Farm Hosp. 2015;**39(2)**:80-91

Farmacia HOSPITALARIA
ÓRGANO OFICIAL DE EXPRESIÓN CIENTÍFICA DE LA SOCIEDAD ESPAÑOLA DE FARMACIA HOSPITALARIA

ORIGINALES

Indirect comparison for Anti-TNF drugs in moderate to severe ulcerative colitis

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Abstract

Objective: To compare the relative efficacy of infliximab, adalimumab and golimumab through adjusted indirect treatment comparisons (ITCs).

Methods: An exhaustive search was performed until October 2013. Databases consulted were MEDLINE, EMBASE, the Cochrane Library, the Centre for Reviews and Dissemination and the Web of Science. Randomized control trials (RCTs) comparing the efficacy of infliximab, adalimumab or golimumab versus placebo, in terms of clinical remission, clinical response and mucosal healing, were included. In the case that more than one RCT fulfilled the inclusion criteria for the same drug, a metanalysis was undertaken using a fixed effects model. ITCs were carried out using the method proposed by Bucher et al.

Results: 6 RCTs published in 5 papers were included: 2 for infliximab (ACT 1 and ACT 2), 2 for adalimumab (ULTRA 1 y ULTRA 2) and 2 for golimumab (PURSUIT-SC y PURSUIT-M).In these RTCs, each biological agent was superior in efficacy to placebo. The results of the adjusted ITC are the following. In relation to the clinical remission, in the induction and maintenance period, there are no statistically significant differences between the three anti-TNF drugs. In relation to the clinical response and mucosal healing, in the induction period, there are statistically significant differences between infliximab and adalimumab.

Conclusion: In view of the results obtained, infliximab, adalimumab and golimumab appear to be similarly effective the-

Fármacos anti-TNF en colitis ulcerosa moderada-grave: comparación indirecta

Resumen

Objetivo: Comparar la eficacia relativa de infliximab, adalimumab y golimumab mediante comparaciones indirectas (CI) ajustadas.

Métodos: Se realizó una búsqueda bibliográfica que abarcó hasta Octubre 2013. Las bases de datos consultadas fueron: *MEDLINE, EMBASE, the Cochrane Library, the Centre for Reviews and Dissemination* y *the Web of Science*. Se incluyeron ensayos clínicos aleatorizados (ECA) que compararan la eficacia de infliximab, adalimumab o golimumab frente a placebo en términos de remisión clínica, respuesta clínica y curación de la mucosa. En el caso de que se incluyera más de un ECA para un mismo fármaco se llevó a cabo un metanálisis utilizado el modelo de efectos fijos. Las CI se realizaron utilizando el método de *Butcher et al.*

Resultados: Se incluyeron 6 ECA publicados en 5 artículos: 2 para infliximab (ACT 1 y ACT 2), 2 para adalimumab (ULTRA 1 y ULTRA 2) y 2 para golimumab (PURSUIT-SC y PURSUIT-M). Los tres agentes biológicos presentaron mayor eficacia que placebo. Los resultados de las CI fueron los siguientes: en relación a la remisión clínica, en el período de inducción y en el período de mantenimiento, no hubo diferencias estadísticamente significativas entre los tres fármacos anti-TNF. En relación a la respuesta clínica y a la curación de la mucosa, en el período de

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Recibido el 10 de octubre de 2014; aceptado el 31 de diciembre de 2014. DOI: 10.7399/fh.2015.39.2.8218

rapeutic alternatives. Therefore, other considerations such as safety, tolerance and cost-effectiveness should be taken into account in order to select the most appropriate treatment.

KEYWORDS
Anti-TNF; Ulcerative colitis; Infliximab; Adalimumab; Golimumab; Indirect treatment comparisons

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inducción hay diferencias estadísticamente significativas entre infliximab y adalimumab.
Conclusiones: En base a los resultados obtenidos (eficacia similar), infliximab, adalimumab y golimumab parecen ser alternativas terapéuticas. Así, otras consideraciones como la seguridad, la tolerancia y el coste-efectividad deben considerarse a la hora de seleccionar el tratamiento más adecuado.

PALABRAS CLAVE
Anti-TNF; Colitis ulcerosa; Infliximab; Adalimumab; Golimumab; Comparaciones indirectas

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Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease of multifactorial aetiology that mainly affects the colon. It has a relapsing-remitting pattern. It could be classified in function of its extension in ulcerative proctitis, left sided colitis or extensive colitis; and in function of its severity in colitis in remission, mild, moderate or severe colitis[1].

Symptoms of active disease or relapse include bloody diarrhoea, an urgent need to defecate and abdominal pain[2].

The incidence in Europe is estimated at 1.5 to 20.3 cases per 100,000 person-years[3]. Disease onset can occur at any age, with a peak incidence between 15 and 25 years and a second smaller between 55 and 65 years[2].

Current medical approaches focus on treating active disease to address symptoms, to improve quality of life, and thereafter to maintain remission. The treatment chosen for active disease is likely to depend on clinical severity, extent of disease and the patient's preference, and may include the use of aminosalicylates, corticosteroids or biological drugs. Surgery may be considered as emergency treatment for severe ulcerative colitis that does not respond to drug treatment[2,4].

