the thrombocytopenia. In this brief overview, there are a number of categories to consider.

One prominent subset is *drug-induced thrombocytopenia* (DIT).[14] It has become clear that ITP occurs frequently in more elderly patients, and therefore the number of medications that patients are on is often not trivial. However, in the absence of diagnostic testing for ITP (which is the current situation) and in the absence of a good way to judge the likelihood of DIT in a given case, the optimal approach appears to be to sequentially change all of a patient's medications to therapeutic equivalents that are biochemically different. In the past this was often arduous, but the increased number of available medications makes this approach currently more feasible.

It is worthwhile commenting briefly on several medications. Heparin-induced thrombocytopenia thrombosis (HITT) is an extremely serious and complex entity and worthy of a separate treatise. It typically occurs in inpatients or those recently discharged. Valproate is almost always a cause of dose-related marrow suppressant and therefore is unusual in that dose reduction to lower the blood level (to less than 100) is usually sufficient and drug discontinuation is not typically required.[15] Diphenylhydantoin is among a small number of drugs known to induce platelet antibodies. In a small number of women, estrogen (whether in oral contraceptives or used unopposed postmenopausally) seems to convert otherwise unexceptional ITP into a refractory state. Discontinuation of estrogen in such a patient (or conversion to only progesterone such as depoprovera) allows the ITP to revert to its ''normal'' form.[16]

Recent studies have highlighted ITP that is not only ''caused'' by *infections* but possibly perpetuated by them. The reported infections capable of causing ITP to appear and persist as long as the infection continues unabated are HIV, Hepatitis C, *Helicobacter pylori*, and cytomegalovirus (CMV); there may well be others. HIV-related thrombocytopenia is well known and the thrombocytopenia was first reported in the early 1980's to respond to viral suppression.[17] The ''disappearance'' of HIV-ITP is a result of the widespread use of HAART.[18] Similarly, hepatitis C has been known to cause thrombocytopenia but the ''one-to-one'' correlation of viral suppression and amelioration of thrombocytopenia has not been as well demonstrated as in HIV infection.[19] Recent studies have demonstrated the variability of response of thrombocytopenia to *H pylori* eradication, seemingly dependent on geography, which may reflect infection with different strains. For example, platelet response rates to *H pylori*

**Box 1**
**ITP: a diagnosis of exclusion**

- Normal complete blood count (CBC) except isolated thrombocytopenia. No other cytopenias (except for possible Fe deficiency).
- Normal peripheral blood smear with some large platelets.
- Normal examination; except signs of bleeding. No splenomegaly.
- *Exclude Secondary ITP*: systemic lupus erythematosus, hypogammaglobulinemia, anti-phospholipid, thyroid disease, Evans syndrome lymphoproliferative disorders, drug-induced.
- Infection: HIV, *Helicobacter pylori*, Hepatitis C, CMV.

eradication in Japan and Italy appear to be far higher than those seen in the United States. Unlike the other infections described and CMV, *H pylori* infection has not been commonly described as an etiology of "refractory" ITP.[20] A recent report on CMV infection has suggested in four cases that immunosuppression, such as steroids used in the treatment of ITP, may in rare cases result in reactivation of CMV infection, which in turn causes a refractory thrombocytopenia. Platelet counts may improve when immunosuppression is stopped and the CMV treated.[21] Human T-cell lymphotropic virus (HTLV1) does not appear to have a similar effect.[22] Other infectious agents have not been carefully studied.

ITP associated with lymphoproliferative disorders is well described. The most prominent are Hodgkin disease and chronic lymphocytic leukemia (CLL). The former is readily recognized but the latter may smolder and not be immediately noticed in all cases. The diagnosis of early-stage CLL requires recognition of the increased number of small lymphocytes and that these cells are of the B-cell lineage. Recent study of Canale-Smith syndrome (ALPS or autoimmune lymphoproliferative syndrome) has suggested that at least a "forme fruste" of it may underlie a substantial fraction of pediatric autoimmune hemolytic anemia (AIHA).[23] Studies of ALPS, an apoptosis defect in autoreactive T and B cells, in patients with ITP have been very limited, but ALPS pathophysiology may have a role in a small fraction of cases.[24]

Finally, *immune deficiency* is well known to be associated with immune thrombocytopenia. The commonest form and best understood is common variable immune deficiency (CVID), also known as hypogammaglobulinemia. At least 10% of patients with CVID develop ITP at one time or another; another 10% of CVID patients may develop AIHA.[25] Among patients with CVID, autoimmunity to platelets and red blood cells occurs more frequently in those with mutations in transmembrane activator and calcium modulator and cyclophilin ligand activator (TACI), a B-cell growth factor receptor.[26] Furthermore ITP does not appear to develop in patients with X-linked agammaglobulinemia (Brutons), presumably because there are no abnormal circulating B cells and T cells to instigate the autoimmunity.

