# Inflammation-Targeted Therapies and Cancer

Joanna Kedra, Gaetane Nocturne, Xavier Mariette, Raphaèle Seror

# Inflammation-targeted therapies and Cancer

**Authors:** Joanna Kedra [1-2], Gaetane Nocturne[1], Xavier Mariette[1] and Raphaèle Seror[1]

1 – Université Paris-Saclay, Assistance Publique-Hôpitaux de Paris (AP-HP), Service de Rhumatologie, Hôpital Bicêtre, INSERM U1184, Fédération Hospitalo-Universitaire CARE (Cancer and Autoimmunity Relationship), Le Kremlin Bicêtre, France

2 - Sorbonne Université, Institut Pierre Louis d'Epidémiologie et de Santé Publique, INSERM UMR S1136, Paris France

**Corresponding author**:

Pr Raphaèle Seror, MD, PhD, Department of Rheumatology, Hôpital Bicêtre, 78 rue du Général Leclerc, 94275 Le Kremlin Bicêtre, France. E-mail: raphaele.seror@aphp.fr

Words: 4117

References: 78

Tables/figures: 6/6

Highlights: cf dedicated file

Key words: cancer, rheumatic diseases, biologics, targeted synthetic DMARDs

## Abstract

Objective: to review and analyze the current knowledge on the risk of malignancy associated with inflammation-targeted therapies in rheumatic diseases.

Methods: We performed a non-systematic literature review on PubMEd MEDLINE by screening randomized controlled trials, meta-analyses, reviews, and observational studies focusing on malignancies and inflammation-targeted therapies including TNF inhibitors, other biologics and JAK inhibitors in rheumatic diseases.

Results: Data from literature are reassuring regarding the overall risk of

incident and recurrent cancer with TNF inhibitors. The risk of lymphoma is more difficult to analyze and data are controversial, however in most of the studies this risk does not seem to be significanlty increased. By contrast, there is probably an increased risk of non-melanoma skin cancer associated with TNF inhibitors, as with other immunosuppressants. There is no signal for an increased risk of malignancies with other biological DMARDs, but additional data are needed. A recent post-marketing surveillance study found out an increased risk of malignancies for tofacitinib compared with TNFi; additional data are therefore urgently needed to confirm or not these results.

Conclusion: Data are presently reassuring regarding the overall risk of cancer, whatever the inflammation-targeted treatment. However, additional data are needed for non-TNF biologics and JAK-inhibitors.

- **Introduction**

The occurrence of cancer in patients with a rheumatic condition always rises several questions, particularly regarding the cause of the cancer, and the relative role of the underlying disease or its treatments. Epidemiologic factors may explain the occurrence of cancer in patients with rheumatic diseases. First, age of onset of some rheumatic diseases, such as rheumatoid arthritis (RA), matches the peak of cancer incidence in the general population. Additionally, some cancers may be associated with factors, which are also risk factors of rheumatic diseases: it is for example the case for smoking, which is an established risk factor of both RA and lung cancer.

Nevertheless, some rheumatic diseases seem to be associated with an increased risk of cancer; thus, the association between active RA, Sjögren's syndrome (SS), systemic lupus erythematosus (SLE) and B-cell lymphoma is now well established (1). To a lesser extent, an increased risk of lymphoma is also suspected in psoriatic arthritis (PsA) (2). Among solid cancers, some studies found an increased risk of lung cancer in patients with systemic sclerosis (SSc) or dermatomyositis/polymyositis (DM/PM) compared with the general population (3), and an increased risk of ovary cancer in patients with SS and DM/PM (3). On the contrary, a decreased risk of breast and colorectal cancer is observed in RA (4). Interestingly, no association has been established to date between ankylosing spondylitis (AS) and solid or hematologic malignancies (2).

The role of rheumatic disease treatments, so called, disease modifying anti-rheumatic drug (DMARD), in the occurrence of cancer has also been discussed during the last decades. In the late 1990s, cases of EBV-induced lymphoma occurring in RA patients treated with methotrexate (MTX) have been reported (5); however, except in two Japanese studies (6, 7), this relationship has not been confirmed in more recent studies (8). An increased risk of cancer is also known with azathioprine, ciclosporin or cyclophosphamide (9). Also, with emergence of inflammation-targeted therapies, acting on the immune system, such as biological DMARDs, and more recently targeted synthetic DMARDs, this question has become even more crucial.

