POSC319

Analysis of Treatment Sequences across Seven Immunological Diseases and the Variability in Efficacy for Patients per Disease: Opportunities for Improvement

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Background

- The full landscape of immune-mediated disorders includes gastrointestinal, dermatological and rheumatological diseases. Patients with these chronic conditions require treatment for prolonged periods of their life and finding effective treatments during the course of their disease can be challenging.
- Whilst multiple new and effective treatment options have become available, uncertainty remains around which treatment should be used first and the optimal order of treatments. Patients often cycle between treatments with the same mechanism of action or start with less effective treatment despite the many advanced options available.
- We developed a model to facilitate decision making regarding likely optimal sequences of treatment to find solutions for this clear and recurring unmet need for patients with immune-mediated diseases.

Objective: To evaluate treatment sequences and to quantify and compare variability in efficacy across seven immune-mediated diseases.

Methods

Model structure

- A state transition model was developed to assess efficacy of treatment sequences in seven immune-mediated diseases: Crohn's disease (CD), ulcerative colitis (UC), plaque psoriasis (PsO), psoriatic arthritis (PsA), rheumatoid arthritis (RA), ankylosing spondylitis (AS) and non-radiographical axial spondylarthritis (NR-AxSpA).
- In accordance with previous modelling in immunology, each treatment line is defined by two treatment phases: induction and maintenance. For treatments that do not utilise an induction period, the maintenance phase starts from initiation of treatment. All treatments with a European Medicines Agency (EMA) marketing authorisation at the end of 2020 were included.

Data inputs and assumptions

- As precise treatment sequencing data are unavailable for these diseases, network meta-analysis informed by trial data was used for the induction and start of the maintenance phase and long-term persistency data informed by published real-world evidence studies were used for the long-term maintenance phase. An overview of comparative evidence used is presented in **Table 1**.
- Efficacy was differentiated between biologic-naïve and biologic-experienced populations. Whenever possible, Kaplan-Meier curves used to model long-term persistency were distinguished between disease areas and treatments.
- Response measures were disease-specific and selected on quality and most frequent availability of data.
- Efficacy variability was calculated as the difference in average number of treatment failures per patient between the best treatment sequence and the worst

Table 1: Overview of comparative evidence used

Disease and Treatment Options	Induction and Maintenance during Trial Period		Long-Term Maintenance
Crohn's Disease (CD)			
Ustekinumab	Reference	UNITI-1 and UNITI-2 trials[1]	Billiet et al.[2]
Adalimumab, Vedolizumab	NMA	Varu et al. (2019)[3]	
Infliximab	Assumed similar to adalimumab as no data available and assumed class effect		
Ulcerative Colitis (UC)			
Ustekinumab	Reference	UNIFI trials[4]	Taxonera et al.[5]
Adalimumab, Vedolizumab, Tofacitinib	NMA	Welty et al. (2020)[6]	
Golimumab, Infliximab	NMA, ORs for experienced vs naïve assumed same as adalimumab as no data available and assumed class effect		
Psoriatic Arthritis (PsA)			
Guselkumab	Reference	DISCOVER 1 and DISCOVER 2 trials[7, 8]	Jacob et al.[9]
Abatacept, Adalimumab, Apremilast, Certolizumab, Etanercept, Golimumab, Infliximab, Ixekizumab, Secukinumab, Tofacitinib, Ustekinumab	NMA	Mease et al.[10]	
Rheumatoid Arthritis (RA)			
Sarilumab	Reference	MOBILITY trial[11]	Jacob et al.[9]
Abatacept, Adalimumab, Baricitinib, Certolizumab, Etanercept, Golimumab, Infliximab, Tocilizumab, Tofacitinib	NMA	Choy et al.[12]	
Plaque Psoriasis (Pso)			
Guselkumab	Reference	VOYAGE 1[13] and VOYAGE 2 trials[14]	Assumed same as ustekinumab
Risankizumab	Assumed same as guselkumab		
Tildrakizumab	NMA	Cameron et al.[15]	
Adalimumab, Apremilast, Etanercept, Infliximab, Ixekizumab, Secukinumab			Lunder et al.[16]
Ustekinumab			
Brodalumab			Assumed same as secukinumab
Certolizumab	Naïve comparison based on available data	CIMPASI-1, CIMPASI-2 and CIMPACT[17]	Assumed same as etanercept
Ankylosing Spondylitis (AS)			
Adalimumab, Etanercept, Golimumab, Infliximab	NMA	Chen et al.[18]	Jacob et al.[9]
Secukinumab	NMA, OR for biologic experienced from trial	Chen et al.[18] MEASURE 2[19]	
Certolizumab	ORs from literature	EMA assessment report of Cimzia[17]	
Non-Radiographic Axial Spondylarthritis (NR-AxSpA)			
Adalimumab, Certolizumab, Etanercept, Golimumab	NMA	NICE appraisal of golimumab (TA497)[20]	Assumed same as AS

Key: NMA, network meta-analysis, OR, odds ratio.

