Supplemental Digital Content 2. Systematic literature review: methodology

Contents

Study Protocol

A full protocol for the systematic literature review was written, detailing the patient population, interventions and study designs to be analysed. A summary version of the original study protocol is provided in Appendix A.

Identification of Studies

A comprehensive search strategy was designed to retrieve relevant data from published literature; details of the search strategy are presented in Appendix B.

The following databases were searched:

- Embase
- Medline (through PubMed)
- Cochrane Database of Systematic Reviews
- Cochrane Central Register of Controlled Trials
- NHS Economic Evaluation Database
- Health Technology Assessment Database

The search of databases other than the above, conference proceedings and hand searching of the indexes of key journals was not conducted as part of this review. However, bibliographies of relevant systematic reviews were scanned to identify any additional studies.

Limitors

The searches were limited to articles published in English and in human populations. The searches included 15 EU countries (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain, Sweden, UK [England, Wales, Scotland] and 7 other countries (Australia, Brazil, Canada, Mexico, New Zealand, Russia and USA).

Study Selection

The inclusion and exclusion criteria required to select studies that met the objectives of this review were based on the 'PICOS principle' (Patient, Intervention, Comparator, Outcome and Study Design) and are described in Table S1.

Table S1: Inclusion Criteria for Studies

	Inclusion Criteria	Implications
Study population	Human	Animal studies were excluded by the searches and rejected during filtering stages.
	Patient population	The searches were performed to include all patients with IBD aged ≥18 years.
Study design	Randomised controlled trials (RCTs) Observational studies Economic evaluations	Pre-specified study types were included by the search terms. All other study types were either excluded by the searches or rejected during filtering stages, e.g. Reviews, editorials, letters and comments. Bibliography of relevant systematic reviews and meta- analyses were scanned for any additional studies.
Intervention	Patients with inadequate response to anti-TNFα	Studies including patients with inadequate response to first/second and/or subsequent TNFα antagonists Studies reporting dose escalation of anti-TNFα, induction/maintenance/re-induction with anti-TNFα, studies reporting patients failing on immunosuppressive agents/corticosteroids/surgery and then initiating anti-TNF therapy will also be included
Other	English language	All other language publications were excluded by the searches and rejected during filtering stages.
	Country	The searches were performed to include countries of interest only. Countries that are not of interest will be excluded during filtering stages.

Data Extraction Strategy

Bibliographic details and abstracts of all citations retrieved by the literature search were downloaded into Endnote version X3.

First Pass of Citations

During this stage, titles and abstracts of citations were screened. Those studies that did not meet the eligibility criteria were excluded at this 'first pass' screening stage. Duplicates of citations (due to overlap in the coverage of the databases) were also excluded during first pass screening. Studies that met the criteria at first pass were included and full text copies were ordered. Full text copies of all references that could potentially meet the eligibility criteria were also ordered at this stage.

Second Pass of Citations

During this stage, the inclusion/exclusion eligibility criteria were applied to the full text citations and the studies presenting relevant data were included for data extraction.

Prioritisation of Studies

Due to the large number of potentially valuable studies identified at the second pass stage, a prioritisation approach was adopted to select the most relevant studies for data extraction. The criteria for prioritisation of studies included:

- Publication year
- Publication type (full text publication/conference abstract)
- Countries
- Disease type
- Interventions
- Sample size
- Anti-TNFα failure (yes/no)
- Dose escalation (yes/no)
- Switching (yes/no)
- Data extraction strategy

Where more than one publication was identified describing a single trial, the data were compiled into a single entry in the data extraction table to avoid double counting patients. Each publication was referenced in the grid to recognise that more than one publication might have contributed to the entry. Studies that did not report data of interest were excluded during the extraction stage.