Currently, three anti-TNF (tumour necrosis factor) drugs have been authorized by the European Medicines Agency (EMA) with the following indication: *treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine or azathioprine, or who are intolerant to or have medical contraindications for such therapies*[5,6,7].

To ensure the rational use of these drugs in clinical practice, aspects such as the efficacy, safety and cost-effectiveness of each drug must be evaluated. No direct head-to-head clinical trials have evaluated the superiority or non-inferiority of these drugs. Given the lack of head-to-head trials comparing biologic agents, indirect treatment comparisons (ITCs) were carried out to explore the relative efficacy of these drugs.

ITCs are relatively new approaches to evaluate the relative treatment effect when two or more interventions have not been compared directly.

An adjusted indirect comparison is an indirect comparison of different treatments adjusted according to the results of their direct comparison with a common control, so that the strength of the randomised trials is preserved. Empirical evidence indicates that results of adjusted indirect comparison are usually, but not always, consistent with the results of direct comparison. Basic assumptions underlying indirect comparisons include a homogeneity assumption for standard meta-analysis, and similarity assumption for adjusted indirect comparison[8].

These approaches are being increasingly used by health technology assessmentl (HTA) agencies[9] as new and existing drugs must be placed within the context of all available evidence for technology appraisals.

The main objective of this study was to compare the relative efficacy of infliximab, adalimumab and golimumab through adjusted indirect comparisons.

Material and methods

A systematic review was carried out to identify relevant studies published between 2005 (when the first trial about the first anti-TNF drug, infliximab, was published) and October 2013. The electronic search was performed by an information specialist in referential sources. Databases consulted were MEDLINE (through OVID), EMBASE, the Cochrane Library, the databases of the Center for Reviews and Dissemination (CRD) and the Web of Science (WOS). Also, Pubmed was revised in order to detect papers not included in MEDLINE (OVID) yet. The search strategies used in the main databases are shown in table 1.

Grey literature was obtained by searching the web sites of the EMA and HTA agencies. Unpublished data were not included in this review.

Studies were chosen for inclusion in the review based on the criteria outlined below:

- Population: adult patients naïve to biological drugs with moderate to severe ulcerative colitis.

- Intervention: infliximab, adalimumab or golimumab.
- Comparator: other anti-TNF-drug (direct comparison between the aforementioned interventions), or placebo.
- Outcomes: clinical remission, clinical response and mucosal healing.
- Study design: randomized controlled trials (RCTs).

Selection, critical appraisal, data extraction, qualitative and quantitative synthesis of the evaluated studies were independently undertaken by two researchers. Any discrepancies between the reviewers were resolved by a third independent reviewer.

The quality of the evidence of the included studies was assessed by the section A of the Critical Appraisal Skills Programme (CASP)[10].

Heterogeneity of included studies was assessed with respect to the trial design and patient populations. For drugs with more than one study, a traditional meta-analysis of the efficacy data was performed, using a

