How to compare drug efficacy in the absence of H2H studies:

Valid tools for the indirect comparison of drugs

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DATE OF PREP: SEPT 2021 UK-GAS-2100103 THE SLIDES HAVE BEEN REVIEWED FOR OFF LABEL INFORMATION BY FERRING PHARMACEUTICALS'

Disclosures

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Clinical scenario

30 year old woman with pan-ulcerative colitis. She has been on 5-ASA and azathioprine for 3 years. Unfortunately, she's symptomatic and a recent sigmoidoscopy has shown active disease

You decide to do some homework

A quick scan of the literature

PubMed.gov

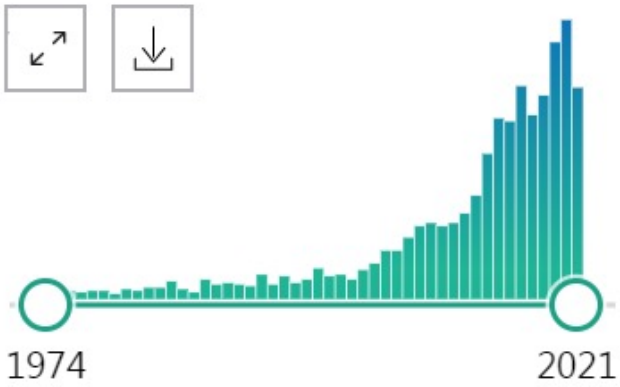
((ulcerative colitis) AND (moderately severe)) AND (treatment)

