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Prevalence and risk factors of infections (excluding tuberculosis) in patients on biotherapy: RBSMR registry

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Abstract: Introduction: *Biologics are used for the treatment of Rheumatoid arthritis (RA), spondylarthritis (SpA) and many other conditions. While the efficiency of biologics has been established, there are adverse effects, which are dominated by infections.* ***Objectives:*** *To assess the prevalence of infections (excluding tuberculosis) in patients with chronic inflammatory rheumatic diseases undergoing biotherapy and to identify infection's predicting factors.* ***Materials and methods :*** *A prospective observational study was carried out on the inclusion on patients followed for chronic inflammatory rheumatic diseases: patients SpA according to ASAS classification criteria 2010 and RA according to ACR/EULAR classification criteria 2009 who were under biotherapy included in the Moroccan RBSMR registry. All the characteristics have been compared between two groups: patients who developed an infection and patients who did not.* ***Results :*** *Among 419 patients, 194 patients had spondylarthritis and 225 had RA. For patients with spondylarthritis the infection rate was estimated at 8.6% (17 patients); they were dominated by urinary tract and respiratory infections. 14 patients (6.2%) with RA presented infections; they were dominated by the ENT sphere, respiratory and urinary tract infections. The data we gathered are consistent with those in the literature; no factors associated with the infection have been found. The bi-variate analysis did not reveal any statistically significant difference between the groups.* ***Conclusion:*** *The literature data suggests that patients with chronic inflammatory rheumatic diseases undergoing biotherapy present an infectious risk. Our study proves that it increases morbidity and mortality risk. In order to screen for infection associated factors, monitoring during follow-ups is required.*

Keywords Spondylarthritis, Rheumatoid arthritis, Infections, Associated factors, RBSMR registry

Abbreviations

Anti CCP = Anti-cyclic citrullinated antibodies
ASAS = Assessment of Spondylarthritis International Society
ASDAS = Ankylosing Spondylitis Disease Activity Score
BASDAI = Bath Ankylosing Spondylitis Disease Activity Index

BASFI = Bath Ankylosing Spondylitis Functional Index

cDMARDs = Conventional disease-modifying anti-rheumatic drugs

CRP = C - reactive protein

DAS = Disease activity score

DMARDs = Disease-Modifying Anti-Rheumatic Drugs
ENT sphere infections: ear, nose and throat infections
ESR = Erythrocyte Sedimentation Rate

HAQ = The Health Assessment Questionnaire
HLA = Human Leukocyte Antigen

NSAIDs = Refractory Nonsteroidal Anti-Inflammatory Drugs
RA = Rheumatoid Arthritis

RBSMR = Register of Biotherapies of the Moroccan Society of Rheumatology

RF = Rheumatic Factor
CIRD = Chronic Inflammatory rheumatic Disease
SpA = SpondylArthritis

Introduction

Rheumatoid arthritis (RA) and spondylarthritis (SpA) are the most frequent and severe chronic inflammatory rheumatic diseases (SCI) [1]. They are well known for the functional limitations that they can induce as well as for their deleterious impact on the quality of life of those affected [2].

Patients with CIRD chronic inflammatory rheumatic disease have a higher infectious risk than healthy subjects [3]. Therefore, higher risks of infectious morbidity and mortality may be incurred by these patients which may be caused by disease related immune dysfunction [4], or by the immunosuppressive effects of therapeutic agents [5]. Infections are generally dominated by respiratory and urinary infections [6, 7]. The main objective of the present work was to review the safety of the biologics available for the treatment of CIRD and to identify the predictive factors of infection in patients on biologics.