Table 1. *Search strategy.*

MEDLINE	EMBASE	WOS
1. *inflammatory bowel diseases/ or *colitis, ulcerative/ **2.** ((colitis and (ulcerati* or ulcero* or mucosal)) or ((procto?colitis or colorectitis) and ulcerati*) or ((chronic adj3 colon) and (ulcerati* or ulcero*))).ti,ab. **3.** (chronic and colon and inflammat*).ti,ab. **4.** 1 or 2 or 3 **5.** *Tumor Necrosis Factor-alpha/ad, ae, ag, ai, ct, de, im, tu **6.** exp Antibodies, Monoclonal/ad, ae, ct, de, im, tu **7.** Anti-Inflammatory Agents/tu **8.** Gastrointestinal Agents/tu **9.** 5 or 6 or 7 or 8 **10.** ((anti?bod* adj3 monoclonal) or (anti?bod* adj3 single?done) or (inmunologic adj2 factor?) or (digestant* or ((gastric or gastrointestin*) adj2 (agent? or Drug?))) or (inflammation or anti?inflammator*) or ((tumo?r adj3 necros*) or tnf?alpha or "tnf")).ti,ab. **11.** (((drug? or pharmaco*) adj3 (treatment? or therap*)) or (pharmaco* adj3 management)).ti,ab. **12.** ((anti?bod* adj3 monoclonal) or (anti?bod* adj3 single?done) or (inmunologic adj2 factor?) or ((tumo?r adj3 necros*) or tnf?alpha or "tnf")).ti,ab. **13.** (((advers* or drug) adj2 effect?) or immunolog* or contra?indicat*).ti,ab. **14.** (10 and 11) or (12 and 13) **15.** (infliximab or adalimumab or golimumab).mp. **16.** 9 or 14 or 15 **17.** 4 and 16 **18.** (letter or "case report*" or "historical article*" or (comment or editorial or in vitro or news)).pt. **19.** ("reference list" or bibliography* or "hand search*" or "relevant journal*" or (manual adj1 search*) or "selection criteria" or "study selection*").mp. **20.** 18 or 19 **21.** humans/ or (animals/ and humans/) **22.** 17 and 21 **23.** limit 22 to (clinical trial, phase iii or clinical trial, phase iv or clinical trial or randomized controlled trial) **24.** 23 not 20 **25.** limit 24 to (english or spanish) **26.** limit 25 to yr="2005 -Current"	**1.** 'ulcerative colitis'/mj OR 'enteritis'/de **2.** colitis:ab,ti AND (ulcerati*:ab,ti OR ulcero*:ab,ti OR mucosal:ab,ti) OR (procto$colitis:ab,ti OR colorectitis:ab,ti AND ulcerati*:ab,ti) OR ((chronic NEAR/3 colon):ab,ti AND (ulcerati*:ab,ti OR ulcero*:ab,ti)) OR (chronic:ab,ti AND colon:ab,ti AND inflammat*:ab,ti) **3.** #1 OR #2 **4.** 'infliximab'/exp OR 'adalimumab'/exp OR 'golimumab'/exp **5.** infliximab OR adalimumab OR golimumab **6.** #4 OR #5 **7.** #3 AND #6 **8.** 7 NOT [medline]/lim **9.** #8 AND ('conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it) **10.** #8 NOT #9 **11.** #10 AND ([english]/lim OR [spanish]/lim) **12.** #11 AND 'human'/de AND (2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py) AND ('clinical trial'/de OR 'clinical trial (topic)'/de OR 'controlled clinical trial'/de OR 'controlled clinical trial (topic)'/de OR 'phase 3 clinical trial (topic)'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial (topic)'/de)	**1.** TI=(colitis AND (ulcerati* OR ulcero* OR mucosal) OR (procto$colitis OR colorectitis AND ulcerati*) OR ((chronic NEAR/3 colon) AND (ulcerati* OR ulcero*)) OR (chronic AND colon AND inflammat*)) OR TS=(colitis AND (ulcerati* OR ulcero* OR mucosal) OR (procto$colitis OR colorectitis AND ulcerati*) OR ((chronic NEAR/3 colon) AND (ulcerati* OR ulcero*)) OR (chronic AND colon AND inflammat*)) **2.** TI=(infliximab OR adalimumab OR golimumab) OR TS=(infliximab OR adalimumab OR golimumab) **3.** TI=(((drug$ OR pharmaco*) NEAR/3 (treatment$ OR therap*)) OR (pharmaco* NEAR/3 management)) OR TS=(((drug$ OR pharmaco*) NEAR/3 (treatment$ OR therap*)) OR (pharmaco* NEAR/3 management)) **4.** ((#3 AND #2 AND #1)) **5.** (#4) AND Language=(English OR Spanish) AND Document Types=(Article OR Review) **6.** TI=(clinical trial OR controlled clinical trial OR randomized controlled trial OR randomization OR single blind procedure OR double blind procedure OR crossover procedure OR placebo OR random* OR placebo OR blind* OR trial) OR TS=(clinical trial OR controlled clinical trial OR randomized controlled trial OR randomization OR single blind procedure OR double blind procedure OR crossover procedure OR placebo OR random* OR placebo OR blind* OR trial) **7.** #6 AND #5 **8.** #7 Databases=SCI-EXPANDED Timespan=2011-2013

fixed-effect model, in the absence of heterogeneity, and the inverse variance method. Analyses were conducted using Epidat version 4.0[11].

Both clinical similarity and methodological similarity should be considered in adjusted indirect comparison. If the trial similarity assumption is not fulfilled, estimates from adjusted indirect comparisons will be invalid and misleading or should be interpreted cautiously.

Finally, adjusted ITCs were conducted based on the relative effects of each biological drug against a common comparator (placebo), following the method proposed by Butcher et al[12]. For the calculation of the risk ratio (RR) (95% CI), the software CIT, developed by the Canadian Agency for Drugs and Technologies in Health (CADTH), was used[13].

Results

A total of 288 citations were found. 6 RCTs published in 5 papers were included: 2 for infliximab (ACT 1 and ACT 2)[4], 2 for adalimumab (ULTRA 1 y ULTRA 2)[14,15] and 2 for golimumab (PURSUIT-SC y PURSUIT-M)[16,17]. The flow diagram illustrates the way in which the trials were selected (Fig. 1).

The quality of the included studies, based on CASP checklist, is detailed in table 2. All of them were of high quality (score 6 out of 6).

Rutgeerts et al reported the results of 2 randomized, double-blind, placebo-controlled trials (ACT 1 and ACT 2) which evaluated the efficacy of infliximab for induction and maintenance therapy in adults with ulcerative colitis[5]. 364 patients were included in each trial. Patients were followed for 54 weeks and 30 weeks in ACT 1 and ACT 2 studies, respectively. The primary endpoint was clinical response at week 8 in both cases.

For adalimumab, 2 randomized, double-blind and placebo controlled trials were included, ULTRA 1 and ULTRA 2[14,15]. The ULTRA 1 study evaluated the efficacy of two dosing regimens of adalimumab in the induction period. A total of 390 patients were included and the primary endpoint was clinical remission at week 8. Moreover, in the ULTRA 2 study, the efficacy of adalimumab in the maintenance period was evaluated. A total of 494 patients were included. However, the subset of patients naïve to biological drugs (the study population in this review) was 295, as patients previously treated with biological agents could be included in the study. The primary end point was clinical remission at weeks 8 and 52.

