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COMMENTARY

# American Society of Hematology 2020 Podcast Collection: Sickle Cell Anaemia

Giovanna Russo · Raffaella Colombatti

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## PODCAST TRANSCRIPT

David Gray (DG): Managing Editor of *Advances in Therapy*

Giovanna Russo (GR): Department of Clinical and Experimental Medicine, University of Catania, Catania

Raffaella Colombatti (RC): Department of Women's and Children's Health, University of Padova, Padova

DG: Hello, and welcome to the Adis Rapid+ 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. On today's podcast we'll be focusing on the sickle cell anaemia data presented at the ASH conference.

Speaking to us today, are Professor Giovanna Russo from the University of Catania and Professor Raffaella Colombatti from the University of Padova. Welcome both to today's podcast, and thank you so much for speaking with us.

Now, obviously, a lot of important data was released at the 2020 conference. So could you just start by talking us through some of your highlights?

RC: Yes. Of course, sickle cell disease is a very complex condition. And clinical features accumulate with age. So it's really, really important that we find treatments that are effective both in preventing and curing the complications. At ASH virtual meeting 2020, there are many reports that highlight both these strategies. We would like to start with commenting on quality of life, because in the past years, sickle cell disease changed from a severe, life-threatening disease of childhood to a chronic, life-lasting condition thanks to significant improvements in care and treatment options.

Now we can see patients that face physical, psychological, and emotional challenges throughout their entire life. And so it's really

G. Russo (✉)
Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy
e-mail: diberuss@unict.it

R. Colombatti
Department of Women's and Children's Health, University of Padova, Padova, Italy
e-mail: Raffaella.colombatti@unipd.it



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important from one side to hear the voice of the patients' report on how they feel, and also to measure quality of life and disease burden in a standardized way.

And we had several reports at ASH that highlighted quality of life and disease burden. The first is from the Sickle Cell World Assessment Survey, the SWAY survey, which was a survey conducted between April and October 2019 involving more than 2000 patients from 16 countries and six regions, involving patients above 6 years of age, and for those patients that were below 12, the completion was by proxy. And so the questionnaires were completed by parents or guardians. And all the symptoms and the complications were self-reported by patients and standardized according to [the] Likert scale.

What is interesting is that the most commonly reported symptom in the past month, before the survey, was fatigue, tiredness [1]. Across all regions, patients reported fatigue and also across all ages although even if it was the top first reported symptom, fatigue across all ages, it was not the first across geographic regions because it was the first in Europe, but in South America and Middle East, the first symptom was bone aches, while in Asia and Africa, among the first three was difficulty in gaining weight. In the United States and North America, it was insomnia. So we had several posters that highlighted quality of life and disease burden across age and geographic regions.

And this is very important. I'd just like to highlight one further thing: is that low mood was reported in adults [2]. And this highlights that not only physical symptoms but also emotional must be considered in sickle cell disease. And all these reports show that there needs to be an increased effort to improve quality of life and reduce disease burden both in the clinical and in the research setting.

GR: I would like to add another piece of evidence that comes also from the SWAY study, that is the poster number 17 [3]. It was reported by El Rassi and colleagues. These authors report on the use of patients who use hydroxyurea versus patients who do not, and very interestingly, they reveal that patients using hydroxyurea that were at 30% had a lower burden of VOC, vaso-occlusive crisis, when compared to patients who do not use hydroxyurea. And this seems a paradox—that patients on therapy perform worse than patients who are not on therapy.

But this finding must be considered with caution since it is possible that patients on hydroxyurea are the ones that are affected by a more severe clinical condition. And therefore, the heavier burden of complaints might be related to the severity of the sickle cell disease itself rather than a consequence of the use of hydroxyurea itself.

And another interesting thing is that the proportion of patients using hydroxyurea at the time... when they completed the questionnaire of the SWAY study was very variable, but low, and not only in countries like Africa where hydroxyurea may be not available but also in other regions, hydroxyurea use was very low. For example, hydroxyurea was not in the top three treatments in Europe or North America. This is a very interesting finding because it highlights that there are other problems also apart from poor access to the drug also, maybe, patients' concerns about side effects or reluctance to take a daily medication.

