Outcomes and safety of TNF inhibitors in reactive arthritis: A nationwide experience from Iceland

Bjarni Thorsteinsson[1,2]
Arni J. Geirsson[3]
Niels S. Krogh[4] https://orcid.org/0000-0002-8520-1674
Bjorn Gudbjornsson[2,5] https://orcid.org/0000-0003-4631-6505
on behalf of ICEBIO

Key words: Reactive arthritis, biologics, TNF-alpha, registry, safety.

[1]Department of Medicine, [2]Center for Rheumatology Research, and [3]Department of Rheumatology, Landspitali University Hospital, Reykjavik, Iceland. [4]Zitelab ApS, Copenhagen, Denmark. [5]Faculty of Medicine, University of Iceland, Reykjavik, Iceland.

Grants or industrial support: None

Conflict of interest: None

B Thorsteinsson, MD; AJ Geirsson, MD, PhD; NS Krogh, MSc; B Gudbjornsson, MD, PhD.

Correspondence:
Bjarni Thorsteinsson
Center for Rheumatology Research, University Hospital, Eiriksgata 5, 101 Reykjavik
bjarnith@gmail.com
+354 694 4031

Running title: TNFi in ReA

Abstract

Objective

Reactive arthritis (ReA) is a spondyloarthritis triggered by a bacterial infection. In cases where nonsteroidal anti-inflammatory drugs and conventional synthetic disease-modifying antirheumatic drugs have failed, biologics such as tumor necrosis factor inhibitors (TNFi) have been used. However, limited evidence exists of the efficacy and safety of these drugs in ReA. We report on Icelandic patients with ReA who have been treated with TNFi, their characteristics, outcomes, and safety.

Methods

We conducted an observational cohort study using the Icelandic nationwide database of biologic therapy (ICEBIO) supplemented with a retrospective study of electronic health record data. Drug efficacy was assessed using disease activity scores and standardized questionnaires within ICEBIO; safety was assessed using ICEBIO and electronic health record data.

Results

Thirty-eight patients with ReA were registered in the database. Eight were given TNFi within one year of symptom onset. At six and 18 months, there was a significant reduction in C-reactive protein (CRP), tender and swollen joints, Visual Analog Scale for pain and fatigue, Disease Activity Score 28-joint count CRP (DAS28CRP), Clinical Disease Activity Index (CDAI), and Health Assessment Questionnaire (HAQ) scores. Seventy-one to 90% of patients were considered treatment responders. Two patients were able to stop biologics due to remission. During the 303 patient years (mean 8, range 1–15) biologics were given, six hospital admissions for infections were noted.

Conclusion

TNFi are safe and effective in ReA, but treatment tends to be prolonged. Further clinical trials are urgently needed in ReA.

Introduction

Reactive arthritis (ReA) is an inflammatory disease arising one to four weeks following a bacterial infection, most commonly of the genitourinary or gastrointestinal tracts. It is classified with the human leukocyte antigen B27 (HLA-B27) associated spondyloarthritides along with axial spondyloarthritis, psoriatic arthritis, and inflammatory bowel disease-associated arthritis. ReA commonly causes oligo- or polyarthritis, mainly of the lower limbs but also extra-articular disease, such as enthesitis, conjunctivitis, and uveitis, as well as symptoms of inflammatory back pain that may result in spondyloarthritis(1,2). The term reactive arthritis represents a spectrum of post-infectious arthritis. Thus, the classic triad of arthritis, conjunctivitis, and urethritis—formerly known as Reiter syndrome—is present only in a subset of patients(3). While ReA is often perceived as mild and self-limiting, a substantial percentage of patients develop chronic inflammatory disease. Indeed, ReA follows a chronic course in up to one-third of patients(4,5).

