Advanced Therapy Treatment Centres

Midlands-Wales Advanced Therapy Treatment Centre

Example Shared Care Guidelines for *in vivo* Gene Therapies using an adeno-associated vector

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Background

In vivo gene therapies are a type of Advanced Therapy Medicinal Product. Many *in vivo* gene therapies use an adeno-associated vector (AAV) to deliver the genetically modified material into the cell. These shared care guidelines describe a typical pathway for an *in vivo* gene therapy utilising an AAV. **It is intended that this guideline is adapted locally, to include details specific to the particular *in vivo* gene therapy being delivered and to accommodate local governance processes.**

Due to the potential for serious adverse effects and the requirement for long term supportive care and follow up, it is vital to establish robust shared care arrangements. This exemplar guideline suggests roles and responsibilities between referring centres and treatment centres. It also outlines common adverse effects associated with *in vivo* gene therapies using an AAV that may occur when patients have returned to their referring centre.

The use of AAV may elicit a neutralising antibody response to the vector capsid and the transgene. With systemic use, this may include immune mediated elevation of transaminases,[1,2] thrombocytopenia, raised troponin and other immune manifestations [2]. The prevalence of pre-existing immunity to AAV varies between serotypes and geographic location.[1,3] Due to an increased risk of immune mediated reaction and risk of loss of transgene expression, patients with substantial levels of antibodies to the specific AAV in use may be unsuitable to receive treatment [2]. To reduce the risk of immune reaction, *in vivo* gene therapies are generally contraindicated in active infection.[2,4]

It is notable that the longer term safety profile of *in vivo* gene therapies using AAV remains unknown, high-lighting the importance of rigorous long term follow up for these patients.

Please note that this guideline describes a typical shared care pathway for an *in vivo* gene therapy using an AAV. The pathways for *in vivo* gene therapies using alternative vectors and for ex vivo (cellular) gene therapies, differ substantially. This guidance should be used as a basis to develop guidance for marketed products only. The investigators brochure must be followed for gene therapy investigational medicinal products.

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1. General Principles of Shared Care for *in Vivo* Gene Therapy AAV Patients

Effective shared care between the treatment centre and the referring centre is essential before, during and after therapy. This requires:

- Good communication between the treatment centre and referring centre, with designated individuals for each centre.
- Intensity of post treatment care is patient dependent and flexibility may be required
- The treatment centre should be contacted to discuss management of any complications after the patient returns to the referring centre

2. Authorised personnel/training required

All healthcare professionals involved in the shared care of patients pre and post treatment with an *in vivo* gene therapy using an AAV should be appropriately trained in common adverse effects of therapy and demonstrate competency.

3. Procedure

This sets out a generic procedure for an *in vivo* gene therapy using an AAV. It will require local adaptation to reflect the particular product and local governance processes. An example of a shared care pathway specific to onasemnogene abeparvovec for spinal muscular atrophy is available in Appendix 1.

3.1 Pre-admission

Preliminary discussion

- Preliminary discussion of potential patients with the treatment centre, with advice given by the treatment centre, where applicable, on testing to be undertaken such as confirmatory genetic testing and adenovirus antibody testing specific to the AAV being used.

Referral to treatment centre/MDT review

- Suspected new diagnosis of an underlying disease requiring treatment with a gene therapy must be referred to the treatment centre as soon as possible
- Referral pathways will differ between gene therapy products, but some may utilise a national electronic referral portal to the national MDT.
- Genetic confirmatory testing and adenovirus antibody testing, where applicable, must be undertaken urgently if not already sent by referring centre
- Once diagnosis confirmed, patients may be reviewed by local MDT for eligibility for treatment and referred on to the national MDT, or for some products, referred directly to the national MDT.

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Midlands-Wales Advanced Therapy Treatment Centre

Timescales

To prevent further complications associated with the patient's diagnosis, it is often vital to initiate treatment as soon as feasible after diagnosis and eligibility confirmed.

Factors that may affect timescales include turnaround times for confirmation of genetic diagnosis and specific AAV antibody testing. Due to high acquisition cost, *in vivo* gene therapies will not be routinely stocked at treatment centres. Stock will only be ordered once baseline investigations complete, diagnostics and AAV antibody status confirmed, national MDT approval and commissioning approval or Blueteq in place and patient confirmed as remaining fit to proceed. It may take around 5-7 working days for an AAV gene therapy product to be received once ordered but this will vary depending on individual product.

