Biological therapy safety in chronic inflammatory arthropathy patients

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Abstract

Objective: The marketing of biological therapies transformed the treatment of rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis. But there is still concern about patient safety and management in daily clinical practice. The aim of this study was to estimate risk factors of the adverse effects in a cohort of Spanish patients with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis.

Methods: A single institution, descriptive, retrospective, cohort study was developed from January 2009 to December 2016. Patients diagnosed with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis on biological therapies were included. Undesirable events affecting patients during biological therapy, their clinical implications and the use of health resources related to adverse effects were collected.

Results: Three hundred and sixty-two patients corresponding to 478 biological therapy lines were analysed. It implied 1192 years of monitoring. There were 57 adverse effects per 100 biological patient-years and 4.8 serious adverse effects per 100 biological patient-years. The only significant factor for a likely serious adverse effect was having a Charlson Index ≥10, OR of 6.2 (CI 95%: 3.4-11.1, p<0.001). Around 15% of patients with adverse effects were admitted to hospital and 25% received attention at the Emergency Department.

Conclusion: Over half of the patients with arthropathies on biological therapy can suffer adverse effect during treatment but only 8.5% of these effects are serious. Special vigilance must be paid to patients with a higher number of comorbidities because they are more likely to experience serious adverse effects.

Keywords: Biological therapy, safety, rheumatic diseases, risk factors

Introduction

Rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA) belong to the group of chronic inflammatory arthropathies (CIAs). The introduction of biological therapies (BTs) approximately two decades ago revolutionized the treatment of many diseases and, more specifically, of CIA. Despite the positive results of these new therapies, there is still some uncertainty in relation to response variability, long-term patient safety, and management in daily clinical practice. Several studies have been published on BT safety in CIA and in particular on the likely repercussions of the use of anti-tumor necrosis factor (anti-TNF) inhibitor drugs (2-5). The risk of infections (6-11), possible malignancy (12-14), adverse effects on the skin (15), or stroke (16) caused by these drugs has been referenced in recent publications.

Notwithstanding, no data have been found on the likely factors leading to a higher risk of adverse effects and on the actual consequences of these during the disease or its treatment. In addition, most published studies focus on serious adverse effects, so there is insufficient literature on all other adverse events.

In our study, we conducted an 8-year follow-up to a cohort of patients with CIA treated with BT on the adverse effects of their therapy at both secondary and primary care levels. This has allowed for a more detailed and comprehensive analysis of all adverse effects, both serious and mild. The study also helped to establish the likely risk factors for the development of any of these events and to estimate the consequences these can entail in clinical terms and in relation to hospital resource use. We believe that the results obtained can provide a thorough overview of the safety of BT in patients with CIA.
The objective of the present study was to estimate the risk factors of the adverse effects of BT in a cohort of Spanish patients with RA, AS, and PsA.

**Methods**

This was a single institution, descriptive, retrospective cohort study. All data on diseases and use of drugs were collected considering standard clinical practice from the hospital electronic medical records. The study was conducted from January 2009 to December 2016 at a tertiary referral hospital complex with a pharmacy department and a day hospital. The study compiled with the Personal Data Protection Act (Act 15/1999, dated December 13). All data were exclusively used for the purpose of the present study and are kept anonymous and confidential. The study was approved by the Research Ethics Committee of Pontevedra, Vigo, and Orense (code 2014/187). Informed consent was not required because some of the patients were already deceased at the time of the study and because data had been encrypted. Inclusion criteria for the study were: (1) diagnosis of RA, AS, or PsA according to the American College of Rheumatology 1987 (17), the classification criterion of the modified New York Assessment of Spondyloarthritides International Society (18-19), and the Classification Criteria for Psoriatic Arthritis (20), respectively, (2) follow-up by the Rheumatology Department, and (3) beginning of BT treatment as of January 2009 and no later than 6 months before the end of the study. Exclusion criterion was taking part in clinical trials either during the study or 3 months before its inception.