Nevertheless, the respective role of the underlying disease and its treatments remains difficult to analyze. Indeed, inflammation-targeted therapies are frequently prescribed in patients with the more severe diseases, who have the most increased risk of inflammation-related malignancies.

Therefore, this review aims to analyze the current knowledge on the risk of malignancy associated with inflammation-targeted treatments in rheumatic diseases, but also to provide some elements to better appraise it and highlight some methodological issues to be kept in mind when evaluating the association between rheumatic diseases, treatments, and the risk of cancer.

- **Cancer risk assessment methods in rheumatic diseases**

Some methodological aspects must be considered when analyzing the risk of cancer in the context of inflammation-targeted treatments.

First, the study design must be appropriate; this point may seem trivial, but it is not easy to implement. Indeed, the occurrence of a treatment-induced cancer is a severe but relatively rare event and may occur years after the treatment exposure or after years of treatments exposures. Thus, randomized controlled trials (RCT), which provide the stronger level of evidence, usually have small sample size and a short duration of follow-up, may fail to capture the onset of such events. To overcome these pitfalls, meta-analyses of RCTs, with larger sample sizes, help to increase the power to analyse these risks. Long-term extension studies increase follow-up duration to identify risks associated with longer exposure, but loose the control group of RCT. Nevertheless, one should keep in mind that RCTs, their meta-analyses and long-term extension studies suffer from a bias in the selection of the study population, given the fact that patients with significant comorbidities (including, previous cancer) are often excluded from these studies, and this limits the extrapolation of the results in “real world” practice settings.

Thus, observational studies provide complementary information on this issue, by analysing these risks in unselected large study populations with a longer follow-up. A first possible design is a prospective cohort study (including biologic registries), which offers the advantage of having detailed data on the underlying disease, treatments, and co-morbidities, and thus limits the risk of unknown confounding factors. Nevertheless, these studies may still be underpowered to detect some rare risks. Another alternative relies on the analysis of health insurance databases; such studies have the greatest power and an incontestable representativeness; however, they usually provide less information regarding the disease of interest and potential confounders. Thus, it appears that all the study designs mentioned previously have advantages and limits and provide complementary information on the risk of cancer (a summary is provided in ***Table 1***). Above all, the concordance of the results of these different studies enables to draw stronger conclusions regarding the relationship between treatments and malignancies.

Another major issue when analysing the risk of treatment-induced cancers is the choice of the comparator group. Two situations must be distinguished, the analysis of the risk of cancer compared to that of the general population or compared to patients suffering from the same rheumatic disease but with no or different treatments. In the first situation, only observational studies may address the question and it is crucial that the general population comparator comes from the same geographic area, thus when they exist, from cancer databases. In France, such database is available from the FRANCIM (France Cancer Incidence and Mortality) network. For multinational studies, two databases are mostly considered: the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute that provides information on cancer statistics among the U.S. population (available from: www.seer.cancer.gov) and the GLOBOCAN (available from: www.globocan.iarc.fr) that provides contemporary estimates of the incidence, prevalence, and mortality from major types of cancer, at the national level, for 184 countries of the world. In rheumatic diseases, most multinational studies use the US SEER as comparator whereas it should be more logical to use the GLOBOCAN which is multinational, or national data when available. Of note, SEER estimates are usually higher than those of GLOBOCAN, providing thus more reassuring data. Moreover, some studies pointed out the fact that the quality of cancer data was variable among countries participating in GLOBOCAN, with lower reliability in low-income countries, which could be a limitation to the estimates (10).

When defining a comparator group to assess the risk of malignancy associated with a specific inflammation-targeted treatment compared to usual care in a specific rheumatic disease, the only study design providing similar characteristics in the exposed and comparator group is RCT, however, it is only guaranteed in the placebo-controlled phase, and not in later phases or extensions. In observational studies, the choice of the comparative drug may be more problematic. Indeed, patients in both groups should have the same degree of disease severity. In rheumatic diseases, the control treatment is often a csDMARD (11), which is not an “ideal” solution given that patients requiring biologics are often in failure of csDMARD and so have a more severe disease.

These methodological aspects being said, we will now discuss the current state of the literature regarding the relationship between cancers and TNFi, other biologics (rituximab, abatacept, tocilizumab) and JAK inhibitors (JAKi). To this end, we screened RCTs, meta-analyses, reviews and observational studies on PubMed MEDLINE regarding cancers and inflammation-targeted therapies.

