Long-term Follow-up of Patients Treated with Cell and Gene Therapy: Scientific and Operational Challenges

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Background

- Regulatory authorities (RA) have issued guidance regarding the need to capture data for up to 15 years following treatment with cell or gene therapy (CGT) to monitor durability of effect as well as safety. Long-term follow-up (LTFU) studies are also useful for Health Technology Assessment (HTA) evaluations, and medical Affairs evidence generation. Execution of LTFU studies, however, poses scientific and operational challenges.

Objectives

- **To analyze the scientific and operational challenges related to LTFU of patients treated with CGT based on our experience**
- **To propose mitigation strategies**

Methods

- Based on our experience conducting LTFU studies of patients treated with gene therapies, we reviewed the context, requirements, designs and operational choices that were made.
- We have identified two main sets of challenges for LTFU of patients treated with CGT and have analyzed their potential consequences and possible mitigation strategies.

Results

Characterization of LTFU

LTFU of patients treated with CGT have several objectives and therefore specific methodological features:

- LTFU are prospective cohort studies including patients who have been treated with CGT as part of a clinical trial or per routine practice.
- Objectives include assessing the long-term safety and effectiveness of the therapy.
- Included patients are often children.
- Required follow-up time is most often 10 to 15 years
- Depending on the treated disease, outcomes can include:
  - Clinical outcomes assessments
  - Patient- or caregiver-reported outcomes
  - Laboratory assessments results
  - Imaging results

LTFU Challenges & Considerations

1 - Patient Retention

Patient retention challenges are multifaceted:

- Patient and caregiver willingness to engage for duration of follow-up
- Pediatric patients mature into adults and might change medical setting
- Patient might experience life events, changes in geography, care settings
- Loss of interest in participation associated with reduction of burden of illness resulting from CGT treatment

2 - Transitions in Care Over Time

CGT is often given in specialized centers and, therefore, multi-disciplinary teams arrange for LTFU of treated patients to capture disease status and late effects of CGT and prior treatments outside of the initial research setting. Transition challenges include:

- Identifying routine care setting for patients and obtaining data (if current setting is not the study site)
- Patient's treatment center may not have access to data at patient's local care facility. LTFU study site may face challenges accessing data from care at non-research centers.
- Physicians and specialized wards may undergo changes such as management change, ward closure, hospital fusion.
- Small numbers of patients per site

Results (cont.)

3 - Incomplete/Missing Data

- LTFU assessments may not be conducted as part of routine care
- Protocol mandated assessments may lead to lack of interest or engagement of LTFU sites over time.

Mitigations

- Limit the study burden on the patients and their caregivers as well as the research sites.
- Consider patient and caregiver's specific needs when finalizing the study design (i.e., assessment schedule, timing and duration of assessments, length of survey completion, reimbursement, etc.) and apply these considerations when implementing strategies for patient recruitment and retention.
- Employ a decentralized patient-centric virtual model where the point of contact is the patient and not the site and where data collection is supported by an external central site model. This approach follows the patient wherever they are without depending on research sites.
- Collect patient/caregiver data using a data collection app to be downloaded on personal mobile devices. Such solutions must be scalable and flexible to adapt to future technological innovations.
- Complete the data collection with data from other sources, e.g. data from existing patient registries; linkage with insurance claims data.

Addressing Additional Challenges in the Post-Marketing CGT LTFU Space

In the case LTFU is required for patients receiving the therapy after marketing authorization (MA), LTFU warrants tailored recruitment strategies for efficient enrollment.

- Consider LTFU studies as product registries and start designing them as such before market authorization. Include stakeholders early by liaising with RAs, HTAs, disease registries, and/or sites likely to prescribe the therapy, as well as patient advocacy groups to organize an early study framework, as recommended by current registry guidance.
- Address the need for consistency in the data collection between LTFU of patients exposed in clinical trials and the LTFU of patients exposed in the post-marketing period to allow pooling of the data in the frequent context of low sample size.

Discussion

- Although LTFUs are usually considered as simple designs, their specific methodological and operational requirements make them at risk of operational challenges that can jeopardize scientific conclusions from these studies.
- Therefore, it is important to anticipate potential issues based on each study's specificity.
- Decentralized/patient-centric approaches have developed quickly these past few years. The possibility to link data and the regulators' openness to patient registries are also assets to decrease the burden of these studies while collecting good quality data for regulatory purposes.

Conclusions

- **LTFU of patients receiving CGT raise specific issues that can be mitigated by latest developments in registry research, via early collaboration and via a virtualization of operations.**

References

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