PURSUIT-SC and PURSUIT-M trials assessed the efficacy of golimumab in the induction and maintenance period, respectively[16,17]. PURSUIT-SC integrated data from phase II and III trials. For phase III, a total of 771 patients, followed for 6 weeks, were included. The primary en-

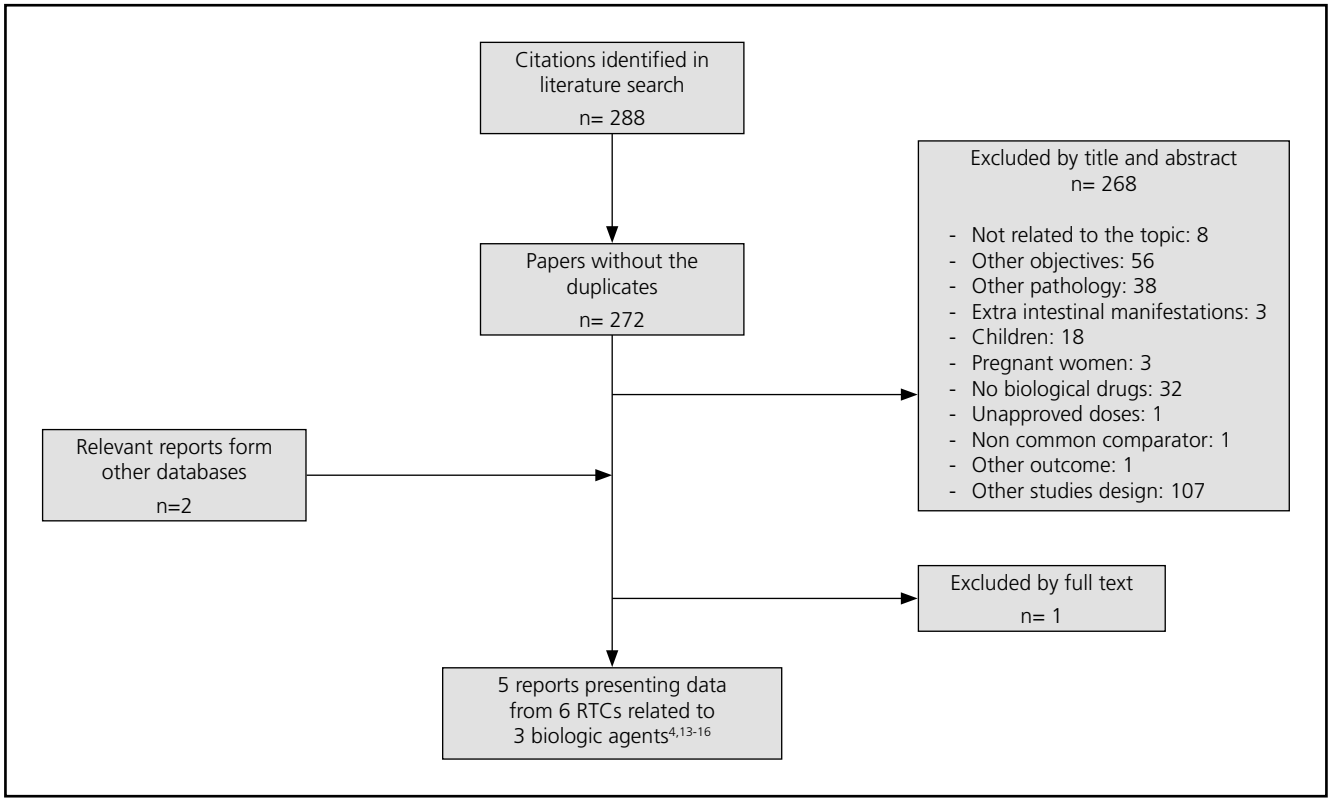

Figure 1. *Literature flowchart for inclusion and exclusion of studies.*

dpoint was clinical response at week 6. PURSUIT-M included 464 patients and the primary endpoint was clinical sustained response through week 54.

Patients baseline characteristics are showed in table 3.

In order to asses the relative efficacy of the biologic drugs in the induction and maintenance periods, relevant and common clinical endpoint in the studies for the three drugs were selected: clinical remission, clinical response and mucosal healing, measured in the 6-8 (induction) and 52-54 (maintenance) weeks.

The efficacy results for the endpoints clinical remission, clinical response and mucosal healing of each clinical trial included are listed in tables 4 and 5, for the induction and maintenance periods, respectively.

The results of the adjusted ITCs (table 6) for the selected outcomes (clinical remission, clinical response and mucosal healing) revealed that:

In the induction period, there were no statistically significant differences between the 3 drugs in terms of clinical remission. In relation to the efficacy endpoints clinical response and mucosal healing, statistically significant differences were observed between infliximab and adalimumab.

In the maintenance period, there were no statistically significant differences between the 3 drugs in terms of clinical remission, clinical response and mucosal healing.

Discussion

In the six RCTs included, patients had similar baseline characteristics and the efficacy outcomes used were the same, although the primary endpoint was not the same in all trials. In addition, the six trials evaluated the results at weeks 6-8 and 52-54 for induction and maintenance periods, respectively. Based on the homogeneity and similarity of the trials, it was possible to realize indirect comparisons between the three biological agents.

The internal validity of the analyses is contingent on three factors: 1) the appropriate identification of the studies that make up the evidence network, 2) the quality of the individual RCTs, and 3) the extent of confounding bias due to similarity violations. Appropriate search and selection methods of all relevant RCTs was conducted. The internal validity of the single RCTs included was high. Studies did not differ with respect to the characteristics of the patients, the way in which the outcomes were measured or defined, the protocol requirements including the concomitant interventions allowed, the length of follow-up as well as differential loss to follow-up.

