Real-World Evidence in Gene Therapies: Recommendations Versus Reality

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Presented at the ISPOR 22 Annual European Congress | Copenhagen, Denmark | 2–6 November 2019

OBJECTIVES

To understand whether real-world evidence recommendations, made by regulatory and reimbursement bodies when evaluating gene therapies, are subsequently addressed by manufacturers.

BACKGROUND

Recent advances in gene therapies have facilitated the generation of effective, novel treatment options for rare and debilitating genetic disorders. However, due to the challenges of evidence generation in small, heterogeneous patient populations, manufacturers may face barriers to generating the robust safety and effectiveness data for these novel treatments that regulatory/reimbursement bodies currently expect.

One solution to these challenges may be the collection of real-world data (RWD). RWD are collected outside the context of tightly monitored trials, and are generally reflective of clinical practice and the long-term observation in which the treatment would be used.

It is widely agreed that manufacturers should use evidence derived from RWD (real-world evidence [RWE]) to supplement trial data in support of regulatory approval and reimbursement.

Despite this agreement, it is unclear whether RWE is being used to support submissions either proactively or reactively, and whether any recommendations for RWE generation are in fact being implemented.

METHODS

In February 2019, the European Medicines Agency (EMA) and Food and Drug Administration (FDA) websites were searched for regulatory documents using terms for gene therapies.

The National Institute for Health and Care Excellence (NICE) and Institute for Clinical and Economic Review (ICER) websites were then searched for related appraisals and reviews, respectively, in May 2019.

The documents retrieved were then searched to identify cases where RWE had been submitted as regulatory/reimbursement documents in the relevant documents were searched for, and the details extracted.

ClinicalTrials.gov was searched on 30 May 2019, for any observational studies, including patient registries, using the gene therapy names.

Finally, results from ClinicalTrials.gov were cross-referenced with the regulatory/reimbursement documents through comparison of expected outcomes, patient numbers and study timelines, in order to establish whether recommendations had been implemented.

RESULTS

Nine gene therapies were identified by searches of the EMA and FDA websites; seven in rare diseases and two in oncology. Eight EMA marketing authorisations were found, though one was subsequently withdrawn (Provenge®) and one expired and was not renewed (Glybera®). Six FDA approvals were found, with four gene therapies currently approved by both the EMA and FDA (Figure 1).

No RWD on the gene therapies was submitted in regulatory applications and a lack of trial data was commonly cited.

Six related NICE appraisals, corresponding to five gene therapies were identified, however, the NICE submission for Provenge® was subsequently withdrawn. Three ICER reviews were identified.

CONCLUSIONS

Although regulatory and reimbursement authorities place importance on RWE for gene therapies, few recommended studies could be identified in ClinicalTrials.gov.

This suggests either barriers to registration of these studies, the use of alternative methods to gather RWE, or that these recommendations are simply not being implemented.

Facilitation of registration of RWE studies, combined with the introduction of formal re-appraisals may be a potential solution to make these recommendations become reality.

Acknowledgements

The authors thank Kevin Racaza, Costello Medical, for graphic design assistance.

References


IMPROVED THERAPY FOR REAL-LIFE PATIENTS

Gene Therapy

RWE was recommended

Gene Therapy

RWE was neither recommended nor submitted

OS registered

FDA

EMA

NICE

Gene Therapy

Withdraw

Imlygic®

Kymriah®

Luxturna®

Shirelle®

Xencor®

Zolgensma®

Zalegenoma®

Glybera®

Provenge®

Graphical Summary

All 9 gene therapies received RWE collection recommendations from regulatory and reimbursement bodies.

Only 3 gene therapies had registered observational studies that could be mapped to a recommendation made by regulatory/reimbursement bodies. No matched observational studies had published results at the time of searching.