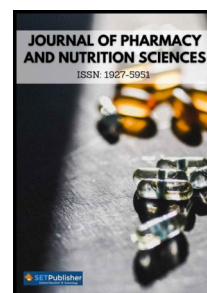




Published by SET Publisher

Journal of Pharmacy and Nutrition Sciences

ISSN (online): 1927-5951



## Persistence, Clinical and Economic Impact of Infliximab CT-P13 in Rheumatoid Arthritis, Psoriatic Arthropathy and Ankylosing Spondylitis Naïve and Switched Patients: After 5 Years of Follow-Up

Joaquín Borrás-Blasco<sup>1,\*</sup>, Alejandro Valcuende-Rosique<sup>2</sup>, Dolores Rosique-Robles<sup>2</sup> and Elvira Casterá<sup>1</sup>

<sup>1</sup>Pharmacy Service, Hospital de Sagunto, Avda Ramon y Cajal s/n, Sagunto, Valencia, Spain

<sup>2</sup>Pharmacy Service, Hospital Universitario de la Ribera, Carretera de Corbera s/n, Alzira, Valencia, Spain

### Article Info:

#### Keywords:

Persistence,  
Infliximab,  
Rheumatoid Arthritis,  
Psoriatic Arthropathy,  
Ankylosing Spondylitis,  
Biosimilar,  
Pharmacoeconomic.

#### Timeline:

Received: October 28, 2022  
Accepted: November 29, 2022  
Published: December 13, 2022

**Citation:** Borrás-Blasco J, Valcuende-Rosique A, Rosique-Robles D, Casterá E. Persistence, clinical and economic impact of infliximab CT-P13 in rheumatoid arthritis, psoriatic arthropathy and ankylosing spondylitis naïve and switched patients: after 5 years of follow-up. J Pharm Nutr Sci 2022; 12: 74-79.

DOI: <https://doi.org/10.29169/1927-5951.2022.12.06>

#### \*Corresponding Author

Tel: + 34 962653809; Fax: + 34 962659428  
E-mail: [jborrasb@gmail.com](mailto:jborrasb@gmail.com)

### Abstract:

**Objective:** Study the economic impact and persistence of Inflectra<sup>®</sup> in rheumatoid arthritis (RA), psoriatic arthropathy (PSA), psoriasis, ankylosing spondylitis (AS) naïve, and Remicade<sup>®</sup> switched patients.

**Methods:** Retrospective observational cohort study of patients treated with Inflectra<sup>®</sup> for more than six months in a five years analysis. We collected age, sex, indication, dose, and persistence (in years) for Inflectra<sup>®</sup> naïve and Remicade<sup>®</sup> switched patients. Efficacy endpoints included a disease activity score calculator for rheumatoid arthritis (DAS28) and bath ankylosing spondylitis disease activity index (BASDAI). Safety was also assessed. We determined each patient's actual cost of Inflectra<sup>®</sup> treatment from individualized IV administration and correlated dates during the study period. We simulated the actual cost of these patients if the patients received Remicade<sup>®</sup>.

**Results:** During five years, 62 patients (38 women; 31 AS, 18 RA, 13 PSA) were treated with Inflectra<sup>®</sup>. 33 (53%) patients were naïve patients, and 29 (47%) were Remicade<sup>®</sup> switched patients. In Sept 2019, 33 patients continued on Inflectra<sup>®</sup> treatment (11 naïve; 22 Remicade<sup>®</sup> switched) in clinical remission. Twenty-nine patients discontinued therapy, 24 due to relapse, and five due to adverse reactions. All patients with Inflectra<sup>®</sup> presented a persistence of 24.4±7.4 months. The persistence in naïve patients was 19.1±4.4 months and in Remicade<sup>®</sup> switched patients was 29.7±5.8 months. The total associated costs of the Inflectra<sup>®</sup> treatment throughout the observation period were 901.840€. If these patients had been treated with Remicade<sup>®</sup>, the total cost of therapy would have been 1.099.803€. The use of Inflectra<sup>®</sup> saved 197,964€ during five years.

**Conclusions:** Inflectra<sup>®</sup> produces similar persistence and substantial cost savings when used in Infliximab naïve patients and Remicade<sup>®</sup> switched patients.

© 2022 Borrás-Blasco *et al.*; Licensee SET Publisher.