Although treating the acute infection with antibiotics seems to lower the likelihood of developing ReA(6), once the disease is established, there generally is no further role for antibiotic treatment(7–9), with the possible exception of Chlamydia-induced ReA(10,11). The first-line treatment of ReA is with nonsteroidal anti-inflammatory drugs (NSAIDs) and local intra-articular steroid injections. Glucocorticoids and conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), such as sulfasalazine and methotrexate, are used in severe or resistant cases(12). Sulfasalazine has been shown to induce remission when started within three months(13) and is effective in chronic ReA(14). High levels of tumor necrosis factor alpha (TNFα) in the circulation and the affected joints of patients with ReA have prompted the use of anti-TNF agents in disease unresponsive to standard treatment(15). Because of the theoretical risk of reactivating the triggering infection, Flagg et al.(16) examined synovial biopsies and clinical response in 10 ReA patients treated with the TNF inhibitor (TNFi) etanercept. Of note, even those

with PCR evidence of bacterial organisms on biopsy before treatment showed clinical improvement.

Few studies have been published on the outcome of patients with ReA receiving TNFi. Meyer(17) and Flagg(16) each reported 10 ReA patients receiving TNFi. In both trials, nine patients responded well to therapy. All 15 ReA patients reported by Brinster(18) showed clinical improvement on TNFi and a third was able to discontinue the medication within a few months. Finally, Courcoul(19) found that three out of 11 patients who had received TNFi for chronic ReA could discontinue the treatment.

The purpose of the present study is to add to the scant evidence of TNFi efficacy and safety in patients with ReA in a larger cohort than earlier reports have presented.

Methods

Data for ReA patients treated with biologic DMARDs (bDMARDs) were extracted from the ICEBIO registry. ICEBIO is a nationwide registry of Icelandic rheumatologic patients treated with bDMARDs that currently includes 98% of this patient group. The registry contains detailed patient characteristics and long-term disease activity scores. The registry was launched in 2007; patients who started biologics earlier were retrospectively entered into the database. ICEBIO is based on the same information technology platform as the Danish Registry DANBIO. ICEBIO has been described in more detail elsewhere(20).

Standard demographic data were obtained from the ICEBIO registry at baseline (start of TNFi therapy) as well as information on the type and dosage of TNFi and the dates of symptom onset, diagnosis, and TNFi administration. The following disease activity markers were collected for each office visit: C-reactive protein (CRP), 28 swollen joint count (SJC), 28 tender joint count (TJC), VAS for pain and fatigue, Disease Activity Score 28-joint count CRP (DAS28CRP), Clinical Disease Activity Index (CDAI), and Health Assessment Questionnaire (HAQ). Three office visits for assessment of disease activity were chosen: baseline (last visit before starting TNFi), six months (closest visit to 180 days (90–210)), and 18 months (closest visit to 540 days (211–660)). Information on HLA-B27 status was gathered from the National University Hospital's Blood Bank, the only laboratory that performs HLA typing in Iceland.

A retrospective study of electronic health record data was used to gather additional information on the patients found in the ICEBIO registry. This included data on the triggering infection, use of antibiotics, clinical symptoms, anti-rheumatic treatment before the initiation of TNFi therapy, recurrence of index infection, and serious adverse events during the TNFi treatment period, which were defined as admissions for infections and death. Further safety data were

extracted from the electronic health record if the patients' ICEBIO data indicated that they stopped or switched biologic agents due to adverse events.

Patients were considered responders if all three of the VAS pain, SJC, and TJC decreased by 30% or more (response criteria adapted from Meyer et al.(17)) or the DAS28CRP score decreased by one or more disease activity categories: remission < 2.6, low activity ≤ 3.2, moderate activity ≤ 5.1, and high activity > 5.2.

Statistical analysis

All data were anonymized before analysis. Microsoft Excel for Mac version 16.29.1 was used for descriptive analysis. Statistical analysis was performed using R version 3.6.1 in a Linux environment. The Kruskal–Wallis test was used to compare variables collected at the baseline, the six-month, and the 18-month visits. The significance threshold was set at .05. Drug survival was demonstrated using a Kaplan–Meier curve.

