Comparison of Methods for Extrapolation of Drug Survival of Biologics in Psoriasis NICE Submission Cost-effectiveness Analyses

EE306

Kazmierska, Paulina[1]; Bungey, George[1]

[1]Evidera Ltd., a business unit of PPD, part of Thermo Fisher Scientific, London, UK

Background

- Current psoriasis National Institute for Health and Care Excellence (NICE) submission models define the proportions of patients remaining on treatment over time using a combination of short-term Psoriasis Area and Severity Index (PASI)-75 response (from network meta-analysis [NMA]) and constant non-treatment-specific drug survival (DS) probabilities derived from UK real-world evidence (RWE).
- However, DS extrapolations based on this approach may differ substantially from parametric extrapolations fitted directly to Kaplan-Meier (KM) data from those RWE studies.

Objectives

This research aimed to:

- Quantify the differences between modeling DS based on PASI-75 data combined with constant probabilities vs. parametric extrapolations.
- Discuss potential reasons behind these differences and implications on cost-effectiveness analyses.

Methods

DS of adalimumab, etanercept, infliximab, and ustekinumab was modeled over 10 years using three approaches:

- Short-term PASI-75 response at 12–16 weeks, depending on intervention, was derived from a published NMA.[1] We assumed that all patients continued treatment during induction, and that those who failed to achieve PASI-75 after 12–16 weeks discontinued treatment. After induction, a constant annual discontinuation probability of 18.7%, sourced from UK RWE data[2] and in line with several recent NICE appraisals[3-5] [**approach 1**], was applied.
- Parametric survival analyses were conducted by fitting a series of distributions to British Association of Dermatologists Biologic and Immunomodulators Register (BADBIR) DS data.[6] KM curves of DS data presenting drug discontinuation for all reasons (including ineffectiveness, safety) were digitized, and six standard parametric functions (exponential, Weibull, lognormal, loglogistic, Gompertz, generalized gamma) and the two-parameter gamma distribution were fitted. Standard parametric survival models were fitted directly to:
  - First-line adalimumab, etanercept, infliximab, and ustekinumab DS data[2] [**approach 2**].
  - Second-line adalimumab, etanercept, and ustekinumab DS data[7] [**approach 3**].
- Models were selected based on statistical fit, visual fit, and comparisons of hazard profiles for the parametric models against smoothed hazard plots for the KM data.
- In line with NICE Decision Support Unit guidance,[8] the same type of parametric model was selected for all comparators in the absence of a strong rationale to support different types.

Results

Parametric Model Selection

- Based on the log cumulative hazard plots and Schoenfeld residuals plots, independent parametric fits were explored for first- and second-line DS data.
- First-line data: Generalized gamma models produced the best statistical fit for adalimumab and etanercept as well as reasonable relative statistical fits for infliximab and ustekinumab. The generalized gamma model also produced good visual fits with hazard profiles aligned with smoothed hazard curves for the KM data. Based on consistency across the independent parametric models, and in the absence of strong rationale for applying different models, generalized gamma independent parametric models were used for all first-line comparators.
- Second-line data: For all three interventions, the generalized gamma model produced the best statistical fit and visual fit, with hazard profiles aligned with the smooth hazard profile of the observed data, and was applied for all treatment arms.

DS Estimates

- Three-, 5-, and 10-year DS estimates are presented in **Table 1**, while **Figures 1** to **4** present a comparison of three approaches over a 10-year time horizon.
- The largest differences in extrapolations were observed for ustekinumab, with approach 1 substantially underpredicting DS compared with approaches 2/3 over 10 years (9.9% vs. 49.0%/59.1%) (**Figure 1**), followed by adalimumab (9.1% vs. 41.6%/29.9%) (**Figure 2**) and etanercept (6.6% vs. 17.7%/15.0%) (**Figure 3**).
- Approach 1 overpredicted DS for infliximab before converging with approach 2 closer to 10 years (10.6% vs. 8.3%) (**Figure 4**).
- Application of the generalized gamma model to first- and second-line ustekinumab data resulted in cross-over of extrapolation curves, with DS of second-line ustekinumab being higher than first-line ustekinumab. Applying a lognormal model to second-line data produced a slightly more conservative estimate with no cross-over; however, the difference between this approach and approach 1 was still substantial (47.5% vs. 9.9% at 10 years).
- Scenario analysis using a lower annual discontinuation rate (14.4%)[9] resulted in slightly smaller differences between approaches 1 and 2/3 for adalimumab, etanercept, and ustekinumab, and produced larger discrepancies between approaches for infliximab (**Table 1**). However, differences in long-term DS estimates were still substantial for adalimumab and ustekinumab.

