

## Malignancies and Biologic Therapy in Rheumatoid Arthritis: A Retrospective Study

Ileana Cosmina FILIPESCU\*, Alexandra OPRIȘ, Horațiu POPOV, and Simona REDNIC

Department of Rheumatology, University of Medicine and Pharmacy „Iuliu Hațieganu” Cluj-Napoca, 4-6 Clinicilor, 400006 Cluj-Napoca, Romania.

E-mails: ileana\_nicoara@yahoo.com (\*); alex\_porfiriu@yahoo.com; ionelpopov@yahoo.com; srednic.umfcluj@gmail.com

\* Author to whom correspondence should be addressed; Tel.: +4-0740-602192; Fax: +4-0264-413040

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### Abstract

*Objectives:* To observe the incidence of malignancies in the group of patients diagnosed with rheumatoid arthritis and treated with biologic therapy. *Methods:* A retrospective study on 157 subjects diagnosed with rheumatoid arthritis (RA) who underwent biologic treatment with Infliximab (IFX), Adalimumab (ADA), Etanercept (ETA) or Rituximab (RTX) was conducted in Rheumatology Clinic from Cluj-Napoca, between June 2012 and August 2012. *Results:* 44% of patients were treated with IFX, 24% with ETA, 10% with ADA and 22% with RTX. Seven malignancies (4.45%) were identified; 2 cases were with basal cell carcinoma of the skin (IFX, after a median duration of 84 months from the start of this therapy). These two malignancies were surgically removed and there was no need to stop IFX. A Bowen tumor was diagnosed after 8 months from the beginning of ETA treatment. Two cases of myeloproliferative disorder were identified after a median of 36 months time from the start of IFX. 1 of these 2 subjects underwent a specific therapy. 2 other female patients were diagnosed with ovarian carcinoma and cholangiocarcinoma respectively, during treatment with RTX (6 months on average after start). These patients have been previously treated with IFX or ETA that were discontinued due to lack of efficacy. Tumors were surgically removed and patients underwent chemotherapy. RTX was stopped. *Conclusions:* The most frequent malignancies in our sample were cutaneous carcinomas and myeloproliferative syndromes; they were not diagnosed in the first year. The treatment duration with different biologic were not related with the occurrence of malignancies.

**Keywords:** Anti-TNF $\alpha$  agents; Rituximab; Rheumatoid arthritis; Malignancy.

### Introduction

More and more studies have been done lately concerning the relationship that exists between rheumatoid arthritis, which is the most frequent rheumatic disease, and different types of malignancies. A great interest upon this aspect is due to the complex pathogenesis of the disease and to the chronic immunosuppression caused by the disease itself and by the specific medication.

The results of some studies which assessed this aspect were contradictory, some of them outline a higher risk of cancer occurrence in patients with active rheumatoid arthritis (RA), other studies deny this fact, but surely there is a predisposition for developing some certain types of malignancies (lymphomas or lung cancer) at patients with active disease [1-6].

Since the biologic era has come up, new chapters were written about RA. Many therapeutic cytokinic targets (TNF $\alpha$ , IL-1, IL-6) and noncytokinic (CD20, costimulating molecules) are involved in the treatment of this disease [1]. The TNF $\alpha$  blockers was proved to be the most efficient in treating chronic inflammation characteristic for RA, but the inhibition of this cytokine may lead to a higher risk for the occurrence of infections and malignancies. Skin cancers (non-melanoma skin cancers), broncho-pulmonary cancers, non-Hodgkin lymphoma may have a strong relationship with this therapy [6,7].

If biologic therapy itself increases the risk of malignancies, if this risk represents an individual characteristic of the biologic class, if the exposure time to this medication has an additive effect, if there might be a predisposition for a certain type of cancers, these are only some of the questions that are still waiting for an answer. Most of the data concerning the relationship between RA and classic remissive therapy or biologic therapy and cancer occurrence, come from the biologic records which include a great number of patients that are monitored in daily practice [7-9].

This is the first retrospective study in Romania, aimed to assess the malignancies diagnosed in daily practice in patients with RA undergoing biologic therapy.

### Objective

To determine the frequency of malignancies in the group of patients with RA that were undergoing biologic treatment and to monitor the type of therapy that were administered in cases with identified malignancies.

### Material and Method

We have carried out a retrospective observational study between June 2012 and August 2012 which included 157 patients with RA diagnosed according to American College of Rheumatology criteria [10]. The subjects in this study have undergone biologic treatment with at least one of the TNF $\alpha$  blockers (infliximab – IFX, adalimumab – ADA, etanercept – ETA) and rituximab – RTX in some cases. The patients were monitored in the Rheumatology Clinic, Cluj-Napoca, during June 2000 and August 2012.

