American Perspective

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New Drugs for ITP- Why wait?

Whenever drugs are first developed they are tested in the patients who seem to have the greatest need and potential benefit. In ITP this is usually the group of patients who have lived with ITP for a very long time or those who have tried many different treatments without success. This is ultimately how agencies arrive at "licensing" drugs for use. It also determines what drugs become available and to which patients. Sometimes this can make it difficult, if not impossible, to obtain drugs if you do not meet the right criteria from the original research trials.

Most of the second-line medications that we use in ITP are only tested in the setting of chronic or refractory disease at first. For example, the first reported trial of rituximab for ITP was 2001 and it was not until 2010, that a study looked at treating patients with newly diagnosed ITP with rituximab in combination steroids. A similar story is true for the testing of the thrombopoietin-receptor agonists (TPO-RAs). All of the original major trials for both eltrombopag and romiplostim in adults and children have been conducted in patients with at least 3 months of ITP and who have failed at least one previous treatment and continue to have a significantly low platelet count. The first studies of eltrombopag and romiplostim were conducted in 2007 and 2008, respectively. Only more recently, in 2014 and 2017, have two trials been published using eltrombopag for initial treatment of ITP.

Learning the best time in a disease course to give medications can be challenging. First, we have to look at the side effects and decide if perhaps there are drugs with fewer side effects that should be tried first because they are safer. Second, we need to evaluate the effect of drugs on all aspects of a disease. Perhaps a particular medication would be really good for patients early in the disease who need an improvement in their quality of life despite not having a platelet count low enough to have gone on to the clinical trials. Lastly, we need to determine if there is a reason to think that medications may have a benefit if given early and used as prevention of chronic disease, as mentioned above for rituximab.

When we look at the TPO-RAs and ask these questions we can see that perhaps they too may have a role early in the course of ITP. The current studies show that for the majority of patients they are well tolerated and may avoid drugs with potential side effects. They may have an impact on quality of life if they can reduce fatigue and improve bleeding symptoms. It is yet to be determined if this profile merits using them before corticosteroids which are far less costly, however any patient who has been on a course of steroids will likely be able to reflect on the side effects that they experienced and the negative impact this had on them. It might also be that these drugs will work up front when combined with steroids in order to prevent chronic disease. This was the goal of one study combining eltrombopag with dexamethasone up front in a small group of patients with ITP. In this small study of 12 patients, 75% had a platelet count over 30 (x $^{109/l}$) at 6 months. There was no comparison group, however this is higher than response rates at 6 months with dexamethasone alone. The small number of patients does not allow us to have an answer to this question yet, but it did show that this approach is safe.

As doctors we all know that patients with ITP can have different concerns regardless of how long they have lived with ITP. The use of medications should be based not only on how long someone has had ITP or what their platelet count is, but also on consideration of other factors such as their quality of life and symptoms. In a review of over 200 patients receiving eltrombopag, 30 patients had ITP less than 3 months before starting eltrombopag. In our pediatric study, 18% of children receiving a TPO-RA had ITP for less than 3 months. Additional studies are needed to look at the potential value of using "second-line" treatments earlier in the course of ITP, with the goal of improving health-related quality of life, avoiding side effects, and more benefits, and possibly preventing the occurrence of chronic disease.

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