- **TNF inhibitors and the risk of cancer**

TNFi are the most ancient biologics and consequently, the most studied to date. These treatments are prescribed in rheumatic diseases such as RA, AS

and PsA, but also in other conditions such as cutaneous psoriasis and inflammatory bowel diseases (IBD). Infliximab, adalimumab, certolizumab and golimumab, are monoclonal antibodies directed against TNF, whereas etanercept is a fusion protein of human p75 soluble TNF receptor and human IgG 1. The relationship between these biologics and cancer has been mostly studied for the 3 most ancient TNFi: infliximab, adalimumab and etanercept.

- ***– Solid cancers***

Data on overall risk of solid and organ specific cancer are provided in ***Table 2*** and ***Table 3***, respectively. The role of TNFi in malignancy onset was suspected for the first time in 2006, after the publication of a meta-analyses of RCTs of adalimumab and infliximab in RA in the JAMA. In this study, an overall increased risk of cancer was found (OR=3.3, 95% confidence interval (CI) 1.2-9.1), updated to 2.4 (95%CI: 1.2-4.8) a few months later with 2 additional trials (12). Nevertheless, in this study, the incidence of cancers was analyzed by randomized patients and not by person-years at risk, which is a major issue. Another meta-analysis, focusing on the risk of breast cancer and overall malignancies, suggested that the risk of cancer was increased for doses of TNFi higher than the marketed dose (13). However, more recent meta-analyses and systematic literature review, did not find such association, whatever the molecule, and whatever the comparator (general population or csDMARD) (14-21).

Data from observational studies did not either show an overall increased risk of solid cancer. Indeed, in a meta-analysis of all RA registries (22) the pooled estimate for the risk of all-site malignancy from seven studies was 0.95 (95% CI 0.85 to 1.05). These results were confirmed by more recent updates from the RABBIT (German), ARTIS (Sweden), ARAD (Australia), BIOBADASER (Spain), LOHREN (Italy), NDBRB (USA), CORRONA (USA) and BSRBR (UK) registries (23-28). Interestingly, a Japanese study based on the SECURE registry found a decreased risk of cancer in TNFi-treated RA patients compared with the general population (SIR = 0.75, 95% CI 0.67–0.83) (29); similarly, a cohort study based on the Registry of Catastrophic Illness Database in Taiwan provided reassuring data regarding the risk of all cancer and solid cancer in RA patients treated with etanercept (HR 0.59, 95% CI 0.36–0.98 and HR 0.46, 95% CI 0.27–0.79, respectively) compared with bionaive patients (30). Actually, this decreased rate of cancer in TNFi-treated patients in registries, case-control or insurance databases studies is not surpising since, before biologic initiation, it is recommended to screen patients for frequent cancers and to exclude patients with a previous cancer in the past 5 years, which is not the case for the comparator control groups remaining on csDMARDs. Thus, one can wonder if an absence of increased risk in many observational studies would not mean an increased risk.

Nevertheless, data regarding other inflammatory diseases treated with TNFi are also reassuring. Indeed, in AS, no increase in the risk of cancer was found associated with TNFi compared to biologic-naïve patients, according to the results from DANBIO registry (RR 0.8 (95% CI 0.7 to 1.0) (31). Similar results were obtained in IBD, whatever the duration of exposure and the age

at the initiation of the first TNFi (32).

Concerning the prognosis of solid cancers occurring in patients with TNFi, a retrospective cohort study of 431 patients with RA and solid malignancies found no statistical difference in terms of overall survival between RA patients treated with TNFi, other biologics or no biologics (hazard ratio (HR), 0.67; 95% confidence interval (CI), 0.31, 1.44; HR, 1.10; 95% CI, 0.26, 4.60 respectively) (33).

In summary, the most recent data regarding cancer onset and prognosis in patients treated with TNFi are reassuring. As a matter of fact, according to the results from CORRONA registry, TNFi remain the most prescribed biologics (53,5%), even in patients with history of solid cancer (34).