Baseline investigations

The following investigations will be undertaken once patient eligibility confirmed, plus any work-up investigations specified for the *in vivo* gene therapy in question

- Weight
- Baseline bloods (as determined by the Summary of Product Characteristics (SPC) for product)
- Clinical examination
- Infection screening
- If pre and post corticosteroid supportive care treatment indicated
  - Review of immunisation schedule (paediatrics)
  - Varicella zoster and measles IgG
- Baseline disease status assessment

Consultation once eligibility for treatment confirmed

- Procedure including adverse effects explained to patient/family or carers
- Patient and family/carers informed of timescales and admission plan
- Patient and family/carers provided with written information on gene therapy treatment pathway, potential adverse effects, risk of shedding and advised management and any required alterations to vaccination schedule where applicable
- Consent process

Communication with other departments/specialities

- Multi-disciplinary review of patients should occur within the treatment centre.
- Healthcare professionals caring for the patient following administration of the *in vivo* gene therapy must be aware of any potential risk of shedding and be familiar with and follow local procedures for management of shedding.

Corticosteroid therapy to reduce the risk of immune mediated reaction

- Schedules and dosing of corticosteroids to reduce the risk of immune mediated reaction are specific to each AAV *in vivo* gene therapy.
- From the products licensed to date, immunomodulatory regimens may start as early as 3 days prior to *in vivo* gene therapy administration and may continue at full dose for up to 30 days post gene therapy administration or longer if adverse effects persist, followed by a period of weaning[2,4]
- Testing for adrenocortical suppression should be considered in accordance with local endocrinology procedures for any patient on prolonged courses of steroids

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3.2 Admission to Treatment Centre for *in vivo* gene therapy administration

Days prior to gene therapy administration (Treatment centre)

- Patient attends/admitted to treatment centre at least 24 hours prior to administration of gene therapy.
- Medical review/examination and baseline monitoring parameters (eg creatinine, liver function tests, full blood count and troponin I for onasemnogene abeparvovec).2
- Confirmation that eligibility criteria still met and patient free from infection.
- Patient re-weighed to ensure gene therapy accurately dosed where applicable.
- Where indicated, corticosteroid therapy to reduce the risk/severity of immune. reaction should be commenced 1-3 days prior to gene therapy infusion as detailed by the product SPC.
- Where applicable the manufacturer's patient alert card should be provided at this point, plus an alert card for patients receiving a prolonged steroid regimen.

Day 1 (Treatment centre)

- Medical review on morning of infusion to ensure patient fit to proceed and no infection present. This may also be confirmed via completion of a Blueteq form depending on the product.
- Preparation of the *in vivo* gene therapy should not commence until medical go-ahead given and confirmation that corticosteroid therapy initiated as appropriate, due to high cost and potential delay in obtaining further stock.
- Most appropriate location for the preparation of the *in vivo* gene therapy should be locally risk assessed by the Trust Genetic Modification Safety Committee.[5]
- *In vivo* gene therapy administered and patient monitoring commenced according to product licence
- Shedding guidance to be followed by hospital staff caring for the patient and by patient's family/carers.

Immediate post infusion monitoring (Treatment centre)

- The patient will remain as an inpatient at the treatment centre for a minimum period following infusion as defined in the product SPC
- Patient continues on immunomodulatory corticosteroid regimen where appropriate
- Patient observed for immune reaction. Monitoring may include:
  - Clinical examination including checking for hepatomegaly and signs of hepatotoxicity
  - Observations – temperature, HR, pulse, oxygen saturation, respiratory rate
  - FBC including platelets
  - Urea and electrolytes
  - Liver function tests, with transaminases in particular being closely monitored
  - Troponin
- Specific time intervals for the above monitoring stated in the specific Summary of Product Characteristics must be closely followed and the patient's treating Consultant urgently informed if abnormal results arise.
- Patients may subsequently be discharged back to their referring hospital or reside in near hospital accommodation whilst monitoring continues