Advanced Create alert Create RSS

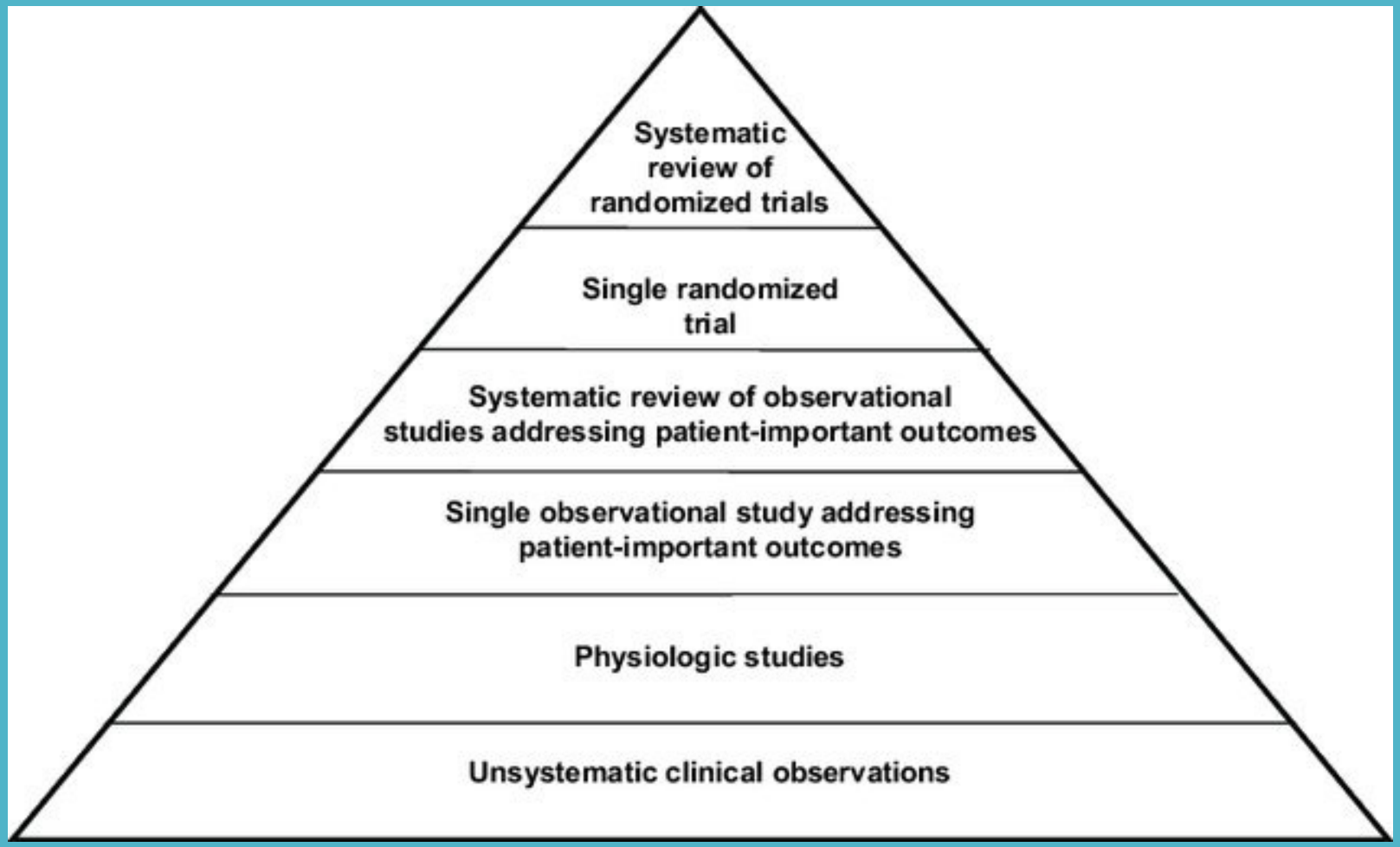
Save Email Send to

1,515 results

RESULTS BY YEAR



Hierarchy of evidence



Systematic review +/- Meta-analysis

Translate large amounts of data into something useable

Grade the quality of evidence

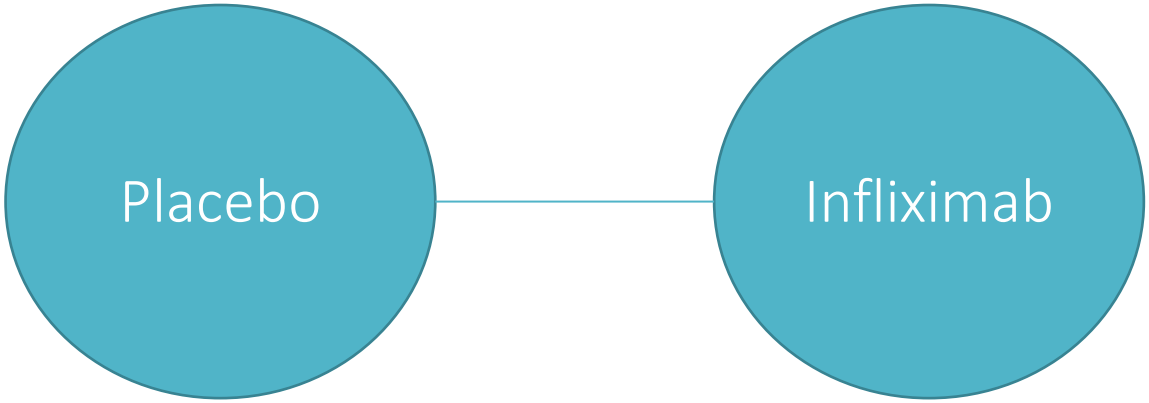
Describe:

