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Therapy

Is there still a place for "old therapies" in the management of immune thrombocytopenia?

S. Audia[a,b,*], B. Godeau[c], B. Bonnotte[a,b]

[a] Service de Médecine Interne et Immunologie Clinique, Centre de Compétences des cytopénies auto-immunes de l'adulte, Hôpital Bocage Central, 14, rue Paul-Gaffarel, 21000 Dijon, France
[b] CR INSERM 1098, Bâtiment B3, rue Angélique-Ducoudray, 21000 Dijon, France
[c] Service de Médecine Interne, Centre de Référence des cytopénies auto-immunes, Hôpital Henri-Mondor, AP–HP, UPEC, 94000 Créteil, France

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ABSTRACT

New molecules such as rituximab or thrombopoietin receptor agonists (romiplostim and eltrombopag) have changed the management of immune thrombocytopenia. Therefore, old drugs which are less expensive and with a well-known benefit/risk ratio are being underused. We aim to define the place of dapsone, danazol, hydroxychloroquine and vinca-alkaloids at the era of targeted therapy in immune thrombocytopenia. With a response rate around 30% to 50%, dapsone is an interesting second-line therapy to be used just after corticosteroids. Patients with positive antinuclear antibodies can benefit from hydroxychloroquine with a 50% response rate. Because of its side effects, mostly virilization, danazol will be preferentially used in the elderly. Vinca-alkaloids could be temporarily used in patients that do not respond to intravenous immunoglobulins or to limit their use to avoid shortage periods.

1. Introduction

Over the last 10 years, the management of immune thrombocytopenia (ITP) has changed with an increased use of rituximab (RTX) [1] and thrombopoietin receptor agonists (TPO-RA) [2,3]. These treatments provide good results but remain expensive (Table 1). Response rates following RTX are 60%, 40% and 20% after 1, 2 and 5 years of follow-up, respectively [4]. Thus, 20% of treated patients could expect to be cured with RTX. Unfortunately, the predictive factors of response have not yet been clearly determined. It has been suggested, however, that short disease duration and a previous response to corticosteroids were associated with a long-term response to RTX [5]. Recently, a study that analyzed drug consumptions in 3000 ITP patients hospitalized each year in France showed that more than 600 were treated with RTX, mostly before splenectomy, and that its use was stable during the last 3 years [6]. Two TPO-RA are currently available: romiplostim, used subcutaneously, and eltrombopag, given orally. The response rate to TPO-RA is around 80% to 90% [7,8]. In Europe, their use is restricted to ITP patients who are refractory to splenectomy or in whom surgery is contraindicated. However, TPO-RA are more and more used in France in persistent ITP before splenectomy. Indeed, they represent 15% of treatments given during the first year following diagnosis of ITP [9]. Furthermore, this percentage will probably increase following the recent publications reporting prolonged remission after temporary use of TPO-RA in 10 to 30% of patients [10,11].

This situation is striking given the current economic context, which imposes a rational use of these expensive drugs. Moreover, even if tolerance to TPO-RA after 5 years of use seems good, long-term toxicity is still not known. In this context, we aim to determine the indication of "old molecules" such as dapsone, danazol, hydroxychloroquine and vinca-alkaloids in ITP management, as their efficacy and side effects are well-known. Moreover, these drugs are quite inexpensive, as reported in Table 1. Although no prospective medical-economic study has been conducted in ITP, data suggest that using RTX before TPO-RA could be less expensive in patients refractory to splenectomy [12].

2. ITP: definitions and current therapeutic strategy

During the past few years, ITP terminology has been clarified [13]. "Newly diagnosed ITP" is used during the 3 months following diagnosis; "persistent ITP" defines the period lasting between 3 to 12 months after diagnosis, and after 1 year of disease

* Corresponding author at: Service de Médecine Interne et Immunologie Clinique, Centre de Compétence des Cytopénies Auto-Immunes de l'adulte, Hôpital Bocage Central, 14, rue Paul-Gaffarel, 21000 Dijon.
E-mail address: sylvain.audia@u-bourgogne.fr (S. Audia).

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Table 1
Cost of the different treatments (molecules only).

Molecule	Dosage	Monthly cost (28 days) or one course treatment (*)
Danazol	200 mg twice or three times a day	€ 51 to 76
Dapsone	100 mg/day	€ 4
Eltrombopag	50 mg/day	€ 2.225
Hydroxychloroquine	200 mg twice a day	€ 10
Intravenous immunoglobulins (IVIg)	1 g/kg for 70 kg weight	€ 2.870*
Rituximab	1 g at day 1 and day 15	€ 5.275*
Romiplostim	3 μg/kg/week (weight < 85 kg) ➔ 250 μg vial	€ 2.773
	3 μg/kg/week (weight > 85 kg) ➔ 500 μg vial	€ 5.381
Vinblastine	5 mg/week	€ 30
	10 mg/week	€ 70
Vincristine	2 mg/week	€ 58

duration, the term "chronic ITP" is used. "Refractory ITP" characterizes patients with thrombocytopenia below 20 G/L and/or bleeding manifestations despite splenectomy [13]. However, this definition should probably be refined and extended to patients that are non-responders to splenectomy, RTX and TPO-RA in succession [14].

