Infliximab Biosimilars in the treatment of inflammatory bowel diseases: a systematic review

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Abstract

Background

Biological therapies represent a fundamental innovation for the management of inflammatory bowel diseases (IBD). However, many biological originators have reached, or are about to, patent expire and long term therapies costs have become progressively unsustainable. CT-P13, a biosimilar of anti-tumor necrosis factor monoclonal antibody infliximab, might represent a significant alternative to its originator, by decreasing the medical care cost and therefore, becoming available for a large number of patients.

Objectives

In this systematic review we analyzed the existing data of available clinical trials that recently investigated the validity of indication extrapolation of CT-P13 for the treatment of IBD in naïve patients and in patients who switched from its originator infliximab, focusing on clinical efficacy, safety and immunogenicity.

Methods

A detailed literature search was developed *a priori* to identify articles that investigated the validity of indication extrapolation of CT-P13 for the treatment of IBD in TNF inhibitor treatment-naïve patients and in patients who switched from the originator infliximab, and applied to Ovid MEDLINE, In-Process and Other Non-Indexed Citation, EMBASE, Cochrane Central Register of Controlled Trials, and Scopus from 2012 to September 2016.

Results

We based our review on the available data from ten studies that included a total of 1007 IBD patients 570 patients suffering from Crohn's disease (294 switched and 276 naïve), 435 patients suffering from Ulcerative Colitis (127 switched and 308 naïve), and 2 IBD unclassified patients (switched). Overall, no significant difference in efficacy and safety

between the originator infliximab and its biosimilar CT-P13 was observed. When assessing the safety of CT-P13, we found that 9.2% of the patients developed any adverse effects, (4.1% infusion related reactions and 4.3% infections, respectively).

Conclusion

The analyzed studies did not report a significant difference in terms of efficacy, safety and immunogenicity when comparing the clinical experience with CT-P13 with the available literature data on originator treatment in IBD. However, some debate still exists on interchangeability and immunogenicity.

Key points

- CT-P13, an anti-tumor necrosis factor monoclonal antibody infliximab biosimilar, might represent a significant cost-effective alternative to its originator for the treatment of autoimmune conditions

- The biological equivalence of CT-P13, in terms of efficacy and safety, has been demonstrated in an equivalence trial conducted in rheumatoid arthritis patients and with a pharmacokinetic study on patients with ankylosing spondylitis.

- Available data suggest that CT-P13 might represent a valid alternative (and potentially cheaper) to its originator for the treatment of IBD. Some debate still exist on interchangeability and immunogenicity.

1. Introduction

Biological therapies represent a fundamental step in the management of several chronic and debilitating immune-mediated inflammatory diseases, including inflammatory bowel diseases (IBD), rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriasis (Ps) and psoriatic arthritis (PsA) [1–3].

Infliximab (brand name Remicade®, Janssen Biotech, Inc. USA)[4] is a human-murine chimeric monoclonal antibody directed against tumor necrosis factor alpha (TNF-α) that has shown a distinct efficacy for patients suffering from Crohn's disease (CD) and ulcerative colitis (UC)[3]. An early treatment with infliximab has been proven to induce clinical remission and to modify disease progression[5], dramatically improving the quality of life of IBD patients and progressively becoming a relevant drug in these patients care[6,7]. Indeed, the advent of biological therapy for IBD has provided more effective control of both underlying diseases, and sustained amelioration of disease activity, compared to the pre-biological era when only anti-inflammatory and immunosuppressant drugs were available[8]. Although the importance of potential improved clinical outcome cannot be overstated, these efficacious treatments for IBD are not without a high cost[9].

In fact, the development of biological drugs and the manufacturing processes are rather complex, which increases the cost of these therapies, making them progressively less sustainable in long-term treatment. Many reference biologicals have reached, or are about to, patents expire. As a result, the production of biosimilar drugs is rising considerable interest, as they potentially reduce the financial burden of the therapy and extend therapeutic alternatives. CT-P13 (Remsima®, Inflectra®, Hospira USA and Celtrion, South Corea)[10,11], was the first infliximab biosimilar to be approved in several countries with the same therapeutic indications as its originator infliximab in September 2013 by the EMA (http://www.ema.europa.eu)[11], and by the FDA in April 2016 (http://www.fda.gov;)'[12].