There are several limitations to consider in these analyses. The study ULTRA 2 included patients who could have been previously treated with anti-TNF drugs. However, the patients were stratified according to prior

Table 2. *Quality of the included studies assessed by Critical Appraisal Skills Programme (CASP)*

	CASP Randomised Controlled Trial					
	Rutgeerts et al 2005 (ACT 1)[4]	Rutgeerts et al 2005 (ACT 2)[4]	Reinisch et al 2011 (ULTRA 1)[13]	Sandborn et al 2012 (ULTRA 2)[14]	Sandborn et al 2014a PURSUIT-SC)[15]	Sandborn et al 2014b (PURSUIT-M)[16]
SCREENING QUESTIONS						
1.- Did the trial address a clearly focused issue?	Yes	Yes	Yes	Yes	Yes	Yes
2.- Was the assignment of patients to treatments randomised?	Yes	Yes	Yes	Yes	Yes	Yes
3.- Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes	Yes	Yes	Yes	Yes	Yes
DETAILED QUESTIONS						
4.- Were patients, health workers and study personnel 'blind' to treatment?	Yes	Yes	Yes	Yes	Yes	Yes
5.- Were the groups similar at the start of the trial?	Yes	Yes	Yes	Yes	Yes	Yes
6.- Aside from the experimental intervention, were the groups treated equally?	Yes	Yes	Yes	Yes	Yes	Yes
CASPe score	6	6	6	6	6	6

Table 3. *Summary of key features of clinical trials of biological agents selected for indirect comparisons*

Study	N	Inclusion Criteria	Patients Baseline Characteristics						Treatment Group	Placebo Group	Primary End Point	Secondary End Points
			Age (mean)	Duration Of Disease (mean)	Mayo Score (mean)	Colonic Area Involved (%)	C Reactive Protein (mean)	Concomitant Medication (%)				
INFLIXIMAB												
Rutgeerts et al 2005 (ACT 1)[4] Phase III (54 weeks)	364	Active ulcerative colitis with a Mayo score of 6 to 12 points and moderate-to-severe active disease on sigmoidoscopy (Mayo endoscopic subscore of at least 2) despite concurrent treatment with corticosteroids alone or in combination with azathioprine or mercaptopurine in ACT 1 or despite concurrent treatment with corticosteroids alone or in combination with azathioprine or mercaptopurine and medications containing 5-aminosalicylates in ACT 2.	41.8	6.8	8.4	Left side (54%) Extensive (45,6%)	1.6	Corticosteroids (61%) 5-Aminosalicylates (69.5%) Immunosuppressants (48.9%)	Infliximab at a dose of 5 mg or 10 mg per kilogram of body weight at weeks 0, 2, and 6 and then every eight weeks through week 22 in ACT 2 or week 46 in ACT 1. ACT 1, n infliximab 5 mg/kg=121; n infliximab 10 mg/kg=122 ACT 2, n infliximab 5 mg/kg=121; n infliximab 10 mg/kg=120	Placebo at weeks 0, 2, and 6 and then every eight weeks through week 22 in ACT 2 or week 46 in ACT 1. ACT 1, n=121 ACT 2, n=123	Clinical response (at week 8).	- Clinical response (at week 8 at 30 in both and at 54 in ACT 1). - Clinical remission (at week 8 at 30 in both and at 54 in ACT 1). - Mucosal healing (at week 8 at 30 in both and at 54 in ACT 1).
Rutgeerts et al 2005 (ACT 2)[4] Phase III (30 weeks)	364		40	6.6	8.4	Left side (60%) Extensive (40%)	1.4	Corticosteroids (51.1%) 5-Aminosalicylates (74.7%) Immunosuppressants (42.9%)				

Table 3. *Summary of key features of clinical trials of biological agents selected for indirect comparisons (cont.)*

Study	N	Inclusion Criteria	Patients Baseline Characteristics						Treatment Group	Placebo Group	Primary End Point	Secondary End Points
			Age (mean)	Duration Of Disease (mean)	Mayo Score (mean)	Colonic Area Involved (%)	C Reactive Protein (mean)	Concomitant Medication (%)				
ADALIMUMAB												
Reinisch et al 2011 (ULTRA 1)[13] Phase III (8 weeks)	390	Adult ambulatory patients with moderately to severely active ulcerative colitis, defined by a full Mayo score (including endoscopic assessment) of 6-12 with an endoscopy subscore of 2-3, despite concurrent and stable treatment with oral corticosteroids and/or immunomodulators.	37.8	6.1	8.8	Left side (38.7%) Extensive (52%) Other (9.2%)	4.3	Corticosteroid (without IMM) (38.4%) IMM (without corticosteroid) (18.2%) Corticosteroid +IMM (21.3%) Aminosalicylates (77.5%)	- Adalimumab 160 mg at week 0, 80 mg at week 2, 40 mg at weeks 4 and 6. - Adalimumab 80 mg at week 0, 40 mg at weeks 2,4 and 6. n=130 in both dosages	Placebo at weeks 0,2,4 and 6. n=130	Clinical remission (at week 8).	- Clinical response (at week 8). - Mucosal healing (at week 8).
Sandborn et al 2012 (ULTRA 2)[14] Phase III (52 weeks)	494 (295 naïve to biological drugs)	Adults with moderately-to-severely active UC for at least 3 months with a Mayo score of 6-12 points (endoscopy subscore of at least 2), despite concurrent therapy with steroids and/ or azathioprine or 6-mercaptopurine.	40.4	8.3	8.9	Pancolitis (48.6%) Descending colon (38.9%) Other (12.6%)	13.8	Corticosteroids (58.7%) Azathioprine/6-MP (35%) Aminosalicylates (60.9%) Azathioprine/6-MP and/or steroids (74.5%) Azathioprine/6-MP +steroids (19.2%) Prior anti-TNF therapy (40.3%)	Adalimumab 160 mg at week 0, 80 mg at week 2 and then 40 mg EOW beginning at week 4. n= 150	Placebo EOW beginning at week 0. n= 145	Clinical remission (at weeks 8 and 52).	- Clinical response (at weeks 8 and 52). - Mucosal healing (at weeks 8 and 52).

