

The False Confidence of Unanchored MAICs: Lessons in Ulcerative Colitis

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Introduction

- Indirect comparisons are used in the absence of RCTs.
- Matching-adjusted indirect comparison (MAIC) helps compare effectiveness of treatments when individual patient data (IPD) are available for one trial and published summaries are available for another.
 - Anchored MAICs** compare treatment effects between studies with a shared common comparator, such as placebo
 - Unanchored MAICs** do not have such an anchor.
- The catch is that unanchored MAICs, despite being less robust and using less information, often yield:
 - Narrower confidence intervals
 - Smaller p-values

Objective

- To compare anchored and unanchored MAICs for ustekinumab versus published ulcerative colitis therapies during induction, focusing on statistical significance and the width of 95% confidence intervals.

Methods

- UC studies are well-suited to this task:
 - Similar placebo-controlled designs
 - Similar eligibility criteria
 - Closely aligned endpoints
- IPD from the UNIFI phase III trial of ustekinumab in moderately to severely active ulcerative colitis (UC), obtained through Yale University Open Data Access Project.

Comparator treatments

- vedolizumab, upadacitinib, mirikizumab, guselkumab, etrasimod, and adalimumab

Outcomes

- Clinical response & clinical remission to induction therapy

Statistical analyses

- Each comparison was performed twice:
 - Anchored: preserved the shared placebo comparator
 - Unanchored: intentionally omitted placebo
- IPD from UNIFI was weighted to match baseline characteristics of each of the comparator trials.
- Results reported on the risk difference and odds ratio scales

Table 1: Baseline Characteristics for UNIFI

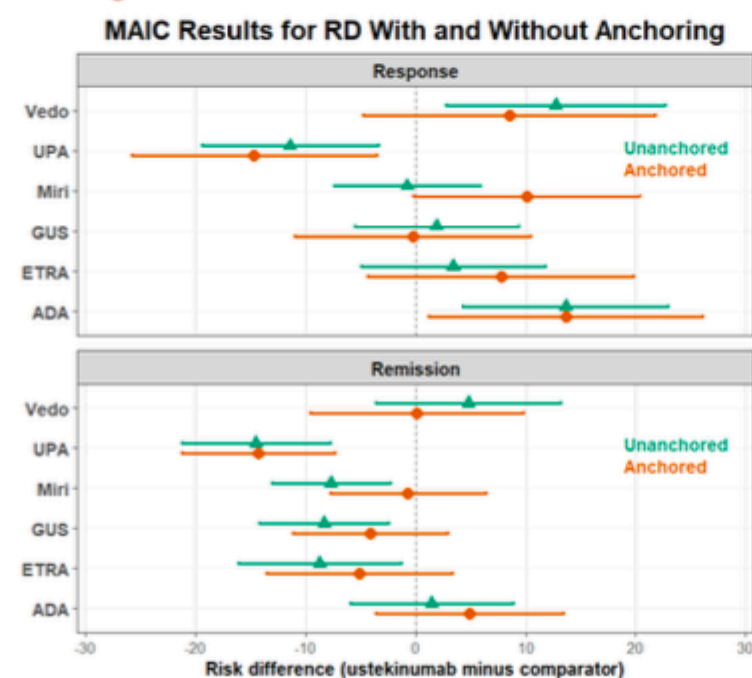
Characteristic	Ustekinumab (6 mg/kg) N = 322	Placebo N = 319
Age	41.7 (13.7)	41.2 (13.5)
Male Sex	195 (61%)	197 (62%)
White Race	243 (76%)	248 (78%)
BMI	24.7 (5.4)	24.5 (4.8)
Left-sided disease	169 (53%)	168 (53%)
Mayo Score	9.0 (1.5)	8.9 (1.6)
Endoscopic subscore = 3	240 (75%)	216 (68%)
Prior Anti-TNF therapy	166 (52%)	175 (54%)
Duration of UC (years)	8.5 (8.0)	8.3 (7.4)
Fecal calprotectin (mg/kg) – Median (IQR)	1586 (740, 3176)	1403 (582, 2563)
CRP (mg/L) – Median (IQR)	5.2 (1.8, 13.7)	5.0 (1.4, 10.7)
Concomitant glucocorticoid use	179 (56%)	161 (51%)
Concomitant ASA use	240 (75%)	207 (65%)
Concomitant immunomodulator use	94 (29%)	90 (28%)

ASA = aminosalicylates; BMI = body-mass index; CRP = C-reactive protein; IQR = interquartile range; TNF = tumor necrosis factor; UC = ulcerative colitis.