The approval of a biosimilar drug has to follow a strict regulatory pathway, that is slightly different between USA and EU. In both cases, extensive physico-chemical and structural analyses and in vitro functional tests to demonstrate quality issues (manufacturing process, comparability exercise versus the originator, analytical methods, physiochemical characterization, biological activity and purity) and non-clinical issues (pharmatoxicological assessment). In addition, clinical studies are needed to test clinical issues (pharmacokinetic, pharmacodynamics and efficacy) and clinical safety issues (pharmacovigilance and immunogenicity). The clinical studies that addressed the equivalence of CT-P13 to its originator in terms of efficacy and safety were one equivalence trial conducted in patients with rheumatoid arthritis (PLANETRA study- Programme evaluating the Autoimmune disease iNvEstigational drug cT-p13 in RA patients)[13] and a pharmacokinetic study on patients with ankylosing spondylitis (PLANETAS study- Programed evaluating the Autoimmune disease iNvEstigational drug cT-p13 in SA patients)[14]. These two trials[13,14] demonstrated the equivalence in terms of efficacy and pharmacokinetics between infliximab and its biosimilar CT-P13 and reported similar safety profiles for the two drugs.

In this review we analyze the existing data of available clinical trials that recently investigated the validity of indication extrapolation of CT-P13 for the treatment of IBD in naïve patients and in patients who switched from its originator infliximab, focusing on clinical efficacy, safety, immunogenicity and therefore compare the results observed in the PLANETRA and PLANETAS studies.

2. Methods

2.1 Literature search

A detailed literature search has been developed *a priori* to identify articles that reported the findings from clinical studies that involved the use of infliximab biosimilar. Key words and

subject terms included: ("infliximab"[MeSH Terms] OR "infliximab"[All Fields]) OR "remicade"[All Fields]) AND biosimilar [All Fields] OR ("CT-P13"[Supplementar Concept] OR "CT-P13"[All Fields] OR "ct p13"[All Fields]). The search strategy applied to Ovid MEDLINE, In-Process and Other Non-Indexed Citation, EMBASE, Cochrane Central Register of Controlled Trials, and Scopus from 2012 to present.

2.2 Study selection

Two independent reviewers (MR and SS) reviewed the potential studies identified with the above strategy. Eligibility was determined by review of the title and abstract and then by full article review. A study was included if (1) reported findings from a clinical study of IBD patients treated with infliximab biosimilar, (2) included more than 5 patients.

The overall quality of the systematic review has been reviewed following the PRISMA checklist.

3. Results

We retrieved 139 articles on the current literature and of those 11 studies[15–25] were eligible for our analysis. The data retrieved from the 11 studies included a total of 570 patients [15–20,22–25] suffering from CD, 294 patients switched from infliximab to its biosimilar and 276 patients naïve to treatment with anti-TNF monoclonal antibody therapy) and 435 patients suffering from UC [15–25] (127 patients switched and 308 patients naïve) and 2 unclassified IBD patients (switched), for a total of 1007 IBD patients treated with of CT-P13. Selection of the included studies is detailed in Figure 1.

3.1 Efficacy

Data regarding the efficacy analysis are summarized in *Table 1*.

Overall, efficacy was assessed at week 6-8 in 3/11 studies, at week 14-16 in 7/11 studies, at week 24 in 1/11 studies and at week 30 in 3/11 studies.

Three studies included patients that switched from an anti-TNF-α monoclonal antibody to CT-P13 [15,24,25] and 8/11 studies reported data of both naïve and switched patients [16–23], while 4/8 studies reported the efficacy data stratifying for naïve and non-naïve patients [17–20].

Disease activity was assessed by the Crohn's Disease Activity Index (CDAI)[26] (in 7 studies out of 11) and by the partial Mayo Scoring System (pMayo)or the Mayo Scoring System (MSS) in patients with CD or UC, respectively [27,28]. Disease activity was estimated at the start and after the induction therapy. CD response was defined as a < 150 points or no fistula drainage as assessed by the Fistula Drainage Assessment. UC response was defined as > 30% decrease in the activity index and a decrease in the rectal bleeding and endoscopy subscores. One study on pediatric patients with IBD assessed disease activity by Pediatric Crohn's Disease Index (PCDAI) [29,30] and Pediatric Ulcerative Colitis activity Index in UC (PUCAI)[31]. Three studies, out of 11, assessed disease activity by Harvey-Brandshaw Index in CD[32]. One study out of 11 assessed the efficacy by Simple Clinical Colitis Activity Index for ulcerative colitis (UC)[33]. One study focused on the mucosal healing of patients suffering from UC and assessed the efficacy by defining the mucosal healing as Mayo endoscopic subscore 0 or 1: complete mucosal healing was defined as Mayo endoscopic subscore 0[34]. Three studies out of eleven included objective as markers of inflammation C-reactive protein (CRP) and fecal calprotectin [15,23,25], 6/11 studies included CRP alone [16,18,19,21,22,24].