Current ITP management [15] could be summarized as follows:

- corticosteroids are the first-line therapy, also used as a diagnostic test, with a response rate around 70% to 80%. Usually, a short treatment duration (3 to 4 weeks) with prednis(ol)one (1 mg/kg/d) is recommended [15]. Dexamethasone, 40 mg/d during 4 consecutive days, also provides good results [16];
- intravenous immunoglobulins (IVIg) should only be used in emergency situations associated with corticosteroids. IVIg are indicated depending on the bleeding score rather than platelet count [17];
- splenectomy is the second-line therapy proposed after 1-year of evolution;
- TPO-RA are used to treat patients who are refractory to splenectomy.

However, the therapeutic strategy during the first year following diagnosis is still not clearly defined, particularly in patients who relapse after steroids, which is a frequent situation. RTX and TPO-RA are more and more used off-label during this phase [9], although old molecules such as dapsone, danazol, hydroxychloroquine and vinca-alkaloids could be useful at this stage.

3. What place remains for the "old therapies"?

3.1. Dapsone

The first use of dapsone during ITP was reported in the 1990's by Durand et al. [18], and its efficacy was further confirmed in larger series (Table 2) [19–27].

The mechanisms of action of dapsone are not well-known. One hypothesis is that the hemolysis induced by the drug (there is usually a decrease of 1–2 g/dL in the hemoglobin level) could limit the phagocytosis of opsonized platelets by splenic macrophages [18]. There is indirect evidence supporting this hypothesis, for example, a greater degree of hemolysis in responder patients and a lower response rate in splenectomized patients [21]. Dapsone is also known to decrease the cytotoxic functions of neutrophils [28], a mechanism that is probably not preponderant during ITP.

The response rate to dapsone is around 30% to 50%, and is only suspensive in most cases [18,19,21]. Once the response is obtained, the drug can be tapered progressively. In rare cases, the response persists after dapsone discontinuation [21,23,25,26]. In cases of relapse, a new response could be achieved by resuming the drug, but sometimes after a long interval [29]. No individual predictive response factors have been identified. In particular, the acetylation profile does not correlate with response rate, even though dapsone is metabolized by N-acetyltransferase [22]. Dapsone can be used after splenectomy, but the response rate is usually half that in non-splenectomized patients [19–21,23]. Dapsone is also effective in secondary ITP, notably due to HIV infection [19,24], in which it will also provide a prophylactic effect against pneumocystosis. Overall, tolerance to dapsone is good, with a discontinuation rate due to side effects of 4 to 24%. It is worth noting that in all studies, patients with glucose-6-phosphate-deshydrogenase (G6PD) deficiency were excluded because of the increased risk of hemolysis. Cutaneous hypersensitivity is a frequent side effect that occurs in 7% of patients [30]. It consists of a rash with pruritus associated with systemic symptoms in the most severe cases, leading to the diagnosis of drug rash with eosinophilia and systemic symptoms (DRESS). Usually, the rash occurs within the first 4 weeks of treatment. Both patients and referent general practitioners must be aware of this potential harmful side effect; discontinuation of the drug is mandatory as soon as these symptoms appear [31].

Proposition: dapsone is a suspensive therapy with a good benefit/risk ratio. The drug constitutes an interesting second-line therapy, particularly in persistent ITP, as recommended [15,32]. A national randomized prospective study (DAPS-ITP study) conducted in France by the French reference center for autoimmune cytopenias will probably confirm the results obtained in retrospective studies. Strong adherence to treatment and good knowledge of the potential side effects (most particularly cutaneous hypersensitivity) are needed. Screening for G6PD X-linked deficiency is important in men, as soon as the diagnosis of ITP is made, in order to start the drug rapidly in case of relapse following steroid discontinuation. As the median response time is 3–4 weeks, concomitant treatment with corticosteroids is usually required. Moreover, it seems that this co-prescription decreases the risk of harmful side effects [30]. Once a stable response is obtained, the drug can be tapered very progressively. We recommend measuring methaemoglobinaemia only in cases of suggestive symptoms such as cyanosis or dyspnea; a blood level below 7% is required for treatment continuation. A full blood count is also needed during follow-up because of the hemolysis induced by dapsone, and agranulocytosis also needs to be checked for. Both hemolysis and methaemoglobinaemia are dose-dependent, thus a decrease in dapsone dosage could be sufficient to reverse these side effects. Interestingly, dapsone can be maintained during pregnancy [33]. Hemolysis and moderate methaemoglobinaemia have been reported in new-borns whose mothers were treated with dapsone during pregnancy. In such cases, these side effects must be checked at birth [34]. Because of the high concentration of the drug in maternal milk, breastfeeding is strongly discouraged (Centre de Référence sur les Agents Pathogènes, French reference center on pathogenic drugs, http://www.lecrat.org). It should be known that as dapsone pills contain iron, they induce black coloration of the feces that should not be misdiagnosed as melena in this context of thrombocytopenia. Moreover, as eltrombopag absorption could be disturbed by concomitant divalent ion intake, the utilization of both molecules simultaneously should be avoided.

3.2. Danazol

Danazol displays multiple immunomodulatory mechanisms. It induces a decrease in Fcγ receptor expression on monocytes [35]