At the start of BT, the following variables were taken into account: demographic (age and sex), smoking habits, and clinical (diagnosis, length of disease evolution, and comorbidities)—analyzed and ranked according to the Charlson Index (21), analytical (C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and hemoglobin (Hb)), and disease activity parameters (Disease Activity Score and Bath Ankylosing Spondylitis Disease Activity Index).

In relation to BT, concomitant treatments at the start of BT (methotrexate, leflunomide, and glucocorticoids), dose regimen, route of administration, and number of BT lines (the length of time in which a patient is on a specific BT drug) were recorded.

An adverse effect was considered any undesirable event affecting patients during BT therapy suspect of being caused by the BT drug. These were classified according to their severity, as serious (requiring hospital admission, an extended hospital stay, permanent disability, or death) and mild (22), and to the type of adverse effect. Data were collected from the clinical records of the patients. When infections were identified, their location and clinical resolution were specified.

**Statistical analysis**

The Statistical Package for the Social Sciences program was used for statistical analysis. A descriptive analysis per disease and BT was made that included all variables considered. Quantitative variables were expressed as mean value±standard deviation (SD) for normal data distribution and as median and interquartile range (IR) for non-normal data distribution. Categorical variables were presented as absolute values and percentages. To establish differences, Student’s t-test, Mann-Whitney, and ANOVA or Kruskal-Wallis was used for quantitative variables, and chi-square test was used for qualitative variables. To evaluate the likely confounders that could affect the results of the study, a multivariate logistic regression analysis was conducted applying those variables that were significant in the univariate analysis. A p value <0.05 was considered as statistically significant.

All data were logged onto an Excel database that could be used and accessed by the study researchers only. Each BT line was assigned a code number to make patient identification impossible.

**Results**

A total of 362 patients were included in the study, which comprised 478 BT lines (250 lines in patients with RA, 119 lines in patients with AS, and 109 lines in patients with PsA). BT line median±SD was 1.7±1.1 per patient. Table 1 shows the characteristics of the patients in the study per disease. Patients with RA represent a more vulnerable population—they are older and present higher comorbidity.

The 478 BT lines comprised a total of 1192 years of monitoring corresponding to: 58 years of treatment with abatacept, 550 years of treatment with adalimumab, 39 years of treatment with certolizumab, 355 years of treatment with etanercept, 75 years of treatment with golimumab, 33 years of treatment with infliximab, 79 years of treatment with tocilizumab, and 1.5 years of treatment with ustekinumab. In 301 (63%) BT lines, there was evidence of some adverse effect in likely relationship with therapy. A total of 683 cases of adverse effects were recorded (57 adverse effects per 100 BT patient-years), of which 58 were considered serious (4.8 cases of serious adverse effects per 100 BT patient-years). A detailed description of the adverse effects of each BT is shown in Table 2.

Overall, all BTs showed a similar safety profile with bacterial infections being the most frequent adverse effect during the study. Certolizumab and abatacept had the highest number of bacterial infections, and infliximab had the lowest number of this type of infections (no significant statistical data available). The locations of infections as registered in patients’ records are shown in Figure 1.

In 455 (79.0%) cases, no information existed on the pathogen causing the infection, and in 16 (2.8%) cases, pathogen culture was negative. Bacteria most frequently isolated were *Escherichia coli* (21 infections, 3.6%), *Streptococcus* sp. (12 infections, 2.1%), and *Staphylococcus* sp. (7 infections, 1.2%). There were 57 opportunistic infections with *Herpes zoster* being the most frequent (13 infections, 2.3%).

Fungal and viral infections represented the second most frequent adverse effects in the study population. However, most of these were not serious, and only one patient had to be admitted as a result.

The occurrence of a cardiovascular adverse effect was 2 per 100 BT patient-years, with abatacept being the drug leading to more adverse effects of this type.