Protocol of infusion for 7/11 studies was 5 mg/kg intravenous infusions of CT-P13 at week #0, #2, #6 and followed by a maintenance regimen every 8 weeks; in one study CT-P13 was infused at week #0, #2, #6, #14 and in 2 studies infusion protocol was not specified but CT-P13 was infused at the standard doses. In details, in one of those studies, efficacy was

assessed after at least 1 infusion of CT-P13 while the other study reported that 78/83 patients completed follow up and received 3 or more CT-P13 infusions. One study reported that, 49% of patients received infusions at 8-week intervals, and 66% of patients received dosages of 4–6 mg/kg. The individual dosage varied between 200 and 900 mg, and the intervals for administration varied between 4 and 12 weeks [25].

Overall, no significant difference in efficacy between the originator infliximab and its biosimilar CT-P13 was observed. Four out of eleven studies reported data of switched patients apart from naïve and 3/4 studies did not show a significant difference between the two groups, with the exception for switched patients that had already developed anti-drug antibodies against the originator infliximab or, in some cases, adalimumab. On the contrary, one study reported a significant difference between the two groups, pointing out a better response in the naïve group compared to the switch group.

3.2 Safety

Nine-hundred forty-four patients with IBD from 10 studies were eligible for this analysis, including 570 patients with CD (294 switched and 276 naïve), 372 with UC (122 switched and 250 naïve) and 2 IBD unclassified patients (switched). Data regarding treatment adverse events (TEAEs) are summarized in *Table 2*. Adverse events analysis included infusion-related reactions, infections, malignancies and death.

Studies differed for TEAEs definition. One study classified TEAEs as mild, moderate and severe according to the Medical Dictionary for Regulatory Activities Version 16.0 (http://www.meddra.org), one study categorized the adverse events according to the Office of Human Research Protection (http://www.hhs.gov/ohrp/) and8/11 studies did not provide specific definition when reporting TEAEs.

No study reported a significant difference between the originator infliximab and its biosimilar CT-P13 regarding the safety analysis. When separating naïve and non-naive patients, [in 6 studies [15,17–20,23]] no significant difference between the two groups was observed. However, a detailed analyses was possible in a limited number of the studies [15,17,18] as only 3 studies reported data of switched patients separated from naïve to treatment and one study reported differentiated the results between the two groups only when analyzing the infusion-related reactions. In details, three of the 8 studies analyzing results from both naïve and switched patients reported the data separately. Infusion related reactions occurred 39/944 patients (4,7%), including 2/944 anaphylactic reactions (0,2%)[17,19]. Infections occurred in 41/944 patients (4,3%), including one patient who experienced a fatal invasive fungal infection[19], and 1 TBC infection (0,1%)[17]. One patient developed a lymphoma and stopped treatment due to the adverse event (0,1%)[25]. No serum sickness like syndrome, no solid malignancies, no drug-induced lupus and no demyelization syndrome were reported in the analyzed data.

3.3 Immunogenicity analysis

Six hundred and seventeen IBD patients from 6 studies were eligible for this analysis, including 390 patients with CD (182 switched and 164 naïve), 268 with UC (99 switched and 179 naïve) and 2 IBD unclassified patients (switched). Data regarding the immunogenicity analysis is summarized in *Table 3*.

Studies were analyzed for titers of antidrug positivity both for naïve patients and for patients that switched for originator infliximab. Drug level monitoring was also taken into consideration when reported.

Two studies reported data only for switched patients, whether 4/6 studies analyzed both naïve and switched patients. Anti-drug antibodies (ADA) level prior to the treatment with CT-

P13 was assessed only in 2/6. One study reported an ADA positivity in the switched group of 25% compared to 4% in the naïve group, whether the other study reported data only of switched patients.