This is an open access article licensed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0/>) which permits unrestricted use, distribution and reproduction in any medium, provided the work is properly cited.

## WHAT IS KNOWN ABOUT THIS SUBJECT?

The long-term Efficacy, safety, and toxicity of infliximab originator are well established, with years of treatment of rheumatic diseases in clinical trials and real-world evidence studies—multicenter randomized phase 3 studies of Inflectra® were conducted in RA and AS patients. Clinical comparability to the originator Infliximab was demonstrated concerning the Efficacy and safety profile for those diseases. Few real-world clinical studies have studied the long-term Efficacy or safety of Inflectra® in naïve, and Remicade® switched patients with rheumatic diseases. Small sample sizes, inconsistent data collection, and low follow-up periods characterize these. Furthermore, only the short-term or related persistence of the Infliximab CT-P13 was studied in Caucasian patients.

## WHAT THIS STUDY ADDS

This study provides long-term real-world data from Spanish naïve, and Remicade® switched patients with AR, PSA, and AS treated with Inflectra®. Furthermore, this study offers important insights into the Efficacy and tolerability of Inflectra® during long-term treatment in naïve and switched patients with AR, PSA, and AS patients.

## INTRODUCTION

Biotherapies significantly impact rheumatology diseases and are associated with a high cost for the health system. Biosimilar drugs contain an active substance version of an already authorized original drug whose patent has expired. Biosimilars are similar to licensed biologic medicines in quality, safety, and Efficacy, but with a lower cost. Therefore, these medicines contribute to lowering the cost of biological medicines with a significant impact on the accessibility of medicines [1].

Infliximab is an alpha tumor necrosis factor approved for rheumatoid arthritis (RA), psoriatic arthropathy (PSA), psoriasis, ankylosing spondylitis (AS), Chron's disease and ulcerative colitis. The objective of treatment with Infliximab is to substantially achieve clinical remission and improve the patient's condition without increasing the risk of serious side effects. The long-term Efficacy, adherence, and safety of infliximab originator are well documented, with years of experience treating rheumatic diseases. Multicenter randomized phase 3 studies of Inflectra® were conducted in RA and AS patients. Clinical

comparability to the Infliximab originator was demonstrated concerning Efficacy as a safety profile for those diseases [2,3]. Open-label extensions to the clinical studies in RA and AS patients showed over 102 weeks, its similar Efficacy and safety of Inflectra® to reference Infliximab maintained [4]. However, few real-world clinical studies have investigated the long-term Efficacy or safety of Inflectra® in naïve and Remicade® switched patients with RA, PSA, and AS. These are characterized by a small sample size, inconsistent data collection, and a low follow-up period [5,6]. Hence questions remain regarding the performance of long-term use of Infliximab CT-P13 in a real-world setting.

In January 2015, the Sagunto Hospital Commission of Biological Therapies approved the implementation of a biosimilar program to use Inflectra® in naïve rheumatology patients and switched rheumatology patients from Remicade® in clinical remission. The study's objective is to determine the persistence, and long-term clinical and economic impact of Inflectra® in RA, PSA, AS naïve, and Remicade® switched patients in a real-world setting during five years of follow-up.

## MATERIALS AND METHODS

We performed an observational, retrospective cohort investigation of patients treated with Inflectra® for at least six months in a five years analysis, Patients with RA, AS, and PSA, defined by ACR criteria [7] and the modified New York criteria [8] respectively, who began Inflectra® therapy were included in the study. Clinical and demographic data were obtained from Rheumatology Department clinical records; age, gender, weight, date of RA AS and PSA diagnosis, naïve to biologics or pretreated with Remicade® and Inflectra® therapy prescribed (type, dose, starting and ending dates of the treatment) and the persistence (in years) of Inflectra® patients (naïve and switched), during the study. Individualized drug dispensations and correlated dates during the study period were collected from Outpatient Clinic Hospital Pharmacy software FARMIST/DISPENSA (Oncopharm® Health Information Technology). We also identified the circumstances surrounding any suspension of Inflectra® and substituting of a different biological medication. Following recommendations from the European League Against Rheumatism (EULAR), the criteria for therapeutic cessation were implemented. [9-11]. Persistence was defined as the length of time on treatment and was calculated from the beginning to the end of Inflectra® therapy. Patients who were still receiving treatment at the time of data extraction and

patients who were lost to follow-up were included in the analysis and were said to have a censored discontinuation time. Regardless of the length of the interruption, data from all patients who temporarily stopped receiving biologic treatment and then resumed it were included in the analysis of the primary outcome. The time it took for patients to quit receiving trial therapies permanently was known as the "time to treatment discontinuation." Furthermore, reasons for treatment discontinuation, comorbidities reported when starting the first or second biological agent, and infections occurring during treatment were recorded.

