The impact of trial design on network meta-analysis and decision-making: a working example in ulcerative colitis

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Introduction

Indirect treatment comparisons are commonly used in health technology assessment (HTA) to compare drugs that have been trialled in the same patient population. Accordingly, new meta-analytic methods have emerged which permit simultaneous comparison of multiple treatments, referred to as *network meta-analysis* (NMA). NMA is commonly used in HTA, when there is a paucity of head to head clinical trial data. However, sometimes this approach may be unsuitable because of differences in trial design[1].

This working example focuses on Ulcerative Colitis (UC), a chronic relapsing-remitting form of IBD[2]. Vedolizumab is a new gut-selective targeted therapy that is indicated for treatment of adult patients with moderately to severely active UC.

The drug manufacturer performed an NMA using RCTs for the same indication in their HTA submission[3].

Objectives

The objective of this study is to assess the impact of trial design on NMA results using NICE appraisal (TA342) considering vedolizumab in UC. The following key differences in trial design were identified:

1. **Induction duration**
2. **Maintenance duration**
3. **TNF inhibitor use**
4. **Re-randomisation**

Methods

The RCT data considered were extracted and assessed alongside structural elements of placebo-controlled trials, visually represented in figure 1. and described in table 1.

Figure 1. Network diagram of RCTs analysed in NMA

Key:
Size of circles represents patient numbers. Each circle represents a different drug or placebo.
Yellow circle is the company's trial. Thickness of line indicates number of trials, also noted by numbers.
*Includes some patients who have taken TNF inhibitors.

Primary endpoint for GEMINI: Clinical remission at week 52.

Note: ACT and PURSUIT endpoint was week 54.

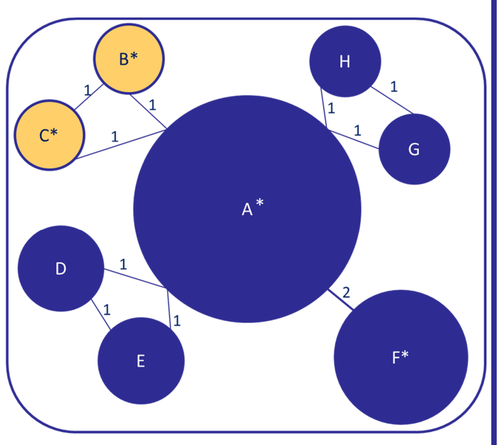


Table 1. Trials included in the company's NMA with the drug manufacturer's trial highlighted in bold.

Trial		Drug	n	% anti-TNF-naïve
All trials	A	Placebo	745	*58-100
GEMINI[3]	**B**	**Vedolizumab (4 weekly)**	**125**	***58-63 (ITT)**
	C	**Vedolizumab (8 weekly)**	**122**	***58-63 (ITT)**
PURSUIT SC/M[4,5]	D	Golimumab (SC) 50mg	154	100
	E	Golimumab (SC) 100mg	154	100
ULTRA 1/ 2[6,7]	F	Adalimumab	248	*58.9-60.5
Suzuki 2014[8]			177	100
ACT 1/2[9]	G	Infliximab (5mg/kg)	121	100
	H	Infliximab (10mg/kg)	122	100

*Exact numbers of anti-TNF-naïve patients were not given.

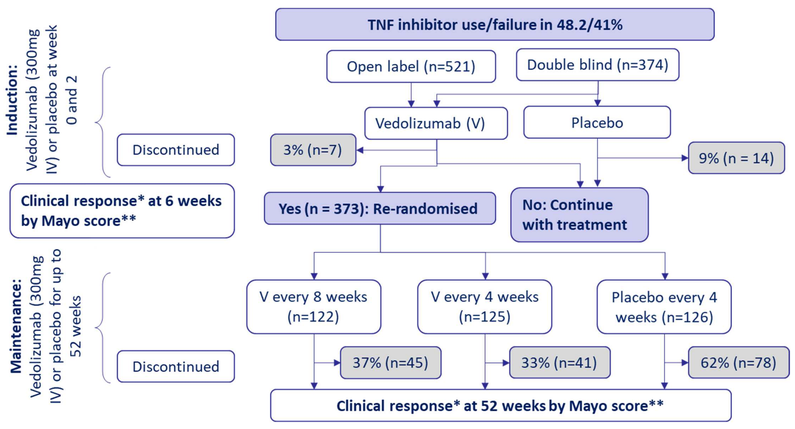
Methods (continued)

- The company performed an NMA with available data, making adjustments for the differences in trial design.
- The ERG stated that different approaches could have been taken in order to address the differences in trial design.
- No significant differences in patient age or gender were identified.

Results

Differences in trial design (duration of induction and maintenance, TNF inhibitor use and re-randomisation) are summarised below (figure 2, bold text) and detailed in sections 1 - 4.