Table 3. *Summary of key features of clinical trials of biological agents selected for indirect comparisons (cont.)*

Study	N	Inclusion Criteria	Patients Baseline Characteristics						Treatment Group	Placebo Group	Primary End Point	Secondary End Points
			Age (mean)	Duration Of Disease (mean)	Mayo Score (mean)	Colonic Area Involved (%)	C Reactive Protein (mean)	Concomitant Medication (%)				
GOLIMUMAB												
Sandborn et al 2014a (PURSUIT-SC)[15] Phase II-III (6 weeks)	168 (Phase II) 771 (Phase III)	Patients had an inadequate response to, or had failed to tolerate, 1 or more of the following conventional therapies: oral mesalamine, oral corticosteroids, azathioprine, and/or 6-mercaptopurine; or were corticosteroid dependent.	40	6.3	8.5	Left side (57,8%) Extensive (42,2%)	11.5	Corticosteroids (excluding budesonide) (42.8%) Budesonide (2.3%) Immunomodulatory drugs (32.4%) 6-MP/azathioprine (31.2%) Methotrexate (1.2%) Mesalamine (81.9%)	Phase III: Golimumab: - 200 mg at week 0 and 100 mg at week 2. - 400 mg at week 0 and 200 mg at week 2. n= 257 and 258 respectively.	Placebo at weeks 0 and 2. n= 256	Clinical response (at week 6).	- Clinical remission (at week 6). - Mucosal healing (at week 6).
Sandborn et al 2014b (PURSUIT-M)[16] Phase III (52 weeks)	464	Participants in PURSUIT-M had completed one of two golimumab induction studies, PURSUITIV or PURSUIT-SC.	40.2	7	8.3	---	9	Corticosteroid (5.,5%) Budesonide (3.2%) Immunomodulatory drugs (31.7%) Aminosalicylates (80.2%)	Golimumab: - 50 mg every 4 weeks through week 52. - 100 mg every 4 weeks through week 52. n= 154 for both dosages.	Placebo every 4 weeks through week 52. n=156	Maintenance of clinical response through week 54.	- Clinical remission (at weeks 30 and 54). - Mucosal healing (at weeks 30 and 54).

Clinical response was defined as a decrease from baseline in the total Mayo score of at least 3 points and at least 30 percent, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or an absolute subscore for rectal bleeding of 0 or 1.
Clinical remission was defined as a total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point.
Mucosal healing was defined as an absolute subscore for endoscopy of 0 or 1.

Table 4. *Efficacy results in the induction period (week 8 for infliximab y adalimumab; week 6 for golimumab).*

	Clinical remission			Clinical response			Mucosal healing		
	Treatment	Placebo	RR (95% CI)	Treatment	Placebo	RR (95% CI)	Treatment	Placebo	RR (95% CI)
INFLIXIMAB (5 mg/kg weeks 0, 2 y 6)									
Rutgeerts et al 2005 (ACT 1)[4]	47/121	18/121	2.61 (1.61-4.23)	84/121	45/121	1.87 (1.44-2.42)	75/121	41/121	1.83 (1.38-2.43)
Rutgeerts et al 2005 (ACT 2)[4]	41/121	7/123	5.95 (2.78-12.75)	78/121	36/123	2.2 (1.62-2.99)	73/121	38/123	1.95 (1.44-2.64)
Metanalysis	---	---	**3.3 (2.19-4.96)**	---	---	**2 (1.64-2.44)**	---	---	**1.88 (1.53-2.32)**
ADALIMUMAB (160 mg at week 1,80 mg at week 2 and 40 mg at week 4 y 6)									
Reinisch et al 2011 (ULTRA 1)[13]	24/130	12/130	2 (1.05-3.83)	71/130	58/130	1.22 (0.96-1,57)	61/130	54/130	1.13 (0.86-1.49)
Sandborn et al 2012 (ULTRA 2)[14]	32/150	16/145	1.93 (1,11-3,37)	89/150	56/145	1.54 (1.20-1.96)	74/150	51/145	1.4 (1.07-1.84)
Metanalysis	---	---	**1.96 (1.29-2.99)**	---	---	**1.37 (1.15-1,63)**	---	---	**1.26 (1.04-1,53)**
GOLIMUMAB (200 mg at week 0 and 100 mg at week 2)									
Sandborn et al 2013 (PURSUIT-SC)[15]	48/257	16/256	**2.99 (1.74-5.12)**	133/257	76/256	**1.74 (1.40-2.18)**	111/257	73/256	**1.51 (1.19-1.92)**