The rheumatologist decided to initiate a biologic TNF $\alpha$  blocker, according to the national guide of RA treatment, in patients who had a suboptimal response at two classic remissive treatments. All of these treatment were taken on a period of minimum 12 weeks [11,12]. Rituximab, an anti-CD20 product was initiated in patients with active RA, who had an inadequate response at one or more TNF $\alpha$  blockers [11-13] (see Table 1).

**Table 1.** Biologic treatment guide in patients diagnosed with rheumatoid

Treatment	Initial	Maintenance
Infliximab (infusion)	3mg/kg body weight at 0, 2, 6 than at 8 weeks	3/5 mg/kg body weight at 6/8 weeks
Etanercept (subcutaneous)	2x25mg or 50mg/week	2x25mg or 50mg/week
Adalimumab (subcutaneous)	40mg at 2 weeks	40mg at 2 weeks
Rituximab (infusion)	1000mg/infusion separated by 2 weeks	1000mg/infusion separated by 2 weeks (after minimum 6 months)

Adapted from Boloșiu et al. [11] and National Health Insurance House [12]

During this study each patient was treated with different anti-TNF $\alpha$  agents and with classic remissive medication such as methotrexate, leflunomide, sulphasalazine, hidroxicloroquine.

The following items were included in the record of all patients with malignancies: demographic data (age ad gender), the type of biologic therapy and the treatment plan used, the period of time that passed from the biologic treatment initiation until the appearance of the malignancy (in

months). It was taken into account the history of classic remissive medication and the previous biologic therapy also.

The research protocol was approved by the Ethics Commission of the "Iuliu Hațieganu" University of Medicine and Pharmacy Cluj-Napoca.

**Statistics.** Qualitative variables were summarized by absolute and relative frequencies (%) with associated 95% confidence interval calculated under assumption of binomial distribution [14,15]. Quantitative variables were summarized by median and interquartile range (first and third quartiles) for variables that have been shown not to be normally distributed, or as mean and standard deviation for normally distributed data. Incidence rate of malignancies are presented as events/1000 person-years with associated 95% confidence interval [95%CI]. This index was calculated for each biologic agent. Data analysis was conducted with Statistica program (v. 8.0) at a significance level of 5%.

## Results

Out of the 157 patients with RA who were included in the study 69 (44% [36.3%-52.2%]) were treated with IFX, 38 (24% [17.8%-31.8%]) with ETA, 14 (10% [5.1%-14.6%]) with ADA and 36 with RTX (22% [16.6%-30.6%]). 88% of the women with the mean age of 57 (with limits between 23 and 75) years. The mean duration of the disease was 9.6 years (with limits between 1.4 and 10.4 years). The most used classic remissive medicine was Methotrexate (83% of the cases of RA).

The main characteristics of the group are presented in Table 2.

**Table 2.** The demographic characteristics of the studied group

	Infliximab (n=69) n, (% [95%CI])	Etanercept (n=38) n, (%[95%CI])	Adalimumab (n=14) n, (%[95%CI])	Rituximab (n=36) n, (%[95%CI])
Age (years)				
< 40	12 (17.4 [8.7-29.0])	7 (18.4 [8.0-34.1])	2 (14.3 [0.5-42.4])	2 (5.5 [0.01-19.4])
40-59	31 (45.0 [33.4-58.0])	9 (23.7 [10.6-39.4])	4 (28.6 [7.7-56.6])	8 (22.2 [11.1-38.8])
> 59	26 (37.6 [26.1-50.7])	22 (57.9 [42.2-73.6])	8 (57.1 [29.1-85.2])	26 (72.2 [55.6-86.0])
Gender				
Female	60 (86 [76.8-94.2])	35 (92.1 [79.0-97.3])	13 (92.9 [64.8-99.5])	30 (83.3 [66.7-94.4])
Male	9 (13 [5.8-23.2])	3 (7.9 [2.7-21.0])	1 (7.1 [0.5-35.2])	6 (16.7 [5.6-33.3])

During this study, 7 cases of malignancies (4.45% [1.92%-8.91%]) were diagnosed. The distribution of the malignancies according to the biologic therapy that was used, the duration of the therapy (patient-years) and the distribution to 1000 patient years is presented in Table 3.

**Table 3.** The distribution of malignancy cases according to the biologic agent and the period of time that was used

Biologic	Total of patients	Number of cases with malignancies	Patient-years	Malignancies/1000 Patient-years [95% CI]
Infliximab	69	4	8934.2	0.4477 [0.4374-0.8851]
Etanercept	38	1	1520.1	0.6579 [0.6340-0.6817]
Adalimumab	14	0	184.4	0.00
Rituximab	36	2	423.5	4.72 [2.70-6.74]

No case of malignancy was recorded at patients treated with ADA. The incidence of cancers reported in 1000 patient-years, in the group treated with IFX was close to the one from ETA group. The number of malignancies reported in 1000 patient-years was higher in RA patients treated with RTX.