The study protocol was approved by the Landspitali University Hospital Bioethics Committee (nr 11/2019).

Results

The total number of patients registered with ReA, as the indication for TNFi treatment in the ICEBIO database, was 40. Two of these were excluded because their registry data did not apply to the first biologic medication given for their ReA. Thus, 38 patients remained for data analysis. Twenty-six (68%) were male, and the mean age at the start of bDMARD treatment was 39 years. Thirty-four patients had failed conventional treatment with NSAIDs and csDMARDs prior to initiation of TNFi (data missing for two patients) (Table 1). The first patient was started on TNFi in 2005 and the last patient in 2018.

Thirty patients were treated with infliximab (79%), six with etanercept (16%), one with adalimumab, and one with golimumab. The starting dose of infliximab was 200 mg in all but one instance, where it was 300 mg, followed by infusions on week 2 and 6 and then on eight-week intervals. The starting dose of etanercept was 25 mg twice a week in three cases, 50 mg once a week in two cases, and an unknown dose in one case. The adalimumab dose was 40 mg every other week, and the golimumab dose was 50 mg monthly. The mean number of days (with 25% and 75% quartiles) from the start of biologic therapy to the six-month visit was 160 days (146; 180) and 441 days (326; 575) to the 18-month visit. Drug survival at 24 months was 78% (Figure 1).

A triggering organism was found in 45% of patients. Salmonella was the most common bacteria identified (comprising 41% of cases with a known infectious agent). Campylobacter, Chlamydia, and Group A Streptococcus were also found (Table 1). Seventy-four percent of patients presented with oligoarthritis and 24% of patients presented with polyarthritis. Enthesitis was present in 24%, and the same percentage of patients had other extra-articular manifestations (Table 2). Of eight patients tested for HLA-B27 status, six were positive.

Ten patients met Braun's criteria for ReA and a further 16 were deemed "very likely ReA." Four patients did not meet these criteria, and data was missing for the remaining eight. However, the patients' practicing rheumatologists assumed that these patients suffered from ReA.

Functional status markers (CRP level, SJC, TJC, VAS pain, VAS fatigue, DAS28CRP, CDAI, and HAQ) improved at six and 18 months compared to baseline (Table 3). Seventy-one percent of patients (15 of 21 with full data available) were good responders to the treatment; they had a 30% or more reduction of SJC, TJC, and VAS pain, at both six- and 18-month visits. Joint count information was available for 23 patients at six months; 18 had no swollen joints and 15 had no tender joints. Of 22 patients with data available at 18 months, 18 had no swollen joints and 16 had no tender joints. Using the DAS28CRP scores entered at baseline and at the follow-up visits, 18 (90%) were considered responders at the six-month visit and 17 (85%) were considered responders at the 18-month visit (i.e., patients with a decrease by one or more disease activity categories of the DAS28CRP). At six and 18 months, 68% and 77% were in DAS28CRP-defined remission, respectively.

Of the 38 patients who received TNFi, eight were treated within one year of symptom onset and five were treated within six months. The mean VAS pain score at 18 months for the group of patients treated with TNFi within six months of symptom onset was 15, within one year was 22, and after one year was 23. Responders defined by a 30% reduction in VAS pain, SJC, and TJC at 18 months were four out of four (with data available) for those who started TNFi within six months of symptom onset, four out of five who started within one year, and 11 out of 16 who started after one year (Table 4).

At the time of data acquisition, biologic therapy had lasted on average eight years (range 1–15). Of the 38 patients, 32 were still receiving biologic therapy. One patient stopped treatment due to a cancer diagnosis and one because of side effects (not requiring hospital admission). Only two were able to stop biologic therapy because of remission. They had started treatment with

etanercept and infliximab at 11 and 12 months from symptom onset, and biologic treatment lasted 1.7, and 12 years, respectively. Data on the current treatment of the remaining two patients were missing. Nineteen patients were still receiving the same initial TNFi. Sixteen patients had switched to another biologic medication; eight because of inefficacy and four due to adverse events. These events were two instances of allergic reactions, one instance of viral meningitis and one unknown event. These four patients had all been treated with infliximab.