Discharge to referring centre or to home

- Prior to discharge, an MDT discussion between the treatment and referring centre will occur, with provision of a written patient pathway, to ensure that both parties are aware of respective responsibilities including;
  - blood test schedule including dates of tests, responsibility for review of results and management of abnormal findings
  - on-going corticosteroid regimen where applicable, including responsibility for prescribing corticosteroid and weaning as determined by the *in vivo* gene therapy SPC.
  - for prolonged steroid courses, assessment of adrenal suppression should be considered according to local guidelines (also consider other side effects of steroids such as effects on blood glucose and bones).
  - monitoring of adverse effects and disease status
  - patient susceptibility to infection whilst on corticosteroid immunomodulatory regimen. The referring centre, patient and carers should be alert to the risk of exposure to infection including varicella zoster and measles.
  - any amendments to the patient's vaccination schedule

- **A discharge summary** documenting inpatient course and medication on discharge to the outpatient setting should be forwarded to the patient's GP and referring centre. All out-patient clinic letters should also be forwarded to the patient's GP and referring centre. Any planned deviations from the normal vaccination programme must also be communicated to the referring centre and the patient's GP

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3.4 Follow up at treatment centre

- Regular treatment centre review is essential in the immediate period post discharge. This may be defined for each individual product, but as an example for onasemnogene abeparvovec, patients may be reviewed at least weekly until 4 weeks post infusion, then every 2 weeks until 3 months post infusion
- Patients experiencing adverse effects, particularly hepatotoxicity or thrombocytopenia will require more frequent follow up and tests.
- Follow-up will continue at the treatment centre for 15 years, as part of post-authorisation safety surveillance, with reporting of patient safety and efficacy data in accordance with relevant registry requirements. Any adverse effects should also be reported as for other medicines via the Medicines Healthcare Regulatory Agency (MHRA) Yellow Card Scheme and to the manufacturer.
- Long term adverse effects of *in vivo* gene therapies using AAV are uncertain and adverse effect profile may develop with more widespread use.

6. Shedding

Vector shedding is the release of virus-based gene therapy products from the patient through one or all of the following routes: faeces, urine, saliva, nasopharyngeal fluids, tears and skin via pustules, sores or wounds.[6]

The degree of shedding, route and duration is product specific. The potential risk to humans and the environment is also product specific and relates to the potential pathogenicity of the AAV, its ability to replicate and the transgene. This should locally risk assessed by the Treatment Centre's Genetic Modification Safety Committee[5] and mitigating measures implemented where necessary. Where patients are discharged to referring centres during the shedding period, the treatment centre should provide advice to the patient, carers and referring centre clinicians on the management of shedding.

7. Organ/Blood Donation

Manufacturers of some AAV *in vivo* gene therapies advise that patients should not donate blood, organs, tissues and cells for transplantation.[4]

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Advanced Therapy Treatment Centres
Midlands-Wales Advanced Therapy Treatment Centre

APPENDIX 1 Example shared care pathway for onasemnogene abeparvovec

Example Patient Pathway for Treatment with Zolgensma in England

Estimated 1-2 weeks

Patient diagnosis confirmed

Blood tests: FBC, U&E, LFT, AAV9 antibodies, Troponin I,
(VZV serology, depending on local preferences)
Cardiac: Echo, ECG (desirable, not mandated unless Troponin I raised)
Vaccine status obtained
Advice given on avoiding infection, where appropriate
SMAREACH Physiotherapy assessment, if possible

Referral made via referral portal

Eligible Group A

Not Group A or unclear if eligible - discuss in national MDT

Not eligible: referrers informed

Infusion centre team ensures all documentation and results have been received. Missing results chased.
Arranges consultation with family

Estimated 1 week

Consultation
Obtain history, explain treatment and process, answer questions

Estimated 1 week

Pre-admission assessment (1 week prior to treatment)
Clinical examination to ensure well, OFC
Observations: HR, BP, RR, Saturations
Infection screen: stool for viruses (including rota virus), NPA, COVID19 (if appropriate)
Nude weight obtained – communicated to infusion team

Estimated 1 week

Infusion team orders Zolgensma based on recent weight

Date arranged for admission for drug administration
NM team communicate date to family by phone
Appointment letter with leaflet posted to family

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Advanced Therapy Treatment Centres