So, overall, we see that barriers still exist for the use of hydroxyurea as already reported in many real-life experiences, also in Italy, where access to cure is not a major issue [4]. So it is very urgent to find and to extend the indication for hydroxyurea.

In this regard, it is interesting to highlight the contribution of two posters, both by Abdullahi and other colleagues, on the use of hydroxyurea in children in Nigeria both in low and moderate dose... in primary prevention and secondary prevention of stroke [5, 6]. And they report that the use of hydroxyurea is effective in lowering the incidence of stroke. So overall, our feeling is that hydroxyurea, the oldest drug that we have for sickle cell disease, is currently underused.

DG: Well thank you so much—surprising insights about hydroxyurea. Let's move on now to some of the drug trials data.

RC: Yes. Crizanlizumab is a drug that is a selective humanized monoclonal antibody that binds to P-selectin, blocking the interaction between activated platelets, sickled red blood

cell leukocyte, and the endothelium. And... it is now an FDA-approved drug for sickle cell disease for the prevention of vaso-occlusive crisis in sickle cell disease for patients above 16 years old. And that was reached thanks to a randomized phase II trial published in 2017 in the *New England Journal of Medicine*, which was the SUSTAIN study [7].

And we had at ASH 2020 several posters that were secondary analyses of this SUSTAIN study that led to the approval of crizanlizumab as an FDA drug in the United States. And of notice, just before ASH 2020, the drug was also approved by EMA in the European Union for the same age range, so above 16. And one of the posters was related to the benefit that crizanlizumab had in the SUSTAIN trial in reducing the number of days requiring opioid use for the management of pain [8]. And interestingly, crizanlizumab reduced the annual number of days where opioids were used to manage pain due to VOCs. And this was a benefit both for parenteral and for oral opioids.

Now, this is very important because in the USA, there is currently an opioid pandemic. So having a drug that prevents VOCs and reduces the opioid use will also help to tackle the opioid pandemic that is a burden on patients with sickle cell disease and the health system in the USA. There are no data yet on opioid use in Europe. And so it would be interesting to address this issue over also in the European Union.

There was also another poster on crizanlizumab, and that was the description of the STEADFAST trial [9]. That's a randomized multicentre open-label phase II study comparing the effect of crizanlizumab plus standard of care versus standard of care alone on renal function in patients with chronic kidney disease due to sickle cell nephropathy. And this was presented by Ataga and colleagues. And it's interesting because also, although sickle cell nephropathy is not a major issue in paediatrics and adolescents with sickle cell disease, it's becoming a very important issue in adults and a major cause of morbidity in adults with sickle cell disease.

And so this is a very welcomed trial that's a phase II and will involve patients—approximately 170 patients with sickle cell disease, with more than 16 years of age, that are receiving at least one standard-of-care drug for sickle-cell-disease-related kidney chronic disease that have a confirmed diagnosis of SS or S $\beta^0$-thalassaemia, so the most severe genotypes of sickle cell disease and that have specific kidney parameters and specific haemoglobin and platelet values.

This is a very welcomed trial that is based on preclinical studies that have demonstrated that the inhibition of P-selectin reduces the infiltration of neutrophils after renal injuries and also protects against acute kidney failures. And so this study provides evidence of the protective effect of crizanlizumab on kidney chronic injury and, hopefully, will reduce morbidity in the long run for this complication.

GR: There's another contribution on crizanlizumab that I would like to comment [on], and it's the trial SOLACE-kids, the first crizanlizumab study in paediatric patients with sickle cell disease that was presented in a poster by Dr. Heeney and colleagues [10]. It is a phase II multicentre open-label study that will enrol more than 100 paediatric patients across 15 countries in three age groups, 12 to 18, 6 to 12, and 6 months to 6 years. So the whole paediatric population.