- Efficacy
- Harms

Liked by policy makers

Highly cited

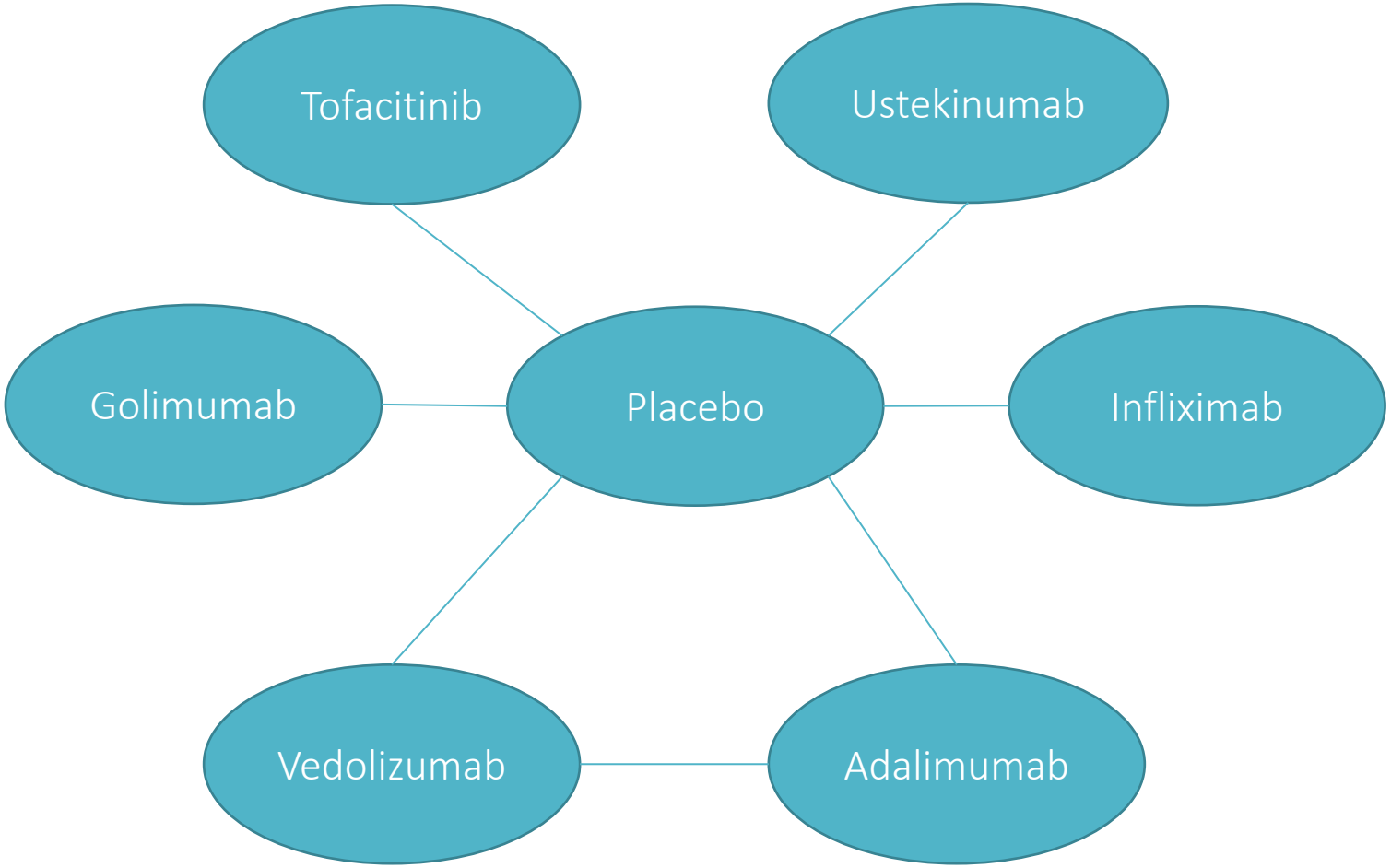
Direct comparison



Clinical question:

Is infliximab more effective than placebo for treating this lady?

