EMA
EUROPEAN MEDICINES AGENCY

Workshop - Challenges in drug development, regulation and clinical practice in haemoglobinopathies

1st July 2024

Virtual meeting

Meeting report: workshop on the challenges in drug development, regulation and clinical practice in haemoglobinopathies

1. Introduction

Haemoglobinopathy is a group of inherited blood disorders and diseases that primarily affect red blood cells. They are single-gene disorders and, in most cases, they are inherited as autosomal co-dominant traits.

There are two main groups: abnormal structural haemoglobin variants caused by mutations in the haemoglobin genes, and the thalassemias, which are caused by an underproduction of otherwise normal haemoglobin molecules. The main structural haemoglobin variants are HbS, HbE and HbC. The main types of thalassemia are alpha-thalassemia and beta thalassemia.

Mutations leading to structural haemoglobin variants and to underproduction can be co-inherited, such in the heterozygous states of S-beta thalassemia. Some haemoglobin variants do not cause pathology or anaemia, and thus are often not classed as hemoglobinopathies.

Recently, new therapies, including gene therapies, have been authorised in the EU and the US and further products are in development.

This workshop was organised to have a multi-stakeholder's perspectives on these diseases before initiating the drafting of new scientific guidelines both in sickle disease (SCD) and beta-thalassaemia in line with the haematology working party work plan for 2024. These guidelines are aimed to define the data needed and clinical requirements for benefit-risk evaluation of new medicines with a view to obtaining a marketing authorisation.

2. Purpose of the Workshop

Overall aims of the workshop:

• To present the epidemiology and disease background in adults and children with sickle cell and thalassemia, the current international treatment guidelines, the unmet medical need, and the overview of the authorised medicines/treatments in the EU and in US for sickle cell and thalassemia.

• To present the challenges in treatment/drug development from a clinicians' perspective with regards to study design and endpoints used in clinical trials as well as the introduction of new therapies such as gene therapy.

• To present additional perspectives from Health Technology Assessment bodies, bioethics for gene editing, and the use of registries in these diseases.

3. Workshop Report

The workshop was organised in the following sessions:

1. **Welcome and opening speech**
2. **Session 1: Patients and clinical perspectives and management of sickle cell and thalassemia diseases**
3. **Session 2: Overview and regulatory consideration of authorised medicines in Sickle Cell Disease and Thalassemia diseases**
4. **Session 3: Additional Perspectives**
5. **Panel Discussion: Clinical Trials and Patient Outcomes**
6. **Closing remarks**

Guidance to the reader: *This report summarises the key aspects which were discussed during each session of the workshop. Abstracts and panel discussions are summarised under each session. This report should not be understood as the official views of the EMA or its scientific committees.*

3.1. Welcome and opening speech

Opening Remarks by Emer Cooke: Emer Cooke, Executive Director of the European Medicines Agency (EMA), welcomed attendees to the workshop on "Challenges in Drug Development, Regulation, and Clinical Practice in Hemoglobinopathies," focusing on both sickle cell disease and beta -thalassemia and emphasised the importance of the workshop. She noted that hemoglobinopathies, which affect approximately 7% of the global population, present significant challenges. Recent advancements, including the approval of gene-editing therapies using CRISPR-Cas9 technology, highlight the evolving landscape of treatment options. Ms. Cooke stressed the importance of the workshop as a platform for discussing pressing issues, learning from shared experiences, and contributing to the development of new scientific guidelines that will support future drug development and regulatory decision-making, ultimately benefiting patients.

Caroline Voltz, from EMA at the advanced therapies and onco-heamatology office extended the welcome to the attendees and highlighted that the workshop would gather multi-stakeholder perspectives, crucial for drafting new EMA guidelines for these conditions. The guidelines aim to define necessary data and clinical requirements for evaluating the benefit-risk ratio of new medicines intended for marketing authorisation. She also outlined the structure of the workshop, which included patient and clinical perspectives, regulatory overviews, and bioethical considerations.

At the beginning of the workshop, Daniela Philadelphy, the chair of the HAEMWP and CHMP member for Austria, welcomed participants and expressed her pleasure in hosting the event. She emphasised that the workshop would serve as the foundation and kick-off for drafting new guidelines to define the clinical requirements for the two conditions discussed. This workshop was considered an essential step in creating scientific guidelines that will guide the evaluation of benefit-risk assessments and support the process of obtaining marketing authorisation for relevant therapies.