Materials and methods

The RBSMR registry

The RBSMR (**R**egistre des **B**iotherapies de la **S**ociété **M**arocaine de **R**humatologie) is a registry of biological therapies in rheumatic diseases of the Moroccan Society of Rheumatology. It is a prospective and multicenter registry, which includes ten departments of rheumatology in the university hospitals of Morocco. The patients entered in the registry are over 18 years old and gave their prior written consent for publication. They were diagnosed for Rheumatoid Arthritis (RA) or Spondylarthritis (SpA) and treated by biotherapy. The inclusion period was from May 2017 to January 2019 and follow-up was 3 years. 440 patients were included in the study, among which 419 patients were validated (225 RA and 194 SpA). The other objectives were to identify the most common side effects in daily practice, to evaluate the effectiveness of biotherapies in Rheumatology and to evaluate the impact of biotherapies on the patients' quality of life. The protocol for the original study was approved by the Ethics Committee of the Faculty of Medicine (Mohammed V, Rabat University (Reference: CERB: 117/17)), as well as the National Committee for the Protection of Personal Data (reference: CNDP: A-RS-308/2017) [8].

Study design and population

Our work is an observational study on patients followed for chronic inflammatory rheumatic disease: SpA and RA under biotherapy included in the RBSMR registry. Our study was conducted at the inclusion of the patients, during this period we proceeded gradually, with many evaluations at 6 months, 12 months and 18 months of treatment.

To this end, the following information from the patient registry was recorded:

- Age, Sex, place of residence (urban or rural), level of education, occupational activity, ethnicity, alcohol and tobacco consumption were also collected.
- Characteristics of RA: We analyzed the family history of RA, the seropositive or seronegative nature of RA assessed by the presence or absence of rheumatic factor (RF) and anti-cyclic citrullinated antibodies (anti CCP), the activity of the disease assessed by the DAS (Disease activity score). Inflammatory syndrome (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), the functional effect of RA which was evaluated by the HAQ (The Health Assessment

Questionnaire). The use of different types of biotherapies in association or not with CDMARDS, as well as the use or not of corticosteroids.

- Characteristics of SpA: We analyzed: the family history of SpA, the duration of development of the disease, the clinical characteristics, the extra-articular manifestations, the disease activity evaluated by the BASDAI (Bath Ankylosing Spondylitis Disease Activity Index). The disease was considered active if BASDAI ≥4. The disease severity defined by the presence of at least one of these criteria: (young age of onset, smoking, coxitis, extra articular manifestations, refractory nonsteroidal anti-inflammatory drugs (NSAIDs), inflammatory Syndrome (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) taken together), and the functional effect of SpA evaluated by the BASFI: Bath Ankylosing Spondylitis Functional Index) in a valid Moroccan version [9]. Use of different treatment modalities: current and previous use of NSAIDs, disease-modifying antirheumatic drugs (DMARDs) and biological therapy.

We divided the patients into 2 groups: patients who presented an infection under biotherapy and patients who did not. The comparison of the two groups has been made on inclusion of the patients.

Statistical analysis

The statistical study was conducted according to the database frozen in January 2019. The statistical analysis was performed using an SPSS (Statistical Package for the Social Sciences) Version 20, with the use of student's khi 2 tests and logistic regression. an overall description of the study population and a bi Analysis and Multivariate were performed and p values less than 0.05 were considered statistically significant.

Results

Among 419 patients included in this study, 194 patients had spondylarthritis and 225 patients had rheumatoid arthritis.

For SpA: A total of 194 patients were included in the study. The average age of all SpA patients was 40.22 years ± 13.68 [18, 69] with a sex ratio Man/Woman equal to 1.7 (123 men and 71 women). In this study 10, 8 % of patients were chronic smokers and 14, 5 % of our patients had a family history of SpA. The mean duration of the disease was 615, 9 weeks ± 349, 12 [104, 2012]. Concerning clinical features, 96.4% of our patients had axial involvement, 70% had peripheral involvement and 61.5% had enthesic involvement. As extra-articular manifestations, 10, 7 % of patients had inflammatory bowel disease and 6, 9 % had psoriasis. Concerning biological features, the mean ESR and CRP were (respectively) 39, 04 mm H1± 27,16 [2, 113] and 32, 87 mg/l ± 38, 77 [0, 334], respectively. HLA B27 was positive in 34 % of patients. Regarding the SpA activity and functional impact, the average ASDAS CRP, BASDAI and BASFI were (respectively) 3,40 ± 1,44 [0, 7.5]; 4,8 ± 1,8 [0, 9] and 5,29 ± 2,21 [0, 10], respectively. SpA was radiographic in 88.1 % of the cases and coxitis was seen in 40.9 %. Concerning the treatment inflicted, 52, 4 % of patients were under NSAIDs and 56, 3 % were under cDMARDs.

