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LETTER TO THE EDITOR

Challenging times: Delivering gene therapies and an opportunity for shared learning

As we embrace the era of precision medicine, gene therapies are the vanguard in the fight to cure rare diseases. While rare diseases are just that, rare, it is suggested that patients with rare diseases worldwide outnumber those with HIV and cancer combined.[1] The development of safe and effective therapies that target genetically driven diseases has progressed significantly since the initial controversies. Now that gene therapies have moved from bench to bedside and achieved regulatory approval, a pipeline of therapies exists providing much needed hope for patients with incurable rare diseases. However, processes to customize the administration of these therapies in a safe, patient-centred and efficient manner are necessary for health care systems. Our recent experience delivering gene therapies, and Zolgensma® specifically, involved many challenges, not least an unprecedented COVID-19 pandemic. Following the recent themed issue on Advanced Therapies in this journal, our experience provides an opportunity to share lessons with international centres who will deliver these therapies.

Zolgensma® (Onasemnogene abeparvovec) is a revolutionary therapy for spinal muscular atrophy (SMA), a fatal neuromuscular disease due to loss-of-function mutations in the survival motor neuron 1 (SMN) gene.[2,3] The therapy delivers the missing gene using an adeno-associated viral (AAV-9) vector which is capable of overcoming the added complexity of crossing the blood brain barrier. Compared with previous SMA therapies, Zolgensma® potentially avoids the requirement for repeated intrathecal injections.[3] The early clinical experience of this therapy is reported elsewhere.[4,5] In addition to the clinical considerations, the administration of Zolgensma® necessitates careful consideration of patient safety, regulatory approval, product preparation, environmental impact and logistics. The administration of advanced therapies in a hectic hospital environment will be a significant challenge for health care providers internationally.

There are two important points to consider when discussing treatment with Zolgensma®. First, there is the patient access to this expensive gene therapy, with a US price tag of $2.1 m.[6] While the product received European Medicines Agency authorization in 2020, funding decisions are ongoing in many jurisdictions. Meanwhile, infants with SMA have a narrow time window in which to receive the product so the benefit is maximized. Therefore, at an individual level, there is a pressing need to treat these children as soon as the product is authorized. While funding applications are evaluated, a managed programme provided immediate access to Zolgensma®.

The second important consideration is the health care context. The delivery of a one-off advanced therapy in a hospital environment is a challenge, not least because it requires considerable resources which must be drawn from other ongoing activities. In addition, gene therapies have specific issues related to their compounding and containment as well as the unfamiliarity of health care providers with their administration. In our hospital, given the complexity of the process to treat patients with Zolgensma®, it was decided to do so in the onsite clinical trial unit, the Wellcome-HRB Clinical Research Facility at St James's Hospital (SJH-CRF). This arrangement facilitated the drug administration in a clinical area which could be ringfenced for administration. The SJH-CRF included access to a dedicated pharmacy and aseptic compounding facility. Also, the SJH-CRF staff had prior experience in the administration of advanced therapies, including gene therapies.

The SJH-CRF is a purpose-built facility with established accessibility pathways for patients entering clinical trials. In Jan 2020, a request was received from a local tertiary-referral paediatric hospital to assist with administration of Zolgensma® to an as yet unborn infant diagnosed with SMA Type 1 in utero. The testing for SMA was performed as the baby's sibling had been diagnosed with SMA. Being aware of the managed access programme for Zolgensma®, the parents requested their baby be considered for treatment. Immediate concerns of the treating team when considering this request included the need for an available aseptic compounding unit with alternate flow capability and the capacity to manage the terms and conditions of an environmental licence for the gene vector product. Of note, the first Zolgensma® treatment at our facility occurred prior to EMA authorization (via the managed access program), while subsequent administrations were after the EMA approval. Also, as the manufacturer rolled out the Zolgensma® access program in early 2020, an unexpected complication arose in the shape of the COVID-19 pandemic.

The challenges for the SJH-CRF to successfully deliver the drug were manifold including

- Regulatory advice regarding the managed access program must be acquired in a timely manner.
- Clinical indemnity and institutional insurance must be requested and confirmed to provide for treatment of a child within an acute adult hospital setting and risk management of drug administration.
- Standard operating procedures (SOPs) for the drug administration must be updated or newly developed.
- Handling and disposal protocols must be compliant with national environmental regulations for genetically modified organisms (GMOs).
- Logistics for the international delivery of GMOs must be arranged.