The 38 patients with ReA received biologics for a total of 303 years. No patient died while on biologic therapy. Six patients had infections requiring hospital admission during their TNFi treatment period. Of the six, there were three cases of appendicitis, of which one was complicated by appendiceal rupture. The other causes for hospital admission were viral meningitis, human metapneumovirus pneumonia, and pyelonephritis. One patient developed metastatic prostate cancer during biologic therapy, which was subsequently stopped. His ReA was originally triggered soon after surgery for prostate cancer.

Discussion

In this nationwide registry study, we report our experience of outcomes and safety of TNFi in a group of patients with ReA. To our knowledge, this is the largest cohort of ReA patients treated with TNFi; reflecting more than 300 patient years. The ICEBIO registry has been used in clinical practice in Iceland since 2007. Treating rheumatologists are required to enter disease information into ICEBIO before applying for a bDMARD treatment license and reimbursement by the Icelandic Health Insurance. Standard follow-up data are then registered annually on clinic visits, irrespective of whether the patient is followed up in a hospital outpatient ward or a private rheumatologist's office(21). This gives us a unique opportunity to examine nationwide data on the treatment of various patient groups with different rheumatic conditions.

In the present study, we focus on ReA, which has been clinically diagnosed by the treating physician, in most cases an experienced rheumatologist. It is important to note that there is no international consensus on the classification or diagnostic criteria for ReA, nor in fact treatment of the disease as there is for rheumatoid arthritis(22), psoriatic arthritis(23), and axial spondyloarthritis(24). However, some attempts have been made in this field and recent studies on ReA have used the Braun criteria(19,25). According to these criteria, a diagnosis of ReA is established if both major criteria and one minor criterion are met, it is considered a very likely diagnosis if both major criteria or one major and one minor criterion are met. The major criteria are firstly an arthritis typical of ReA and secondly preceding enteritis or urethritis. The minor criteria are microbial evidence of Chlamydia in the urogenital tract or positive stool culture for bacteria associated with ReA. Of the 30 patients with data available, only four did not meet these criteria. Reflective of the lack of validated criteria, this study focuses on real-world prescribing for a presumed diagnosis of ReA.

Our main finding is that the large majority of patients experienced low disease activity or remission, according to DAS28CRP, or achieved good response on various patient reported outcome measures a few months after starting treatment with TNFi. These findings are in accordance with previously discussed studies(17,18) that have reported favorable outcomes of TNFi treatment in ReA. Furthermore, safety was acceptable with six hospital admissions due to infections and no deaths during the 303 years of biologic treatment and no documented reactivation of the triggering infection. Two patients had to switch to another biologic after an allergic reaction. Drug survival was good and similar to drug survival reported in other spondyloarthritides(26).

To our surprise, only two patients (5%) were able to stop the TNFi therapy on the basis of remission. This is lower than previous studies have suggested. Meyer(17) reported that three out of 10 could discontinue TNFi without relapse, and in Brinster's(18) study, five patients of 15 could stop the medication. It is likely that our cohort had a lower rate of treatment stop due to remission because it had a larger percentage of chronic ReA patients with a more established spondyloarthritis (79% treated after one year from symptom onset). As a result, there were fewer patients who would have achieved remission irrespective of treatment as a natural course of their disease.

It has been hypothesized that there might be an advantage to giving TNFi within a few months of symptom onset; a "window of opportunity" to avert a chronic course of disease. Although data is limited, the literature does not seem to support this notion. In Courcoul's study, only one out of five early-treated patients (< 3 months) was able to stop treatment(19). Our study adds two cases. Both patients treated within three months of symptom onset were unable to discontinue treatment and were still receiving a TNFi at the time of data acquisition, three and a half and four and a half years later. Thus, the available data does not support the idea that early treatment of ReA with TNFi halts progression to spondyloarthritis. Although our sample size is

small, our data does seem to suggest that treating soon after symptom onset might result in lower disease activity. Indeed, all four patients with available data treated within six months were considered treatment responders.