Clinical activity was evaluated using clinical activity indexes DAS28 and BASDAI on starting Inflectra® and when the final assessment was made (or before if Inflectra® had to be discontinued earlier). We mimicked the cost of Infliximab treatment for these patients as if they had received Remicade® for each of their Inflectra® treatment periods. Prices for Remicade® and Inflectra® were obtained from the price bulletins published by the Spanish Medicines Agency (ex-factory price + VAT as of September 2022).

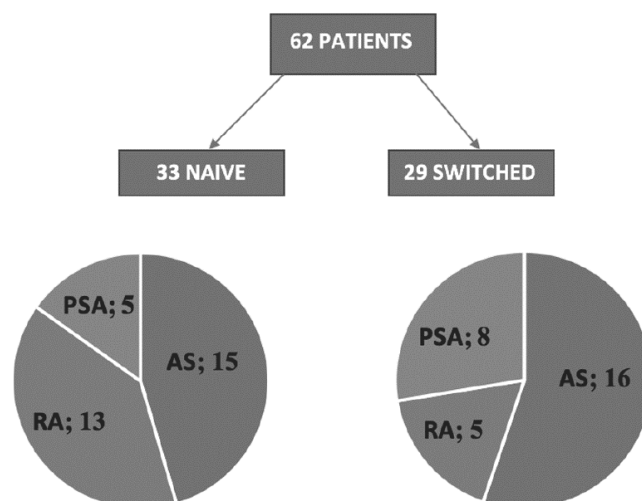
All the patients who belonged to the study were invited to participate voluntarily and signed informed consent at the start of treatment. Since the data used for this study were de-identified and only aggregated results were reported, the study was exempt from review by the Institutional Review Board.

## RESULTS

During this period, 62 patients (38 women), aged  $52 \pm 20$  years and weight of  $75 \pm 27$  kg, received Inflectra® for at least six months: 31 AS patients (50%), 18 RA patients (29%) and 13 PSA patients (21%). Of the 62 patients, 33 were Inflectra® naïve patients (54%), with 34% of these patients naïve to biologics; 15 patients with AS, 13 patients with RA, and five patients with PSA. 29 patients were switched from Remicade® (46%) with 51% naïve to biologics; 16 patients with AS, five patients with RA and eight patients with PSA. The distribution of naïve and switched patients according to their diagnosis is presented in Figure 1.

At the end of the study, 33 patients (54%) continued with the Inflectra® treatment; 23 naïve patients (12 AS patients, 9 RA patients, and 2 PSA patients) and 10 switched Remicade® patients (7 AS patients, 2 RA patients, and 1 PSA patients). All patients that continued on Inflectra® therapy showed up DAS values

of  $28 < 2.6$  [12] or a BASDAI  $< 2$  [13,14]. Twenty-nine patients discontinued Inflectra®; 10 naïve patients (3 AS patients, 4 RA patients, and 3 PSA patients) and 19 switched patients (9 AS patients, 3 RA patients, and 7 PSA patients), 24 patients due to a relapse in their rheumatic disease and five patients due to adverse effects (1 patient suffered rash, three upper chest infections and 1 with persistent diarrhea).



**Figure 1:** Distribution of Naïve and Switched patients according to their diagnosis.

The median persistence on I Inflectra® was  $24.4 \pm 7.4$  months (range = 1 to 5.5 years). The total persistence of AS patients was  $22.7 \pm 3.7$  months. RA patients of  $19.2 \pm 5.4$  months and PSA patients had persistence of  $31.7 \pm 16.7$  months. The median retention duration of naïve Inflectra® patients was  $19.1 \pm 4.4$  months. AS patients had a median persistence of  $19.1 \pm 4.7$  months, RA patients  $13.8 \pm 3.2$  months, and PSA patients  $24.5 \pm 15.4$  months. The median persistence on switched Inflectra® patients was  $29.7 \pm 5.8$  months. AS patients had a median persistence of  $26.5 \pm 6.5$  months, RA patients  $24.6 \pm 7.2$  months, and PSA patients had a persistence of  $37.9 \pm 18.1$  months (Table 1).