*Third*, how does one decide who to treat? This has been considered in depth in "How I Treat ITP" in *Blood* 2005.[27] On the one hand, there is hemorrhagic morbidity and especially mortality in patients with low platelet counts and bleeding symptoms.[28] On the other hand, one study suggested that death as a consequence of infection related to therapy occurs at least as frequently as hemorrhage.[29] Clearly this depends on the treatment in question and in particular the greatest morbidity is related to the persistent use of corticosteroids. As indicated previously, the clinical algorithm has become more complicated by the inclusion of HRQoL into the treatment equation. A surprising example is noted that some students with ITP want treatment to increase their platelet count before examinations because they can "think better when their counts are higher." The issue of treating versus not treating has been best considered in pediatric ITP, but no clear consensus has been reached there.

The rest of this article is devoted to which patients with chronic ITP need to receive treatment because with low platelets, bleeding symptoms and/or HRQoL issues to consider, it may be difficult to judge by the treating physician. For the sake of consensus, this would usually involve a platelet threshold of 20,000 to 30,000/$\mu$L, but as discussed in "How I Treat ITP,"[27] it is occasionally appropriate to select a higher target count for a number of reasons. Certain issues discussed earlier in this article affect treatment. If there is secondary ITP, then treating the underlying disease, such as infection or an immune defect, is usually the optimal approach. This section will assume that appropriate evaluation has been undertaken and patients with secondary causes of ITP will have been managed accordingly.

The previous discussion may make it seem as if the identification of secondary ITP is straightforward and clinically obvious; it is often not. One critical issue is the decision in which patient to do which tests. In other words, should certain testing be done ''blindly'' with no clinical indication? This is an evolving field in which there is not any resolution at this time, in large part because there are no data to inform the decision. Our approach has been to do a battery of tests in all patients with chronic ITP to explore the possibility of CVID, hypothyroidism, Evans syndrome, and other entities even without direct clinical history suggestive of these possibilities. Other centers may advocate hepatitis C testing (as transaminases may be normal in infected patients) and also to look for *H pylori*.

Laboratory testing in a complex patient often requires not only a careful history but often two rounds of testing: a screening set of tests and then follow-up exploration. Testing that depends on IgG antibodies may be false positive for months following IVIG. However CVID can be considered based on IgA and IgM levels and other testing such as *H pylori* done by the breath test and stool antigen, and hepatitis C, HIV, and CMV done by polymerase chain reaction (PCR). Bone marrow evaluation typically requires at least an aspirate, biopsy, and cytogenetics focused on myelodysplasia; flow cytometry is less useful in the absence of a monoclonal population in the marrow, although some investigators have documented small populations of CLL lymphocytes in the marrows of older ITP patients. All of these and other tests are not diagnostic of ITP and are intended to exclude other specific diagnoses linked to apparent ITP. The only specific test that ''includes'' ITP (although it does not distinguish primary from secondary ITP) is response to ITP-specific therapy (prednisone, IVIG, or IV anti-D). If response is substantial even if transient and if the response is repeated, then this is a strong argument for the presence of immune thrombocytopenia. The issue of diagnostic testing is further delineated in the new International ITP Guidelines scheduled to appear in *Blood* in late 2009.

If a patient has chronic ITP, the utility of repeated IVIG and IV anti-D is usually limited. Further steroids typically are fraught with increasing toxicity and less efficacy. It is ''too late'' for high-dose dexamethasone to have other than rare curative effects. Therefore other therapies need to be considered.[30]

The gold standard is splenectomy. Unlike what many patients believe based on Internet misinformation, the 5- to 10-year efficacy is approximately 65% for all patients and 85% in the first week after surgery.[31] Laparoscopic splenectomy does not result in additional complications, such as an increased need for accessory splenectomy, or loss in efficacy. The issues deterring at least some patients are:

(1) Knowledge that other patients who have undergone splenectomy have failed to be ''cured'' of their ITP. This remains active in Internet communication, whereas those who are cured typically do not report this. This means that patients seeking guidance from other patients are often counseled not to undergo the procedure because ''splenectomy does not work.''
(2) Patients do not wish to undergo an operation without being assured that it will work 100% of the time. There are no good, readily available predictors at this time. Platelet site of destruction studies remain controversial.
(3) The long-term outcome is not known. Specifically 20- to 30-year follow-up data are absent. Concern has been raised about dementia in one small group of patients.[32] A conundrum here is that efficacy decreases as the age of the patient increases above age 45 years.[31] This means that the higher response rates are in the patients with the most potential for late side effects because they are younger and should have the longest lifespan post splenectomy.