Continuous variables are presented with mean and standard deviation unless otherwise specified.

Minimal missingness was handled using a single random-forest imputation; values may differ slightly from published Table 1.

Figure 1 – Results for RD with and without anchoring

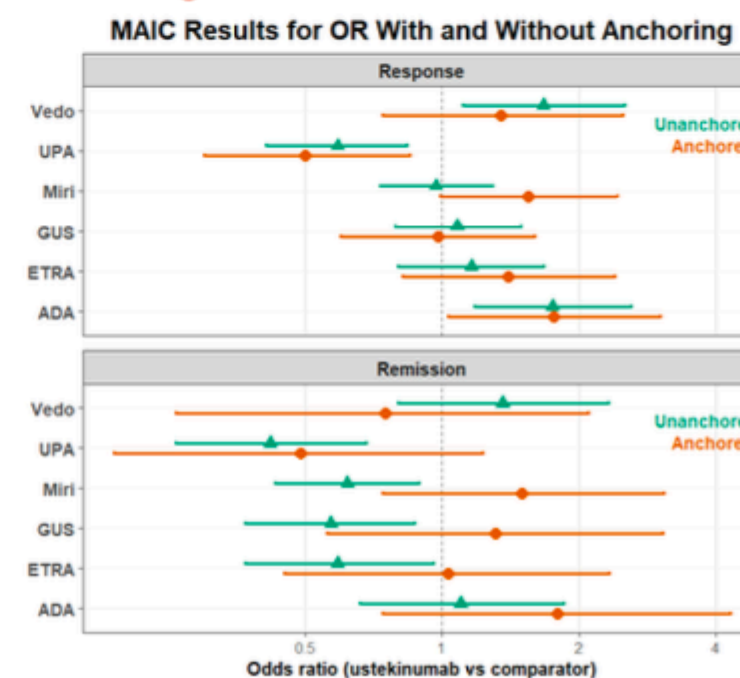


Results

Table 2: Raw Outcomes for Each Trial

Comparator	Active %	Placebo %	Naïve Unanchored RD	Naïve Anchored RD
Clinical response to induction therapy (USTE 61.8%; placebo 31.3%)				
Vedolizumab	47.1%	25.5%	14.7%	8.8%
Upadacitinib	73.6%	26.2%	-11.8%	-17.0%
Mirikizumab	63.5%	42.2%	-1.7%	9.2%
Guselkumab	61.5%	27.9%	0.3%	-3.2%
Etrasimod	62.3%	37.2%	-0.5%	5.4%
Adalimumab	50.4%	34.6%	11.4%	14.6%
Clinical remission to induction therapy (USTE 15.5%; placebo 5.3%)				
Vedolizumab	16.9%	5.4%	-1.4%	-1.3%
Upadacitinib	29.8%	4.3%	-14.3%	-15.4%
Mirikizumab	24.2%	13.3%	-8.7%	-0.7%
Guselkumab	22.6%	7.9%	-7.0%	-4.5%
Etrasimod	26.0%	10.9%	-10.5%	-4.9%
Adalimumab	16.5%	9.3%	-1.0%	3.0%

Figure 2 – Results for OR with and without anchoring



- Mean CI width was smaller for **unanchored vs anchored MAICs** on both scales:

- RD:** 15.2 vs 19.6
- log(OR):** 0.82 vs 1.40

Conclusions

- Unanchored MAICs produce narrower confidence intervals and smaller p-values than their anchored counterparts even though they use less data and rely on stronger assumptions.**
- Additional caution should be taken when interpreting unanchored MAICs, recognizing these limitations and the increased chance for bias.**
- Researchers and analysts should never deliberately use an unanchored MAIC when an anchored one is feasible merely to gain precision.**

Disclosures

Bret Zeldow completed this work while employed by Genesis Research Group, not in connection with his current affiliation. Craig Parzynski is an employee of Genesis Research Group.

Acknowledgement

This study, carried out under YODA Project #2025-0432, used data obtained from the Yale University Open Data Access Project, which has an agreement with Johnson & Johnson. The interpretation and reporting of research using these data are solely the responsibility of the authors and do not necessarily represent the official views of the Yale University Open Data Access Project or Johnson & Johnson.

References

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