



# American Society of Hematology 2020 Podcast Collection: Immune Thrombocytopenia

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## PODCAST TRANSCRIPT

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DG: Hello and welcome to the *Adis Rapid Plus* podcast series. We're bringing you a selection of podcasts focused on the American Society of Hematology 2020 Conference, discussing the highlights of the data released during the event. Today's podcast will be focusing on the immune thrombocytopenia data presented at the ASH Conference.

Speaking to us today are Dr. Sabine Eichinger and Dr. Johanna Gebhart from the Hematology and Hemostasis Department at the Medical University of Vienna. Welcome both to today's podcast. And thank you so much for speaking with us.

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Now, a lot of important data were released at the 2020 conference. So, could you just introduce us to some of the highlights?

SE: Thank you so much for these introductory remarks. My name is Sabine Eichinger. And I am Professor of Hematology at the University of Vienna in Austria. I am currently a board member of the European Hematology Association. And I was chair of the Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis.

As we already heard, we will cover major topics on ITP, mainly—or exclusively—in adult patients that have been presented at last year's 2020 ASH meeting.

As you know, ITP is an acquired autoimmune disorder, and it is characterized by a low platelet count. This low platelet count results not only from peripheral platelet destruction, but also stems from impaired platelet production in the bone marrow. ITP is quite rare, with the prevalence estimated to be 2 to 5 per 100,000 persons in the general population.

Because of this low frequency, large randomized trials on the management of ITP are lacking. There are significant controversy and variation in daily routine practice. And for that I wish to draw your attention to the clinical guidelines of the American Society of Hematology that were published in 2019.

They summarize available evidence and recommendations regarding management of ITP

in adults and children. And as I already said, this broadcast will cover recent findings in adult patients only.

So, Dr. Gebhart, quality of life for ITP patients was a key topic at this year's conference. And the results from the ITP World Impact Survey have been presented. What was it that we learned about quality of life for these patients? They all have long-term treatments. And what can physicians do practically with the information going forward?

JG: Dear Professor Eichinger, thank you very much. Indeed, health-related quality of life in daily clinical practice as well as at the ASH conference is a very hot topic in ITP patients. And there were a few very, very interesting data presented on this topic.

So, first of all, I'd like to point out the presentation by Al-Samkari, who presented a literature review on outcome reporting and tools used for outcome reporting on platelet counts, bleeding, and health-related quality of life in adult and pediatric ITP patients [1]. In this literature review, he analyzed 168 manuscripts and could show that only 9% of these studies reported on health-related quality of life outcomes in ITP patients.

And [what] was really interesting was that eight different tools were used to report health-related quality of life. So, I think this is the first obstacle we're faced with: that we don't have a systematic approach to record health-related quality of life in our ITP patients. And that's a broad variety, which, of course, impairs the comparability of clinical data on health-related quality of life in these patients.

So, of course, further very interesting studies were presented, such as. The I-WISH study, the ITP World Impact Survey, which is an online tool that was applied in certain countries and reported data on over 1500 ITP patients and over 470 ITP-treating physicians. The aim of this study was to summarize the impact of ITP on various aspects or dimensions of a patient's health-related quality of life.

Furthermore, I found it a very interesting approach to compare patients' and physicians' perceptions of symptoms and disease management. So, there were three posters presented on

the I-WISH study. I'd like to just point out the main findings.

The first poster was on the emotional well-being of ITP patients [2]. It was quite astonishing that 49% of the patients reported that their emotional well-being was impacted by the diagnosis of ITP.

So, the main worries that were reported by these patients were disease worsening or fluctuations in platelet counts, which were reported by over 60% of patients. Furthermore, which was kind of surprising because it was a very high rate, 41% of patients reported that they were worried about dying.

Interestingly, these patients that reported a very high emotional burden also had a higher symptom burden, including ITP-related symptoms like fatigue. So, another poster exclusively reported on fatigue [3]. Interestingly, in this poster, the patient's and the doctor's perspectives were compared. The main finding was that the rate of fatigue is pretty underestimated by ITP-treating physicians because only 31% of the doctors perceived fatigue as a very bothersome symptom, whereas 50% of the patients reported it.