Our clinical trials unit was accustomed to the provision of novel therapies, and its location within Ireland's largest hospital provided support in terms of access to pharmacy, radiological and intensive care expertise if they were required.

At the centre of all considerations was the requirement for the children with SMA to be treated in a time critical manner.[5] To date, four babies have received Zolgensma® at the SJH-CRF. Therefore, the challenges above have been overcome, providing an opportunity to share lessons with an international community who will treat patients with SMA with Zolgensma®. Indeed, our unit has advised other European units on the complexities of Zolgensma® delivery, and we are committed to helping other institutions on request. The lessons may be more broadly applicable to centres commencing the administration of gene therapies in the setting of a clinical trial, compassionate access program or a service to deliver advanced therapies.

First, a multidisciplinary and cross-institutional project leadership team was assembled. The team was focused on the task at hand and dedicated significant time in their schedules to prepare for the Zolgensma® dosing. The team assigned the necessary clinical staff required to treat the babies with SMA including paediatric and clinical trial specialists. The latter were chosen based on their previous experience administering gene therapies in the clinical trial setting. The project required resourcefulness, collaboration and learning-by-doing approach from all staff involved.

Second, key stakeholders were identified by the leadership team at the planning stage so that the process to deliver the therapy was considered in its entirety and potential pitfalls were identified. For example, clinical indemnity was required for the treating physician. Given the unique nature of the project at the time, the decision makers in terms of indemnity were involved at an early stage. Also, it was essential to include the hospital management who were agreeable and willing to invest time into the endeavour.

External stakeholders, including governmental agencies and statutory bodies, were identified and briefed. Which agencies to involve was determined by the relevant legislation in our jurisdiction and so will vary depending on the context elsewhere. The EMA drug approval process for gene therapies includes an environmental risk assessment because they are GMOs.[7] As the first Zolgensma® treatment was administered before the drug had EMA approval, the medicines regulator in Ireland, the Health Products Regulatory Agency, was consulted for advice. Importantly, the project also required the involvement of our Environmental Protection Agency (EPA) for the first dose. The leadership team were careful to brief all relevant stakeholders as the project evolved so that communication was maintained.

Next, a number of SOPs were written to enable Zolgensma® dosing. These were prepared with information drawn from our institutional knowledge of gene therapy delivery in clinical trials, Zolgensma® prescribing and MAP protocols, a visit to observe the dosing of a gene therapy at a UK site as well as drawing from freely available resources such as those provided by the Advanced Therapy Treatment Centres and the Pan UK Pharmacy Working Group. Specific pharmacy protocols were drafted, reviewed and authorized. These included the SOPs on dose preparation and administration. Advance planning was required to ensure the required materials were in stock and that the compounding technicians were trained on how to prepare the product. Essential steps in the preparation were detailed such as product labelling and inspection of the dose. Accountability and chain of custody documents were also introduced. The compounding isolator and cleanroom were cleaned and monitored to an agreed standard before and after dose preparation. Careful inspection and checking of the product are inherent in the administration procedure and were stipulated.

The administration procedure focused on patient safety, drawing on the SJH-CRF's commitment to safety and quality when performing clinical trials. Acute toxicities following gene therapy are well described. These can be vector related with a significant viraemic response, drug-related immune responses or thrombocytopaenias and/or related to inappropriate handling or administration. To mitigate the risk of acute toxicities corticosteroids were administered from 1 day prior to dosing for 30 days in line with the company's prescribing information. A plan for escalation of care in the event of a serious reaction was described and agreed upon. A care team was assembled including a consultant paediatrician, a paediatric anaesthetic, nurse specialists and paramedics.

Patient monitoring was also detailed in the SOPs including ongoing measurement of platelets and liver function. The SOPs were supported by a flow sheet which required review of the patient on arrival (vital signs, clinical exam, intravenous access and blood results), an equipment check (paediatric resuscitation kit, emergency drugs and consumables) and patient monitoring during and after drug administration (vitals and clinical examination). Importantly, the creation of SOPs for Zolgensma® was supported by the existing SJH-CRF SOPs such as those related to our Advanced Therapy Medicinal Product (ATMP) Clean Room.