Intravenously crizanlizumab will be administered on week 1, day 1; week 3, day 1; and then every 4 weeks thereafter for up to 2 years with a starting dose of 5 mm/kg. And then those will be adjusted based on population PK models.

The primary objectives are to confirm the dosing of the drug in the paediatric patients and assess safety. Secondary objectives include assessment of crizanlizumab long-term efficacy in the paediatric population such as the annualized rate of VOCs, hospitalization, and ER visits. As of January 28, already 59 patients have been enrolled. But we do not have info on the analysis of this data. So we are waiting.

And as paediatricians, we wait for these results. Since the evaluation of the clinical use for crizanlizumab among the paediatric population is quite urgent, in order to have the possibility to offer such therapy also to children with sickle cell disease as already Dr. Colombatti mentioned, the drug is approved for patients aged above 16 years of age. So we wait with

some anxiety to have this, too, also as paediatricians.

There's another interesting drug, a new drug, that offers a different therapy—that is voxelotor, a very promising new agent. This is a sickle haemoglobin polymerization inhibitor that was approved by the FDA in November 2019 for the treatment of sickle cell disease in adults and adolescents aged more than 12 years. Under an accelerated approval, based on the results of the HOPE study; in this study, voxelotor increased average haemoglobin by 1.1 g/dL from baseline.

At ASH 2020, Shah and colleagues presented a poster on real-world evidence of prescription patterns and effects of voxelotor for patients with sickle cell disease [11]. And they reviewed patient records from five comprehensive sickle cell centres. Overall, 60 patients were prescribed voxelotor. And 80% were already on hydroxyurea.

Among these 31 patients, more or less 50% did not begin the drug or did not return for follow-up. This is another piece of evidence on how difficult it is to actually administer a potentially useful drug to patients with sickle cell disease. The chronic nature of the disease, the barrier to access, the burden of monitoring, I think these are all critical points that need to be considered.

Another consideration on the data that were presented is that most patients prescribed the voxelotor were the HbSS genotype on hydroxyurea and with a mean baseline haemoglobin level below 7.5 g/dL, so indicated an initial focus on more severe patients and especially more anaemic patients. And this is in perfect agreement with the results of the whole trial.

RC: There was also another report on the real-world effectiveness of voxelotor. And, in fact, Zaidi et al. reported on effectiveness of voxelotor for treating sickle cell disease patients in the US for 1275 patients [12]. So it's not a small cohort of patients. And in 22 patients of this cohort, the mean baseline haemoglobin was 8 [g/dL]. And there was a mean increase from baseline of 1.1 during follow-up to a maximum of 1.3.

So this is very important because it confirms the results of the HOPE trial outside a clinical trial setting, but in the real world, that the rise in haemoglobin is true and can happen in real life. But also, the demonstration from this poster is that the mean overall transfusion rates declined from 0.45 to 0.31 and also in occasionally transfused patients as well as regularly transfused patients.

And so it is a drug that can reduce transfusion burden by increasing the rate of anaemia. And this also has, we imagine, an effect on quality of life and costs. Moreover, after voxelotor initiation, there was a reduction in annualized rates of VOC, although the reduction was not statistically significant. But we hope that with more data, this result can be achieved.

DG: Now, there was also an interesting phase I study looking at a PKR [pyruvate kinase-R] activator. Can you tell us a bit more about that?

RC: Yes. Dr. Brown, in his oral presentation on December 7, gave an insight on the phase I study with FT-4202 [13]. And the reason for which this drug might be of benefit is that we know that the loss of oxygen promotes a polymerization of HbS [haemoglobin S], resulting in RBC [in red blood cell] sickling and membrane damage, which lead to haemolysis and vaso-occlusion.

Now, sickle cell red cells contain more 2,3-DPG [2,3-disphosphoglycerate] than healthy red blood cells and resulting in decreased oxygen affinity for haemoglobin increased p50 early release of $O_2$, leading to deoxygenization of HbS polymerization, sickling, etc. So FT-4202 is an oral activator of pyruvate kinase. And its beneficial effect could be related to its ability to decrease 2,3-DPG, therefore reducing HbS polymerization and sickling.