The study sample was divided into two groups: (1) patients who had an adverse effect and those who did not and (2) patients who had a serious adverse effect and those who did not. In the univariate study, disease-related aspects, such as disease duration, Hb value, and CRP or...
Table 1. General characteristics of the study population broken down per disease: Rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis.

|                          | RA (n=250) | AS (n=119) | PsA (n=109) | p  |
|--------------------------|------------|------------|-------------|----|
| **Age (year), mean±SD**  | 53.8±13.9  | 42.6±12.2  | 47.6±12.1  | 0.000 |
| **Sex, n (%)**           |            |            |             |     |
| Female                   | 173 (69.2) | 25 (21.0)  | 58 (5.2)    | 0.000 |
| Male                     | 77 (30.8)  | 94 (79.0)  | 51 (46.8)   |     |
| **Length of disease evolution in years, mean±SD** | 8.6±7.8 | 7.6±8.2 | 8.0±8.1 | 0.057 |
| **Comorbidities (Charlson Index)** |          |            |             |     |
| Between 0 and 3          | 70 (28.0)  | 56 (47.4)  | 45 (41.3)   | 0.000 |
| Between 4 and 9          | 121 (48.4) | 51 (42.8)  | 52 (47.7)   |     |
| ≥10                      | 59 (23.6)  | 12 (10.0)  | 12 (11.0)   |     |
| **Smoker, n (%)**        |            |            |             |     |
| Yes                      | 40 (16.0)  | 32 (26.8)  | 23 (21.1)   | 0.017 |
| No                       | 135 (54.0) | 54 (45.3)  | 38 (34.8)   |     |
| No data available        | 75 (30.0)  | 33 (27.7)  | 48 (44.0)   |     |
| **DAS28/BASDAI, mean±SD**| n=134     | n=67       | n=36        | ~d  |
|                          | 5.2±1.1    | 6.0±1.6    | 5.2±1.5     |     |
| **ESR (mm/h), median (IR)** | n=235  | n=112      | n=100       | 0.000 |
|                          | 28 (2–140) | 13 (1–140) | 19 (1–101)  |     |
| **CRP (mg/l), median (IR)** | n=232 | n=116      | n=96        | 0.039 |
|                          | 9 (0–144)  | 7 (0–120)  | 5 (0–143)   |     |
| **Hemoglobin (mg/dl), mean±SD** | n=243 | n=115      | n=103       | 0.000 |
|                          | 13.1±1.5   | 14.2±1.5   | 13.2±1.6    |     |
| **Concomitant MTX, n (%)** | n=247  | n=76       | n=109       | 0.000 |
|                          | 126 (51.0) | 6 (7.9)    | 54 (49.5)   |     |
| **Concomitant leflunomide, n (%)** | n=237 | n=116      | n=108       | 0.000 |
|                          | 32 (13.5)  | 1 (0.9)    | 8 (7.4)     |     |
| **Concomitant GC, n (%)** | n=242   | n=117      | n=104       | 0.000 |
|                          | 204 (84.3)| 19 (16.2)  | 62 (59.6)   |     |
| **Daily GC dose (mg), mean±SD** | n=242  | n=117      | n=104       | 0.000 |
|                          | 7.4±5.7    | 1.4±3.6    | 4.6±5.1     |     |
| **Biological therapy, n (%)** |         |            |             |     |
| Adalimumab               | 82 (32.8)  | 58 (48.7)  | 56 (51.4)   | ~f  |
| Etanercept               | 65 (26.0)  | 43 (36.1)  | 29 (26.6)   |     |
| Abatacept                | 34 (13.6)  | 0 (0.0)    | 0 (0.0)     |     |
| Tocilizumab              | 28 (11.2)  | 0 (0.0)    | 3 (2.8)     |     |
| Infliximab               | 7 (2.8)    | 1 (0.8)    | 4 (3.7)     |     |
| Golimumab                | 15 (6.0)   | 13 (10.9)  | 11 (10.1)   |     |
| Certolizumab             | 19 (7.6)   | 4 (3.4)    | 3 (2.8)     |     |
| Ustekinumab              | 0 (0.0)    | 0 (0.0)    | 3 (2.8)     |     |

The total number of BT lines was 478. The values in this table represent the number of lines for which data were available. AS: ankylosing spondylitis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CRP: C-reactive protein; DAS28: Disease Activity Index 28; ESR: erythrocyte sedimentation rate; GC: glucocorticoid; IR: interquartile range; n: number of BT lines; PsA: psoriatic arthritis; RA: rheumatoid arthritis; SD: standard deviation.