Concerning the biological treatment, 33% of cases (64 patients) were on Etanercept, 30.40% of cases (58 patients) were on Adalimumab, 13.40 % of cases (26 patients) were on Infliximab (REMICADE), 12.90% of cases (25 patients) were on Infliximab (REMSIMA), 9.80% of cases (19 patients) were on Golimumab, 1.50% of cases (2 patients) were on Secukinumab

In this group of patients with SpA, the frequency of infections was estimated at 8.6%, i.e., 17 patients : 14 patients had presented a bacterial infection: (5 patients presented an urinary tract infection, 3 patients presented a respiratory infection, 2 patients presented a digestive infection, 2 patients presented an ENT infection, 1 patient presented an articular infection and 1 patient presented a skin abscess), 2 patients presented a viral infection: (1 patient having presented chickenpox and 1 patient having presented shingles), while 1 patient presented a fungal infection. Note that all the patients were on anti-TNF alpha: 7 patients on Adalimumab, 5 patients on Etanercept, 4 patients on Infliximab: 3 patients on REMICADE, 1 patient on REMSIMA, and 1 patient on Golimumab.

The bivariate analysis did not reveal any factors associated with the onset of infection in spondylarthritis patients undergoing biotherapies, in particular with regard to average age ($p = 0.29$), gender ($p = 0.57$), duration of disease progression ($p = 0.21$), comorbidities ($p = 0.14$), presence of HLA B 27 ($p = 0.325$), axial involvement ($p = 0.483$) , radiographic spondylarthritis ($p = 0.607$), ASDAS CRP ($p = 0.37$), taking CDMARDS ($p = 0.06$), taking corticosteroids ($p = 0.067$), the duration of taking biological ($p = 0.09$) (Table 1)

For patients with rheumatoid arthritis: the average age was 54.94 years ± 11.3 [18, 69], the sex ratio woman / man (W / M) was 7. The rheumatoid factor was positive in 85.3% of cases, Anti-CCP was positive in 67.1% of cases, mean DAS CRP was 3.5 +/- 0.7. 79.2% of patients were on corticosteroid therapy and 92% of cases were on cDMARDS.
Compared to biologicals, 60.30% of cases or 135 of patients were on Rituximab, 23.20% of cases or 52 of patients were on Tocilizumab, 8% of cases or 18 patients were on Etanercept, 6.30% of cases or 14 patients were on Adalimumab, 0.90% of cases or 2 patients were on Infliximab (REMICADE), 0.90% of cases or 2 patients were on Infliximab (REMSIMA) and 0.90% of cases or 2 patients were on Golimumab.

14 patients with Rheumatoid arthritis presented infections under biotherapy, i.e. 6.2% of cases: with 5 cases presenting an infection of the ENT sphere, 3 cases presenting a respiratory infection, 3 cases presenting an urinary tract infection, 1 case with digestive infection and 2 cases with skin infection (1 case with erysipelas and the other with folliculitis).

Compared to biologicals: 6 patients were on Rituximab, 4 patients were on Tocilizumab, 4 patients were on anti-TNF alpha (2 patients were on Adalimumab and 2 patients were on Etanercept).

The bivariate analysis did not show any predictive factors for infection in patients with rheumatoid arthritis. In particular with regard to the average age (p = 0.817), gender (p = 0.5), comorbidities (p = 0.633), rheumatoid factor positivity (p = 0.36), inflammatory syndrome: CRP (p = 0.194), sedimentation rate (p = 0.49), functional impact HAQ (p = 0.714), activity evaluated by DAS CRP (p = 0.115), corticosteroid intake (p = 0.067), cumulative dose of corticosteroids (p = 0.068), duration of biotherapy (p = 0.059) (table 2).