The plot thickens

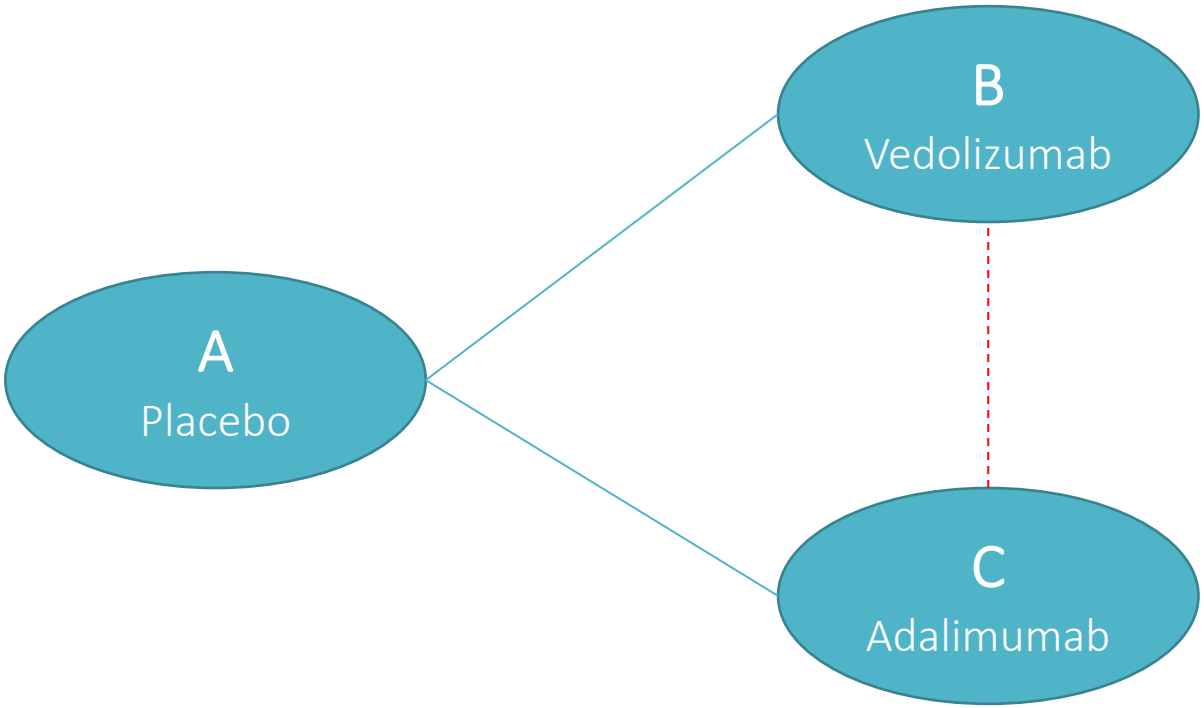


Direct versus indirect evidence

Direct evidence is evidence that directly proves a key fact

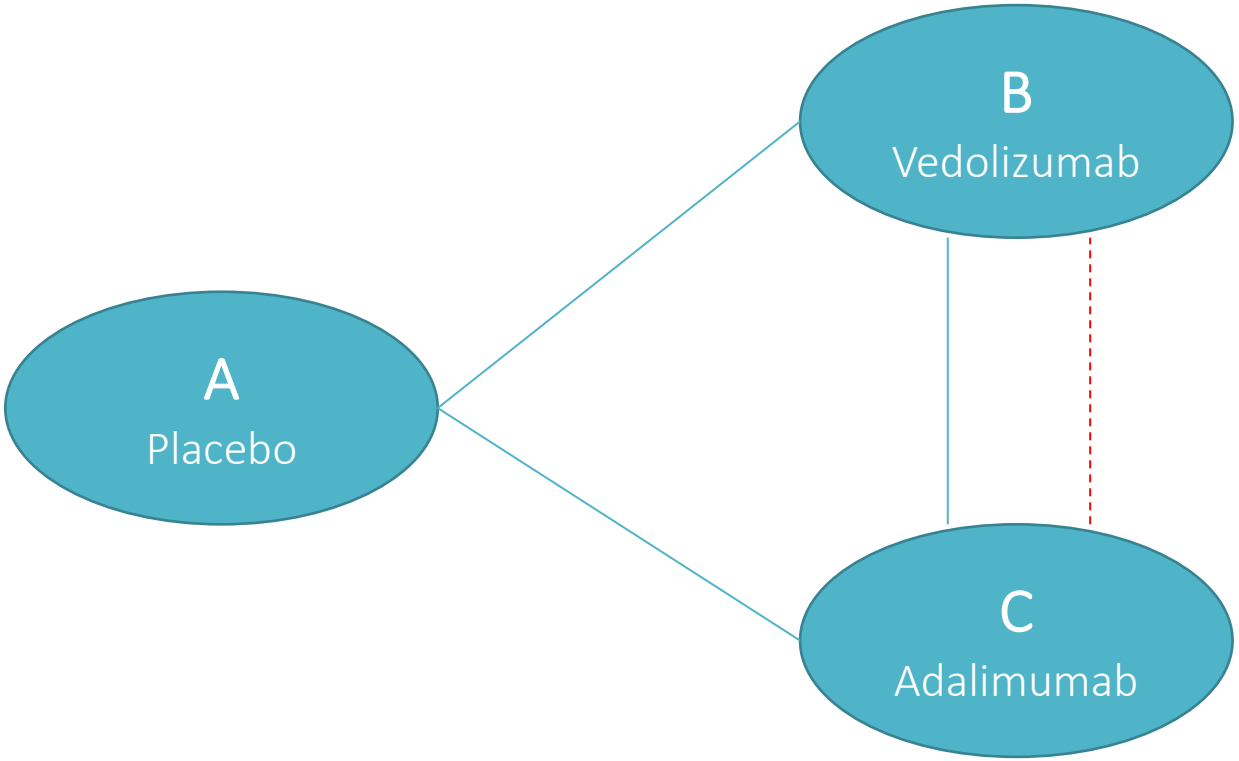
Indirect evidence (circumstantial evidence), is a set of facts that, if they are true, allows a person to infer the fact in question

Indirect evidence: Network meta-analysis



BC = AC - AB

Mixed effects



More precise

Benefits of network meta-analysis

Estimate the relative efficacy without head-to-head studies

Increase the confidence in an estimate

Single, coherent ranking of treatments

May be misleading

Caveats

Represents randomisation but **NOT** randomisation

Validity assumptions

- Transitivity
  - *Should these studies be combined?*
- Consistency
  - *Does the direct and indirect evidence agree?*

Transitivity assumptions

Patient groups the same?

Disease the same?

Treatments the same?

Outcomes the same?