Midlands-Wales Advanced Therapy Treatment Centre

Summary of administration process

Paediatric Ward / Day Care Unit, depending on infusion centre practice

Admission to Infusion Centre Day 0

Inform NM Team of arrival. Physiotherapy review to confirm previous findings
PCCU - Clerking, examination, occipitalfrontal circumference, observations

Repeat bloods: FBC, U&E, LFT, Troponin I

Administration of steroids (prednisolone 1mg/kg/day enterally once a day)
GI protective drugs (lansoprazole or omeprazole as per BNFc)

Family given advice on safe disposal of nappies. Box of gloves given to family

Alert card given. Alert inserted in medical notes

Infusion D1

Two cannulae placed in child

Infusion given over 1 hour according to pharmacy protocol

Continue steroids

Observations

Follow-up D2

Review by NM Team

Observations

FBC, U&E, LFT, Urine dipstick

Continue steroids

Continue safe disposal of nappies / waste

Discharge D3

As per day 2, including investigations

Review by NM Team - discharge letter prepared and sent to referring centre

Hospital Accommodation / Hotel unless lives near hospital or agreement with local NM centre

1 Week Post-Zolgensma (Monday)

Review by NM Team, including observations, OFC

FBC, U&E, LFT, Troponin I, Urine dipstick

1 Week Post-Zolgensma (Thursday)

*may be omitted if infusion centre thinks once a week satisfactory

Review by NM Team, including observations, OFCFBC, U&E, LFT

2 Weeks Post-Zolgensma (Monday)

Review by NM Team, including observations, OFC FBC, U&E, LFT, Troponin I, Urine dipstick

Discharge letter

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Follow-up after administration of Zolgensma

3 Weeks Post-Zolgensma - Sheffield Clinic

Examination, HR, BP, RR, Saturations, OFC
Bloods – FBC, U&E, LFT, Troponin I
(Echocardiography and ECG if Troponin raised at any point)

(Further cardiac testing may be required if Troponin I is raised)

4 Weeks Post-Zolgensma - Sheffield Clinic

Examination, HR, BP, RR, Saturations, OFC
Bloods – FBC, U&E, LFT, Troponin I
Consider weaning prednisolone if transaminase <2xULN
Advice that normal handling of nappies and waste can resume

6 Weeks Post-Zolgensma – Local team

Examination, HR, BP, RR, Saturations, OFC
Bloods – FBC, U&E, LFT, Troponin I

8 Weeks Post-Zolgensma - Sheffield Clinic

Physiotherapy assessment
Examination, HR, BP, RR, Saturations, OFC
Bloods – FBC, U&E, LFT, Troponin I
Review vaccination advice

10 Weeks Post-Zolgensma – Local team

Examination, HR, BP, RR, Saturations, OFC
Bloods – FBC, U&E, LFT, Troponin I

12 Weeks Post-Zolgensma - Sheffield Clinic

Physiotherapy assessment Examination, HR, BP, RR, Saturations, OFC
Bloods – FBC, U&E, LFT, Troponin I
Vaccination advice review

Discharge to local neuromuscular team, if agreement with local team

Remains well

Discharge to local neuromuscular team, if they are in agreement

Side effects / Unwell

Ongoing management from infusion centre, duration dependent on clinical case

*The number of clinic appointments may differ: patients who experience side-effects, such as thrombocytopenia or hepatotoxicity, will require additional appointments and tests

Example Shared Care Guidelines for *in vivo* Gene Therapies using an adeno-associated vector

Advanced Therapy Treatment Centres

Midlands-Wales Advanced Therapy Treatment Centre

Longer term follow-up in SCH if required or if local patient

16 Weeks Post-Zolgensma - Sheffield Video Clinic

(unless blood tests are required)

20 Weeks Post-Zolgensma - Sheffield Video Clinic

(unless blood tests are required)

6 Months Post-Zolgensma (around week 24-26) - Sheffield Clinic

Physiotherapy assessment
Examination, HR, BP, RR, Saturations, OFC
Bloods – If previously abnormal
Vaccine advice

9 Months Post-Zolgensma (around week 36-38) - Sheffield Video Clinic

(unless blood tests are required)

12 Months Post-Zolgensma - Sheffield Clinic

Physiotherapy assessment
Examination, HR, BP, RR, Saturations, OFC
Bloods – If previously abnormal
Echocardiography and ECG Vaccine advice

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