Challenges in comparing remission outcomes in network meta-analyses in ulcerative colitis

L. Nelson[1], A. Curry[2], S. Ralston[2].
[1]SIRIUS Market Access, Newcastle-upon-Tyne, United Kingdom
[2]SIRIUS Market Access, London, United Kingdom. email: info@siriusmarketaccess.com

PRM13

Objectives

The goal of treatment in mild-moderate ulcerative colitis (UC) is the induction and maintenance of remission, however, there is currently no fully validated definition of remission in UC[1]. This research aimed to explore the definitions of remission used in clinical trials, and implications this may have for indirect treatment comparison and Health Technology Assessment (HTA) decisions.

Introduction

UC is the most common form of inflammatory bowl disease. It is a chronic, life-long condition, characterised by alternating periods of remission and relapse[1]. The symptoms of UC are debilitating, and correlated with the extent of inflammation and the location of disease[1,2]. First-line treatment for UC is generally oral and/ or topical 5-ASA (mesalazine) treatment, followed by steroid treatment if there is insufficient response.

Methods

A pragmatic search was conducted in the MEDLINE database for phase 3 trials in mild-moderate UC that involved steroid or 5-ASA (mesalazine) treatments. No year or geographical limit was placed. Electronic searches were supplemented by references lists of identified systematic reviews in UC. Trials that included remission as a primary or secondary outcome were included if a definition of remission was given.

Results

Table 1: Trials identified by pragmatic literature search

Ref.	Active drug	Definition of remission	N
D'Haens (2017)	Oral mesalazine	Mayo: ≤2 points with no individual sub-score > 1.	817
Sun (2016)	Oral mesalazine	UCDAI: ≤2 and a bloody stool score of 0.	251
Sandborn (2015)	Budesonide foam	Mayo: endoscopy subscore <1, rectal bleeding subscore 0, improvement or no change from baseline in stool frequency subscore.	265
Sandborn (2015)	Budesonide foam	Mayo: endoscopy subscore <1, rectal bleeding subscore 0, improvement or no change from baseline in stool frequency subscore.	281
Jiang (2015)	Diosmectite + mesalazine	Mayo: total score ≤2 with no individual subscore >1 point, or an absolute rectal bleeding subscore of 0 or 1.	120
Travis (2014)	Budesonide MMX	UCDAI: total score ≤1, rectal bleeding score 0, stool frequency score 0, mucosal appearance score 0 and ≥1 point reduction in baseline endoscopic index (EI).	512
Wantanabe (2013)	Mesalazine suppository	UCDAI: ≤2 and a bleeding score of 0.	129
Sandborn (2012)	Budesonide MMX	UCDAI: total score ≤1, rectal bleeding score 0, stool frequency score 0, mucosal appearance score 0 and ≥1 point reduction in baseline EI.	
Hiwatashi (2011)	Oral mesalazine	UCDAI 0-1.	123
Andus (2010)	Mesalazine suppository	UCDAI: < 4.	354
Kruis (2009)	Oral mesalazine	CAI: ≤4.	380
Lichtenstein (2007)	Mesalazine MMX	UCDAI: ≤1, rectal bleeding 0, stool frequency 0, no mucosal friability, and ≥1 point reduction from baseline.	280
Kamm (2007)	Mesalazine MMX	UCDAI: ≤1, rectal bleeding 0, stool frequency 0, no mucosal friability, and ≥1 point reduction from baseline.	343

Results

Table 1 (cont.): Trials identified by pragmatic literature search

Ref.	Active drug	Definition of remission	N
Gibson (2006)	Eudragit-L coated mesalazine	CAI: ≤4.	258
Gross (2006)	Budesonide foam	CAI: ≤4.	541
Marteau (2005)	Mesalazine enema	UCDAI: <2.	127
Marakouski (2005)	Mesalazine pellets	CAI: ≤4.	233
Bar-Meier (2003)	Budesonide foam	UCDAI: ≤3.	251
Ardizzone (1999)	Mesalazine foam	CAI <4 and EI <6.	195
Williams (1987)	5-ASA suppositories	UCDAI.	27

Figure 1: Criteria used to assess remission in clinical trials of mild-moderate UC

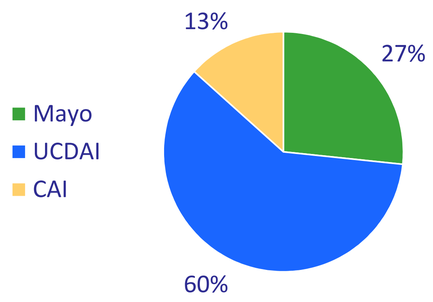
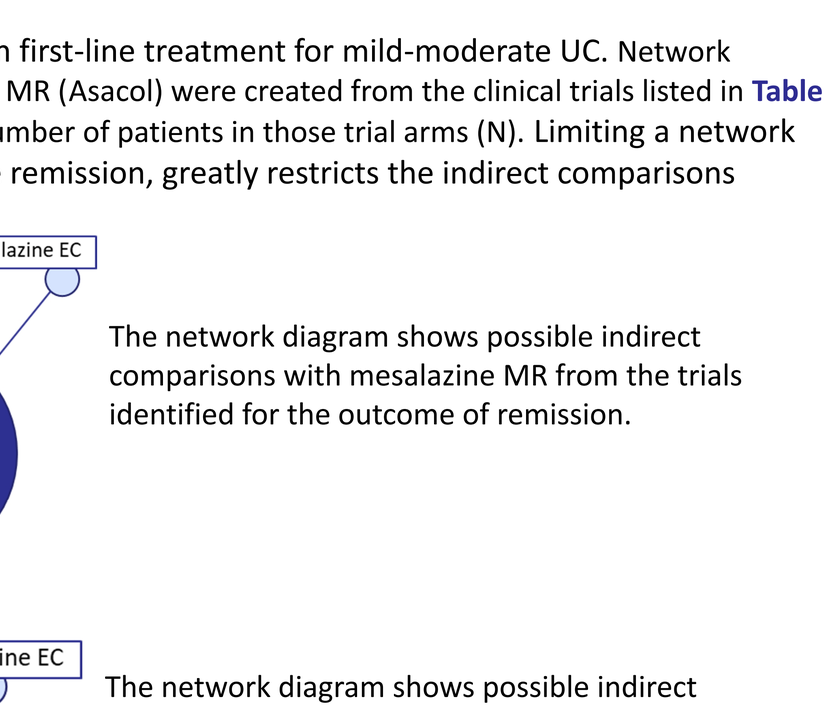


