Using clinical trial and real world data to bridge efficacy to effectiveness of fingolimod in multiple sclerosis patients

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Introduction

As more treatments come to market, demonstration of how efficacy results from clinical trials (CT) can translate to effectiveness in the real world (RW) prior to launch is necessary to minimize negative clinical outcomes and prevent further progression of disease.

- Multiple sclerosis (MS) affects 400,000 people in the United States (US) and 2.5 million people worldwide and approximately 85% of patients have relapsing-remitting multiple sclerosis (RRMS).
- Relapse frequency and severity vary considerably among MS patients, and increased relapse frequency is associated with a higher risk of disease progression.
- Multiple disease modifying treatments (DMTs) for MS are currently used to manage patients' care. The typical first line of DMTs, called BRACE treatments, are injectables. The typical second line treatments are oral treatments, interferon-based, or another BRACE therapy (Figure 1).

Objective

- We proposed and implemented an efficacy to effectiveness (E2E) causal methodological approach to predict the RW effectiveness of fingolimod, an oral MS treatment prior to launch using CT data and pre-launch RW observational data.

Data Sources & Sample Selection

- Two data sources were used to implement E2E (Figure 2).

1. The first source was for patients with a diagnosis of MS (ICD-9-CM: 340.xx) within the pre-index period; evidence of relapse in the RW data was not used. The model estimated RW RP between 0.13 (moderate-severe relapses) and 0.27 (moderate relapses).
2. The second source was for patients with a diagnosis of MS (ICD-9-CM: 340.xx) within the pre-index period; evidence of relapse in the RW data was used. The model estimated RW RP between 0.13 (moderate-severe relapses) and 0.27 (moderate relapses).

Results

- Our model estimated the RP in the RW to be between 0.13 and 0.27. This compares to the 0.13 to 0.22 seen in the CT.
- The treatment effect seen in MS on relapses in the RW is similar to that seen in the CT.
- This may also suggest that the correction for the difference in joint distributions of covariates between CTs and RW data is large, which allows making a population level prediction of effectiveness in the RW.
- The authors thank Daniel Shenfeld of GNS Healthcare (Cambridge, MA, USA) for intellectual and technical support and Maninder Reddy Karka for designing the model.

Conclusions

- We implemented an E2E approach to estimate endpoints of interest (RP) of fingolimod in MS by standardizing to the reference population, which allows making a population level prediction of effectiveness in the RW while the drug is still in the development stage.
- It should be noted that a previously conducted RW study has shown that the treatment effect seen in MS on relapses in the RW is similar to that seen in the CT. This may also suggest that the correction for the difference in joint distributions of covariates between CTs and RW data is large, which allows making a population level prediction of effectiveness in the RW.
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This project demonstrates that these mappings can be developed in the MS space. Further research of this type in other disease areas is needed to know the extent of general applicability that can be achieved.

References

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Figure 1. Treatments of newly diagnosed MS patients

Figure 2. Data sources used to implement E2E analysis

Figure 3. Population comorbidity categories in pre-index period

Figure 4. Model covariates and endpoints

Table 1. CT and pre-launch RW populations used in modeling

Table 2. Means for REFS selected model covariates in the CT data before and after weights application

Table 3. Probability of relapse (RP) and annualized relapse rate (ARR) of moderate/severe relapses in the RW when compared with CTs

Table 4. RP and ARR validation model estimates and observed values (post-2010)

Acknowledgement

The authors acknowledge the support of GNS Healthcare Cambridge, MA, USA for developing the technical infrastructure and Senior Regulatory for designing the model.