3.2. Session 1: Clinical and Patient Perspectives

Thalassemia: The session commenced with a presentation by Professor Ali Taher from the American University of Beirut, who provided a detailed examination of thalassemia, particularly emphasising the significance of hepatic and cardiac iron levels as critical indicators of patient morbidity and mortality. Prof. Taher highlighted the variations in transfusion practices across different regions, pointing out the challenges patients face in adhering to iron chelation therapy. He stressed the importance of adopting a holistic approach to patient care, which goes beyond managing iron overload to addressing the broader spectrum of health challenges faced by individuals with thalassemia. He also discussed the forthcoming 2024 treatment guidelines by TIF, which aim to standardise and improve patient care globally.

Sickle Cell Disease (SCD): Following this, Professor John Porter from University College London provided an overview of the complexities associated with SCD. He elaborated on the variability in disease expression and the severe complications that affect patients, particularly as they transition from childhood to adulthood. Prof. Porter discussed the range of management strategies currently available, including anti-sickling agents, gene therapy, and preventive approaches. He underscored the critical need for improving non-curative therapies and enhancing healthcare systems to better address the needs of SCD patients, many of whom suffer from significant health inequities.

Pediatric Perspectives: Professors Marianne de Montalembert from France and Raffaella Colombatti from Italy jointly provided a pediatric perspective on SCD and thalassemia, drawing attention to the disparities

in care and access to treatment across different regions. They highlighted how disease expression varies across the lifespan, which complicates treatment. Their presentations underscored the significant unmet medical needs in paediatric populations (e.g. cerebral vasculopathy, need for biological markers, quality of life, markers of organ damage) and the need for greater international collaboration to improve treatment outcomes.

Patient Perspective: Loris Brunetta, representing the Thalassaemia International Federation, provided a poignant patient perspective, sharing his personal experiences living with thalassemia. He expressed optimism about the advances in treatment but also highlighted ongoing unmet needs, particularly the need for a more patient-centered approach that considers the psychological and social aspects of the disease. Loris emphasized the need of a more appropriate QoL measurements with patient involvement by having PRO, PED and RWE validated so that they can be used in decision-making. There are still unmet medical needs with regards to osteoporosis prevention and pain issue in older patients. His presentation was a compelling reminder of the importance of involving patients in the decision-making process.

3.3. Session 2: Regulatory Perspectives

FDA Approvals: Patricia O'Neil and Megha Kaushal from the FDA provided a thorough review of the agency's approach to approving treatments for beta-thalassemia and SCD. They discussed the various therapeutic options that have received FDA approval, including iron chelators and novel gene therapies. Their presentation addressed the challenges of selecting appropriate outcome measures for clinical trials, as well as the long-term safety concerns associated with emerging therapies.

EMA Overview: Johanna Lähteenvuo from the Finnish Regulatory Agency and alternate member of CHMP as well as member of the scientific advice working party (SAWP) offered insights into the EMA's evaluation process for new treatments for SCD and beta-thalassemia. She highlighted the importance of reliable and meaningful endpoints in clinical trials, particularly in the context of rare diseases where data is often limited. She also discussed the challenges regulators face in assessing the benefit-risk profiles of new therapies, given the complexities and variability of these diseases. This was supported by examples from approved products.

Project OPEN: Radhouane Cherif from EMA's International Affairs department introduced the EMA's OPEN framework, aimed at achieving regulatory convergence and facilitating the global approval of new medicines. He emphasised the importance of collaboration between regulatory bodies worldwide to ensure that patients gain timely access to safe and effective treatments. The project seeks to facilitate sharing of scientific expertise to tackle common challenges and alignment of regulatory approaches between regulatory authorities to streamline the approval process for innovative therapies, particularly for rare diseases like SCD and thalassemia.

3.4. Session 3: Additional Perspectives

Bioethics in Gene Editing: Laurence Lwoff from the Council of Europe addressed the ethical considerations surrounding gene editing technologies, which are increasingly being explored as potential treatments for genetic disorders like SCD and thalassemia. She emphasised the need for clear ethical guidelines that respect human dignity and ensure that gene editing is conducted responsibly and transparently. In this respect Laurence referred to the relevant statements and clarifications adopted at intergovernmental level in relation to relevant legal provision laid down in the Convention on Human rights and Biomedicine.