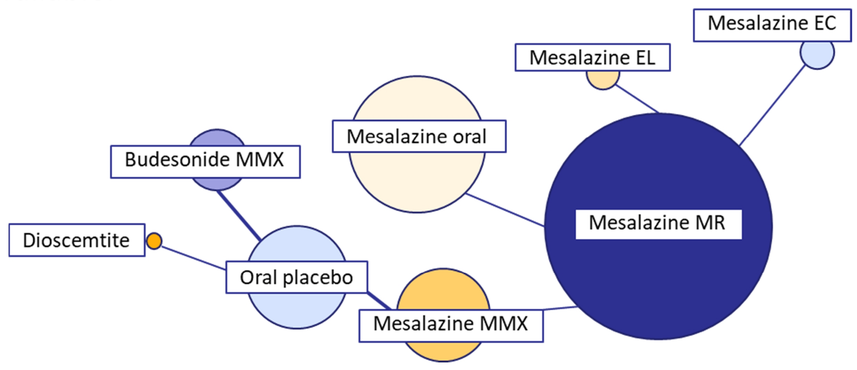
Figure 1 shows the variation in the criteria used to measure remission. Variation over time in the methods used to identify and quantify remission is shown in **Figure 2**.

Figure 2: Changes over time of the methods used to assess remission in clinical trials of UC

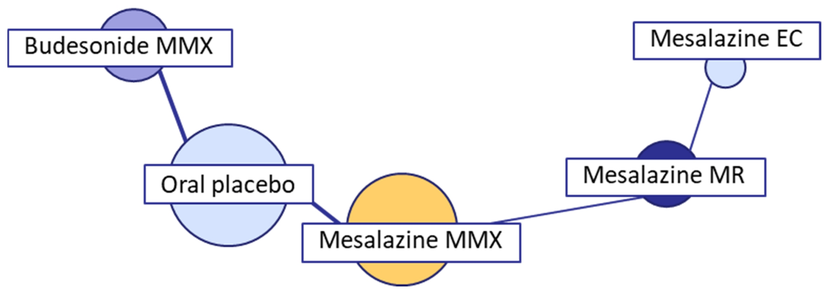


Example of network diagrams for indirect treatment comparisons

Mesalazine modified release (MR) (Asacol) is a common first-line treatment for mild-moderate UC. Network diagrams for indirect treatment comparison to mesalazine MR (Asacol) were created from the clinical trials listed in **Table 1.** The size of the treatment nodes is proportional to the number of patients in those trial arms (N). Limiting a network diagram to trials which used the same criteria to define remission, greatly restricts the indirect comparisons available.



The network diagram shows possible indirect comparisons with mesalazine MR from the trials identified for the outcome of remission.



The network diagram shows possible indirect comparisons with mesalazine MR from the trials identified for the outcome of remission as measured by the UCDAI.

Conclusions

- The goal of treatment in UC is to induce and maintain remission, however, there is no fully validated definition of remission in UC.
- The variation in definition of remission across clinical trials limits the ability to perform indirect comparisons for efficacy.
- Variations over time in definition of remission may impact the ability to compare outcomes of earlier trials in indirect comparisons.
- In HTAs, it may be easier to compare treatments for UC when considering tolerability rather than efficacy. Indeed, a contributing factor to the approval of budesonide MMX for UC in Sweden and Scotland was its association with fewer adverse events when indirectly compared to oral systemic corticosteroids.
- The first International Consensus on the definition of endoscopic remission in UC was published in 2017, and a draft FDA Guide for Industry for clinical trial endpoints in UC was released in 2016. This may lead to greater consistency in the definition of remission in future UC clinical trials.

References: 1. Magro et al (2017) European Crohn's and Colitis Organisation [ECCO] consensus guideline, *Journal of Crohn's and Colitis*; 2. Dignass et al (2012) *Journal of Crohn's and Colitis, 6.*

Abbreviations: CAI: clinical activity index; DAI: Disease Activity Index; EC: ethylcellulose-coated; EI: endoscopic index; EL: eudragit L-coated; FDA: Food and Drug Administration; HTA: Health Technology Assessment; MMX: multi-matrix; MR: modified release; UC: ulcerative colitis; UCDAI: ulcerative colitis disease activity index.

SIRIUS MARKET ACCESS