Interestingly—and this was also shown in other studies—the fatigue, this chronic fatigue syndrome, was not related to platelet counts or platelet count increases.

Another poster focused also on the comparison between patients' and doctors' perspectives and focused on the treatment-associated side effects [4]. I thought the main finding was that, for corticosteroids, the perception of side effects was pretty comparable between doctors and patients except for fatigue, which was reported also by one third of the patients under corticosteroid treatment, whereas in anti CD20 antibody treatment or TPO receptor agonist treatment, the reported side effects differed between patients and treating physicians.

For example, for the anti-CD20 antibodies, doctors were more afraid, of course, of side effects that were related to the infusion or the immunosuppressive effect, whereas patients also reported fatigue as the most bothersome side effect of anti-CD20 treatment.

So, I think this is probably the main message from this huge survey, which really pointed out

very interesting things: that the doctors' perceptions in ITP are very much different from patients' perspectives in many aspects. And I think this is very important that we as treating physicians are aware of this discrepancy so we can probably target, or just talk to our patients about, their anxieties about their fears and about their symptoms more concretely.

DG: Now in addition to this fascinating insight, the virtual visitors at last year's conference also had the chance to learn more about some of the novel treatments emerging from the trials landscape. So, could you talk us through some of the highlights?

SE: One of the major highlights was, of course, presentation of novel data on rilzabrutinib [5]. Rilzabrutinib is an oral inhibitor of the protein tyrosine kinase. And it targets mechanisms of platelet destruction.

The minimally effective dose of rilzabrutinib in a previous dose escalation study was 400 mg given twice daily. Now, in an open-label phase 1 and 2 study, rilzabrutinib was evaluated in adult patients with ITP. Those patients had to have an inadequate response to corticosteroids or thrombopoietin receptor agonists.

The primary endpoint of the study was a platelet count of more than 50,000 per microliter and an increase of more than 20,000 per microliter from baseline. More than 30 patients were included in that study. They all got oral rilzabrutinib 400 mg twice daily for a median duration of 18 weeks.

Rilzabrutinib treatment achieved a clinically significant platelet response in these patients. And it has to be noted that all of these patients had been heavily pre-treated.

The good response was also seen in patients who had been splenectomized or had a lack of response to several prior ITP therapies. The patients maintained this good response for the majority of time in the study.

We also know that platelet counts lower than 50,000 per microliter would be sufficient to avoid harmful bleeding episodes. In this respect, it is relevant that more than two thirds of the patients in this study achieved a clinically meaningful response such that they had no or very mild bleeding during that time.

Of course, one important aspect with all novel therapies is side effects. The treatment-related adverse events were all rather mild and only grade 1 and maximum grade 2. One patient had grade 1 diarrhea and another one grade 1 hypophosphatemia. These were patients who had been included in the extension phase of the study, so there was a subpopulation of patients who had been given the opportunity to continue treatment with rilzabrutinib for periods longer than 6 months. Also in these patients, the safety profile was excellent.

So, these are very promising findings in these patients who are otherwise refractory to currently available first- and second-line ITP treatments. Of course, we are now awaiting more data that demonstrate the durability of rilzabrutinib's benefit.

So, let's see what the future of these studies will bring so that we have more tools in our hands for this very vulnerable patient cohort.

JG: For me, I can continue by talking about another very interesting treatment approach for chronic multi-refractory ITP patients, which is sutimlimab, a monoclonal antibody which inhibits the activation of the classical complement pathway. Also here, data on the phase 1 study were presented and were updated in this ASH meeting [6].

So, the background of that is that circa 50% of ITP patients showed activation of the classical complement pathway *in vitro*. The hypothesis is that inhibition of the classical complement pathway might lead to a platelet count increase. The authors reported data on 12 patients also with chronic multi-refractory ITP, which required treatment. This phase I study was divided into two parts, a treatment part and one long-term extension phase after a washout period.