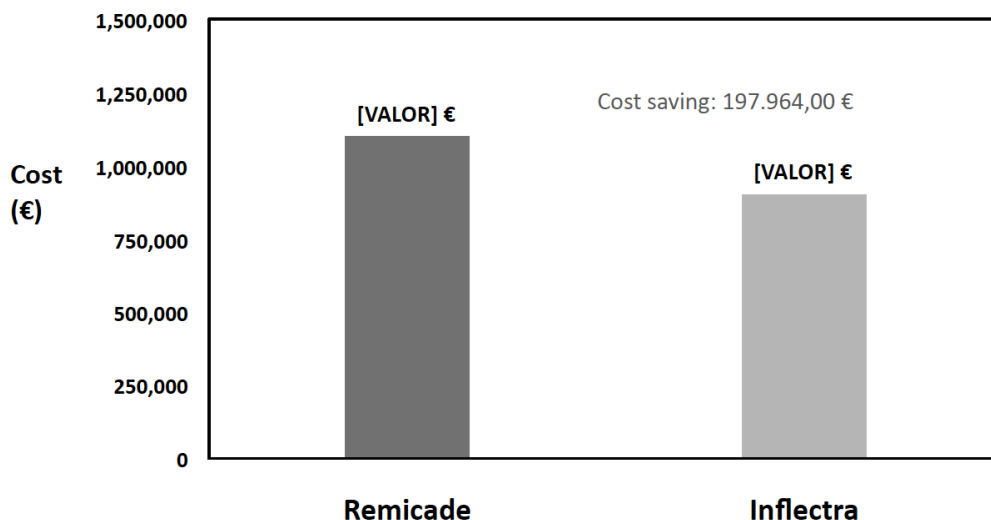
During the study period, if the patients in the Inflectra® group had been treated with Remicade®, the total cost of therapy would have been 1.099.803 €. Implementing the use of Inflectra® has meant a saving of 197.964 euros over the 5-year duration of the study. Figure 2 shows the total Inflectra® cost savings per year.

## DISCUSSION

In this retrospective real-world observational cohort study, we demonstrate that Inflectra® can be effective in naïve and switched patients from various rheumatic

**Table 1: Inflectra® Persistence in Naïve and Switched Patients**

	Median	AS	RA	PSA
Naïve patients persistente (month)	19.1±4.4	19.1±4.7	13.8±3.2	24.5±15.4
Switched patients persistente (month)	29.7±5.8	26.5±6.5	24.6±7.2	37.9±18.1
All patients persistente (month)	24.4±7.4	22.7±3.7	19.2±5.4	31.7±16.7

**Figure 2:** Costs due to the use of Remicade® and Inflectra® during 5 years.

pathologies. Sixty-two patients (33 naïve and 29 switched) were followed over five years, making it a long-term data study. At the end of the study, 54% of the patients continued with I Inflectra®. The Majority of Inflectra® discontinuations (82%) were due to a relapse in their rheumatic pathology. In a Spanish single-center study, the most common reason for discontinuation of TNF inhibitor therapy in RA and AS patients was lack of efficacy [12]. In the literature, the evidence of real-world clinical studies that have investigated the persistence, long-term Efficacy, or safety of Inflectra® in Caucasian naïve and switched patients with RA, PSA, and AS is scarce. A real-world study, which included 109 patients with AS/PSA, found that 2-year drug retention rates were higher among patients receiving CT-P13 as their first Infliximab product than those receiving Infliximab original [13].