Table 1. Estimated drug survival at 3, 5, and 10 years

Year	NMA + extrapolation [approach 1, base case][a]	NMA + extrapolation [approach 1, scenario][b]	RWE extrapolation: Warren 2015[2] [approach 2]	RWE extrapolation: Iskandar 2018[7] [approach 3]
Adalimumab				
3	38.7%	44.4%	60.0%	50.4%
5	25.6%	32.5%	51.6%	40.8%
10	9.1%	14.9%	41.6%	29.9%
Etanercept				
3	27.9%	32.2%	41.0%	28.2%
5	18.4%	23.6%	29.5%	21.6%
10	6.6%	10.8%	17.7%	15.0%
Infliximab				
3	45.0%	51.6%	35.6%	-
5	29.7%	37.8%	22.0%	-
10	10.6%	17.4%	8.3%	-
Ustekinumab				
3	42.4%	48.7%	74.9%	72.5%
5	28.0%	35.7%	64.5%	66.7%
10	9.9%	16.4%	49.0%	59.1%

[a]Constant annual discontinuation probability of 18.7%[2]

[b]Constant annual discontinuation probability of 14.4%[9]

Abbreviations: NMA = network meta-analysis; RWE = real-world evidence

Results (cont.)

Figure 1. Estimated DS of Ustekinumab

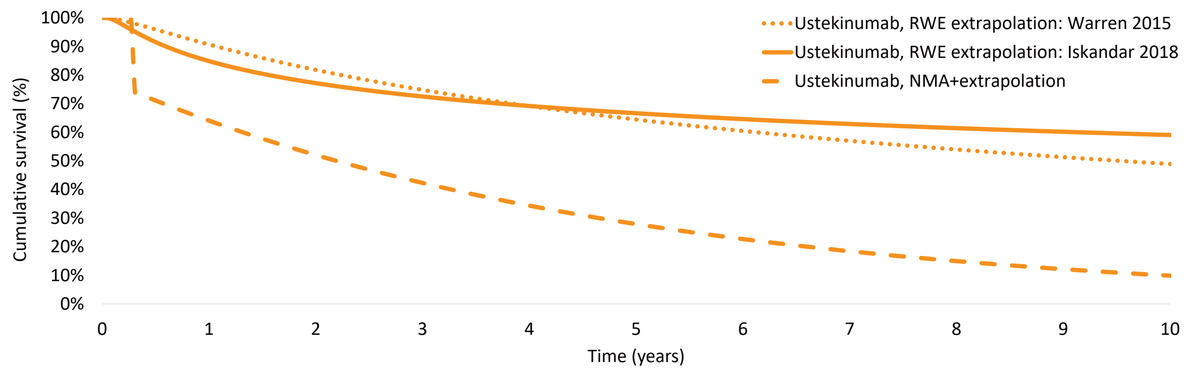


Figure 2. Estimated DS of Adalimumab

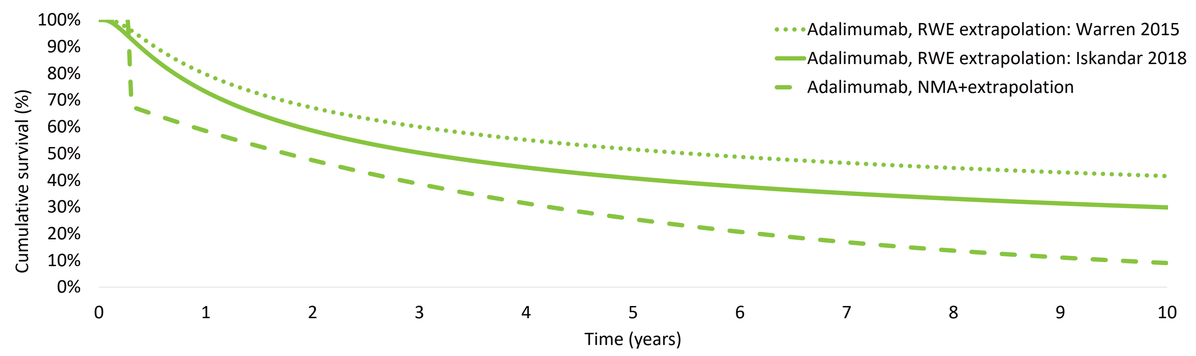


Figure 3. Estimated DS of Etanercept

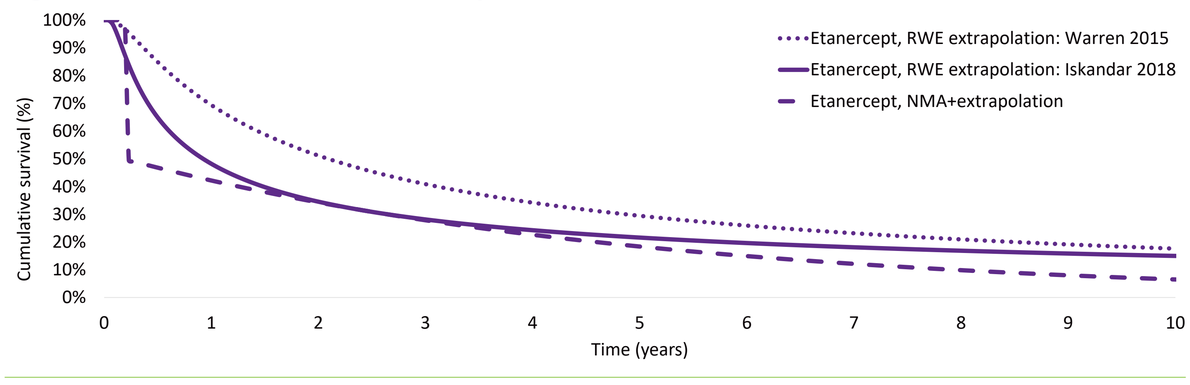
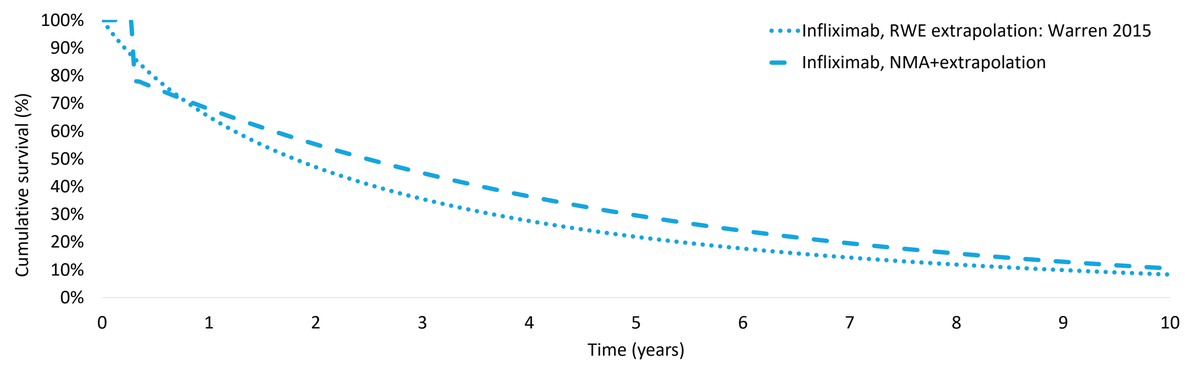


Figure 4. Estimated DS of Infliximab



Abbreviations: NMA = network meta-analysis; RWE = real-world evidence

Limitations

- Approaches 2 and 3 used slightly older BADBIR publications for real-world DS estimates, with more recent BADBIR publications not presenting KM curves for drug discontinuation for all reasons. As a result, newer biologic or oral therapies were not included in this analysis.

Conclusions

- Differences in DS extrapolations may result in substantially different predictions of treatment line distributions over time if used in psoriasis cost-effectiveness models, and therefore may impact estimation of the most cost-effective treatment sequences. Given more recent biologics recommended by NICE have demonstrated stronger efficacy than adalimumab and ustekinumab in clinical trials, differences in NICE submission model predictions and RWE may also be substantial for other biologics if similar plateaus in RWE DS curves are observed.
