

EDITORIAL

Updated treatment options for immune thrombocytopenia

We would like to update readers on the treatment landscape for severe chronic immune thrombocytopenia (ITP) in the wake of recent welcome changes to the Pharmaceutical Benefits Scheme (PBS) reimbursement criteria in Australia and since the publication of our consensus treatment guidelines.¹

First, splenectomy is no longer required to access thrombopoietin receptor agonists (TPO-RAs) such as romiplostim and eltrombopag. This change aligns with management guidelines and clinical data showing no difference in outcome between patients with splenectomy versus those without splenectomy receiving TPO-RAs and permits ITP treatment selection best tailored towards patient preferences and clinical factors.^{1–4}

Second, a new TPO-RA avatrombopag is now PBS listed as an alternative to romiplostim and eltrombopag. There are no head-to-head data to suggest superiority of one TPO-RA over another, but differing administration routes, dose schedules, interactions and side effect profiles may assist clinician–patient decision-making with treatment selection. Table 1 highlights the main differences between the available TPO-RA agents.

Third, switching between TPO-RAs for any reason including tolerance or failure is now permissible at any time. Previously, switching was not allowed after 24 weeks of therapy, even after the development of an unanticipated adverse event or eventual loss of response. Although one may anticipate an equivalent TPO-RA class effect with these agents, retrospective data demonstrate switching between these drugs for inadequate responses can be successful with improved platelet counts and reductions in concomitant medications.^{5,6} Thus, with the relaxation of switching rules and the PBS listing of avatrombopag, we now have an additional line of therapy rather than just another oral alternative to romiplostim or eltrombopag.

Fourth, a clinical response as determined by the treating physician is sufficient to warrant ongoing PBS reimbursement in lieu of absolute platelet targets that were insensitive to clinically apparent improvements in bleeding and quality of life (QoL). Previously, the threshold for some patients to meet platelet response criteria devised for clinical trial environments was extremely difficult to achieve for PBS reimbursement purposes, even though there was clear benefit for patients in terms of reduced bleeding, improved platelet counts and lower concomitant ITP therapies. Along with penalising

patients who needed intermittent rescue therapies, these measures had seemed to restrict TPO-RA access for the patients with the most severe disease. This has now been rectified as the threshold for ongoing use is clinically determined by the treating physician most cognisant of their patients' medical priorities.

Finally, rituximab (intravenous B-cell depleting anti-CD20 monoclonal antibody) is now unrestricted on the PBS. Previously, off-label rituximab use was either self-funded or compassionately supported with a bias towards lower dosing schedules that were more cost-effective.⁷ Any new enthusiasm for PBS-reimbursed rituximab is probably balanced by recent coronavirus disease 2019 (COVID-19) pandemic concerns and tempered by previous analyses demonstrating only a modest long-term success rate, particularly when administered in monotherapy.^{8,9}

There are still many uncertainties ahead for optimal ITP management such as targeting the natural history of ITP before it becomes chronic, exploring the role of TPO-RAs in earlier stages of ITP, predicting and targeting patients at the highest risk of bleeding and rationally drafting the optimal sequence or combination of novel and existing therapies for severely refractory patients.

Data from the iWISh survey suggest that patients prefer to halt the progression or worsening of their ITP above QoL and bleeding, in contradistinction to their physicians.¹⁰ The ultimate goal for most patients is to optimise initial therapy of newly diagnosed ITP to prevent progression to the chronic phase. The recent FLIGHT (Newly Diagnosed Immune Thrombocytopenia Testing the Standard Steroid Treatment Against Combined Steroid & Mycophenolate) study, which explored the addition of mycophenolate mofetil to corticosteroids in first-line therapy, demonstrated an improved response and a halving of the progression rate to chronic ITP. This was at the expense of worsened patient-reported QoL measures at the end of the study¹¹; however, it seems reasonable to expect that the longer-term impact on cumulative disease and treatment burden by preventing the development of chronic ITP will eventually lead to better QoL.

Treatment strategies addressing the pervasive but insidious symptom of fatigue in ITP are also lacking. Patients with newly diagnosed ITP remain vulnerable to the uncertainties of their diagnosis, anxious about their

Table 1 PBS-listed TPO-RA available for use in chronic ITP

	Description	Mode of delivery	Dose schedule	Metabolism	Interactions	Toxicities
Romiplostim	Fc-peptide fusion protein	Subcutaneous injection	Weekly, 1-10 mcg/kg [†]	$t_{1/2} = 3.5$ days	Other Fc receptor-binding therapies	Bone marrow reticulin Thrombosis Rebound thrombocytopenia Risk of progression of myeloid malignancies
Eltrombopag	Nonpeptide small molecule	Oral tablet	Daily, 25-75 mg [‡]	$t_{1/2} = 26-35$ h, CYP1A2 and CYP2C8	Chelates polyvalent cations (such as calcium and iron) OATP1B1 and BCRP substrates caution (e.g. ciclosporin) Reduce statin dose	Hepatotoxicity Cataracts Thrombosis Rebound thrombocytopenia Bone marrow reticulin Risk of progression of myeloid malignancies
Avatrombopag	Nonpeptide small molecule	Oral tablet	Daily, 20-40 mg [‡]	$t_{1/2} = 19$ h, CYP2C9 and CYP3A4	CYP2C9 and CYP3A4 inhibitors may increase avatrombopag levels (e.g. fluconazole) CYP2C9 and CYP3A4 inducers may reduce avatrombopag levels (e.g. rifampicin)	Bone marrow reticulin Thrombosis Rebound thrombocytopenia Risk of progression of myeloid malignancies

[†]Some authors prefer to start at 200 to 250 mcg sc weekly and titrate by 50- to 100-mcg increments.

[‡]Although on-label dosing for new patients begins daily, careful titration is possible with alternate day dosing (e.g. increase avatrombopag from 20 mg daily to 20 mg/40 mg alternate days) and tapering off may be achieved by increasing dosage intervals up to once weekly before trialling cessation.

BCRP, human breast cancer resistance protein; CYP1A2, cytochrome P450 family 1 subfamily A member 2; CYP2C8, cytochrome P450 family 2 subfamily C member 8; CYP2C9, cytochrome P450 family 2 subfamily C member 9; CYP3A4, cytochrome P450 family 3 subfamily A member 4; ITP, immune thrombocytopenia; OATP1B1, organic anion transport proteins 1b1; PBS, Pharmaceutical Benefits Scheme; TPO-RA, thrombopoietin receptor agonist.

prognosis, and still have limited treatment options available to them.

Despite these therapeutic challenges, we welcome these updates to the PBS listings for the TPO-RAs. We look forward to the promise of these and other novel agents in the modern treatment landscape ahead. Amongst newer therapies, fostamatinib (spleen associated tyrosine kinase inhibitor) was listed by the Food and Drug Administration for chronic ITP in 2018 but remains unavailable in Australia. Clinical trials in ITP have recently been completed for rilzabrutinib (Bruton's tyrosine kinase [BTK] inhibitor) and efgartigimod (neonatal Fc receptor [FcRn] inhibitor).^{12,13} As new clinical trials are opening across Australia now with B-cell activating factor [BAFF] and a proliferation-inducing ligand [APRIL] inhibitors, the prospect of better targeting the immune lesion in ITP beckons.

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