Health Technology Assessment (HTA) Perspectives: Anja Schiel from the Norwegian Medical Products Agency discussed the role of health technology assessment (HTA) in evaluating the cost-effectiveness of

new treatments. She focused on the importance of quality-adjusted life years (QALYs) as a metric in decision-making, particularly in the context of high-cost gene therapies. She highlighted the challenges that HTA bodies face in balancing innovation with affordability, especially when considering long-term outcomes and societal benefits.

Experience from Registries: Dr. María del Mar Mañú Pereira presented findings from the RADeep Registry, the European patients registry that collects standardised real-world data on patients with SCD and thalassemias, and other rare anemia disorders. She emphasised the value of such data in supporting clinical research and informing regulatory decisions. Pereira's presentation demonstrated how registries can provide insights into disease progression, treatment patterns, and patient outcomes, which are critical for advancing care and improving guidelines.

Challenges in Drug Development: Antonella Isgrò from the Italian Regulatory Agency (AIFA) spoke on the challenges associated with drug development for hemoglobinopathies like SCD and thalassemias. Over the past few years, there has been an increased understanding of the SCD pathophysiology, with several treatment approaches proposed for modulation of Hb polymerization, prevention of vasal occlusion by inhibiting cell-cell interactions, prevention of endothelial dysfunction and modulation of inflammation. Also, for β-thalassemia several treatments have been proposed for ineffective erythropoiesis and anaemia associated with TDT and NTDT, to modify iron metabolism or the globin gene expression. However, evidence from Academic and Pharma industrial research for translation needs to be solid in every step of drug development, until approval and patient access. She highlighted the need for validated endpoints in clinical trials and the importance of international collaboration to overcome these challenges. She further stressed that the clinical outcome assessments selected should be suitable for regulatory use, be valid assessments of important and relevant aspects of the disease, and that input be obtained from clinicians experienced in caring for patients with the target disease. Antonella also discussed the regulatory hurdles that companies face when developing new therapies and the need for ongoing dialogue between regulators, clinicians, and patient groups.

3.5. Panel Discussion: Clinical Trials and Patient Outcomes

The panel session during the workshop focused on defining relevant parameters and outcome measures for clinical trials, particularly in the context of sickle cell disease and thalassemia. The session was co-chaired by Caroline Voltz and Daniela Philadelphy and included all speakers and additionally Jennica Leah and Chris Sotirelis, patients' representatives.

Key topics included the importance of considering both the perspectives of physicians and patients when identifying treatment goals, as well as recognising the heterogeneity in patient populations, which demands tailored approaches in clinical trials. Hemoglobinopathies have a substantial genotypic and/or phenotypic heterogeneity. Moreover, the variability in thalassemias and SCD expression is only partially explained by genetics, as socioeconomic and environmental factors can also contribute to the heterogeneity. Therefore, the panel emphasised the necessity of accounting for this heterogeneity when defining the study population and the importance of considering baseline patients' characteristics (e.g. previous treatment(s) already received) to select relevant endpoints. The impact of genetic variability on pharmacokinetics, pharmacodynamics, safety and efficacy needs to be carefully considered. Panellists emphasised the importance of incorporating patient perspectives into trial design, particularly in terms of reducing pain and preventing long-term organ damage.

The discussion also highlighted the importance of differentiating between the needs of patients with sickle cell disease and those with thalassemia. Starting with the patient perspective, Jennica Leah stressed the expectation for treatments that genuinely reflect the needs of the broader sickle cell community, underscoring the importance of patient-centered outcome measures. Loris Brunetta highlighted the

importance of having several treatments options. Preventing long term complications arising from long-term blood transfusions was also emphasised. Differentiation between transfusion dependent and transfusion non-dependent patients should also be made.