Appendix A. Study Protocol

Objectives and research questions	
Primary study question	To define the "anti-TNFα failure" patient population, treatment patterns, place in therapy and to generate data (clinical and economic) that supports changing the common clinical practice of "TNF cycling" in support of Vedolizumab for the treatment of CD and UC
Studies to include	
Population	Age: Adult ≥ 18 years Gender: No limits, non-pregnant females Disease area: Inflammatory bowel disease (CD and UC) Treatment status: Only patients who have failed prior anti-TNFα therapy
Intervention	No limitations
Comparators	No limitations
Outcomes	Treatment patterns Clinical outcomes Adverse events Cost outcomes
Study designs	Included: Randomised controlled trials Non-randomised trials Observational studies Excluded: Review, comments, case reports, editorials NB: Bibliographic searches of identified systematic reviews will be conducted
Language	English language only
Publication timeframe	No limits
Data sources	
Databases	Medline Embase Cochrane Library NHSEED
Other	Bibliographic searching of identified relevant systematic reviews
Information to extract	
Study information	Study objectives Study country/ies/region Study design and methods Number of patients screened and included Interventions (as per categories) Study endpoints Conclusions drawn by investigators

Baseline data	Age Gender, Presence of co morbidities Baseline severity of disease Baseline demographics Number of years on anti-TNFα therapy Number of anti-TNFα treated patients
Clinical outcomes	Treatment pattern Clinical response/remission Inadequate response to anti-TNFα Other clinical outcomes
Safety and Tolerability Outcomes	Total withdrawals for RCTs Withdrawals due to lack of tolerance to treatment/any adverse events/ serious adverse events related to inadequate treatment response AEs related to anti-TNFα therapy Other AEs
Economic outcomes	Monitoring costs (routine tests, labs etc.) Direct costs - associated with treatment/management, concomitant medications, adverse events, office visits, hospitalisations related to "anti-TNFα failure patients" Indirect costs (productivity loss/ absenteeism) for anti-TNFα inadequate responders/failure Overall total drug costs and total costs of patients initiating anti-TNFαs

Analyses

Qualitative- summaries of study characteristics including critical appraisal

Reporting

As per flowchart for preferred reporting items for systematic reviews and meta-analyses (PRISMA) as presented in Figure 1.
MS Word
PDF

Appendix B. Search Strategy

B.1 (Medline + PubMed)
Total number of hits: 3721

Sr. No.	Search String	Hits
1.	'crohn disease'/exp OR 'Crohn disease' OR 'Crohns disease'	56543
2.	'Ulcerative Colitis'/exp OR 'UC'	73351
3.	'inflammatory bowel disease'/exp OR 'inflammatory bowel disease' OR IBD:ab,ti	368185
4.	'colitis'/exp OR colitis:ab,ti	131809
5.	'ileitis'/exp OR 'ileitis':ab,ti	4703
6.	#1 OR #2 OR #3 OR #4 OR #5	398325
7.	'anti-tumour necrosis factor alpha' OR 'anti tumor necrosis factor alpha' OR 'anti-tumour necrosis factor alpha antibody' OR 'anti tumor necrosis factor alpha antibody'	548
8.	'anti-tumour necrosis factor antibody' OR 'anti tumor necrosis factor antibody' OR 'anti TNF' OR 'anti TNF alpha'	11256
9.	Infliximab OR Remicade	26759
10.	Certolizumab OR Natalizumab	6608
11.	Adalimumab OR Humira	13196
12.	Golimumab OR Simponi	1627
13.	Onercept OR Etanercept	17558
14.	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	45563
15.	'Treatment pathways' OR 'treatment sequence' OR 'treatment switch'	1278
16.	'treatment patterns' OR 'treatment paradigm'	4255
17.	'treatment failure'/exp OR 'treatment failure':ab,ti OR 'TNF cycling':ab,ti OR 'TNF failure':ab,ti	85056
18.	'Dose escalation' OR de-intensification OR 'medical diagnosis' OR 'prior treatments' OR 'previous treatments'	29546
19.	'cost'/exp OR 'health care cost'/exp OR 'cost of illness'/exp OR 'direct costs' OR 'indirect costs'	254902
20.	'quality of life'/exp OR 'quality of life':ab,ti OR qol:ab,ti	285315
21.	hospitalization:ab,ti OR employment:ab,ti OR productivity:ab,ti	174758
22.	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	781288
23.	#6 AND #14 AND #22	6672
24.	'austria'/exp OR austria:ab,ti OR 'belgium'/exp OR belgium:ab,ti OR 'denmark'/exp OR denmark:ab,ti OR 'finland'/exp OR finland:ab,ti OR 'france'/exp OR france:ca,ab,ti OR 'germany'/exp OR germany:ca,ab,ti OR 'greece'/exp OR greece:ab,ti OR 'ireland'/exp OR ireland:ab,ti OR	5571890