- ***–Skin cancers***

An increased risk of non-melanoma skin cancers (NMSC) is probable with TNFi (***Table 4***) (35). Indeed, the largest meta-analysis to date on this topic, which considered 76 trials, found a hazard ratio (HR) of 2.02 (95%CI: 1.11, 3.95) (16). However, this result was not confirmed by other smaller meta-analyses (17-19). Recently, a meta-analysis including 6 studies with 123,031 RA patients found an increased risk of squamous skin cancer in TNFi-treated patients compared with TNFi-naïve patients (RR 1.30, 95% CI 1.09 to 1.54), but there was no increase of risk for basal cell skin cancer (RR 1.13, 95% CI 0.97 to 1.31) (3). Registry-based studies provided complementary information: according to the data from the Danish registry, it seems that the risk of NMSC is increased with TNFi only when compared with general population (SIR 1.92, 95% CI: 1.4 - 2.6), and this increased risk is the same in patients treated with csDMARD (SIR= 1.76 (95% CI: 1.3 - 2.5 (36). This finding is concordant with other studies regarding the risk of NMSC with MTX (37). In addition, according to the results from the ARTIS registry, the risk of squamous skin cancer is increased in TNFi-treated patients compared with the general population but also compared with biologic-naïve patients (HR 1.88 (95%CI 1.74 to 2.03) and HR 1.30 (95%CI 1.10 to 1.55) respectively); consequently, it appears that there is an additional risk of squamous skin cancer with TNFi use (38). A similar trend was recently observed in the BSRBR with patients with severe PsA treated with TNFi, with a SIR of 2.12 (95% CI: 1.19, 3.50) for NMSC occurrence (39). Thus, anti-TNF, as almost all other immunosuppressants, moderately increased the risk of NMSC.

Regarding melanoma, results from the literature are discordant (***Table 4***). On one hand, in the ARTIS registry, a significant increased risk of invasive melanoma (but not in situ melanoma) was observed in patients treated with TNFi compared to patients treated by csDMARDs (HR= 1.5 (95%CI:1.0-2.2)) (40). On the other hand, a combined analysis of 11 European registries did not find any increased risk of melanoma with TNFi (41). These results are supported by a recent case-control study performed by the Mayo Clinic (42). A meta-analysis of 7 cohort studies did not find either a significantly increased risk of melanoma in patients with RA, IBD or psoriasis (43). In IBD as in

rheumatic diseases, data regarding the risk of melanoma with TNFi are discordant (44). Interestingly, studies which found a significant association were mostly performed in Scandinavian populations; thus, these results could be at least partly explained by the Scandinavian patients' phototype, as Northern Europeans are more at risk of melanoma.

- ***– Cervix cancer***

Regarding the specific risk of HPV-related cervix cancer that is also recognized to be increased by immunosuppressants, data are more discordant. On the one hand, no increased risk of cervix cancer was found in the DANBIO and BSRBR registries (45, 46). On the other hand, in the ARTIS registry, there was no statistically significant difference in risk for CIN 1 (HR 1.23, 95% CI 0.87 to 1.74), but a higher rate of CIN 2+ (HR 1.36, 95% CI 1.01 to 1.82) and a doubled risk of invasive cervical cancer were observed in the TNFi cohort (HR 2.10, 95% CI 1.04 to 4.23). Similar findings were observed even when restricting to individuals with a normal screening test at the last screening before start of follow-up (47).

- ***- Lymphoma***

As mentioned above, an increased risk of lymphoma is well known in some rheumatic diseases and was also suspected with csDMARD (1, 5). The meta-analysis published in 2006 in JAMA also raised the question for TNFi (10). Indeed, in this metaanalysis, the inceased risk of cancer was mainly driven by an increased risk of lymphoma. However, more recent meta-analyses based on RCTs did not find such association ***(Table 5)***; nevertheless, it has to be recalled that the number of events in RCTs is very low, the duration of exposition is limited, and thus they are usually underpowered (17, 20, 48-50).

The results from the French observatory RATIO suggested that the risk might be different according to the mechanism of action of the TNFi; indeed, the risk of lymphoma was increased with the two monoclonal antibodies (SIR = 3.7; 95% CI 2.6-5.3), but it was not the case for etanercept (SIR = 0.9; 95% CI 0.4-1.8) (51). Of note, the risk with adalimumab and infliximab was that expected in a population of severe RA patients. Similar findings were reported in the Japanese SECURE registry (29). However, a more recent study by the EULAR & RODS study group brought more reassuring conclusions; indeed, among the 124,997 RA patients followed-up in this study, 533 cases of lymphoma occurred, and the incidence rate of lymphomas occurring in TNFi-treated patients was lower than in the total population as well as in bionaïve patients (81/100,000, 85/100,000, and 89/100,000 patient-years, respectively) (52). Recently, a Swedish cohort study even stated that biologics may reduce the risk of lymphoma in RA, compared with bionaive patients (adjusted hazard ratio [aHR]=0.69, 95% CI: 0.47, 1.00) or with patients switching from one csDMARD to another (aHR=0.46, 95% CI: 0.28, 0.73) (53).