Other factors

- Geographical location
- Timeframe

This information should be in the protocol

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Systematic Reviews and Meta-analyses

First- and Second-Line Pharmacotherapies for Patients With Moderate to Severely Active Ulcerative Colitis: An Updated Network Meta-Analysis

Siddharth Singh *, ‡, Mohammad Hassan Murad §, Mathurin Fumery ||, Parambir S. Dulai *, William J. Sandborn *

First- and Second-Line Pharmacotherapies for Patients With Moderate to Severely Active Ulcerative Colitis: An Updated Network Meta-Analysis

Efficacy and safety of different therapies as first and second-line agents for moderate-severe UC

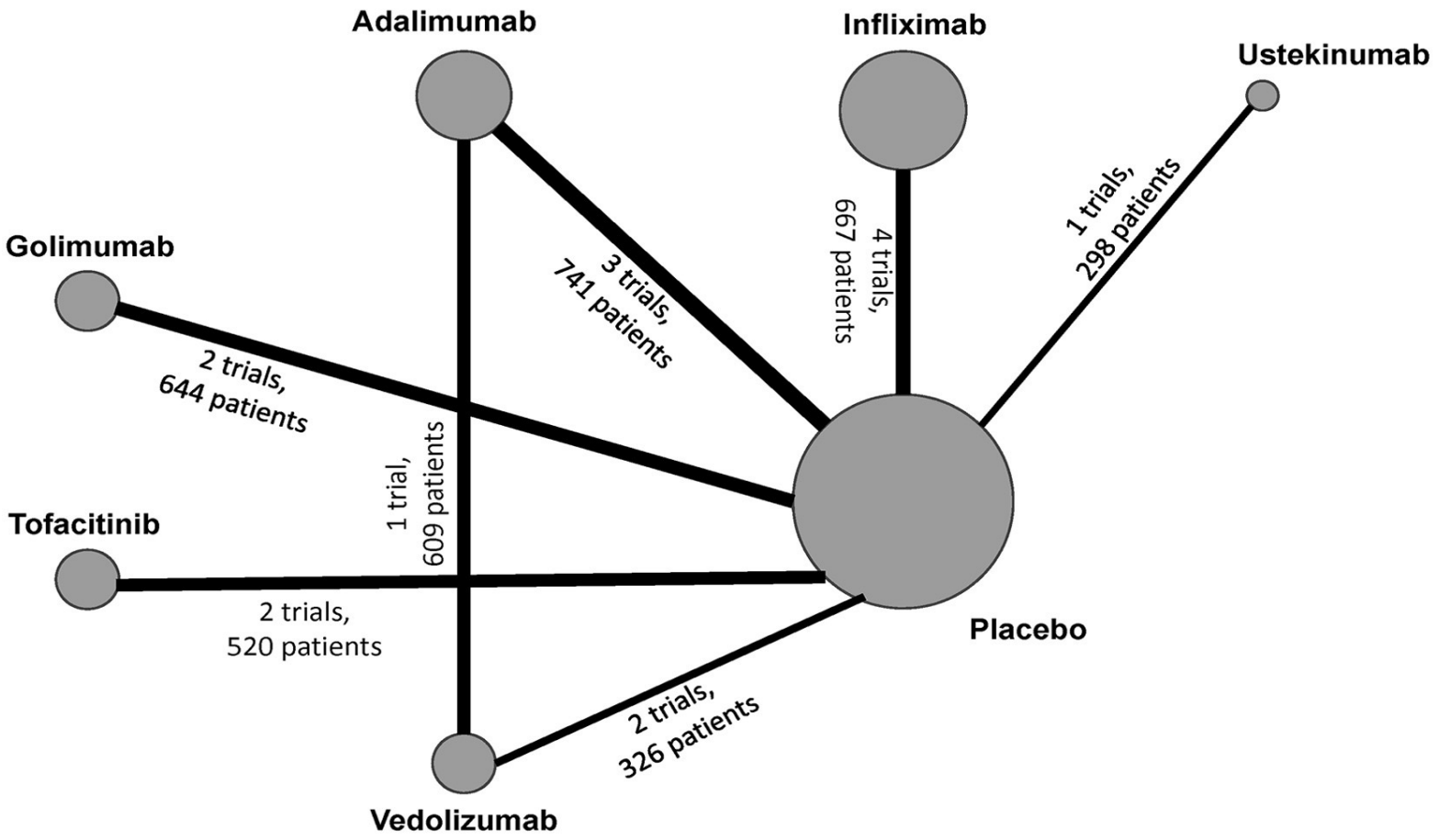
Biologic naïve patients

- 15 trials
- 1 head-to-head trial

Previous anti-TNF exposure

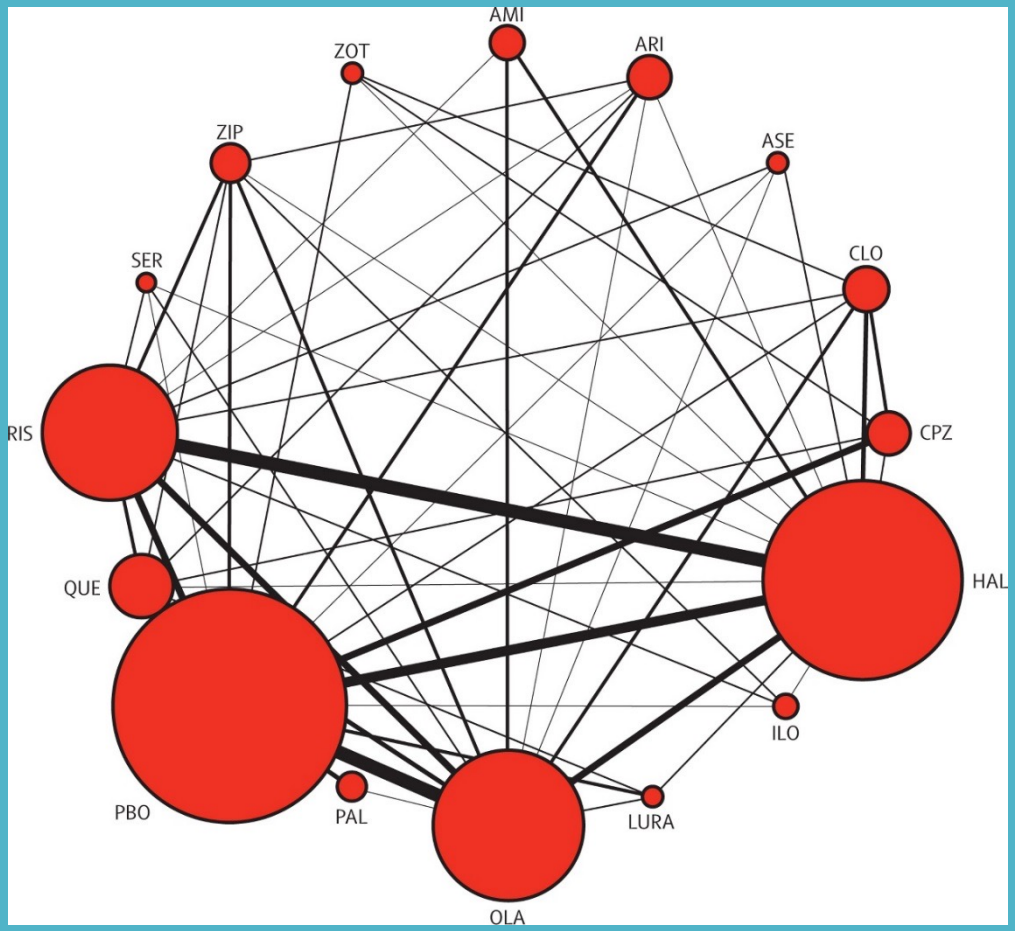
- 7 trials
- One head-to-head

Network plot



Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis

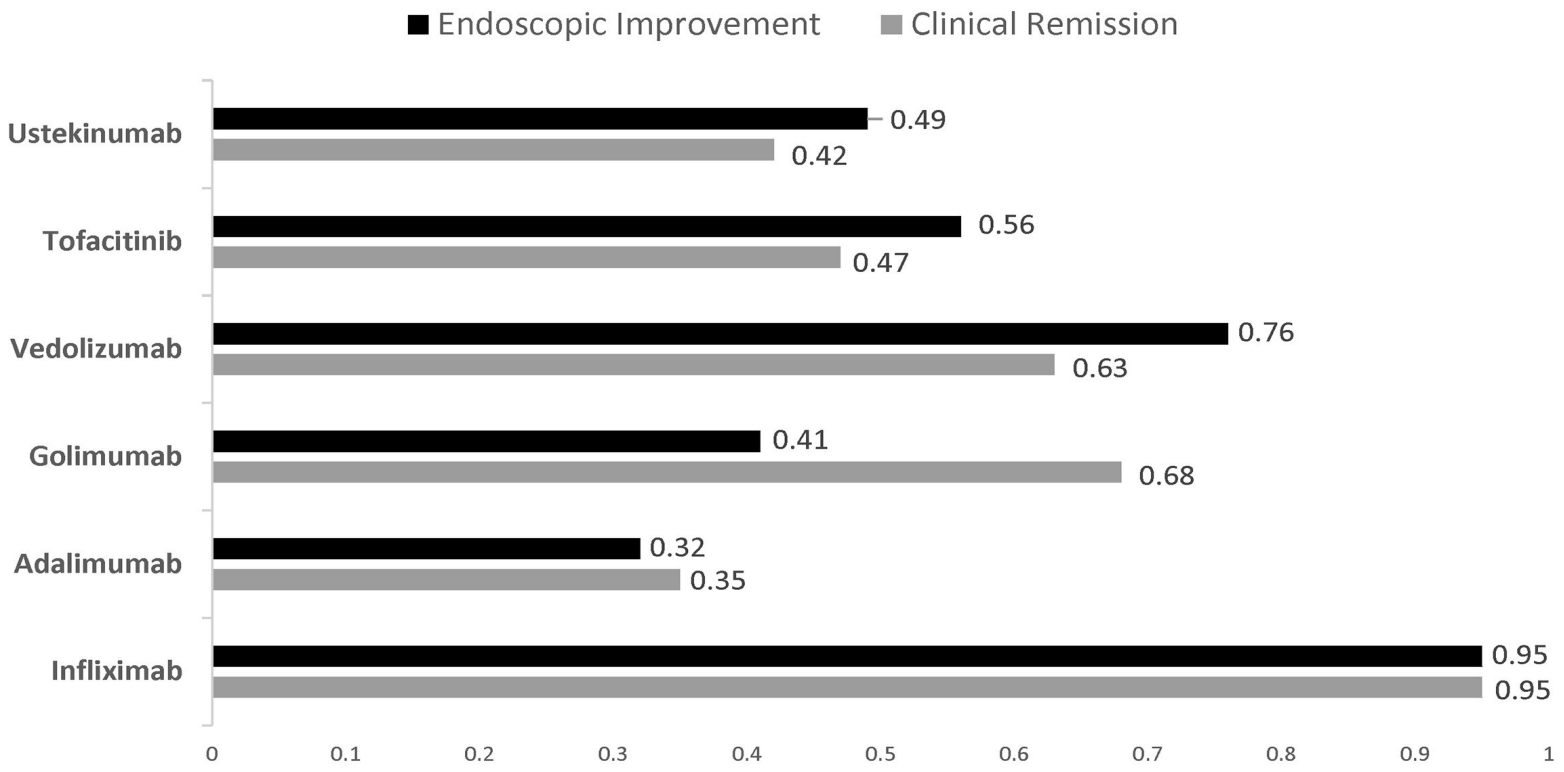
Leucht, The Lancet 2013



Study characteristics

Trial name	Design	Interventions	Other treatments allowed	Clinical remission definition	Endoscopic remission definition	Induction endpoint (weeks)	Maint. endpoint (weeks)
ACT-1	Parallel	Infliximab 5mg/kg, 10mg/kg & placebo		Total Mayo ≤ 2 with no subscore >1	Mayo ≤ 1	8	54
GEMINI	Adaptive	Vedolizumab 300mg v placebo	5-ASA, immunomodulator, corticosteroids	Total Mayo ≤ 2 with no subscore >1	Mayo ≤ 1	6	52
OCTAVE 2	Adaptive	Tofacitinib 10mg v placebo	ASA, corticosteroids	Total Mayo ≤ 2 with no subscore >1 and rectal bleeding score of 0	Mayo ≤ 1	8	NA
VARSITY	Parallel	Vedolizumab 300mg IV v adalimumab	ASA, immunomodulator, corticosteroids	Total Mayo ≤ 2 with no subscore >1	Mayo ≤ 1	14	52

Treatment rankings – Surface under the cumulative ranking curve (SUCRA)