All 6 studies assessed ADA levels after therapy with CT-P13, and all studies showed no significant difference in terms of immunogenicity between the originator infliximab and its biosimilar CT-P13. Four out of 6 studies reported a higher, but not significant, incidence of ADA levels in the switched group compared to the naïve patients, especially in the patients that had previously developed ADA against the originator infliximab. One study [19] reported a significance difference between the naïve and switched group reporting an higher incidence of ADA levels in the switched group.

4. Discussion

In our analysis considering 1007 patients with IBD, including 570 patients with CD (48% naïve) and 391 with UC (71% naïve), we observed a similar efficacy profile in patients treated with CT-P13 when compared to studies including patients who received originators[6,35,36]. Similarly, when assessing the safety of CT-P13, we found that 9.2% of the patients developed any adverse effects, (4.1% infusion related reactions and 4.3% infections, respectively) and this incidence is comparable to those observed in RTCs with originators anti-TNF[37]. In fact, among others, Colombel and co-workers in a cohort of 500 consecutive patients with IBD treated with infliximab at the Mayo Clinic found that acute infusion reactions and infections occurred in 3.8% and 8.2%, respectively[7]. Interestingly, no patients treated with CT-P13 included in our analysis developed during the observation time serum sickness like syndrome, , drug-induced lupus or demyelization syndrome.

Our results are in line with recent extension studies of both PLANETRA and PLANETAS reporting over the course of 2 years of the same cohorts of patients that were analyzed the equivalence to its originator infliximab in AR and AS patients, respectively[38,39]. Over 2 years of treatment, comparable results between groups of patients (patients treated with originator infliximab and with the biosimilar CT-P13) of efficacy, tolerability and immunogenicity were observed, in patients who switched from infliximab to its biosimilar for an additional year (for the PLANETAS study) and in those who had long term CT-P13 treatment for 2 years.

The extended results of these two studies are very promising, however they represent the sole trials on which the biosimilar equivalence was tested and demonstrated on two specific cohort of patients. When extrapolating a drug for other indications, the selection of the patient population is crucial. Better results are showed when a high difference in efficacy between a test drug and placebo is present. RA for infliximab, of 6 of its indications, revealed the smallest placebo-adjusted response, making the population of patients suffering from RA a less sensible model to demonstrate a possible difference in the bioequivalence of CT-P13 and its originator infliximab[40].

Regarding immunogenicity, we found that all 5 studies assessed ADA levels after therapy with CT-P13 showed no significant difference in terms of immunogenicity between the originator infliximab and its biosimilar CT-P13. Immunogenicity profiles between various patient populations should be a matter of focus when extrapolation of indication is considered. Indeed, as CD population has showed the highest incidence of immunogenicity up to 61%[41], whether the lowest was demonstrated in the RA population, less than 10%[42], further studies addressing differences in immunogenicity profiles in patients with different diseases are warranted.

Similarly, the issue of switching from a reference product to its biosimilar is still on debate. The PLANETAS study has shown promising results after one year of treatment in patients who switched to CT-P13 from its originator, similar results were described by Ruiz and al.[43] that evidenced identical reactivity towards biosimilars in a cohort of patients with rheumatic diseases treated with infliximab. However the concerns of immunogenicity in switched patients might represent an unsolved problem, as we found a significance difference between the naïve and switched group reporting an higher incidence of ADA levels in the switched group[19]. However, more data are needed to confirm this observation.

4.1 Limitations of the study

The present systematic review has several limitations. In fact, most of the analyzed studies have a retrospective design, posing some caution when interpreting results. Furthermore, the present systematic review is based on uncontrolled studies, as no randomized controlled studies up to date have evaluated the treatment of IBD with CT-P13 in comparison with its originator infliximab. Additionally, the results were in some cases heterogeneous by using different classifications, methods and criteria for assessing efficacy, safety and immunogenicity. Moreover, the follow up time of the studies was relatively short: long-term consequences should be evaluated with studies with a longer follow up.

While we cannot exclude that some patients included in the two studies by Farkas and colleagues [16,21] and the study by Gecse et al. [19], this has not been clearly stated in the manuscripts. Furthermore, due to the intrinsic limitation of the studies (different number of patient included, heterogeneity in terms of protocol and study design), the risk of bias in individual studies could not be assessed.