'italy'/exp OR italy:ca,ab,ti OR 'luxembourg'/exp OR luxembourg:ab,ti OR luxemberg:ab,ti OR 'netherlands'/exp OR netherlands:ca,ab,ti OR 'portugal'/exp OR portugal:ab,ti OR 'spain'/exp OR spain:ca,ab,ti OR 'sweden'/exp OR sweden:ab,ti OR 'united kingdom'/exp OR 'united kingdom':ca,ab,ti OR england:ca,ab,ti OR wales:ab,ti OR scotland:ab,ti

25.	'canada'/exp OR canada:ca,ab,ti OR 'australia'/exp OR australia:ca,ab,ti OR 'new zealand'/exp OR 'new zealand':ab,ti OR 'mexico'/exp OR mexico:ab,ti OR 'russia'/exp OR russia:ab,ti OR 'brazil'/exp OR brazil:ab,ti	1344351
26.	'united states'/exp OR 'united states':ca,ab,ti	6207349
27.	#24 OR #25 OR #26	12914291
28.	#23 AND #27	4968
29.	#28 AND [humans]/lim AND [english]/lim AND [abstracts]/lim	3721

B.2   The Cochrane Library

Total number of hits: 131

Sr. No.	Search String	Hits
1.	MeSH descriptor: [Crohn Disease] explode all trees	895
2.	MeSH descriptor: [Colitis, Ulcerative] explode all trees	856
3.	MeSH descriptor: [Inflammatory Bowel Diseases] explode all trees	1801
4.	MeSH descriptor: [Colitis] explode all trees	960
5.	MeSH descriptor: [Ileitis] explode all trees	46
6.	'Crohn disease' OR 'Crohns disease' OR 'Ulcerative Colitis' OR UC OR 'inflammatory bowel disease' OR IBD OR colitis or ileitis	6575
7.	#1 OR #2 OR #3 OR #4 OR #5 OR #6	6579
8.	'anti-tumour necrosis factor alpha' OR 'anti tumor necrosis factor alpha' OR 'anti-tumour necrosis factor alpha antibody' OR 'anti tumor necrosis factor alpha antibody'	1008
9.	'anti-tumour necrosis factor antibody' OR 'anti tumor necrosis factor antibody' OR 'anti TNF' OR 'anti TNF alpha'	1131
10.	Infliximab OR Remicade	721
11.	Certolizumab OR Natalizumab OR antegren OR tysabri OR 'certolizumab pegol' OR cimzia	181
12.	Adalimumab OR Humira	395
13.	Golimumab OR Simponi	69
14.	Onercept OR Etanercept	599
15.	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	2463
16.	'Treatment pathways' or 'treatment sequence' or 'treatment switch'	15032
17.	'treatment patterns' or 'treatment paradigm'	10730

18.	MeSH descriptor: [Treatment Failure] explode all trees	2540
19.	'treatment failure' or 'TNF cycling'OR 'TNF failure'	27261
20.	'Dose escalation' OR de-intensification OR 'medical diagnosis' OR 'prior treatments' OR 'previous treatments'	53899
21.	MeSH descriptor: [Costs and Cost Analysis] explode all trees	20266
22.	MeSH descriptor: [Quality of Life] explode all trees	13023
23.	cost OR 'health care cost' OR 'cost of illness' OR 'direct costs' OR 'indirect costs'	47688
24.	'quality of life' OR QoL:ti,ab,kw	27659
25.	hospitalization OR employment OR productivity	19331
26.	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25	139164
27.	#7 AND #15 AND #26	229
28.	austria OR belgium OR denmark OR finland OR france OR germany OR greece OR ireland OR italy OR Luxembourg OR luxemberg OR netherlands OR portugal OR spain OR sweden OR 'united kingdom' OR england OR wales OR Scotland OR canada OR australia OR 'new Zealand OR mexico OR russia OR brazil OR 'united states'	202026
29.	#27 AND #28	131

B.3   NHSEED

Total number of hits: 40