However, in another study based on the French national claim

database called Système National des Données de Santé (SNDS) and focusing on patients with IBD, the risk of lymphoma was higher among those exposed to thiopurine monotherapy (aHR=2.60; 95% CI, 1.96-3.44), TNFi monotherapy (aHR=2.41; 95% CI, 1.60-3.64), and mainly in patients exposed to association of these two classes of treatments (aHR=6.11; 95% CI, 3.46-10.8) (54). Nevertheless, no other study found such association, in the context of rheumatic diseases. Thus, further data are needed and results from the French SNDS for patients with rheumatic diseases are ongoing.

- ***– Recurrent cancer***

According to the last recommendations, TNF inhibitors are contra-indicated in patients with a history of cancer in the 5 previous years. However, in some situations, these treatments are the main or only therapeutic options. Therefore, the question of cancer recurrence with TNFi is an important issue. The latest results from the Swedish registry ARTIS suggested that TNFi do not increase the risk of recurrent cancer compared with patients with the same cancer history (HR=1.06, 95% CI, 0.73 to 1.54) (55). Similar conclusions were drawn from the BSRBR registry (23). More recently, a meta-analysis of observational studies did not find neither any significant association between new and recurrent cancer and TNFi compared to other therapies (incident risk ratio [IRR] 0.90, 95%CI 0.59-1.37) (56). Moreover, TNF-inhibitors may be used in rheumatic or gastrointestinal immune-related adverse events caused by checkpoint inhibitors, without consequences on the underlying cancer progression (57).

- ***– Pediatric cancer***

Few data are available for pediatric cancers. According to the recent results from a Canadian single center study, 6 rheumatology pediatric patients among 357 developed a cancer while on TNFi between 1997 and 2013 (58). The cancers types were: 2 renal clear cell carcinoma, 1 pilomatricoma, 1 nasopharyngeal carcinoma, 1 Ewing's sarcoma, 1 hepatic T-cell lymphoma, 1 lymphoproliferative disease. Thus, the malignancy rate in this study was relatively low, however the authors underlined the fact that more than half of the neoplasms identified were rare and unusual in the pediatric population. Other studies found increased rates of lymphoma (mainly Hodgkin's), with higher incidence rates than those reported in general population (59). Thus, it seems that the overall incidence of malignancy for pediatric patients appeared to be higher than expected in the overall pediatric population. Regarding the specific role of inflammation-targeted treatments in the occurrence of pediatric cancers, a study based on US Medicaid and MarketScan claims found an overall increased risk among patients with juvenile idiopathic arthritis, pediatric IBD or pediatric plaque psoriasis (SIR= 2.9 [1.6-4.9]) and among those who did not receive any medications of interest (SIR=2.1 [1.5-2.9]), compared to general population (60). Additionally, this study did not find an increased risk of incident malignancies following treatment with TNFi compared to children who did not receive this bDMARD

(HR=1.58 [0.88-2.85]). However, in pediatric IBD, TNFi use with thiopurine use was associated with a higher risk of cancer (SIR=6.0 [1.2-17.5]) than TNFi use without thiopurine use (SIR=2.5 [0.7-6.4]), compared to general population.

- **Other biologics and the risk of cancer**

Fewer data on cancer risk are available for other biologics. Main findings are summarized in ***Table 6***. Studies regarding these treatments often suffer from lack of power, given that they have been marketed later than TNFi and that less patients are undergoing these therapies.

- ***– Rituximab***

To date, no worrying signal regarding rituximab and cancers has been reported in the literature (28, 61). Recently, a post-marketing study involving 409,706 RA patients treated with rituximab found a rate of malignancies worth 7.4 per 1000 patient-years, which was within the expected range (62). In fact, rituximab is a treatment also used in several hematological malignancies since 1997 without any safety concern regarding cancer, and therefore is considered in situations when other biologics are contraindicated due to cancer history. As a matter of fact, rituximab is recommended by learned societies when biologics are indicated in patients with malignancy history (63, 64).