Two cases of basal cell carcinoma and two myeloproliferative syndromes were recorded in the patients with RA treated with IFX. In the group of patients undergoing ETA one case of Bowen's disease was diagnosed. Other solid cancers were also identified in patients treated with RTX: an

ovarian malignant tumor and a cholangiocarcinoma.

No case of malignancy was diagnosed in the first year of treatment with TNF $\alpha$  blockers ( table IV). Concerning anti CD20 therapy, the two malignancies were diagnosed after 6 months of treatment initiation, but in both of the situations, patients have previously undergone other TNF $\alpha$ -blockers (IFX respectively ETA).

**Table 4.** The relationship between the type of malignancy, treatment duration and the biologic type

Type of malignancy (gender, age in years)	Period of time (months)	Biologic	Observations
Basal cell carcinoma 1, (F, 68)	66	Infliximab	
Basal cell carcinoma 2, (F, 71)	102	Infliximab	
Bowen's carcinoma (F, 72)	8	Etanercept	Previously has undergone 16 months of infliximab
Myeloproliferative syndrome 1 (M, 64)	22	Infliximab	
Myeloproliferative syndrome 2 (F, 62)	50	Infliximab	
Ovarian carcinoma (F, 57)	2	Rituximab	Previously has undergone 12 months of infliximab
Cholangiocarcinoma (F, 61)	10	Rituximab	Previously has undergone 12 months of etanercept

Females were the most affected. 6 out of 7 malignancies (85.7%, 95%CI [44.9%-98.0%]) have occurred in women. One of the myeloproliferative syndromes was detected in a man with RA after 22 months of treatment with IFX. In this case, specific immunosuppressive therapy was needed with a good evolution after that. In the two cases of myeloproliferative syndromes, the IFX therapy was stopped because of loss of efficiency and treatment was continued with rituximab.

Basal cell carcinomas and Bowen's disease were surgically removed. An interruption of the biological therapy was not needed. The cancers that were diagnosed in patients treated with RTX were also surgically removed and are now under specific chemotherapy. No deaths were recorded.

Because this is a retrospective study and sometimes the symptoms of the active disease might overlap to those of a malignant disorder, reporting them might not be that exact (in time). Also, it is difficult to prove the role of RTX therapy in the appearance of malignancies, mainly because the subjects had also previously undergone several other biologic therapies. In the absence of a control group, it is hard to conclude if biologic therapy has an important role in the appearance of malignancies.

## Discussion

The quality of life of patients with rheumatoid arthritis has greatly improved after treatment with biologic agents. But as any other medication this one has its own side effects and risks. The first reports about the occurrence of malignancies in rheumatic patients, or with gastroenterological or dermatological diseases, have appeared soon after the beginning of these therapies [16-18].

Chronic arthritis with its prolonged inflammation may lead to the proliferation of certain lymphocyte populations: B cells, a fact which may also lead to malignant transformations. A strong relationship was not clearly established, but a study conducted by Smitten et al, has proved a three times greater risk for developing certain types of cancers (lymphoma or lung cancer) in patients with chronic arthritis [19].

Besides the risk related to the biologic therapy, there is another one related to the disease itself and also the risk implied by the classic remissive therapy. 8-10 cases of malignancies at 1000 patient-years have been identified in the group of subjects with RA treated only with methotrexate [5,20,21].

The conclusion of an observational study which took place in 2009, in which were included

patients from the French registry of biological therapy, was that patients with RA receiving biological therapy do not have an increased risk of developing malignancies. The incidence of all types of malignancies in patients with RA receiving TNF $\alpha$  blockers therapy was of 0.3-1.6/1000 patients- years, compared with the incidence of 0.73- 1.51/1000 patients- years in patients treated with classic remissive medication [22].

In another observational study, recently published in 2011, Mariette et al, confirmed an incidence of malignancies of 7.40 (5.81- 8.99) in subjects with RA, the estimated risk of malignancy was 0.95 (0.85-1.05) compared to the biologic naive population [7].

Another research done by Wolfe et al. revealed that the relative risk of developing cancers in patients with RA and biologic therapy was of 1.0 (95% CI 1.0-1.1) – compared to general population [21].

Due to some possible common mechanisms of the rheumatoid arthritis and malignancies, an explanation would be the implication of the TNF $\alpha$ , a proinflammatory cytokine that has a key role in RA, but also in infectious defense and in tumoral cell apoptosis [23,24].