Table 5. *Efficacy results in the maintenance period (week 54 for infliximab and golimumab; week 52 for adalimumab).*

	Clinical remission			Clinical response			Mucosal healing		
	Treatment	Placebo	RR (95% CI)	Treatment	Placebo	RR (95% CI)	Treatment	Placebo	RR (95% CI)
INFLIXIMAB (5 mg/kg every 8 weeks)									
Rutgeerts et al 2005 (ACT 1)[4]	42/121	20/121	2.1 (1.31-3.36)	55/121	24/121	2.29 (1.52-3.45)	55/121	22/121	2.5 (1.63-3.83)
ADALIMUMAB (40 mg every 2 weeks)									
Sandborn et al 2012 (ULTRA 2)[14]	33/150	18/145	1.77 (1.05-3)	55/150	35/145	1.52 (1.06-2.17)	47/150	28/145	1.62 (1.08-2.44)
GOLIMUMAB (50 mg every 4 weeks)									
Sandborn et al 2013 (PURSUIT-M)[16]	50/151	34/154	1,50 (1.03-2.18)	---	---	---	---	---	---
GOLIMUMAB (100 mg every 4 weeks)									
Sandborn et al 2013 (PURSUIT-M)[16]	51/151	34/154	1,53 (1.06-2.22)	---	---	---	---	---	---

Table 6. *Results of the adjusted indirect comparisons*

	Induction period	Maintenance period
Clinical remission RR (95% CI)	Infliximab vs adalimumab: 1.68 (0.94-3.03) Infliximab vs golimumab: 1.10 (0.56-2.17) Adalimumab vs golimumab: 0.66 (0.33-1.30)	Infliximab vs adalimumab: 1.19 (0.59-2.40) Infliximab vs golimumab 50 mg: 1.40 (0.77-2.56) Infliximab vs golimumab 100 mg: 1.37 (0.75-2.50) Adalimumab vs golimumab 50 mg: 1.18 (0.62-2.25) Adalimumab vs golimumab 100 mg: 1.16 (0.61-2.20)
Clinical response RR (95% CI)	Infliximab vs adalimumab: **1.46 (1.12-1.90)** Infliximab vs golimumab: 1.15 (0.85-1.55) Adalimumab vs golimumab: 0.79 (0.59-1.04)	Infliximab vs adalimumab: 1.51 (0.87-2.60)
Mucosal healing RR (95% CI)	Infliximab vs adalimumab: **1.49 (1.12-1.98)** Infliximab vs golimumab: 1.25 (0.91-1.71) Adalimumab vs golimumab: 0.83 (0.61-1.14)	Infliximab vs adalimumab: 1.54 (0.86-2.79)

exposure to the same or not, and the results were reported independently for each subgroup of patients. Moreover, in this study, patients not responding to adalimumab treatment could continue with it, but they entered to an open trial, assuming these losses as treatment failure (this does not happen with trials of infliximab and golimumab). Finally, the Mayo score was calculated in ULTRA 2 as the worst score of the last three days for stool frequency and rectal bleeding, while in RCTs of infliximab and golimumab was calculated as the average score of the last three days for these items.

The statistical approach that we employed is widely accepted by agencies such as the National Institute for Health and Care Excellence (NICE), and the CADTH. However, many clinicians may be unfamiliar with this approach and few guides are available to critically appraise such studies. The ITCs rely on many of the same assumptions as a standard pair-wise meta-analysis. There is a necessary consideration that the trials of each agent are sufficiently similar to pool together in terms of populations, interventions and outcomes. A further necessary consideration is that these similarities exist across the different agents.

For both infliximab and golimumab, the results of ACT 1 and ACT 2 and PURSUIT-SC and PURSUIT- M, were consistent with each other respectively. However, in the case of adalimumab, in ULTRA 1 and ULTRA 2, the results for the primary endpoint (clinical remission at week 8) were similar, but these studies differed in the results of the secondary endpoints. In ULTRA 1, there were no statistically significant differences between adalimumab and placebo for clinical response and mucosal healing at week 8, while in ULTRA 2 there were. This discrepancy may be due to higher response rates in the placebo group in ULTRA 1.

The three biological agents showed statistically superior efficacy to placebo. The available evidence is limited, as there are no comparative head to head trials.

The results of the adjusted ITCs for the outcomes evaluated were heterogeneous and insufficient to suggest differences between the three drugs. Therefore, they can be considered therapeutic alternatives with similar efficacy.

The results of the RCTs can be extrapolated to the population of interest, because the baseline characteristics of the patients do not have substantially differences with the patients treated in the routine clinical practice. Moreover, the end points used in the studies are the recommended for this condition.

Given the lack of ITCs related to biological agents in Spain, this work could be an important contribution for the evidence available so far. Nevertheless, a network meta-analysis[18], which includes vedolizumab (a biological agent recently approved by EMA), had been published after we finished our systematic review. This new meta-analysis concludes that biological agents are effective treatments for UC. However head-to-head trials are necessary to select the best treatment option.