Two real-world studies were published regarding the persistence, long-term Efficacy, or safety of Inflectra® in Asian naïve and switched patients with RA and AS patients. Kim *et al.* reported the long-term drug retention, Efficacy, and safety of the Inflectra®CT-P13 in 244 AS Korean patients. All patients were naïve to Infliximab. The overall median duration of CT-P13 treatment was 2.05 (0.04–4.18) years. After up to 4

years of follow-up, the retention rate of CT-P13 was 66% in the overall patient population. Lack of Efficacy was the most common reason for treatment changes, whereas adverse effects were the most common single cause of discontinuation [14]. A non-interventional retrospective analysis investigated drug survival and long-term safety and effectiveness of CT-P13 in patients with RA or AS in the Republic of Korea. Four hundred ninety-one patients were treated with CT-P13 (154 RA patients [135 Infliximab-naïve; 19 switched from reference Infliximab]; 337 patients with AS [219 Infliximab-naïve; 118 switched from reference Infliximab]). Drug survival was similar in naïve and switched patients. The authors concluded that drug survival and safety were similar in naïve patients and switched groups, supporting switching from reference infliximab to CT-P13 [15]. The results of the NOR-SWITCH extension trial aimed to assess Efficacy, safety, and immunogenicity in patients on CT-P13 throughout the 78-week study period confirmed that there was no difference in safety and Efficacy between patients who maintained CT-P13 and patients who switched from originator infliximab to CT-P13, supporting that switching from originator infliximab to CT-P13 is safe and efficacious [16].

In our study, the median Inflectra® treatment persistence was more than 24 months for all patients. In the naïve cohort, the median persistence was more than 19 months; in the switched cohort, the median persistence was more than 29 months. The persistence in switched patients was significantly higher because the switched patients were in clinical remission.

This is probably due to the most naïve to biologics patients in the Inflectra® naïve patient group. In the literature, several reports stated that the persistence of the first biologic is more central than the second and the beginners [17].

Because they are less expensive than RPs, biosimilars could have significant economic advantages. Several studies assessing the economic impact of switching from Infliximab RP to CT-P13 in various indications provide compelling evidence of the cost savings of CT-P13, even though there are currently no cost analyses explicitly examining the use of CT-P13 in the treatment of patients with AS [18]. In our study, we demonstrated that Inflectra® has similar Efficacy to Remicade® at a lower cost, allowing a larger number of patients to be treated. Implementing the procedure to use Inflectra® for all prescriptions of Infliximab in these patients saved 197,964€ during five years.

This study has some limitations: there are no data on the presence or absence of concomitant synthetic disease-modifying drugs such as methotrexate. Also, it is necessary to consider that the small number of patients could affect the results' consistency. Finally, in the persistence calculation, we assumed that patients were adherent to treatment if the medication was dispensed in the pharmacy service. However, the dispensing of medication does not necessarily imply medication administration.

The main contribution of our study is to provide long-term real-world data from Spanish naïve and switched patients with AR, PSA, and AS receiving treatment with Inflectra®. Our analysis provides essential information on the long-term Efficacy and tolerability of Inflectra. These data could counteract clinicians' concerns about switching patients to a biosimilar, including the potential loss of Efficacy, changes in immunogenicity, and unanticipated differences in safety profile compared to the original drug. Furthermore, these results add to the results previously published, in which only the short-term or related persistence of the Infliximab CT-P13 was studied in Caucasian patients.

## CONCLUSIONS

When the cost of therapy is an unavoidable component of healthcare treatment decisions, Inflectra® could be a cost-effective option for selected patients with RA, PSA, and AS by achieving similar persistence and cost savings when used in infliximab-naïve patients and patients who have switched from Remicade.

## CONFLICT-OF-INTEREST STATEMENT

To the best of our knowledge, no conflict of interest exists.

## AUTHOR CONTRIBUTIONS

Joaquín Borrás-Blasco, Alejandro Valcuende-Rosique, Dolores Rosique-Robles, Elvira Casterá, substantially contributed to the conception and design of the study, acquisition, analysis and interpretation of data; all authors drafted the article and made critical revisions related to the intellectual content of the manuscript, and approved the final version of the article to be published.