*Values were considered statistically significant when p<0.05.

†Validated index to measure prognostic comorbidity in clinical studies

‡Active smoker at the beginning of biological treatment

§No statistical test could be used because of the differences between the scores applied in each disease.

‖All glucocorticoid doses were converted to an equivalent prednisone dose.

Test could not be conducted because some of the observed values in each cell were<5.

Discussion

According to our results, patients on BT treatment whose drugs are administered every 7 or 14 days are at a higher risk of suffering any adverse effect. This could be the result of injection-related reactions. However, when only serious adverse effects are considered, patients with multiple comorbidities are at a higher risk of a hospital admission, a longer hospital stay, or death.

Our study shows that infections are the most frequent adverse effect in patients with CIA on BT treatment. According to data from the Spanish Registry BIOBADASER (6), the number of infections for every 1000 patient-years was estimated at 53.1. The registry found that the most frequent infections were pneumonia, cystitis, tuberculosis, and skin and joint infections. The infection percentage obtained by the registry is significantly lower than that reached in our study (39 bacterial infections per 100 BT patient-years). This might be because their data are dependent on notification from ESR at the onset of the study, did not have an impact in relation to adverse effects.
clinicians, and thus all those infections are likely to be severe. The infection profile from the registry also varies in relation to our data (in our study, respiratory and genitourinary infections were the most frequent) possibly due to the same factor.

Viral and fungal infections were the second and third most frequent causes of adverse effects (51 and 52 cases per 100 BT patient-years, respectively). No data supporting this frequency have been found as published data are based on serious adverse effects frequency only. However, according to the published literature, the risk of opportunistic infections in these patients is higher than that in a healthy population. Herpes zoster is the most frequent pathogen in these types of infections (23). Our study recorded a total of 4 patients diagnosed with tuberculosis (0.3 cases per 100 BT patient-years). This value is similar to published data in Spain: 3.5 cases per 1000 patient-years in Spain (6), although according to the British Registry, the rate of tuberculosis in patients with RA on BT treatment is 38 cases per 100,000 patient-years (23).