There were many researches that were done in order to determine if the risk of malignancy is a characteristic of the biologic class or if it occurs individually. A meta-analysis which included 9 randomized clinic trials, in which were included 5014 subjects with RA undergoing IFX or ADA therapy, compared with the MTX group, hasn't proved a raised incidence of cancers in the biologic group [8]. Another research on a greater number of patients with RA and TNF $\alpha$  blockers, compared to the ones undergoing MTX, estimated a relative risk of malignancy occurrence of 0.99 (95% CI 0.51-1.56), after excluding non-melanomas [5].

Bongartz et al. in 2009, have detected 26 malignancies in the group of patients treated with ETA (10.47/1000 patient-years) compared to 7 malignancies (6.66/1000 patient-years) diagnosed in the group of patients treated with classic remissive medications (control group) [25]. Also, some other recent observational studies done by Askling et al., respectively Mariette et al have outlined the fact that there is no difference in the risks of malignancies induced by anti- TNF $\alpha$  class [5,7].

Similar observation was found in our study. The incidence of malignancies in the group of patients treated with IFX is not significantly different compared to the ones undergoing ETA (0.44 respectively 0.65/at 1000 patient-years). Infliximab is the first biologic that was approved in Romania, exposure to this medicine is longer and also the number of patients who have taken this TNF $\alpha$ -blocker is greater.

There aren't many recent data published yet about the risk of malignancies in patients with RA and treated with RTX. In 2010 van Vollenhoven et al have included in a research 2578 patients with RA that have undergone at least one cycle of treatment with RTX and diagnosed 42 cancers (0.84/1000 patient-years). The majority of them were lymphomas [26].

In our group 2 patients that were undergoing RTX therapy were diagnosed with cancer, but none of them was a lymphoma. Establishing a correlation between the risk of malignancies and RTX therapy is difficult due to the fact that all the patients had also undergone other types of anti-TNF $\alpha$  treatments.

Although it's supposed that TNF $\alpha$  blocker therapy has biologic effects on oncogenesis and on tumoral progression, the length of time when the biological therapy was applied has not been proved to have a correspondence with malignancy occurrence. This comes as a conclusion of monitoring patients with RA on a long period of time, treated with TNF $\alpha$  blockers, and with RTX respectively [5,27,28]. Another conclusion of these studies was that the majority of malignancies have occurred in the first year of biologic treatment.

This aspect hasn't been outlined in our research, where cutaneous carcinomas were diagnosed after 84 months (as a mean) and 36 months for myeloproliferative syndromes.

Concerning some certain types of malignancies that are more frequently diagnosed in patients with RA, it is known that lymphoproliferative disorders are highly associated with the severity and intense activity of the disease [13,29]. An increased risk of developing malignancies in patients with RA and biologic therapy can be explained due to an intense activity of RA- Wolfe et al [9]. The risk is not statistically significant, but it is also known that these patients have a greater incidence of hepatosplenic lymphoma with T cell [9,25]. The occurrence of cutaneous non-melanomic carcinomas seems to be more frequent in patients with RA undergoing biologic therapy compared

to those who have classic remissive medication, especially in the first year of treatment [7,29]. An increased risk of 1.79 (0.92-2.67) was recorded, inclusive for malignant melanoma [27].

In our group, myeloproliferative syndromes and cutaneous carcinomas had the greatest frequency too, but have appeared late in the evolution of the disease treated with biologic therapy.

A Scottish observational study outlined that the malignancy risk in patients with RA and biologic treatment is increased for lymphoproliferative disorders (1.76), lung (1.44) and prostate (1.26) and low for colorectal cancer (0.71) and stomach (0.70) [30].

There might be a relationship between the occurrence of malignancies and the biologic therapy, but this aspect has not been proved yet. More studies are needed to evaluate these connections.

Our results should be interpreted with caution, due to the following constraints: small size of the group of patients, the difference in the treatment duration and lack of a control group.

## **Conclusions**

The most frequent diseases observed in our sample were cutaneous carcinomas and myeloproliferative syndromes.

In our study the malignancies were not diagnosed in the first year.

We did not find any lymphoma secondary to biologic therapy.

The number of cancer reported at 1000 patients-years is quite similar between group treated with IFX and ETA.

Different duration of exposure to the three TNF $\alpha$  blockers did not significantly increase the risk of malignancy in our study.

Two malignancies were diagnosed in patients treated with RTX, but all of these subjects were treated before with TNF $\alpha$  inhibitors.

## **Conflict of Interest**

The authors declare that they have no conflict of interest.

## **Authors' Contributions**

IF defined the aim of research, designed experiment, analyzed and interpreted the data and wrote the manuscript. AO analyzes the data. HP participated at the acquisition of data. SR coordinated and helped to draft the manuscript. All authors read and approved the final manuscript.

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