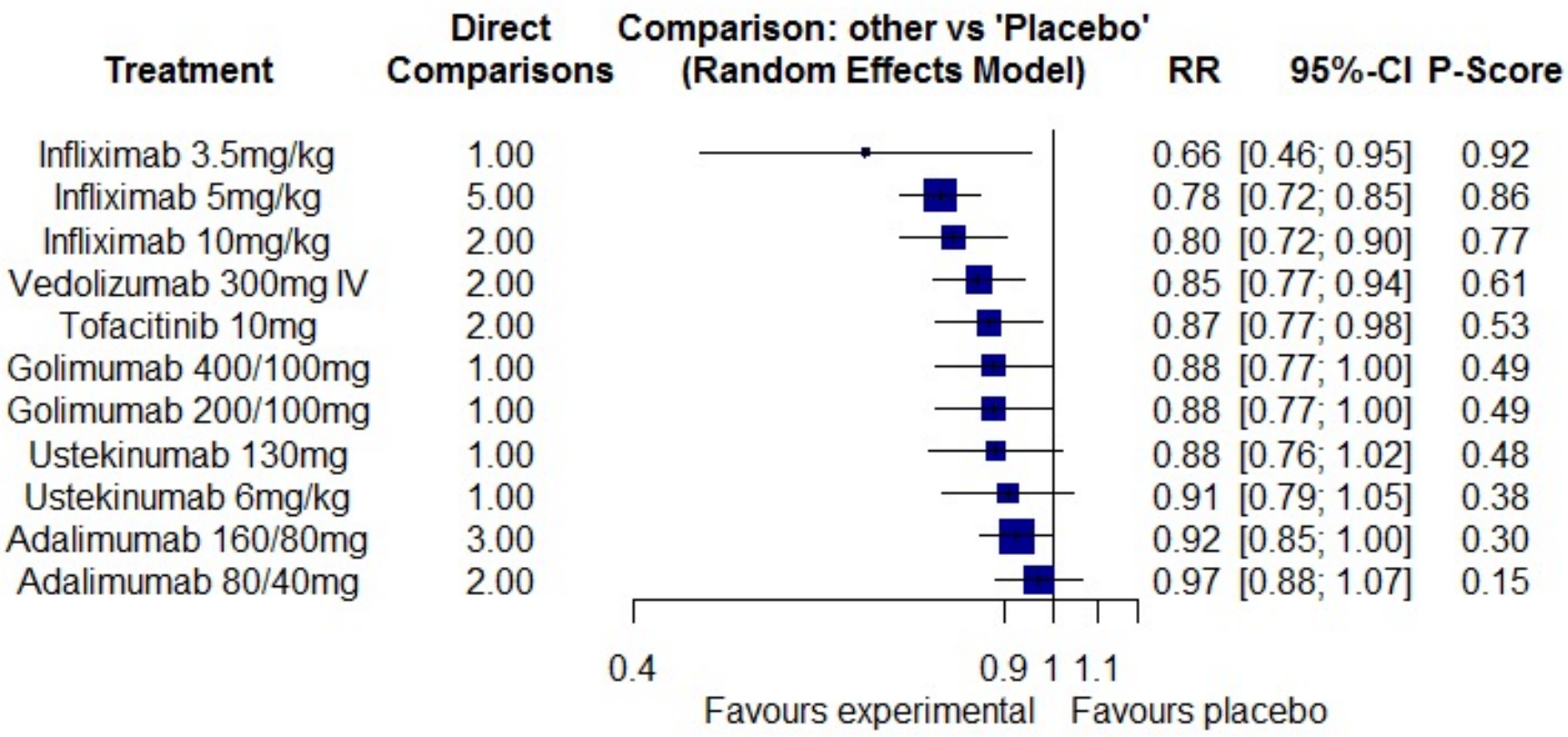
Biologic naïve patients with mod-severe UC

League table

Induction of clinical remission

Induction of endoscopic improvement					
Ustekinumab	0.96 (0.4–2.5)	0.80 (0.4–1.8)	1.05 (0.5–2.3)	0.50 (0.2–1.1)	**2.04 (1.0–4.1)**
0.92 (0.45–1.89)	Tofacitinib	0.84 (0.4–1.8)	1.10 (0.5–2.3)	0.52 (0.2–1.1)	**2.12 (1.1–4.0)**
0.74 (0.36–1.51)	0.80 (0.4–1.6)	Vedolizumab	1.31 (0.9–2.0)	0.62 (0.3–1.2)	**2.54 (1.6–4.0)**
1.17 (0.65–2.13)	1.28 (0.7–2.3)	1.59 (0.9–2.8)	Adalimumab	**0.48 (0.3–0.9)**	**1.94 (1.3–2.9)**
0.56 (0.30–1.04)	0.61 (0.3–1.1)	0.76 (0.4–1.4)	**0.48 (0.3–0.7)**	Infliximab	**4.07 (2.7–6.2)**
1.86 (1.11–3.13)	**2.03 (1.2–3.3)**	**2.52 (1.5–4.1)**	**1.58 (1.2–2.1)**	**3.32 (2.4–4.6)**	Placebo

Induction of clinical remission for moderate to severe UC



Include observational data?

Can be done

Uses more data

Weighted evidence

- RCT weighted highest
- Observational data weighted on quality (ROB)

Need to be extremely careful (transitivity again)

Conclusions

Useful addition to the evidence base
- Even with head-to-head trials

Questions:
- Should these studies be combined? (transitivity)
- How good are the studies? (quality/GRADE)
- Do the results make sense? (consistency)
- Are the results generalisable?

Other things to consider
- Costs
- Tolerability
- Number needed to treat / harm
- Special situations

They are here to stay
- Adopted by NICE, Cochrane and WHO (amongst others)
- Add in observational data……..

Questions?