Discussion

The chemical therapeutic arsenal of spondylarthritis which remains active despite the use of conventional treatments has been enriched by anti TNF alpha that were the first molecules available, and then by other molecules including anti IL 17 (Secukinumab). [10]. In our study, the frequency of infections for patients with spondylarthritis was estimated at 8.6%.

Seauve had carried out a systematic review of the literature in the Pubmed and Cochrane databases until March 2021 concerning patients with spondyloarthropathy, who were put on biologicals and had presented an infection, a meta-analysis had first shown that the infectious risk is very high especially with anti TNF alpha with an RR at 1.23 and with Secukinumab with an RR at 1.28 and secondarily that these infections were mainly pulmonary and ENT [11]. On the other hand, Hynes et al. also carried out a study on 8722 patients and found that there were statistically significant increase in infection rates for infections on Secukinumab versus placebo for upper respiratory tract infections, nasopharyngitis and all infections [12]. The relative risks for secukinumab versus placebo were 1.57 (1.19 to 1.97) and the absolute risk was 1.79% [12]. The number needed to harm was 56, 24 and 29 for URTI, nasopharyngitis and all infections, respectively. [12]

Our study had objectified that all the spondylarthritis patients having presented an infection were all under an anti-TNF alpha. Moreover, no patient had presented an infection under Secukinumab, therefore our results compared to Secukinumab are not consistent with the literature; this could be due to the too small number of patients who were put on Secukinumab in our study or to the Moroccan context. Our results also showed that bacterial infections were the most frequent with 14 cases, followed by viral infections with 2 cases and by fungal infections with a single case.

Currently, several biological molecules are available for the treatment of severe forms of Rheumatoid arthritis resistant to conventional DMARDs, including Rituximab, anti-TNFα and anti-IL6 [13]. Patients with RA have also a higher infectious risk than healthy people [3]. In our study, the frequency of infections for those patients was estimated at 6.2 %.

We have also shown that for patients with Rheumatoid arthritis, Rituximab had the highest rate of infection occurrence for 6 cases, followed by Tocilizumab and anti-TNF alpha (Adalimumab: 2 cases and Etanercept: 2 cases) with similar rates (4 cases). Moreover, it was shown that the ENT sphere infections were the most frequent followed by Respiratory and urinary tract infections. Gottenberg had carried out a study on 4498 Rheumatoid arthritis patients who had been put on biological (Abatacept, Tocilizumab, Rituximab) with a follow-up of 02 years. At month 24, 513 patients (6.7 / 100 patient-years) had experienced at least one of the adverse events of specific interest including serious infection: 255 in the Rituximab registry (7.3 / 100 patient-years), 116 in the Abatacept registry (6.4 / 100 patient-years), and 142 in the Tocilizumab registry (6.0 / 100 patient / years) [13], which is consistent with our results showing higher incidence in patients on Rituximab. Furthermore, in this study, the 2nd position was ensured by Tocilizumab and the 3rd position by Abatacept [14].
Rekik et al. carried out a study of 120 files over a period of 6 years. Among the 120 files included, they had identified 21 infections in 16 patients (13.33%) who presented at least one infection under biotherapy, 11 patients presenting a Rheumatoid arthritis and 5 patients having a spondylarthritis [15]. The infections occurred under Infliximab in 38% of cases, under Etanercept in 23.8% of cases, under Adalimumab in 9.5% of cases (i.e., a total of 71.42% of cases under anti-Tumor Necrosis Factor), under Tocilizumab in 23, 8% of cases and under Rituximab in 4.76% of cases. The infection was of bacterial origin in 76.19% of cases: 7 urinary tract infections (including 5 under Infliximab, one under Tocilizumab and one under Rituximab), 2 bronchial infections (one under Etanercept and the other on Tocilizumab), 2 pulmonary tuberculosis (one on Infliximab and the other on Tocilizumab), sore throat