The strength of the present study is, firstly, that it is an unselected population of patients with ReA who are treated with TNFi and the largest to date. Secondly, it describes treatment efficacy in a group with relatively long symptom duration and established disease. Finally, it reports detailed outcome measures not previously published in ReA. Besides the common limitations of observational registry studies, such as missing data entries, and retrospective study of medical records, a drawback to this report is the fact that a number of the outcome measures are not validated for use in ReA. Of note, the 28-joint SJC and TJC are not ideal in ReA since they omit the foot and ankle joints, which are commonly affected in the disease. The 28-joint index was used in this study since it is by far the most used in the ICEBIO database. Thus, the disease activity index for the assessment of reactive arthritis (DAREA), proposed by Eberl et al. in 2000(27), could not be used as it relies on the total joint count. The HAQ, CDAI, and DAS28 were developed and validated for rheumatoid arthritis(28) but are commonly used in randomized clinical trials of spondyloarthritides such as psoriatic arthritis(29). It is therefore reasonable to assume that these measures could be reliable in ReA. It should be mentioned that while a significant proportion of the patients had back pain and extra-articular manifestations, there was no way of specifically quantifying their response to treatment other than what surrogate markers, such as VAS pain, could provide.

Three of the included patients in this study were treated with TNFi for post-Streptococcal ReA (PSRA), which is generally regarded as a separate entity from urogenital and enteric ReA(30). Indeed, these patients had an upper limb oligoarthritis, an equal upper and lower limb oligoarthritis, and a polyarthritis, respectively. The only extra-articular manifestation noted was erythema nodosum in one patient. The patients had all been treated with antibiotics for their

pharyngitis. All three received infliximab, and two were treated within one year from symptom onset. Only one of the three PSRA patients was considered a responder at the 18-month visit. There was no recorded reactivation of Streptococcus or other severe infections during biologic therapy. To our knowledge, these are the first reported cases of PSRA treated with TNFi in the literature.

In conclusion, we have demonstrated in our group of 38 patients with ReA that TNFi are safe and effective. The data also seems to suggest that lower disease activity might be achieved if the active anti-inflammatory treatment with TNFi is initiated as soon as traditional treatment options do not result in remission. However, as in other spondyloarthropathies, biologic therapy in ReA tends to be prolonged.

Acknowledgements

The authors would like to thank the patients who recorded their symptoms in ICEBIO and to all rheumatologists in Iceland who are part of the ICEBIO group. We would also like to thank Elinborg Stefansdottir, RN, for practical help and Thorarinn Jonmundsson at the University of Iceland for help with statistical analysis.

References

1. Leirisalo-Repo M. Reactive arthritis. Scand J Rheumatol 2005;34:251-9.
2. Selmi C, Gershwin ME. Diagnosis and classification of reactive arthritis. Autoimmun Rev 2014;13:546-9.
3. Rothe MJ, Kerdel FA. Reiter Syndrome. Int J Dermatol 1991;30:173-80.
4. Leirisalo-Repo M. Prognosis, course of disease, and treatment of the spondyloarthropathies. Rheum Dis Clin North Am 1998;24:737-51.
5. Uotila TM, Antonen JA, Paakkala AS, Mustonen JT, Korpela MM. Outcome of reactive arthritis after an extensive Finnish waterborne gastroenteritis outbreak: A 1-year prospective follow-up study. Clin Rheumatol 2013;32:1139-45.
6. Bardin T, Enel C, Cornelis F, Salski C, Jorgensen C, Ward R, et al. Antibiotic Treatment of Venereal Disease and Reiter's Syndrome in a Greenland Population. Arthritis Rheum 1992;35:190-4.
7. Fryden A, Bengtsson A, Foberg U, Svenungsson B, Castor B, Karnell A, et al. Early antibiotic treatment of reactive arthritis associated with enteric infections: clinical and serological study. BMJ 1990;301:1299-302.
8. Yli-Kerttula T, Vainionpää R, Toivanen A, Luukkainen R, Yli-Kerttula U, Möttönen T, et al. Effect of a three month course of ciprofloxacin on the outcome of reactive arthritis. Ann Rheum Dis 2000;59:565-70.
9. Zhang Y, Gripenberg-Lerche C, Söderström KO, Toivanen A, Toivanen P. Antibiotic prophylaxis and treatment of reactive arthritis: Lessons from an animal model. Arthritis Rheum 1996;39:1238-43.
10. Lauhio A, Leirisalo-Repo M, Lähdevirta J, Saikku P, Repo H. Double-blind, placebo-controlled study of three-month treatment with lymecycline in reactive arthritis, with special