What the authors could report was that they achieved very fast- within 24 hours- and high response rates in 42% of the patients in 42% of the patients. One third of the patients even reached a complete response in respect to an increase of the platelet counts over 100,000 on two consecutive occasions. This was very astonishing and promising, also considering the multi-refractory [nature] of these patients.

Also, in the extension part of the washout period, the patients' responses were comparable. What the authors also investigated was whether the platelet count increase was correlated with the activity of the classical complement pathway; they could show that it was inversely correlated. So, when you inhibited the activity of the classical complement pathway, the platelet counts did increase.

Also, this treatment was actually pretty well tolerated. There was only one severe adverse event, which was considered possibly related to sutimlimab. This was an episode of migraine. So, this is a very, very interesting treatment approach for chronic and multi-refractory ITP patients.

DG: Thank you very much, Dr. Gebhart and Dr. Eichinger. Did you also want to talk about the combination therapy data you looked at from the FLIGHT trial?

JG: Yes. Sure. Of course. This was a very interesting presentation, which was given by Professor Bradbury in the late-breaking abstract session on December 8th [7]. They presented the results from the FLIGHT trial with the hypothesis that the combination treatment of mycophenolate and corticosteroids might be superior in first-line treatment of ITP patients to the standard of care, meaning corticosteroid treatment alone. Thus, the authors performed a multicenter, open-label, randomized trial in a pretty large cohort of ITP patients, including 120 patients.

They really could show that there were fewer treatment failures in the group of patients that were treated with mycophenolate together with corticosteroids. So, they had treatment failures occurring in 22% of this patient group in comparison to 44% of treatment failures in the corticosteroid-only treated group.

Furthermore, the treatment was very well tolerated by the patients. There was almost no difference in main side effects, although over 40% of patients that were included and investigated in the study were older than 70 years. It was a pretty old cohort.

That's why the authors concluded that mycophenolate might be a very good add-on treatment to standard of care in the first-line setting and might be even superior to the

current standard of care. So, this was also a very, very interesting approach, especially as this treatment was very well tolerated and is not very expensive and might really increase response rates in the first-line setting.

DG: Thank you very much. Now, you did look at the real-world data for fostamatinib and avatrombopag. Could you tell us what was learned here?

SE: Yes. There were several studies presented at the ASH meeting that focused on not only real-world data, but also on long-term outcome data from original phase 3 studies, particularly with fostamatinib [8]. Interestingly, these data not only focused on patients with ITP, but these treatment options have meanwhile been extended also to other disease entities, for example, to patients with hemolytic anemia or rheumatoid arthritis.

The safety profile of these which have been shown in these studies is very consistent with the original clinical trials. The safety profile is very good for fostamatinib, and also for avatrombopag [9]. There is not any significant signal that shows differences from the original data when it comes to real-world experience.

The main side effects are, for example, with fostamatinib—diarrhea, nausea, hypertension. But this is not different from what we already know with this drug. And this is not different from what has been previously described. So, no unexpected signals here.

It is also similar to other disease entities when it comes to side effects. And the same is true for avatrombopag. So, in general, all these treatment options are very well tolerated in the patients.

I just want to come back to the issue of quality of life-related side effects, the major one, which is fatigue—chronic fatigue syndrome, as it may be called. This interestingly also has been described, or has come up, in the long-term outcome studies and in the real-world experience where this is something which affects the patients and which is not as good when treated with the new therapies.

So, the mechanism is obscure, still obscure, and obviously something which is not related to the increase in the platelet count because the effects of these novel therapies and also the

meanwhile established therapies on platelet counts are very, very good. But this is in contrast to this fatigue syndrome patients complain about. And there has to be future research to unravel the pathophysiologic mechanisms and hence treatment options.

DG: Well, thank you both so much. I'm afraid that is all that we've got time for in this episode. But please do check back for more episodes in the ASH 2020 podcast series.

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## FUNDING

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