In tandem with the clinical and pharmacy SOPs, protocols were required to ensure the environmental impact was assessed and minimized. This was aided by advice from the EPA as well as the hospital's Infection Control and Occupational Health departments. The EPA gave consent to proceed with Zolgensma® dosing with a number of conditions. These included the limited timeframe for the EPA consent, appropriate recording of GMO use, reporting requirements, containment measures, staff safety, prevention of contamination and waste disposal. The regulation surrounding ATMPs classified as GMOs has been identified as an issue for ATMP adoption in Europe.[8] Thankfully, the EMA now provides guidance on a streamlined approach to assess the environment risk of medicines containing GMOs. To meet the EPAs conditions, Zolgensma® required additional specific protocols to detail processes for its receipt, handling, storage, internal transport and disposal. For example, the exact access point and delivery route through the hospital building was mapped. Also, the personal protective equipment (PPE) to be worn when handling Zolgensma® was carefully described. Contingencies were considered in the event of an incident such as a spill or accidental exposure and SOPs were prepared accordingly. This level of detail ensured that planning of an in-depth step-by-step process occurred, and the potential critical issues had been identified.

To ensure these procedures were correctly implemented, staff training was essential. Training was delivered to the CRF staff in a multimodal manner. A 'read and understand' approach was used for the new Zolgensma® specific SOPs for CRF staff already familiar with the administration of gene therapies. The visiting paediatric clinical team required instructor led training on the new SOPs as well as those required for CRF induction. In addition, all staff attended a session to familiarize themselves with the timetable for the day of dosing, their responsibilities and the procedures for dosing. Importantly, the plan of action in the case of a clinical event, for example an acute toxicity, was presented at this session. Therefore, staff training was more in keeping with the standard required in preparation for a clinical trial rather than a routine clinical service.

Lastly, the logistical operation of importing a novel gene therapy with a GMO classification across international borders was completed. The choice of delivery service may be informed by the manufacturers experience or that of the administering facility. After the first Zolgensma® dose in February 2020, the COVID-19 pandemic began to loom large in Europe. Therefore, the delivery of Zolgensma® was extremely urgent so that a significant delay to dosing did not occur while a baby's health deteriorated. Thankfully, with the cooperation of the manufacturer and the delivery firm, the dose arrived before international parcel services were affected.

And so, we are at the beginning of an exciting era of curative therapies which have been promised for decades but are now being realized. Health systems internationally must adapt to complete the translation of advanced therapies from scientific successes to effective health interventions. The difficult process of delivering Zolgensma® to an infant with SMA has taught us numerous lessons which we wish to share. The challenges we encountered spanned the health care context, national and international regulations, environmental impact and protection as well as funding approval and access to treatment. To these, a pandemic has been added for good measure. However, at the centre of this complex milieu are the young patients who benefit from these novel therapies. Keeping the latter at the forefront of our considerations, and those of all stakeholders, ensured the babies successfully received their Zolgensma® doses.

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The authors declare no competing interest.

Cormac Kennedy[1,2]
Edel O'Dea[2]
Derval Reidy[2]
Jeremy Towns[2]
Maria Pigott[2]
David Kevans[2,3]
Declan O'Rourke[4]
Martina Hennessy[1,2]

[1]*Department of Pharmacology and Therapeutics, Health Sciences Centre, Trinity College, Dublin, Ireland*
[2]*Wellcome-HRB Clinical Research Facility, St James Hospital, Dublin, Ireland*
[3]*Department of Gastroenterology, St James Hospital, Dublin, Ireland*
[4]*Department of Neurology, Children's Health Ireland at Temple Street, Dublin, Ireland*

Correspondence
Cormac Kennedy, Department of Pharmacology and Therapeutics, Trinity Centre for Health Sciences, St James Hospital, Dublin 8, Ireland.
Email: cormackennedy1@gmail.com; kennec30@tcd.ie

If further detail is required by a reader, please contact the corresponding author. We would be delighted to share our experience with other centres.

ORCID

Cormac Kennedy https://orcid.org/0000-0002-2577-0242

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