- Each treatment sequence included up to three biologic treatments and one blended biologic line, followed by best supportive care (**Table 2**).
- To model the final blended line, the average of the efficacy inputs (duration of the induction phase, duration of the trial period, percentage of responders and persistency curve) of all biological treatments not previously used in first, second or third line, was applied.
- Although surgery can be a viable treatment for UC and CD, we assumed it to be a rarely used option within the time horizon and therefore excluded it from the analysis. Wash-out periods between two biological treatment lines were assumed to be short enough to be negligible over the time horizon.
- Based upon these constraints, a list of all possible sequences for each disease was generated, and an estimate of their effectiveness was computed using the state transition model with a 3-year time horizon.

Table 2: Model assumptions, constraints, and number of sequences

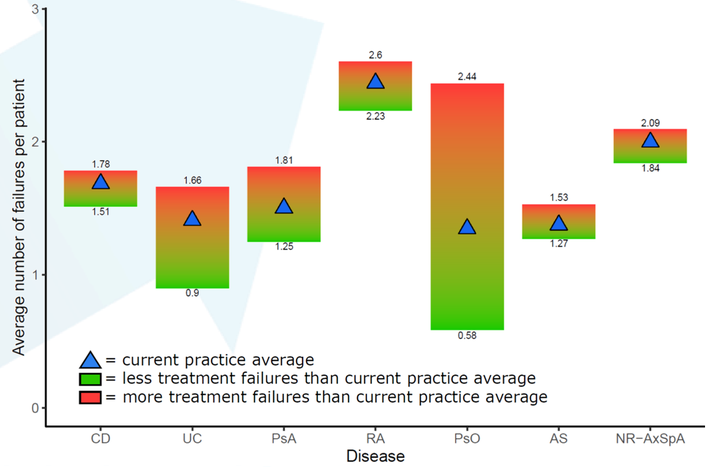
Disease	Response Measure	Maximum instances per…		Number of treatment-specific lines	Blended line	Number of INNs	Number of sequences
		INN	MOA				
CD	CDAI-100	1	2	3	No	4	24
UC	Clinical response	1	2	3	No	6	114
PsA	ACR20	1	2	3	Yes	12	1260
RA	ACR70	1	2	3	Yes	10	660
PsO	PASI90	1	2	3	Yes	12	1284
AS	ASAS20	1	3	3	No	6	120
NR-AxSpA	BAISDAI50	1	3	3	No	4	24

Key: ACR, American College of Rheumatology; ASAS, Assessment in SpondyloArthritis International Society; BAISDAI, Bath Ankylosing Spondylitis Disease Activity Index; CDAI-100, Crohn's Disease Activity Index 100; INN, international non-proprietary name; MOA, mechanism of action; PASI, Psoriasis Area and Severity Index;

Results

- In **Figure 1**, the variation in efficacy between treatment sequences is displayed. The blue triangle captures average prescribing behaviour in this example country, and the green part of the bars display the room there is to reduce the number of treatment failures experienced by patients. A larger variation indicates a greater opportunity for improvement.
- For PsO, 1,284 treatment sequences were possible, and the estimated average number of treatment failures ranged from 0.58 to 2.44, translating to an efficacy variability of 1.86 failures per patient over three years. The number of possible sequences and efficacy variability for the other diseases are as follows: UC- 114 and 0.76; PsA- 660 and 0.56; RA- 660 and 0.37; CD- 24 and 0.27; AS- 120 and 0.26; NR-AxSpA- 24 and 0.25.

Figure 1: Efficacy variation across diseases



Limitations and Conclusions

- The key limitations of this analysis relate to the availability of published data. This analysis will therefore be strengthened by including real-world evidence studies that will help provide more robust data in place of some of the sequence-related efficacy assumptions.
- The model results suggest that the treatment sequences that exhibited the greatest variability in efficacy were those for PsO, UC, and PsA, while those for RA, CD, AS and NR-AxSpA demonstrated the least variability.
- The greatest improvement in patient outcomes from consistent selection of optimal treatment sequences may be achieved in PsO, UC, and PsA given the extent of efficacy variability observed for these diseases.
- Our work suggests that providing clinicians with the ability to prescribe more efficacious treatments earlier in the course of therapy provides a greater opportunity to minimize treatment failures and therefore maximize outcomes for patients.

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