Event report

Gene therapy – Where do we stand

Tuesday 27 October 2020, Virtual event

EXECUTIVE SUMMARY

This EHC Roundtable aimed to shed light on the benefits and pertinent challenges of gene therapy within the haemophilia community. In this regard, current and future implications were addressed, generating key considerations that would impact trajectory of this novel treatment.

The event featured presentations featuring the following main conclusions:

1. Issues of reliability, variability, durability and safety need to be addressed in order to optimise the viability of gene therapies.
2. Gene therapy licensing is evolving in nature to promote patient access and protection, whilst ensuring innovation.
3. The budget impacts and cost vs value differentials impacting the affordability of gene therapies could be addressed through social contracts.
4. Clear professional-patient communication is necessary to ensure that patient-related and treatment-related facets are understood.

The event also featured two interventions by MEPs Manuel Pizarro and Katalin Cseh who pledged their political support to the haemophilia community, advocating for more action at the European level.

I. ABOUT THE EVENT

On Tuesday 27 October 2020, the European Haemophilia Consortium (EHC) organised a roundtable discussion entitled *Gene therapy – Where do we stand.* Moderated by Brian O'Mahony - CEO of Irish Haemophilia Society and EHC member of the Medical and Scientific Advisory Group, the event took place virtually, bringing together attendees from patient, industry and research backgrounds. MEPs Manuel Pizarro and Katalin Cseh were also in attendance. The event's agenda can be found in the final part of this report.

II. WELCOME SPEECH

Guest speakers: MEP Manuel Pizarro and MEP Katalin Cseh

MEP Pizarro (S&D, Portugal) opened the roundtable discussion by remarking that gene therapies offer very promising prospects to the rare bleeding disorders patients, potentially enabling them to live disease-free. He nonetheless noted that there are also unique challenges related to safety, efficacy and affordability. Dr Pizarro emphasised the need to involve the EU in healthcare matters and build a European Union of Health, as announced by European Commission President Ursula Von der Leyen.

Dr Cseh explained that gene therapies will have far-reaching positive consequences not only for haemophilia patients, but for the rare diseases field at large. Having experienced first-hand the resilience and solidarity shown within the haemophilia community, the MEP noted that the policy-makers' job is not done until patients are able to live a life of the highest quality, without the pressure of their underlying conditions. As such, EU policymakers are always open to input on how they can contribute to the efforts of the haemophilia community.

III. GENE THERAPY FOR HAEMOPHILIA – STATE OF PLAY

Dr David Lillicrap, *Associate Head, Research and Professor at Queen's University, Canada*

Dr Lillicrap's presentation focused on the relevance of gene therapy for haemophilia patients and the key concerns that have shaped the current state of play. With 5 ongoing haemophilia A gene therapy studies and 4 in haemophilia B, the professor noted four key questions that arise when using adeno-associated-virus (AAV)-mediated haemophilia gene therapy: 1) reliability in the vector doses, 2) variability of doses in Factor VIII and IX expressions, 3) durability of gene therapy responses and 4) safety issues arising from potential side-effects. It was also noted that all trials require 2 years to mature for efficacy evaluation, since immune obstacles, biological knowledge of gene delivery and expression processes need to be comprehended to a greater degree. Nonetheless, Dr Lillicrap emphasized that these hurdles should not inhibit the licensing of a gene therapy product.

IV. SAFETY, EFFICACY, LICENCING AND AFFORDABILITY OF NOVEL THERAPIES

Dr Glenn Pierce*, World Federation of Haemophilia (WFH) Board of Directors*; ***Caroline Voltz****, European Medicines Agency (EMA);* ***Declan Noone,*** *EHC President*

Gene Therapy Safety and Efficacy considerations

Dr Glenn Pierce remarked that the variability and predictability of gene therapy response may be problematic for decision making processes. These issues have been progressively addressed through gene therapy, but studies have yet to determine the exact interaction between AAV and the host. Progress on biology is indeed far behind clinical trial development. Dr Pierce additionally noted that, before introducing a medical product on the drug market, developers face a dilemma of having to predict market needs 7 to 10 years ahead. Finally, for AAVs, improvements in delivery path, contributors to factor production, and understanding the human host response to this viral vector would seem necessary as the price of entry.