Figure 2. GEMINI trial design, bold text indicates difference in design between other trials



*Clinical response defined as: a reduction in the Mayo score of at least 3 points and a decrease of at least 30% from baseline, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an overall rectal bleeding subscore of 1 point or less.
**Mayo score: included assessment of stool frequency, rectal bleeding, an endoscopic assessment and a global assessment by a clinician.

1. Induction duration

Clinical response* at 6 weeks: GEMINI and PURSUIT

vs.

Clinical response* 8 weeks: ULTRA 1; ACT 1

At 6 weeks patients received:

- 2 doses of vedolizumab and golimumab
- 4 doses of adalimumab
- 3 doses of infliximab

The ERG has since stated that 10 weeks should be used to assess the clinical effectiveness during induction to maintain parity between treatments.

Outcome:

By assessing clinical response at 6 weeks the efficacy of vedolizumab may have been underestimated.

2. Maintenance duration

52 weeks: GEMINII, ULTRA 2; Suzuki (2014);

vs.

54 weeks: ACT 1; PURSUIT-SC/M

52 vs 54 weeks was considered to have no impact on the results.

Outcome:

The committee agreed.

3. Re-randomisation after induction

Re-randomised: GEMINII, PURSUIT-SC/M

vs.

Randomised at baseline only: ACT 1/2; ULTRA 1/2; Suzuki (2014);

Re-randomising only patients who responded at 6 weeks means late responders are excluded; potentially under estimating the efficacy of vedolizumab.

Results (continued)

Equally, by only selecting responders, this may generate better results.

Outcome:

It was not clear whether the results in GEMINI or PURSUIT-M over- or underestimated the treatment effect of vedolizumab relative to the comparators in the maintenance phase.

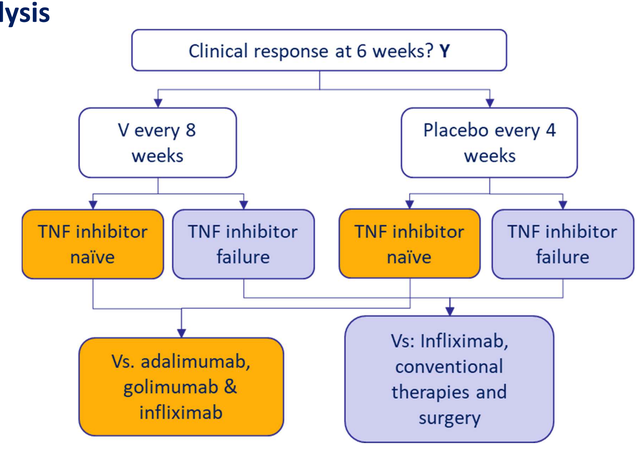
4. TNF inhibitor use

Where TNF inhibitors have failed, UC is considered more difficult to treat[3].

Manufacturer's approach:

- The company analysed these sub-groups separately according to figure 3. using a fixed effect model (no data for TNF inhibitor failure for adalimumab or golimumab).

Figure 3. Clinical responders from GEMINI and subgroup analysis



ERG response:

- A random effects model would have been more appropriate, as fixed effect models cannot capture the uncertainty in treatment effect due to differences in trial design.
- A random effects model does not presume that all trial populations are the same and allows for differences in treatment effect between trials (due to variables that cannot be controlled for).
- A fixed effect model would underestimate uncertainty in this example.

Outcome:

- A disadvantage of not comparing all subgroups is that interaction between treatment and subgroup cannot be explored - this could have been done using meta-regression.
- The Committee concluded that vedolizumab was clinically effective in the whole population, and in both subgroups, compared with conventional therapy.

Conclusions

- Whilst the fixed effect NMA was still assessed, NICE recommended vedolizumab largely based on tolerability and patient QoL considerations related to corticosteroids and invasive surgery, rather than the comparability of vedolizumab to TNF inhibitor alternatives for treating this patient group.
- Although NMA is important for HTA purposes it assumes no significant trial heterogeneity. Where trial designs differ, this may have an important influence on NMA results, and therefore should be given careful consideration alongside other factors such as tolerability during decision making.

Abbreviations: AE, adverse event; ERG, Evidence review group; HTA, Health technology appraisal; NICE, National institute for health and care excellence; NMA, network meta analysis; QoL, Quality of life; RCT, randomised control trial; TNF, tumour necrosis factor; UC, ulcerative colitis.

References
1. Brown et al (2014) Systematic reviews. 3:110; 2. Burness and Keating (2013) BioDrugs. 27 (3): 247-62; 3. NICE [TA342] (2015) Vedolizumab for treating moderately to severely active ulcerative colitis; 4. Sandborn et al. (2014) Gastroenterology. 146:96-109; 5. Sandborn et al. (2014) Gastroenterology. 146: 85-95; 6. Reinisch et al. (2011) Gut. 60: 780-787; 7. Sandborn et al. (2012) Gastroenterology. 142: 257-265; 8. Suzuki et al. (2014) Gastroeneterology. 49: 283-294; 9. Rutgeerts et al. (2005) 353: 2462-2476.

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