4.2 Future challenges

Biosimilars form of biological drugs are rising interest in the scientific community and new forms of biosimilars are either under development, testing for regulation approval or awaiting extrapolation approval. Currently, physicians are facing the challenge of choosing among a biological drug or its biosimilar or switching from an originator to its biosimilar. In the future, physicians might also have to undergo the decision of switching back to the originator from its biosimilar (reverse-switch) or to switch to a different biosimilar drug (cross-switch). Further efforts are underway to develop new classes of biosimilars, such as the so called bio-betters, which have the objective to rise above their originators, in terms of clinical profile, through altering their chemical composition and their formulation [44].

However, the necessity and challenge of further standardization of international guidelines and regulatory legislation still exist. Prospective randomized phase III trials are needed in order to ensure efficacy and safety of biosimilars, as well as their interchangeability. An ongoing study, the NOR-SWITCH, a randomized, double-blind, parallel group, non-inferiority study, has the aim to assess the safety and efficacy of switching from infliximab to the biosimilar treatment in patients with rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, ulcerative colitis, Crohn's disease and chronic plaque psoriasis (ClinicalTrials.gov identifier: NCT02148640). Furthermore, an ongoing phase III study, is currently aiming to assess noninferiority in efficacy and to assess overall safety of CT P13 compared to infliximab in patients with active Crohn's disease up to Week 54 (ClinicalTrials.gov identifier: NCT02096861).

5. Conclusion

Despite no trial has addressed the use of CT-P13 in IBD in a randomized fashion, the current literature, including observational studies about the clinical experience of CT-P13, is promising. The analyzed studies did not report a significant difference in terms of efficacy, safety and immunogenicity when comparing the clinical experience with CT-P13 with the available literature data on originators treatment in IBD. However, some debate still exists on interchangeability and immunogenicity.

Legend

Figure 1. Research strategy of the included studies

Table 1. Data summarizing the efficacy analysis

Table 2. Data summarizing the safety analysis

Table 3. Data summarizing the immunogenicity analysis

Authors' contributions

MR, SS, DR and MJC conceived of the manuscript, and participated in its design and coordination. MR and SS performed the literature search for relevant publications on the topic. MJC, DR participated in drafting the manuscript and provided critical insights. All authors read and approved the final manuscript.

REFERENCES

1   Wiens A, Venson R, Correr CJ, *et al.* Meta-analysis of the efficacy and safety of

        adalimumab, etanercept, and infliximab for the treatment of rheumatoid arthritis.

        Pharmacotherapy 2010;**30**:339–53. doi:10.1592/phco.30.4.339

2   Bansback N, Sizto S, Sun H, *et al.* Efficacy of systemic treatments for moderate to severe

        plaque psoriasis: systematic review and meta-analysis. *Dermatology* 2009;**219**:209–18.

        doi:10.1159/000233234

3   Billiet T, Rutgeerts P, Ferrante M, *et al.* Targeting TNF-α for the treatment of

        inflammatory bowel disease. *Expert Opin Biol Ther* 2014;**14**:75–101.

        doi:10.1517/14712598.2014.858695

4   Changes M. Infliximab (remicade) anti-TNF. *Interactions* 1998;**50**:1–25.

5   Schnitzler F, Fidder H, Ferrante M, *et al.* Long-term outcome of treatment with

        infliximab in 614 patients with Crohn's disease: results from a single-centre cohort. *Gut*

        2009;**58**:492–500. doi:10.1136/gut.2008.155812

6   Targan SR, Hanauer SB, van Deventer SJ, *et al.* A short-term study of chimeric

        monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's

        Disease cA2 Study Group. *N Engl J Med* 1997;**337**:1029–35.

        doi:10.1056/NEJM199710093371502

7   Colombel JF, Loftus E V., Tremaine WJ, *et al.* The Safety Profile of Infliximab in Patients

        with Crohn's Disease: The Mayo Clinic Experience in 500 Patients. *Gastroenterology*

        2004;**126**:19–31. doi:10.1053/j.gastro.2003.10.047

8   Kuek A, Hazleman BL, Ostör AJK. Immune-mediated inflammatory diseases (IMIDs) and

        biologic therapy: a medical revolution. *Postgrad Med J* 2007;**83**:251–60.

doi:10.1136/pgmj.2006.052688

9   Liu Y, Wu EQ, Bensimon AG, *et al.* Cost per responder associated with biologic therapies for Crohn's disease, psoriasis, and rheumatoid arthritis. *Adv Ther* 2012;**29**:620–34. doi:10.1007/s12325-012-0035-7