Alternatively, PKR activation increases ATP, promoting the repair of the red blood cells and reducing haemolysis. So, of course, this background is promising. And this first data from the phase I trial demonstrate the ability of FT-4202 in decreasing 2,3-DPG and normalize the affinity—the oxygen affinity curve for HbS. The drug is also able to increase ATP and improve membrane function. What is important is also that in this first group of patients that were enrolled, more or less nine patients, the trial showed a favourable safety profile.

So based on this encouraging preliminary data, there was also another poster on FT-4202 presented by Dr. Kenneth Wood, the design of an adaptive randomized placebo-controlled double-blind multicentre study of oral FT-4202, a part of it kinase-activated in patients with sickle cell disease. It's the PRAISE study [14]. Now, what I forgot to mention while presenting Dr. Brown's result is that this is an oral drug that will be administered only once a day. And this, we know, might help compliance for sickle cell disease patients. The PRAISE study will enrol 344 adults and adolescents with sickle cell disease. And it's a phase II/III study with several co-primary endpoints.

Again, this is very interesting because it's not common to have co-primary endpoints. And so the co-primary endpoints are the Hb response, I think 24. And it's an increase in 1 g/dL from baseline haemoglobin. And the other co-primary endpoint is the annualized VOC rate during the blinded treatment period.

And so it's a trial that wants to achieve both an effect on haemoglobin anaemia and haemolysis and on vaso-occlusive crisis and pain. The safety points are also included. And the anticipated clinical outcomes are an increase in haemoglobin and a decrease in vaso-occlusion simultaneously. There have been various sites already selected in the US. And site identification at the global level is ongoing.

DG: Well, thank you, both, so much for joining me today. Unfortunately, we are coming to the end of the podcast. But before you go, what questions do you think still remain unanswered at the end of last year's conference?

GR: Well, thank you for this question because we think that we have several drug options that were presented. And even if most countries have implemented strategies to offer appropriate care to sickle cell disease patients, we see that there are many unmet needs and many unanswered questions.

How do we fit curative treatments in the era of multiple options? How do we incorporate the newly approved options—and I refer to L-glutamine, crizanlizumab, voxelotor—into a regular management? How do we help our patients to choose these treatments?

Can we use multiple agents simultaneously or sequentially? How can we combine then the different options? How can we choose? And as Dr. Colombatti highlighted, the compliance for the patients is a very hot topic.

So with more complicated regimens, will we have a greater pill burden that will influence compliance? Will we have separate options or cocktails for acute events or for chronic therapy? And so far we talked only about drugs, pills, and what about other options? Haematopoietic cell stem transplantation is far from being an option for most patients. We have many challenges with access, donor availability, toxicity, cost. So there is a lot to explore.

RC: Yes, and I also can add that we must not forget to mention gene therapy and gene editing. And there were also many oral presentation and abstract at ASH. And I'd like to recall, as a concluding remark, the presidential session in which Dr. Haydar Frangoul presented their encouraging data on safety and efficacy of CTX001 in transfusion dependently to thalassaemia and sickle cell disease [15]. And he presented the early results from the CLIMB THAL-111 and CLIMB SCD-121 studies for autologous CRISPR-Cas9-modified CD34 cells, haematopoietic stem, and progenitor cells. And the data was so encouraging that they were published the same day in the *New England Journal of Medicine*.

So yes, as we discussed today, there are many pharmaceutical options, disease-modifying options, that are reaching the real world but also promising results from the curative option that are reaching the real world for sickle cell disease patients.

DG: Fantastic. Thank you both so much for that amazing roundup of the sickle cell anaemia highlights from ASH 2020. Thank you for joining us today and giving us your time. I know that this will be really helpful for our listeners. Please do look out for other podcasts in the ASH 2020 coverage collection.

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