- Differences in DS estimates may be partially explained by differences in treatment stopping rules recommended by NICE for clinical practice, which are based on achieving PASI-75 or PASI-50 combined with a 5-point reduction in Dermatology Life Quality Index, rather than PASI-75 alone.
- Further research should be conducted into comparisons of overall DS for newer biologic therapies and compared against NICE submission model DS extrapolations, and methods for more accurate DS prediction from short-term trial data using RWE sources.

References

1. Armstrong A, et al. Dermatol Ther (Heidelb). 2022;12(8):1777-1792. 2. Warren RB, et al. J Invest Dermatol. 2015;135(11):2632-2640. 3. NICE. Brodalumab for treating moderate to severe plaque psoriasis. Technology appraisal guidance [TA511]. 2018. 4. NICE. Tildrakizumab for treating moderate to severe plaque psoriasis. Technology appraisal guidance [TA575]. 2019. 5. NICE. Risankizumab for treating moderate to severe plaque psoriasis. Technology appraisal guidance [TA596]. 2019. 6. Burden AD, et al. Br J Dermatol. 2012;166(3):545-554. 7. Iskandar IYK, et al. J Invest Dermatol. 2018;138(4):775-784. 8. Latimer N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011. https://www.ncbi.nlm.nih.gov/books/NBK395885/pdf/Bookshelf_NBK395885.pdf 9. Yiu ZZN, et al. Br J Dermatol. 2020;183(2):294-302.

Disclosures/Acknowledgments

The authors would like to thank Michail Galanakis of Evidera, a business unit of PPD, part of Thermo Fisher Scientific for support with conducting parametric survival analysis, and Michael Grossi and Shani Berger of Evidera, for their editorial and graphic contributions.

PK and GB are employees of Evidera. The views expressed in this study are those of the authors and not necessarily those of Evidera. The authors do not have any conflicts of interest.

Funding provided by Evidera Ltd., a business unit of PPD, part of Thermo Fisher Scientific