Further, the panel explored the challenges of balancing the pursuit of long-term outcomes with the urgency of getting medicines to patients faster. The discussion recognised that while short-term studies often dominate, there is a need to have long-term data. From the physician perspectives for SCD, the most frequently used measures are vaso-occlusive crises (VOC) rates and can reflect the impact on some health systems (e.g. admissions in hospitals). Although pain assessment is very subjective, pain and its consequences could be further explored as an endpoint. However, it was considered that the most relevant endpoint could be the long-term effects on the sickling process and the impact on organ damage, acknowledging the time needed to have these data. For ß-thalassemia, Hb levels are considered an adequate surrogate measure. Measurement of pain is highly subjective therefore it is extremely difficult to use pain as an endpoint. In addition, children have different trigger for pain in comparison to adults, as an example adults are most likely to have neuropathic pain. Measurements of Foetal haemoglobin (HbF) is often used as well. In addition, attendees recognised that patients may be hesitant to enter clinical trials. The decision to give long-term transfusions would not be the same amongst health care givers and would not be the same for all patients. Notably, ongoing clinical trials mostly recruit patients who are not receiving transfusion. There are currently different views with regards to using biomarkers in SCD amongst the medical community (e.g. does an improvement in haemoglobin translate in an improvement in the clinical state?). According to a recent publication from the British journal of pharmacology (Assessment of fatigue in adult patients with sickle cell disease: Use of the functional assessment of chronic illness therapy-Fatigue (FACIT-fatigue) questionnaire, Cheminet G, e*t al* JB.Br J Haematol. 2024 Jul;205(1):335-342. doi: 10.1111/bjh.19568. Epub 2024 May 27. PMID: 38802081), there is no apparent relationship between fatigue and anaemia. With regards to anaemia and its clinical consequence for SCD patients, it has been demonstrated that anaemia only had an impact on stroke and renal disease. Cerebral vasculopathy has been neglected in clinical trials. Complications of stroke would be also very important to investigate.

From a HTA's perspective, it is also important to get data on the natural course of the disease for example if patients are reluctant to participate in clinical trials. It is important when designing clinical trials to also take into consideration the HTA needs. Using registries would be useful to collect data on natural course of the disease. At present, there are missing data in the patients' registries and dataset currently available. Standardisation of data reporting is also paramount to be able to rely on these data.

With regards to ß-thalassemia, the main issue is the low level of haemoglobin. For children, increasing the haemoglobins levels with low side effects, reduce the need for transfusions and associated complications linked to long-term use of transfusion. Switching a patient with a high transfusion state to less transfusions, the patients need to generate more red blood cells and therefore increase the risk of Extra Medullary Haematopoiesis (EMH). Another risk is that patients could be at risk of thrombosis which would translate into the need for transfusions because of thrombotic episodes. There might be different needs for paediatric patients that could also depend on their baseline characteristics. Patient representative highlighted the differences in patients care in other regions of the world where alternative care is provided (e.g. holistic and nutritional considerations), when quality of life aspects is considered. Intra-patients' comparison could also be used to determine the effects of medicines, such as in haemophilia. From a HTA perspective, it is important to consider patients' needs and long-term data are considered important to be able to measure the impact of treatments on patients.

FDA colleagues clarified that Zynteglo is authorised in children and other gene therapy medicines approved for SCD and β-thalassemia include an indication for children above 12 years of age. Data on new therapies regarding children are currently limited and access to new therapeutic approaches in children is delayed since most clinical trials involve adults first. FDA recently issued a guideline on diversity and inclusion in

clinical trials. FDA, EMA and HC participated to a project initiated by the American Society of Haematology (ASH) on diversity and inclusion in clinical trials. This is also an area of interest in ACT EU.

The panellists also addressed the importance of aligning clinical trial endpoints with what patients perceive as beneficial, a task deemed easier for thalassemias compared to sickle cell disease.

Lastly, the session concluded with a reflection on the need for comprehensive guidelines that define safety, efficacy, and long-term outcomes, all while incorporating the patients' voice. The outcome of this panel will serve as a foundation for drafting new guidelines aimed at improving the evidence generated for benefit-risk assessment for new treatments in these conditions.

3.6. Conclusion

The workshop underscored the critical importance of multi-stakeholders' collaboration in addressing the complex challenges associated with SCD and thalassemia. By bringing together clinical experts, regulators, ethicists, and patient representatives, the Haematology Working Party of the EMA has gathered multi-stakeholders' input that can be used as a sound basis to develop guidelines that define the data needed for benefit-risk assessment by reflecting the needs of all involved. Moving forward, the insights gained from this workshop is expected to play a crucial role in shaping the future of treatment options and care for patients living with these debilitating conditions. It was also emphasised that there is a need for continuing multistakeholder discussions.