10   CHMP. Remsima, INN: infliximab. 2013.

11   CHMP. Inflectra; INN: infliximab. 2013.

12   Press Announcements - FDA approves Inflectra, a biosimilar to Remicade.

13   Yoo DH, Hrycaj P, Miranda P, *et al.* A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. *Ann Rheum Dis* 2013;**72**:1613–20. doi:10.1136/annrheumdis-2012-203090

14   Park W, Hrycaj P, Jeka S, *et al.* A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. *Ann Rheum Dis* 2013;**72**:1605–12. doi:10.1136/annrheumdis-2012-203091

15   Smits LJT, Derikx LAAP, de Jong DJ, *et al.* Clinical Outcomes Following a Switch from Remicade® to the Biosimilar CT-P13 in Inflammatory Bowel Disease Patients: A Prospective Observational Cohort Study. *J Crohns Colitis* Published Online First: April 2016. doi:10.1093/ecco-jcc/jjw087

16   Farkas K, Rutka M, Bálint A, *et al.* Efficacy of the new infliximab biosimilar CT-P13 induction therapy in Crohn's disease and ulcerative colitis - experiences from a single center. *Expert Opin Biol Ther* 2015;**15**:1257–62. doi:10.1517/14712598.2015.1064893

17   Park SH, Kim Y-H, Lee JH, *et al.* Post-marketing study of biosimilar infliximab (CT-P13) to evaluate its safety and efficacy in Korea. *Expert Rev Gastroenterol Hepatol* 2015;**9**:35–44. doi:10.1586/17474124.2015.1091309

18   Jung YS, Park D Il, Kim YH, *et al.* Efficacy and safety of CT-P13, a biosimilar of infliximab, in patients with inflammatory bowel disease: A retrospective multicenter study. *J Gastroenterol Hepatol* 2015;**30**:n/a-n/a. doi:10.1111/jgh.12997

19   Gecse KB, Lovász BD, Farkas K, *et al.* Efficacy And Safety Of The Biosimilar Infliximab CT-P13 Treatment In Inflammatory Bowel Diseases: A Prospective, Multicentre, Nationwide Cohort. *J Crohn's Colitis* 2015;:jjv220. doi:10.1093/ecco-jcc/jjv220

20   Kang YS, Moon HH, Lee SE, *et al.* Clinical Experience of the Use of CT-P13, a Biosimilar to Infliximab in Patients with Inflammatory Bowel Disease: A Case Series. *Dig Dis Sci* 2015;**60**:951–6. doi:10.1007/s10620-014-3392-z

21   Farkas K, Rutka M, Golovics PA, *et al.* Efficacy of Infliximab Biosimilar CT-P13 Induction Therapy on Mucosal Healing in Ulcerative Colitis. *J Crohns Colitis* Published Online First: April 2016. doi:10.1093/ecco-jcc/jjw085

22   Keil R, Wasserbauer M, Zádorová Z, *et al.* Clinical monitoring: infliximab biosimilar CT-P13 in the treatment of Crohn's disease and ulcerative colitis. *Scand J Gastroenterol* 2016;**5521**:1–7. doi:10.3109/00365521.2016.1149883

23   Jahnsen J, Detlie TE, Vatn S, *et al.* Biosimilar infliximab (CT-P13) in the treatment of inflammatory bowel disease: A Norwegian observational study. *Expert Rev Gastroenterol Hepatol* 2015;**9 Suppl 1**:45–52. doi:10.1586/17474124.2015.1091308

24   Sieczkowska J, Jarzębicka D, Banaszkiewicz A, *et al.* Switching Between Infliximab Originator and Biosimilar in Paediatric Patients with Inflammatory Bowel Disease.

Preliminary Observations. *J Crohns Colitis* 2016;**10**:127–32. doi:10.1093/ecco-jcc/jjv233

25 Buer LCT, Moum BA, Cvancarova M, *et al.* Switching from Remicade® to Remsima® is well tolerated and feasible: a prospective, open-label study. *J Crohn's Colitis* 2016;:jjw166. doi:10.1093/ecco-jcc/jjw166

26 Best WR, Becktel JM, Singleton JW, *et al.* Development of a Crohn's Disease Activity Index. *Gastroenterology* 1974;**70**:439–44. doi:10.1016/S0016-5085(76)80163-1

27 Lee K-M, Jeen YT, Cho JY, *et al.* Efficacy, safety, and predictors of response to infliximab therapy for ulcerative colitis: a Korean multicenter retrospective study. *J Gastroenterol Hepatol* 2013;**28**:1829–33. doi:10.1111/jgh.12324