Gene Therapy Licencing - the EMA view

Strong EMA support was shown in the development of gene therapy medicines, and has been further demonstrated by the publication of overarching and specific guidelines[1]. General requirements for gene therapies incorporate key learnings from EU experience, focusing on safety considerations for quality levels and key points of contention for advanced therapy medicinal products (ATMP) approval (such as product consistency, challenges related to starting materials and insufficient long-term follow-up). Specific requirements for haemophilia gene therapies include procurement of data from phase 3 clinical studies (which are generally conducted in an open-label, single-arm and single-dose manner) and the EMA has also extended the long-term follow-up from clinical AAV studies to at least 10 years. Extrapolation of adult data to paediatric population is not straightforward and developments in younger age groups will require finalisation of adult patients' data, with available and clear positive benefit/risk results. Overall, gene therapy licencing presents an evolving role for the EMA in order to progress from research and development to patient access and to protect patients whilst enabling innovation.

GT Affordability – Possible payment mechanisms

Two systematic challenges are presented in terms of gene therapy affordability: budget impact and the cost vs value differential. Mr Noone demonstrated the cost-effectiveness of gene therapy vs FVIII prophylaxis and presented contracting as a viable solution, which would require planned assessments and incentives to countries for assessing therapy value regularly. The co-creation of contracts between the patient and clinician or healthcare provider could enable pragmatic outcome collection and account for long-term uncertainties (such as treatment avoidance or proven lack of toxicity).

V. DISCUSSING GENE THERAPY CHALLENGES WITH PEOPLE WITH HAEMOPHILIA

***Prof Wolfgang Miesbach**, Department Head at the Goethe University Hospital*

Noting that there are many issues that healthcare practitioners must discuss with their patients, Prof Miesbach outlined the importance of individualized information for every patient enrolling, undergoing or considering gene therapy. He stated that prior to therapy administration, patients should understand how gene transfer works, what the possible clinical benefits are, the level of follow-up required, the variability in desired outcomes and associated potential risks. Following gene therapy, the patient must be informed about the changes in bleed risk and precautionary requirements, and should also be encouraged to an open conversation about any emotional problems.

In addition to this, Prof Miesbach maintained that the limited patient eligibility should also be considered, as patients with a history of AAV inhibitors do not make suitable candidates. Furthermore, following gene therapy administration, patient-related and treatment-related variabilities, such as possible side-effects, durability, anxiety, lifestyle changes and life-long monitoring could add pressure onto the patient.

[1] List of EMA scientific guidelines on gene therapies: https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/multidisciplinary/multidisciplinary-gene-therapy

VI. CONCLUSION

Although a number of key considerations would need to be addressed, speakers estimated that potentially 10-20% of severe haemophilia A patients and 20-30% of severe haemophilia B patients may consider this treatment by 2030. In summary, the following important points were highlighted during the event:

- Although advances have been made in gene therapy, fundamental questions concerning reliability, variability, durability and safety need to be addressed. Nonetheless, these obstacles should not impede the licencing of gene therapies in the next years.
- More liver biopsies are essential for a better assessment of integration, host-response to the viral vector and processing of FVIII and FIX genes. Each company needs to take the responsibility in implementing and proceeding with regular and sufficient liver biopsies studies in each trial.
- Gene therapy licencing is taking on an evolving role within the EMA so as to guarantee patient access and protection whilst ensuring that innovation is also placed at the forefront.
- Systematic problems relating to affordability, notably budget impact and the cost vs value differential, can be potentially overcome with the creation of social contracts for patients.
- A two-way communication stream between medical professionals and patients is essential to ensure that any challenges are accounted for when considering or administering gene therapy.

European Haemophilia Consortium Round Tables of Stakeholders
27 October 2020
Virtual event

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AGENDA

(CET)

14.25-14.30	**Opening & Instructions**
14.30 – 14.35	**Welcome and introductions** *Brian O'Mahony - EHC MASAG member* *MEP Manuel Pizarro, MEP Katalin Cseh*
14.35 – 15.00	**Gene therapy for haemophilia – state of play** *Dr. David Lillicrap*
15.00 – 15.45	**Gene Therapy Safety and Efficacy considerations** *Dr. Glenn Pierce* **GT Licencing - the EMA view** *Caroline Voltz* **GT Affordability – Possible payment mechanisms** *Declan Noone*
15.45 – 16.00	**GT Challenges - Discussing Gene Therapy with people with Haemophilia** *Dr. Wolfgang Miesbach*
16.00-16.25	**Q&A and discussions**
16.25-16.30	**Conclusions**