There is no evidence to suggest the superiority of one drug over the other. In view of the results obtained, infliximab, adalimumab and golimumab appear to be similarly effective therapeutic alternatives. Therefore, other considerations such as safety, tolerance and cost-effectiveness should be taken into account in order to select the most appropriate treatment for individuals with ulcerative colitis.

Bibliography

1. Gomollón F, García López S, Sicilia B, Gisbert JP, Hinojosa J, Spanish Group for Working on Crohn'sDisease and Ulcerative Colitis (GETECCU). Therapeutic guidelines on ulcerative colitis: a GRADE methodology based effort of GETECCU. Gastroenterol Hepatol. 2013; 36: 483.e1-e46.
2. National Clinical Guideline Centre (NICE). Ulcerative colitis: management in adults, children and young people [Internet]. Londres: NICE, jun 2013 [cited 2013 4 October]. 37 p. NICE clinical guideline 166. Available from: http://www.nice.org.uk/nicemedia/live/14189/64216/64216.pdf
3. European Medicine Agency (EMA). Scientific discussion. Humira® (adalimimab) [Internet]. Londres: EMA; nov 2007 [cited 2013 4 October]. 19 p. Procedure number: EMEA/H/C/481/II/38. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion_-_Variation/human/000481/WC500050876.pdf
4. Rutgeerts P, Sandborn WJ, Feagan MD, Reinisch W, Olson A, Johanns J et al. Infliximab for Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med. 2005;353:2462-76.
5. European Medicine Agency (EMA). Summary of product characteristics: Remicade® (infliximab) [Internet]. Londres: EMA; ago 2013 [cited 2013 4 October]. 59 p. EMEA/H/C/000240 -WS/0400. Available from: http://www.ema.europa.eu/docs/es_ES/document_library/EPAR_-_Product_Information/human/000240/WC500050888.pdf
6. European Medicine Agency (EMA). Summary of product characteristics: Humira® (adalimumab) [Internet]. Londres: EMA; oct 2013 [cited 2013 4 October]. 250 p. EMEA/H/C/000481 -II/0120. Available from: http://www.ema.europa.eu/docs/es_ES/document_library/EPAR_-_Product_Information/human/000481/WC500050870.pdf
7. European Medicine Agency (EMA). Summary of product characteristics: Simponi® (golimumab) [Internet]. Londres: EMA; 2013 [cited 2013 4 October]. 207 p. EMEA/H/C/000992 -IAIN/0051. Available from: http://www.ema.europa.eu/docs/es_ES/document_library/EPAR_-_Product_Information/human/000992/WC500052368.pdf
8. Jansen JP, Fleurence R, Devine B, Itzler R, Barret A, Hawkins N et al. Interpreting Indirect Treatment Comparisons and Network Meta-Analysis for Health-Care Decision Making: Report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: Part 1. Value Health. 2011; 14:417-28.
9. European Network for Health Technology Assessment (EUnetHTA). Comparators & Comparisons. Direct and indirect comparisons. Final version [Internet]. Copenhagen: EUnetHTA. February 2013. [cited 2014 15 April]. URL: European network for Health Technology Assessment. Febrero 2013. [Internet]. Available from: https://5026.fedimbo. belgium.be/ sites/5026.fedimbo.belgium.be/files/Direct and indirect comparisons.pdf
10. CASP Randomised Controlled Trial . [Internet] 2013. [cited 2013 20 December]; Available from: http://www.casp-uk.net/wp-content/uploads/2011/11/CASP-Randomised-Controlled-Trial-Checklist-31.05.131.pdf
11. Dirección Xeral de Innovación e Xestión da Saúde Pública, Xun-

ta de Galicia; Organización Panamericana de la Salud. Epidat 4.0 [Internet]. A Coruña: Sergas 1991- [cited 2013 18 November]. Available from: http://www.sergas.es/MostrarContidos_N3_T01.aspx?IdPaxina=62714.

12. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 1997;50 :683-91.
13. Wells GA, Sultan SA, Chen L, Khan M, Coyle D. Indirect Treatment Comparisons (ITC) [software on internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health; c2012 [cited 2013 4 October]. Available from: http://www.cadth.ca/en/resources/about-this-guide/download-software.
14. Reinisch W, Sandborn WJ, Hommes DW, D´Haens G, Hanauer S, Schreiber S et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. Gut. 2011;60:780-787.
15. Sandborn WJ, Assche GV, Reinisch W, Colombel JF, D´Haens G, Wolf DC, et al. Adalimumab Induces and Maintains Clinical Remission in Patients With Moderate-to-Severe Ulcerative Colitis. Gastroenterology. 2012; 142:257–265.
16. Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J et al. Subcutaneous Golimumab Induces Clinical Response and Remission in Patients With Moderate to Severe Ulcerative Colitis. Gastroenterology. 2014; 146: 85-95.
17. Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J et al. Subcutaneous Golimumab Maintains Clinical Response in Patients with Moderate-To-Severe Ulcerative Colitis. Gastroenterology. 2014; 146: 96-109.
18. Danese S, Fiorino G, Peyrin-Biroulet L, Lucenteforte E, Virgili G, Moja L, et al. Biological agents for moderately to severely active ulcerative colitis: a systematic review and network meta-analysis. Ann Intern Med. 2014; 160 :704-11.