reference to Chlamydia arthritis. Arthritis Rheum 1991;34:6-14.

11. Carter JD, Espinoza LR, Inman RD, Sneed KB, Ricca LR, Vasey FB, et al. Combination antibiotics as a treatment for chronic Chlamydia-induced reactive arthritis: A double-blind, placebo-controlled, prospective trial. Arthritis Rheum 2010;62:1298-307.
12. Lucchino B, Spinelli FR, Perricone C, Valesini G, Di Franco M. Reactive arthritis: current treatment challenges and future perspectives. Clin Exp Rheumatol 2019;37:1065-76.
13. Clegg DO, Reda DJ, Abdellatif M. Comparison of sulfasalazine and placebo for the treatment of axial and peripheral articular manifestations of the seronegative spondylarthropathies: A Department of Veterans Affairs Cooperative Study. Arthritis Rheum 1999;42:2325-9.
14. Clegg DO, Reda DJ, Weisman MH, Cush JJ, Vasey FB, Schumacher HR, et al. Comparison of sulfasalazine and placebo in the treatment of reactive arthritis (Reiter's syndrome). Arthritis Rheum 1996;39:2021-7.
15. Butrimiene I, Jarmalaite S, Ranceva J, Venalis A, Jasiuleviciute L, Zvirbliene A. Different cytokine profiles in patients with chronic and acute reactive arthritis. Rheumatology 2004;43:1300-4.
16. Flagg SD, Meador R, Hsia E, Kitumnuaypong T, Schumacher HR. Decreased pain and synovial inflammation after etanercept therapy in patients with reactive and undifferentiated arthritis: An open-label trial. Arthritis Care Res 2005;53:613-7.
17. Meyer A, Chatelus E, Wendling D, Berthelot JM, Dernis E, Houvenagel E, et al. Safety and efficacy of anti-tumor necrosis factor α therapy in ten patients with recent-onset refractory reactive arthritis. Arthritis Rheum 2011;63:1274-80.
18. Brinster A, Guillot X, Prati C, Wendling D. Anti-TNF treatment of reactive arthritis. A monocentric experience. Joint Bone Spine 2017;84:237-8.
19. Courcoul A, Brinster A, Decullier E, Larbre JP, Piperno M, Pradat E, et al. A bicentre retrospective study of features and outcomes of patients with reactive arthritis. Joint Bone

Spine 2018;85:201-5.

20. Runarsdottir EE, Gunnarsdottir AI, Love TJ, Gunnarsson PS, Gudbjornsson B. The majority of patients with psoriatic arthritis are not eligible for randomised clinical trials. Clin Exp Rheumatol 2018;36:1068-73.

21. Glintborg B, Gudbjornsson B, Krogh NS, Omerovic E, Manilo N, Holland-Fischer M, et al. Impact of different infliximab dose regimens on treatment response and drug survival in 462 patients with psoriatic arthritis: Results from the nationwide registries DANBIO and ICEBIO. Rheumatology 2014;53:2100-9.

22. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569-81.

23. Helliwell PS, Taylor WJ. Classification and diagnostic criteria for psoriatic arthritis. Ann Rheum Dis 2005;64:ii3-8.

24. Rudwaleit M, Van Der Heijde D, Landewé R, Listing J, Akkoc N, Brandt J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): Validation and final selection. Ann Rheum Dis 2009;68:777-83.

25. Braun J, Kingsley G, Van der Heijde D, Sieper J. On the difficulties of establishing a consensus on the definition of and diagnostic investigations for reactive arthritis. Results and discussion of a questionnaire prepared for the 4th international workshop on reactive arthritis, Berlin, Germany, July 3. J Rheumatol 2000;27:2185-92.

26. Aaltonen K, Heinonen A, Joensuu J, Parmanne P, Karjalainen A, Varjolahti-Lehtinen T, et al. Effectiveness and drug survival of TNF-inhibitors in the treatment of psoriatic arthritis: A prospective cohort study. Semin Arthritis Rheum 2017;46:732-9.

27. Eberl G, Studnicka-Benke A, Hitzelhammer H, Gschnait F, Smolen JS. Development of a

disease activity index for the assessment of reactive arthritis (DAREA). Rheumatology 2000;39:148-55.

28. Anderson J, Caplan L, Yazdany J, Robbins ML, Neogi T, Michaud K, et al. Rheumatoid arthritis disease activity measures: American college of rheumatology recommendations for use in clinical practice. Arthritis Care Res 2012;64:640-7.

29. Michelsen B, Fiane R, Diamantopoulos AP, Soldal DM, Hansen IJW, Sokka T, et al. A comparison of disease burden in rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis. PLoS One 2015;10:e0123582.

30. Mackie SL, Keat A. Poststreptococcal reactive arthritis: What is it and how do we know? Rheumatology 2004;43:949-54.

Table 1

Baseline characteristics of 38 patients with reactive arthritis who received treatment with TNF inhibitors and were registered in ICEBIO.

	n (%)
Total number of patients	38
Male	26 (68)
Age (years), mean (range)	39 (20–61)
Symptom duration (years), mean (1st and 3rd quartiles)	6 (1; 9)
BMI (kg/m2), mean (1st and 3rd quartiles)	29 (26; 30)
Known focus of infection	31 (82)
Enteric	20 (65)
Urogenital	8 (26)
Respiratory	3 (10)
Known pathogen	17 (45)
Salmonella	7 (41)
Campylobacter	3 (18)
Chlamydia	4 (24)
Streptococcus Group A	3 (18)
Satisfies Braun Criteria (established or likely; data missing: 8)	26 (87)
Antibiotic treatment given for triggering infection (data missing: 19)	15 (79)
Failure of NSAIDs and csDMARDs (data missing: 2)	34 (94)
Biologics given within 1 year of symptom onset	8 (21)
0-6 months	5 (13)
6-12 months	3 (8)

Abbreviations: BMI: body mass index; csDMARDs: conventional synthetic disease-modifying antirheumatic drugs.

Table 2

Clinical features of 38 patients with reactive arthritis who received treatment with TNF inhibitors and were registered in ICEBIO.

	n (%)
Arthritis	38 (100)
Monoarthritis	1 (3)
Oligoarthritis, predominantly of the lower limb	24 (63)
Oligoarthritis, other	4 (11)
Polyarthritis	9 (24)
Back pain	14 (37)
Enthesitis	10 (26)
Dactylitis	5 (13)
Extra-articular features	10 (26)
Uveitis	7 (18)
Conjunctivitis	3 (8)
Balanitis	3 (8)
Prostatitis	2 (5)

Table 3

Disease activity of 38 patients with reactive arthritis treated with TNF inhibitors at baseline and the 6-month and 18-month visits, according to data from ICEBIO.