### Table 2. Adverse effects of each biological therapy.

| Description                                | ABA          | ADA          | CER          | ETA          | GOL          | INF          | TOC          | UST          | Total         |
|--------------------------------------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|---------------|
| **N=55**                                   | **N=196**    | **N=26**     | **N=137**    | **N=39**     | **N=12**     | **N=31**     | **N=3**      | **N=478**    |               |
| Bacterial infection, n (e)                 | 40 (68.5)    | 209 (38.0)   | 32 (81.5)    | 123 (34.6)   | 33 (43.8)    | 8 (24.0)     | 23 (29.3)    | 1 (66.7)     | 469 (39.3)    |
| Viral infection, n (e)                     | 5 (8.6)      | 22 (4.0)     | 7 (17.8)     | 9 (2.5)      | 3 (4.0)      | 3 (9.0)      | 2 (2.5)      | 0 (0)        | 51 (4.3)      |
| Fungal infection, n (e)                    | 5 (8.6)      | 0 (0)        | 2 (5.1)      | 17 (4.8)     | 6 (8.0)      | 0 (0)        | 2 (2.5)      | 0 (0)        | 52 (4.3)      |
| Infusion-injection-related response, n (e) | 2 (3.4)      | 15 (2.7)     | 0 (0)        | 13 (3.7)     | 1 (1.3)      | 0 (0)        | 0 (0)        | 0 (0)        | 31 (2.6)      |
| Cardiovascular disorders, n (e)            | 7 (12.0)     | 0 (0)        | 1 (2.5)      | 9 (2.5)      | 2 (2.7)      | 0 (0)        | 0 (0)        | 0 (0)        | 28 (2.3)      |
| Dermal toxicity, n (e)                     | 1 (1.7)      | 6 (1.1)      | 0 (0)        | 3 (0.8)      | 2 (2.7)      | 0 (0)        | 1 (1.3)      | 0 (0)        | 13 (1.1)      |
| General symptoms, n (e)                    | 3 (5.1)      | 3 (0.5)      | 2 (5.1)      | 3 (0.8)      | 0 (0)        | 1 (3.0)      | 0 (0)        | 0 (0)        | 12 (1.0)      |
| Solid tumors, n (e)                        | 0 (0)        | 4 (0.7)      | 0 (0)        | 1 (0.3)      | 0 (0)        | 0 (0)        | 0 (0)        | 0 (0)        | 5 (0.4)       |
| Tuberculosis, n (e)                        | 0 (0)        | 0 (0)        | 1 (2.5)      | 1 (0.3)      | 0 (0)        | 2 (6.0)      | 0 (0)        | 0 (0)        | 4 (0.3)       |
| Interstitial lung disease, n (e)           | 0 (0)        | 3 (0.5)      | 0 (0)        | 1 (0.3)      | 0 (0)        | 0 (0)        | 0 (0)        | 0 (0)        | 4 (0.3)       |
| Hematological toxicity, n (e)              | 0 (0)        | 0 (0)        | 1 (2.5)      | 3 (0.8)      | 0 (0)        | 0 (0)        | 0 (0)        | 0 (0)        | 4 (0.3)       |
| Hematological tumor, n (e)                 | 0 (0)        | 2 (0.3)      | 0 (0)        | 0 (0.00)     | 0 (0)        | 0 (0)        | 0 (0)        | 0 (0)        | 2 (0.2)       |
| Liver toxicity, n (e)                      | 0 (0)        | 1 (0.1)      | 0 (0)        | 0 (0)        | 0 (0)        | 0 (0)        | 1 (1.3)      | 0 (0)        | 2 (0.2)       |
| Respiratory system disorders, n (e)        | 0 (0)        | 0 (0)        | 0 (0)        | 1 (0.3)      | 1 (1.3)      | 0 (0)        | 0 (0)        | 0 (0)        | 2 (0.2)       |
| Anaphylaxis, n (e)                         | 0 (0)        | 0 (0)        | 0 (0)        | 1 (0.3)      | 0 (0)        | 0 (0)        | 0 (0)        | 0 (0)        | 1 (0.1)       |
| Psychiatric disorders, n (e)               | 0 (0)        | 1 (0.2)      | 0 (0)        | 0 (0)        | 0 (0)        | 0 (0)        | 0 (0)        | 0 (0)        | 1 (0.1)       |
| Lipidic disorders, n (e)                   | 0 (0)        | 0 (0)        | 0 (0)        | 0 (0)        | 0 (0)        | 0 (0)        | 1 (1.3)      | 0 (0)        | 1 (0.1)       |

Total, n (e) 63 (107.9) 266 (48.3) 46 (117.2) 186 (52.3) 48 (63.8) 14 (41.9) 30 (38.2) 1 (66.7) 683 (57.3)

ABA: abatacept; ADA: adalimumab; CER: certolizumab; ETA: etanercept; GOL: golimumab; INF: infliximab; n: number of BT lines; n (e): number of adverse effects (number of adverse effects per 100 patient-years of BT); TOC: tocilizumab; UST: ustekinumab.

Figure 1. Location of infections in chronic inflammatory arthropathies and biological therapy patients.
Table 3. Differences between BT lines in patients who had an adverse effect and those who did not and patients who had a serious adverse effect and those who did not (univariate study).