(on Infliximab), tuberculous septic arthritis of the elbow (on Etanercept), liver abscess (on Adalimumab), knee abscess (on Etanercept) and ungueal whitlow (on Infliximab) [15]. A viral origin of the infection was noted in 14.28% of cases: 2 cases of shingles (one under Adalimumab and the other under Etanercept) and pulmonary virosis (under Etanercept). Fungal infections were noted in 2 cases: oral candidiasis and skin dermatophyte (both under Tocilizumab) [15]. Therefore, the infections reported in this series were much more frequent under anti-tumor necrosis factor treatment, which is consistent with our results obtained in patients with spondylarthritis, followed by Tocilizumab while Rituximab was the biologic treatment with the least infectious side effects; bacteria are the most implicated pathogens in this series and infections are dominated by urinary and respiratory tract infections, which is consistent with the results of our study. In this series the C-reactive protein was frequently elevated unlike the number of white blood cells whose elevation does not appear correlated with infections [15].

Maatallah et al. did a 36-month study of 298 patients (175 RA and 123 SpA) who received biologicals. Anti-TNFs were prescribed in 87.9% of patients: (24.5% Etanercept; 21.6% Infliximab, 26.2% Adalimumab, 27.7% Certolizumab), Tocilizumab in 10.4% of patients and Rituximab in 5% of patients. An infection under biotherapy was recorded in 9 patients (3.1%) with 13 infectious episodes: a pulmonary infection in 38% of cases, urinary infection in 15% of cases, skin infection in 23% of cases, ENT infection in 8% of cases and cardiac one in 8% of cases [16]. The infection was bacterial in 92.3% of cases and viral in 7.7% of cases [16]. No fungal infection has been identified. Infections were significantly more frequent with Tocilizumab than with anti-TNF and Rituximab. Moreover, bacterial infections were the most reported [16].

Pinheiro had carried out a study until August 2019 including 88 patients with RA and 20 patients with SpA. Infections were noted in 23.1% under Etanercept, 21.5% under Rituximab, 19% under Adalimumab, 17% under Tocilizumab, 10.7% under Golimumab, 8.3% under Infliximab 2.3% under Certolizumab and 0 .8% under Abatacept [17]. This study also demonstrated that the risk of severe infection seems to be determined mainly by concomitant corticosteroid therapy, in a dose-dependent manner, with no difference depending on the bDMARDs [17].

Derbel et al. studied the profile of infectious complications in 31 patients with CIRD treated with biotherapy over a period of 11 years. The molecules used were Infliximab in 17/31 cases (54.8%), Etanercept in 5/31 cases (16.1%), Rituximab in 5/31 cases (16.1%) and Adalimumab in 4/31 cases (12.9%) [18]. Among the 31 patients treated with biotherapy, 11 infectious complications were identified in 9 patients [18]. The indications for biotherapies were Crohn's disease, Rheumatoid arthritis and Ankylosing spondylarthritis in all these 3 cited cases [18]. The infection was bacterial in 7 cases with 2 cases of pulmonary tuberculosis, one under Infliximab and the second under Adalimumab, one case of lymph node tuberculosis under Etanercept, two cases of skin infections (one erysipelas and one impetigo) under Adalimumab and Etanercept, one case of sinusitis on Infliximab and bacterial pneumonia on Infliximab [18]. Two cases of viral infection were noted: diaper shingles under rituximab and CMV infection under Infliximab. One case of intestinal amebiasis under Infliximab and one case of pulmonary aspergillosis under Adalimumab were also observed [18]. This serie confirms that susceptibility to infections in patients treated with biotherapy is increased by prior use of corticosteroids and immunosuppressants and by patient comorbidities [18].

Our series did not reveal any particular risk factors for infections in patients treated with biotherapy. The unequal use of the different biotherapies in our study does not make it possible to incriminate one molecule more than another in the occurrence of infectious complications.

Conclusion

The infectious risk in patients with chronic inflammatory rheumatic disease under biotherapy is present according to the data in the literature as our study also proves it and increases the risk of morbidity and mortality. Our study was carried out on the inclusion of patients, monitoring at follow-up was required in order to screen for factors associated with the infection.

Consent For Publication

The authors have equal contribution in this study. This project has been reviewed and accepted by the scientific committee of the RBSMR study. Moreover, this committee has reviewed this current manuscript and has agreed upon its submission to your journal. Written consent for publication has been obtained by the patients

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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