28 Sands BE, Anderson FH, Bernstein CN, *et al.* Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med* 2004;**350**:876–85. doi:10.1056/NEJMoa030815

29 Hyams J, Markowitz J, Otley A, *et al.* Evaluation of the Pediatric Crohn Disease Activity Index: A Prospective Multicenter Experience. *J Pediatr Gastroenterol Nutr* 2005;**41**:416–21. doi:10.1097/01.mpg.0000183350.46795.42

30 Turner D, Griffiths AM, Walters TD, *et al.* Appraisal of the Pediatric Crohn's Disease Activity Index on Four Prospectively Collected Datasets: Recommended Cutoff Values and Clinimetric Properties. *Am J Gastroenterol* 2010;**105**:2085–92. doi:10.1038/ajg.2010.143

31 Turner D, Hyams J, Markowitz J, *et al.* Appraisal of the pediatric ulcerative colitis activity index (PUCAI). *Inflamm Bowel Dis* 2009;**15**:1218–23. doi:10.1002/ibd.20867

32 Harvey RF, Bradshaw MJ. Measuring Crohn's disease activity. *Lancet (London, England)*

1980;**1**:1134–5.

33   Walmsley RS, Ayres RC, Pounder RE, *et al.* A simple clinical colitis activity index. *Gut*
      1998;**43**:29–32.

34   Rutgeerts P, Sandborn WJ, Feagan BG, *et al.* Infliximab for induction and maintenance
      therapy for ulcerative colitis. *N Engl J Med* 2005;**353**:2462–76.
      doi:10.1056/NEJMoa050516

35   Ljung T, Karlén P, Schmidt D, *et al.* Infliximab in inflammatory bowel disease: clinical
      outcome in a population based cohort from Stockholm County. *Gut* 2004;**53**:849–53.

36   Zhou Z, Dai C, Liu W. Anti-TNF-A Therapy about Infliximab and Adalimamab for the
      Effectiveness in Ulcerative Colitis Compared with Conventional Therapy: A Meta-
      Analysis. *Hepatogastroenterology* 2015;**62**:829–37.

37   Khanna R, Feagan BG. Safety of infliximab for the treatment of inflammatory bowel
      disease: current understanding of the potential for serious adverse events. *Expert Opin
      Drug Saf* 2015;**14**:987–97. doi:10.1517/14740338.2015.1029915

38   Park W, Yoo DH, Miranda P, *et al.* Efficacy and safety of switching from reference
      infliximab to CT-P13 compared with maintenance of CT-P13 in ankylosing spondylitis:
      102-week data from the PLANETAS extension study. *Ann Rheum Dis*
      2016;:annrheumdis-2015-208783. doi:10.1136/annrheumdis-2015-208783

39   Yoo DH, Prodanovic N, Jaworski J, *et al.* Efficacy and safety of CT-P13 (biosimilar
      infliximab) in patients with rheumatoid arthritis: comparison between switching from
      reference infliximab to CT-P13 and continuing CT-P13 in the PLANETRA extension
      study. *Ann Rheum Dis* 2016;**13**:annrheumdis-2015-208786. doi:10.1136/annrheumdis-
      2015-208786

40   Lee H. Is extrapolation of the safety and efficacy data in one indication to another appropriate for biosimilars? *AAPS J* 2014;**16**:22–6. doi:10.1208/s12248-013-9534-y

41   Baert F, Noman M, Vermeire S, *et al.* Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med* 2003;**348**:601–8. doi:10.1056/NEJMoa020888

42   Flood J. Tumor necrosis factor inhibitors in the treatment of chronic inflammatory diseases. A review of immunogenicity and potential implications. *Manag Care* 2009;**18**:1–5.

43   Ruiz-Argüello MB, Maguregui A, Ruiz del Agua A, *et al.* Antibodies to infliximab in Remicade-treated rheumatic patients show identical reactivity towards biosimilars. *Ann Rheum Dis* 2016;:annrheumdis-2015-208684. doi:10.1136/annrheumdis-2015-208684

44   Danese S, Bonovas S, Peyrin-Biroulet L. Biosimilars in IBD: from theory to practice. *Nat Rev Gastroenterol Hepatol* Published Online First: 2016. doi:10.1038/nrgastro.2016.155