	*Nr**	*Baseline*	*Nr*	*6 months*	*Nr*	*18 months*	*P-value*
CRP	31	26 (6; 42)	23	6.0 (3.0; 7.0)	22	5.6 (1.0; 4.5)	<.001
SJC – 28 joint count	32	2.8 (0; 3)	23	1.3 (0.0; 0.0)	22	0.5 (0.0; 0.0)	<.001
TJC – 28 joint count	32	3.8 (1.0; 4.3)	23	0.7 (0.0; 1.0)	22	0.9 (0.0; 0.8)	<.001
VAS pain	30	68 (55; 80)	23	22 (5.0; 25)	23	22 (6.5; 43)	<.001
VAS fatigue	28	57 (41; 77)	23	25 (8.0; 29)	23	29 (8.5; 54)	<.001
DAS28CRP	30	4.1 (3.3; 4.9)	22	2.2 (1.5; 3.0)	22	2.2 (1.3; 2.5)	<.001
CDAI	23	20 (13; 24)	16	4.7 (1.0; 6.5)	20	4.5 (1.0; 6.0)	<.001
HAQ	29	0.99 (0.50; 1.50)	24	0.31 (0.00; 0.41)	23	0.35 (0.00; 0.69)	<.001
Responders, defined by:**							
VAS, SJC, TJC			21	15 patients, 71%	21	15 patients, 71%	
DAS28CRP			20	18 patients, 90%	20	17 patients, 85%	

Notes: *Nr denotes number of patients with data available for each parameter. Data presented as means and 25% and 75% quartiles in parenthesis. **Responders defined as having a 30% or more reduction in VAS pain, SJC and TJC, or a DAS28CRP score decrease by one or more disease activity category. The Kruskal–Wallis test found a significant difference for all variables.

Abbreviations: SJC: swollen joint count; TJC: tender joint count; VAS: visual analog scale; DAS: Disease Activity Score; CDAI: Clinical Disease Activity Index; HAQ: Health Assessment Questionnaire; Nr: number.

Table 4

Clinical outcomes at the 18-month follow-up visit of 38 patients with reactive arthritis with respect to time from symptom onset to the start of TNF inhibitor therapy.

	*Nr**	*< 12 months*	*Nr*	*> 12 months*	*P-value*
Total n	8		30		
CRP	6	2.5 (2.3; 3.0)	16	6.8 (1.0; 7.0)	0.97
SJC – 28 joint count	6	0.3 (0.0; 0.0)	16	0.5 (0.0; 0.0)	0.87
TJC – 28 joint count	6	0.5 (0.0; 0.8)	16	1.1 (0.0; 0.5)	1.00
Patient VAS pain	6	22 (4.8; 33)	17	23 (7.0; 45)	0.89
Patient VAS fatigue	6	41 (15; 64)	17	24 (4.0; 46)	0.18
DAS28-CRP	6	2.1 (1.5; 2.3)	16	2.2 (1.3; 2.8)	0.66
CDAI	5	2.6 (1.0; 4.0)	15	5.2 (1.2; 6.2)	0.66
HAQ	6	0.25 (0.00; 0.09)	17	0.38 (0.00; 0.75)	0.72
Responders, defined by:**					
VAS, SJC, TJC	5	4 responders (80%)	16	11 responders (69%)	
DAS28CRP	5	4 responders (80%)	15	13 responders (87%)	

Notes: *Nr denotes number of patients with data available for each parameter. Data presented as means and 25% and 75% quartiles in parenthesis. **Responders defined as having a 30% or more reduction in VAS pain, SJC and TJC, or a DAS28CRP score decrease by one or more disease activity category. The Kruskal–Wallis test did not find a significant difference for the variables.

Abbreviations: SJC: swollen joint count; TJC: tender joint count; VAS: visual analog scale; DAS: Disease Activity Score; CDAI: Clinical Disease Activity Index; HAQ: Health Assessment Questionnaire; Nr: number.

Figure 1

Kaplan–Meier plot for survival of first TNF inhibitor in 38 patients with reactive arthritis.