|                          | Total of adverse effects | Serious adverse effects |
|--------------------------|--------------------------|-------------------------|
|                          | Yes n=301                | No n=177                | Yes n=58 | No n=420 | p\(^a\) |
| Age, n (%)               |                          |                         |          |          |        |
| <65 years                | 250 (83.1)               | 148 (8.6)               | 0.490    | 38 (65.5) | 360 (85.7) | <0.001 |
| ≧65 years                | 51 (16.9)                | 29 (16.4)               |          | 20 (34.5) | 60 (14.3)   |        |
| Sex, n (%)               |                          |                         |          |          |        |
| Female                   | 167 (55.5)               | 89 (50.3)               | 0.157    | 33 (56.9) | 223 (53.1) | 0.344  |
| Male                     | 134 (44.5)               | 88 (49.7)               |          | 25 (43.1) | 197 (46.9) |        |
| Smokerb, n (%)           |                          |                         |          |          |        |
| Yes                      | 60 (28.8)                | 35 (30.7)               | 0.411    | 6 (13.0)  | 89 (32.2)  | 0.005  |
| No                       | 148 (71.2)               | 79 (69.3)               |          | 40 (87.0) | 187 (67.8) |        |
| Pathology, n (%)         |                          |                         |          |          |        |
| RA                       | 164 (54.5)               | 86 (48.6)               | 0.363    | 38 (65.5) | 212 (50.5) | 0.084  |
| AS                       | 69 (22.9)                | 50 (28.2)               |          | 9 (15.5)  | 110 (26.2) |        |
| PsA                      | 68 (22.6)                | 41 (23.2)               |          | 11 (19.0) | 98 (23.3)  |        |
| Comorbidity (Charlson Index)c, n (%) |                |                         |          |          |        |
| Between 0 and 9          | 242 (80.7)               | 152 (85.9)              | 0.092    | 30 (51.7) | 364 (86.9) | <0.001 |
| ≧10                      | 58 (19.3)                | 25 (14.1)               |          | 28 (48.3) | 55 (13.1)  |        |
| BT type, n (%)           |                          |                         |          |          |        |
| Anti-TNF group           | 258 (85.7)               | 152 (85.9)              | 0.538    | 45 (77.6) | 365 (86.9) | 0.049  |
| No anti-TNF group        | 43 (14.3)                | 25 (14.1)               |          | 13 (22.4) | 55 (13.1)  |        |
| BT dose optimization, n (%) |                          |                         |          |          |        |
| Optimized                | 79 (26.2)                | 43 (24.3)               | 0.359    | 16 (27.6) | 106 (25.2) | 0.404  |
| Not optimized            | 222 (73.8)               | 134 (75.5)              |          | 42 (72.4) | 314 (74.8) |        |
| BT dose regimen at onset, n (%) |                |                         |          |          |        |
| Every 7 days or 14 days  | 251 (83.4)               | 132 (74.6)              | 0.014    | 46 (79.3) | 337 (80.2) | 0.493  |
| Every ≧28 days           | 50 (16.6)                | 45 (25.4)               |          | 12 (20.7) | 83 (19.8)  |        |
| Place of BT administration, n (%) |             |                         |          |          |        |
| Outside of hospital      | 271 (90.0)               | 153 (86.4)              | 0.147    | 49 (84.5) | 375 (89.3) | 0.191  |
| At day hospital          | 30 (10.0)                | 24 (13.6)               |          | 9 (15.5)  | 45 (10.3)  |        |
| Concomitant MTX at onset, n (%) |                |                         |          |          |        |
| Yes                      | 120 (44.9)               | 66 (40.0)               | 0.182    | 29 (55.8) | 157 (41.3) | 0.035  |
| No                       | 147 (55.1)               | 99 (60.0)               |          | 23 (44.2) | 223 (58.7) |        |
| Concomitant GC at onset, n (%) |                |                         |          |          |        |
| Yes                      | 176 (60.7)               | 109 (63.0)              | 0.346    | 37 (68.5) | 248 (60.5) | 0.166  |
| No                       | 114 (39.3)               | 64 (37.0)               |          | 17 (31.5) | 161 (39.4) |        |
| Concomitant leflunomide at onset, n (%) |               |                         |          |          |        |
| Yes                      | 21 (8.0)                 | 9 (5.6)                 | 0.227    | 5 (9.8)   | 25 (6.7)   | 0.284  |
| No                       | 242 (92.0)               | 153 (94.4)              |          | 46 (90.2) | 349 (93.3) |        |
| No. of BT lines, n (%)   |                          |                         |          |          |        |
| First-line               | 184 (61.1)               | 92 (52.0)               | 0.032    | 30 (51.7) | 246 (58.6) | 0.198  |
| Second and successive lines | 117 (38.9)              | 85 (48.0)               |          | 28 (48.3) | 174 (41.4) |        |

The percentage values were calculated by dividing the number of events by the total number of adverse or non-adverse effects.