(4) Patients are concerned about "post splenectomy sepsis." On the one hand this is quite rare. On the other hand, if or when a fever occurs, it is mandatory to urgently and emergently receive parenteral broad spectrum antibiotics that are effective against pneumococcus. This is true no matter how many years post splenectomy it is when the fever occurs.

Nonetheless the answer to the question *What is the best way to "cure" ITP?* is splenectomy!

Rituximab, anti-CD20 therapy has advantages and disadvantages. It is the answer to the question "*what is the likeliest way to cure ITP if one does not wish to do splenectomy*." It is estimated that approximately one third of patients will have a complete response (CR) (unmaintained normal platelet count) following a standard treatment with 375 mg/m$^2$ weekly for 4 weeks.[4] Virtually all of these patients in CR will maintain their response for at least 1 year. The current estimate is that after that time approximately one half will lose their response within 4 more years, most by 3 years from initial treatment. Therefore it has high utility to maintain a normal platelet count for 1 to 3 years, but the patient should know that a complete response is not a cure and ITP will often relapse. Repeat treatment for the relapsed complete responder can result in a high rate of repeat response.[33] However, essentially all patients will relapse again after approximately the same time interval, so that one may have to plan on regular repeated treatments. Unfortunately, the optimal approach to patients achieving an initial CR and then relapsing remains to be discovered. The safety of repeated courses of rituximab has not been evaluated. Concerns include development of progressive multifocal leukoencephalopathy (PML)[34] and reactivation of hepatitis B, but the former seems vanishingly rare in patients not receiving multiple chemotherapies with rituximab. Reactivation of hepatitis B does not seem to be very common and will be even less so in the era of hepatitis B vaccination. In addition, it can be monitored so that reactivation could be treated early before serious liver damage occurs. Common but less serious toxicity includes first infusion reactions such as fever and chills, and serum sickness; the latter especially in children.[35] Finally, patients cannot mount humoral responses to vaccines for months after rituximab; but contrary to expectation despite elimination of B cells in the peripheral blood, overall immunoglobulin levels rarely decrease. Newer human or humanized anti-CD20 monclonal antibodies have been and are being developed, but whether their efficacy has been altered by humanizing them or by engineering to affect antigen and/or Fc receptor binding is not clear. Toxicity has been ameliorated by intramuscular injection, which reduces infusion reactions and greatly speeds up administration. This may however lower the dosage because of volume limitation, but it can be argued that the optimal dose of rituximab for the treatment of ITP remains unknown.

The newest development involves thrombopoietin receptor agonists. The rationale for their use, their structure, their biology, and clinical effects in normal volunteers is described in the article by Kuter-Gernsheimer in this issue. There are a series of publications on romiplostim (AMG531) and eltrombopag, which are the first two such agents that are approved for treatment of refractory ITP, at least in the United States. As described by Kuter-Gernsheimer, the current second generation agents were initially evaluated in refractory ITP.

AMG531 (romiplostim, Nplate):

(1) The first study using AMG531 was published in 2006 and had two parts.[36] The first part was a cohort dose increase study that showed a clear dose response in the effective range between 1 and 10 μg/kg. Counts in good responders at the highest dose levels only began to increase on day 5 and peaked after day 8. The second

part of the study was a 6-week, repeated weekly injection study in two groups of 8 patients, one group at 1 μg/kg and the second group at 3 μg/kg. It was demonstrated that at these treatment doses patient platelets counts often increased to higher than 50,000/μL, but with a high degree of fluctuation from one week to the next.

(2) The second publication described two pivotal, randomized, controlled studies that were identical, with one study in splenectomized patients and the other study in nonsplenectomized patients.[37] Both involved slow dose increases week to week depending on the platelet count. There was also the ability to use rescue medication for too low counts and/or bleeding and, after response, to discontinue concomitant prednisone. In both parallel trials, unequivocal efficacy was demonstrated by all efficacy end points: durable response (platelets $\geq$50,000/μL for 6 of the last 8 weeks and no rescue therapy), overall response (platelet counts $\geq$ 50,000/μL on 4 of 24 weeks), reduction in the use of concomitant medications such as prednisone; and less use of rescue medications (IVIG, anti-RhD, or prednisone). No tachyphylaxis was seen over the 6 months of the study and no important toxicity emerged such as an increased incidence of thromboembolic events. AMG531 (romiplostim, Nplate) was licensed in August 2008 based on these two studies.

(3) Patients who entered one of the previous studies were eligible to enter the long-term maintenance study, which was recently published representing up to 3 years of follow-up of patients on weekly AMG531.[38] Overall, the study showed that long-term use of AMG531 as a maintenance therapy was feasible from many aspects: platelet counts could be maintained for years; no dose increase was required over time; responses were consistent within most patients; patients could learn to give 3 of 4 weekly injections at home; and no important toxicity developed. This study was the first one to address reticulin fibrosis in the marrow and reported nine cases. Further studies need to be performed to clarify this issue as to whether there is a high potential for important marrow damage or not, although at this time it does not appear to result in permanent injury.