## REFERENCES

- [1] Martínez-López de Castro N, Matilla-Fernández MB, Fraga-Fuentes MD, *et al.* Spanish Society of Hospital Pharmacy position paper on biosimilar medicines. *Farm Hosp* 2018; 42: 180-183.
- [2] Park W, Hrycaj P, Jeka S, *et al.* A randomized, 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. <https://doi.org/10.1136/annrheumdis-2012-203091>
- [3] 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 PLANETA study. *Ann Rheum Dis* 2013; 72: 1613-20. <https://doi.org/10.1136/annrheumdis-2012-203090>
- [4] Park W, Yoo DH, Miranda P, Brzoska M, Wiland P, GutierrezUrena S, *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* 2017; 76: 346-54. <https://doi.org/10.1136/annrheumdis-2015-208783>
- [5] Nikiphorou E, Kautiainen H, Hannonen P, *et al.* Clinical effectiveness of CT-P13 (Infliximab biosimilar) used as a switch from Remicade (Infliximab) in patients with established rheumatic disease. Report of clinical experience based on prospective observational data. *Expert Opin Biol Ther* 2015; 15: 1677-83. <https://doi.org/10.1517/14712598.2015.1103733>
- [6] Glintborg B, Sorensen IJ, Loft Ag *et al.* A nationwide non-medical switch from originator infliximab to biosimilar CT-P13 in 802 patients with inflammatory arthritis: 1-year clinical outcomes from the DANBIO registry. *Ann Rheum Dis* 2017; 76: 1426-31. <https://doi.org/10.1136/annrheumdis-2016-210742>

- [7] Arnett FC, Edworthy SM, Bloch DA, *et al.* The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-24.  
<https://doi.org/10.1002/art.1780310302>
- [8] Van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984; 27: 361-8.  
<https://doi.org/10.1002/art.1780270401>
- [9] Smolen JS, Landewé RBM, Bijlsma JWJ, *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis* 2020; 79: 685-99.
- [10] Van der Heijde D, Ramiro S, Landewé R *et al.* 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. *Ann Rheum Dis* 2017; 76: 978-91.  
<https://doi.org/10.1136/annrheumdis-2016-210770>
- [11] Coates LC, Gossec L, Ramiro S *et al.* New GRAPPA and EULAR recommendations for the management of psoriatic arthritis. *Rheumatology (Oxford)* 2017; 56: 1251-53.  
<https://doi.org/10.1093/rheumatology/kew390>
- [12] García-Lagunár MH, Gutiérrez-Cívicos MR, García-Simón MS *et al.* Reasons for discontinuation and adverse effects of TNF- $\alpha$  inhibitors in a cohort of patients with rheumatoid arthritis and ankylosing spondylitis. *Ann Pharmacother* 2017; 51: 388-93.  
<https://doi.org/10.1177/1060028016682330>
- [13] Nikiphorou E, Hannonen P, Asikainen J, *et al.* Survival and safety of infliximab biooriginal and Inflectra®(CT-P13) in usual rheumatology care. *Clin Exp Rheumatol* 2019; 37: 55-9.
- [14] Kim HA, Lee E, Lee SK, *et al.* Retention rate and long-term safety of biosimilar CT-P13 in patients with ankylosing spondylitis: data from the Korean College of Rheumatology Biologics registry. *Clin Exp Rheumatol* 2020; 38: 267-74.  
<https://doi.org/10.55563/clinexprheumatol/z0va6o>
- [15] Kim TH, Lee SS, Park W, *et al.* A 5-year Retrospective Analysis of Drug Survival, Safety, and Effectiveness of the Inflectra®CT-P13 in Patients with Rheumatoid Arthritis and Ankylosing Spondylitis. *Clin Drug Investig* 2020; 40: 541-53.  
<https://doi.org/10.1007/s40261-020-00907-5>
- [16] Goll GL, Jørgensen KK, Sexton J, *et al.* Long-term Efficacy and safety of biosimilar infliximab (CT-P13) after switching from originator infliximab: open-label extension of the NOR-SWITCH trial. *J Intern Med* 2019; 285: 653-69.  
<https://doi.org/10.1136/annrheumdis-2018-eular.4620>
- [17] González-Fernández MÁ, Villamañán E, Jiménez-Nácher I, *et al.* Persistence of biological agents over an eight-year period in rheumatoid arthritis and spondyloarthritis patients. Persistencia de medicamentos biológicos durante ocho años en pacientes con artritis reumatoide y espondiloartritis. *Farm Hosp* 2019; 43: 24-30.
- [18] Jha A, Upton A, Dunlop Wc, *et al.* The budget impact of biosimilar infliximab (Remsima) for the treatment of autoimmune diseases in five European countries. *Adv Ther* 2015; 32: 742-56.  
<https://doi.org/10.1007/s12325-015-0233-1>