Anti-TNF: anti-tumor necrosis factor; PsA: psoriatic arthritis; RA: rheumatoid arthritis; AS: ankylosing spondylitis; GC: glucocorticoid; MTX: methotrexate; n: number of patients; BT: biological therapy.

*p<0.05 was considered statistically significant.

Active smoker at onset of BT.

Validated index to measure prognostic comorbidity in clinical studies.
Dermatological and other types of reactions related to BT injection or infusion are a very significant factor in relation to safety of this type of therapies, and all of them share a degree of toxicity in this regard (24). BT administered intravenously has shown infusion reactions with a frequency of 0.6 cases per 100 patient-years for abatacept and of 1 case per 100 patient-years for tocilizumab (25). These data are similar to those obtained in our study. In the case of infliximab, no infusion reaction was detected in our patients notwithstanding the fact that such type of reaction has been described in the published literature (26) as have dermatological reactions in subcutaneously administered BT (27). In our study, both adalimumab and etanercept showed a similar number of reactions related to the injection, whereas other BT drugs that have been commercialized more recently (e.g., golimumab, certolizumab, abatacept, tocilizumab, or ustekinumab) did not have such an adverse effect. This could be explained by the improved administration device of more recently marketed BT.

Patients with RA have an increased risk of suffering a cardiovascular disease (48% higher than the non-RA population) due to the inflammation usually caused by the disease and to lipidic disorders (28). In some studies, the use of anti-TNF drugs has resulted in a decrease in cardiovascular risks according to surrogate markers of the disease (blood pressure or ventricular mass index) (29, 30). However, high-density lipoprotein-cholesterol and low-density lipoprotein-cholesterol levels increase according to another study (31). The cardiovascular effect of no anti-TNF drugs has raised some controversy because when tocilizumab was first introduced into the market, several cases of lipidic parameters increase occurred although this did not result in any cardiovascular event (32, 33). However, a different study in which abatacept was compared with anti-TNF drugs concluded that the latter presented an increased cardiovascular risk of 28% higher than abatacept (34). In our study, the BTs that were associated with a higher number of cardiovascular events were etanercept and abatacept, suggesting that this type of adverse effect is not related to drug class. However, the sample size of our cohort is too small to draw conclusions on this.

Another safety aspect characteristic of patients with CIA is a higher risk of malignancy (35-36). The increase of solid tumor risks in BT patients is an area of contention. However, the use of anti-TNF drugs could have a real influence in the case of hematological cancers (14).

During our study, 5 solid tumors (2 lung carcinomas, 1 prostate cancer, 1 breast cancer, and 1 benign uterine leiomyoma) appeared, all of them in anti-TNF patients. During the study, a total of 2 hematological cancers (1 acute myeloid leukemia and 1 follicular lymphoma) were diagnosed. Although no clear relationship can be established between the development of these types of cancer and BT, monitoring of this type of patients is essential to continue collecting long-term safety-related data.

One of the limitations of our study could be that given its limited sample size, we may not have detected all confusion factors.

No publication has been found to compare the predicting factors of adverse effects of BT. Data collected for our study suggest that their impact at the healthcare service is significant and these aspects should be taken into consideration in the daily management of these patients.

Bacterial infection is the most frequent adverse effect in patients with CIA on BT. Over half of these patients can suffer some adverse effect during treatment, but only 8.5% of these are serious. Health professionals must make a special monitoring of patients with chronic arthropathies on BT with multiple medical comorbidities due to the higher risk of adverse effects. This could lead to the prevention and early detection of adverse effects, which would contribute to reduce the use of health resources in these patients.

**Ethics Committee Approval:** Ethics Committee Approval was received from the Research Ethics Committee of Pontevedra, Vigo, and Orense (code 2014/187).

**Informed Consent:** Informed consent was not required because some of the patients were already deceased at the time of the study and because data had been encrypted.

**Peer-review:** Externally peer-reviewed.

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