(4) Other studies have been reported in abstract form including a 22-patient study in children preliminarily demonstrating safety and efficacy and a study exploring the utility of presplenectomy use of AMG531 to delay or prevent splenectomy in which splenectomy was performed more often and earlier on the standard-of-care arm.

Eltrombopag (Promacta)

(1) The first study published was a 6-week study at four (daily) doses: placebo, 30 mg, 50 mg, and 75 mg.[39] Responses were seen in 70% to 80% of patients at the two highest doses compared with 11% in placebo. No important toxicity was seen in the study and bleeding decreased as the platelets increased. A second study in the same issue of the *New England Journal of Medicine* reported similar impressive results for thrombocytopenic patients with hepatitis C infection allowing continued antiviral chemotherapy without dose reduction or interruption.[40]

(2) The second study was a confirmatory 6-week randomized placebo-controlled trial comparing 50 mg of eltrombopag to placebo.[41] The results were again striking with 59% response on the eltrombopag arm to a level higher than 50,000/μL compared with 16% on placebo. Bleeding manifestations again were decreased in responders and increased back to baseline after the medication was discontinued and the platelet counts returned to baseline. In this study, rebound thrombocytopenia was a rare problem on drug withdrawal and no statistically significant specific organ toxicity was seen. However, some patients have developed significant elevations in liver enzymes requiring cessation of medication.

(3) Other eltrombopag studies have been reported only in abstract form. These include a 6-month randomized study with results comparable to the AMG531 pivotal trials described previously and a repeated use study (three cycles of 6 weeks on, 4 weeks off), which showed super-imposable findings for each of the cycles, demonstrating no loss of efficacy with duration of treatment or repeated use.

Single-agent treatment of ITP with agents such as azathioprin, danazol, cyclophosphamide, cyclosporine, and mycophenalate mofetil, to name the most commonly used agents, has been difficult. One review by Berchtold and McMillan[42] suggested that no single agent is effective in more than 30% of cases and this is especially true in chronic cases, particularly those refractory to splenectomy. In the post-splenectomy refractory patients, the higher response rates reported in the patients treated with the thrombopoietin receptor agonists suggest that these would be the drugs of choice for this group of patients (discussed previously). In addition, the use of these agents, by increasing platelet counts in the post-splenectomy patients, allowed for a reduction in the use of concomitant immunosuppressive drugs. This can reduce the infection risk in this high-risk patient population. In general, therefore, single-agent therapy often is ineffective. Even autologous stem cell transplants have only been found to have a 25% to 33% response rate without multiyear follow-up.[43] Individual agents are analyzed and their efficacy and toxicity considered in the soon to be published International Guidelines on ITP.

Combination therapy has been approached in some situations to increase response rate and decrease toxicity of single agents whose dosage must be increased to the maximum to maintain any efficacy. The first report involved a patient with Hodgkin disease and refractory ITP whose thrombocytopenia responded to six cycles of chemotherapy protocol consisting of cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP). Treatment of further patients resulted in important toxicity, but good responses in certain patients[44] Long-term follow-up showed that all but one responder maintained the response over many years.[45] Boruchov and colleagues[46] tried multiagent therapy with initial IVIG, IV methylprednisolone, and IV anti-D, vincristine, or all four together followed by danazol and azathioprin in combination. The latter was effective in 13 of 17 patients with the only important exclusion being abnormal liver testing before initiation of treatment. Other combinations may be demonstrated to be useful in the future.

Mechanism of therapeutic effect can now be targeted more specifically and this could lead to the development of ''intelligent'' combinations. The most obvious would be combining an agent that inhibits platelet destruction, such as IVIG, IV anti-D, or the Rigel syk inhibitor,[47] with an agent that stimulates platelet production (AMG531 or eltrombopag). Although this would not be a ''curative'' approach, it is potentially a highly effective treatment strategy.

## SUMMARY

In summary, diagnosis and management of chronic ITP requires experience and the appropriate use of the laboratory despite the absence of a diagnostic test for ITP. The diagnostic test valuable above all others is response to ITP-specific therapy as it is the only test that ''includes'' ITP, rather than excluding other entities in the differential diagnosis. Consideration of secondary ITP is very important because identification of immunodeficiency or of infections or of lymphoproliferative disorders would change the management approach to a given patient. The development of

newer therapies such as rituximab and the thrombopoietic agents have had a major impact on the management of ITP. Further exploration of how to optimize curative effects of any and all therapies remains an important consideration. In the future, additional combinations of agents may be a critical approach although the schedule and dosing remains difficult to establish. Finally, current studies to augment therapy in the newly diagnosed ITP patients to prevent chronic disease may lessen the number of patients in chronic disease category.

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