Safeguarding public health

MHRA

Gene Therapy Case Studies

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CAT-ESGCT WORKSHOP ATMPs: from regulation to reality

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DISCLAIMER

The views expressed are mine and not to be taken as representative of MHRA/EMA

Gene Therapy License Applications

- Experience to date:
  - Sitimagene ceradenovec (Cerepro)
  - Contusugene ladenovaec (Advexin) x2
  - Alipogene tiparvovec (Glybera)

- All products received negative opinion

Contusugene ladenovaec

- Adenovirus with P53 gene
- Indicated for recurrent/refractory head and neck cancer
- CHMP opinion
  - Not shown to be beneficial
  - Insufficient evidence to demonstrate the product was
    - Safe
    - Could be made reliably
    - Not harmful to the environment

Cerepro

- Adenovirus with thymidine kindase gene
- Indicated for high-grade glioma
- CHMP/CAT opinion
  - Not demonstrated to be effective
  - Increased risk of serious AEs eg, hemiparesis, seizures
  - Side effects a concern, considering the lack of proved efficacy

Fictionase deficiency syndrome

- Muscle pain and weakness, lethargy, fatigue
- Debilitating, but near normal life-span
- Prevalence 5–10/million
- No specific licensed treatment
- NSAIDs used with some success

Product

- Retrovirus with fictionase gene
- Currently in Phase III with pre-commercial product
- 10% process and product related impurities
- Non-clinical: no oncogenicity seen in immunocompromised animals

Clinical trial

- 40 patients
- Single-arm trial
- Multiple intramuscular injections over 3 days
- Follow-up data up to 1 year for all patients

End-points

- Fictionase levels in blood
- Gene expression in muscles
- Muscle strength
- 6-minute walking test

Results

- Doubling of fictionase levels at 3 and 6 months, but decreasing at 12 months
- Gene expression +ve in 50% muscle biopsy samples
- Muscle strength and 6-MWT increased by 25% at 6/12
- Not statistically significant

Safety

- Infusion reaction in 80% of patients
- Muscle pains with raised CK in 50%
- Joint pains 30%
- Raised LDL-C 20%
- 1 case of anaphylactoid reaction

Immunogenicity

- Low titre IgG Ab in 90%
- T-cell immunity in 40%

Aspects to resolve

- Quality comparability issue
- Effect of impurities
- Tumourigenicity
- Limited exposure
- Fictionase levels
- 25% clinical benefit – clinical relevance
- Increase in LDL
- Anaphylactoid reaction

Aspects to be further addressed

- Overall impact on patient's life
- Is readministration possible?
- Effect of immunogenicity
- Long-term safety, including tumour risk
- Plans to demonstrate comparability