- ***– Tocilizumab and other anti-interleukines***

Data regarding tocilizumab are somewhat discordant. Indeed, a first long-term extension study did not reveal an increased risk of overall malignancies (SIR=0.80, 95% CI, 0.78, 0.82) (65) but a more recent update showed a SIR for all malignancies, excluding non-melanoma skin cancer, of 1.36 (95%CI 1.01-1.80) compared to SEER database and 1.81 (95%CI 1.44-2.23) compared to GLOBOCAN, suggesting an increased risk of malignancies (66). A Japanese study including 5573 patients treated with tocilizumab found a decreased risk of all malignancies (SIR 0.79, 95% CI, 0.66 to 0.95) but an increased risk of lymphoma (3.13, 95% CI, 1.82 to 5.39) compared with the Japanese general population (67). More recently, a cohort study based on 3 American insurance claims databases included 13,102 tocilizumab users and matched them to 26,727 TNFi users and did not find an increased risk of cancer (HR =0.98, 95%CI 0.80-1.19) (68). Additionally, tocilizumab may be considered to treat rheumatic adverse events occurring with checkpoint inhibitors and is part of recommended biologics in case of malignancy history (63, 64).

Fewer data are available for other anti-interleukines, such as secukinumab or ustekinumab. However, to date, long-term safety studies did

not find any signal of increased risk of malignancy with these treatments (69).

- ***– Abatacept***

As for tocilizumab, contradictory data are available for abatacept. First meta-analyses of trials and observational studies did not find an association between abatacept and the occurrence of malignancies (5, 70). However, according to a population-based comparative cohort study, the use of abatacept as first biologic in the treatment of RA was associated with a slight increased risk of cancer overall (aHR 1.17; 95% CI 1.06, 1.30) and particularly non-melanoma skin cancer (aHR=1.20; 95% CI 1.03, 1.39), compared with other biologics (71). Additionally, compared with other biologics, exposure to abatacept in RA patients was significantly associated with an increased risk of reporting melanoma (Reporting Odd Ratio ROR= 1.58, 95% CI 1.17 to 2.08) (72). This increased risk could be related to the properties of abatacept (CTLA-4 agonist) since it has an opposite action than ipilimumab, an antibody that blocks CTLA-4 and is approved for the treatment of malignant melanoma (73). However, further investigations are needed to draw any conclusion.

- **JAK-inhibitors and the risk of cancer**

JAK-inhibitors are small molecules which emerged during the last years as a new option of treatment for RA, IBD, psoriasis or AS. These molecules are: tofacitinib (anti-JAK1 and 3), baricitinib (anti-JAK1 and 2), filgotinib and upadacitinib (anti-JAK1). Particular concerns about the risk of malignancy in patients treated with tofacitinib have been raised, given that this molecule inhibits signal transduction of several cytokines, such as type I and type II interferons, and may decrease the function of NK cells, both of which are relevant to the elimination of transformed cells in the process of cancer immunoediting (74, 75). Results are presently discordant regarding these treatments. Indeed, a meta-analysis of 113 RCTs regarding the risk of cancer with biologics and tofacitinib (17/113 RCTs) did not find a significant association between tofacitinib and overall risk of cancer (OR= 2.39 (0.50, 11.5)) (76). Another meta-analysis, comprising 66,159 patients treated with JAK-inhibitors for various immune-mediated diseases, did not find either any increased risk of malignancies with these molecules (RR=1.05 (0.45-2.35) for NMSC and RR=1.39 (0.68-2.85) for other malignancies) (77). However, a recent post-marketing surveillance study for tofacitinib conducted in 4,362 RA patients found out an increased risk of malignancies (excluding NMSC) for both dosages of tofacitinib compared with TNFi: HR=1.47 (1.00-2.18) for 5 mg twice daily, HR=1.48 (1.00-2.19) for 10 mg twice daily, and HR=1.48 (1.04-2.09) for tofacitinib doses combined (78). Additional data are therefore urgently needed to confirm or not this data that are crucial for our patients.

- **Conclusion**

The risk of cancer associated with inflammation-targeted treatments has been largely studied, particularly for TNFi. The data currently available are generally reassuring, except perhaps for an increased risk of non-melanoma skin cancer with TNFi and abatacept. The risk of cancer recurrence with biologics also appears to be low, whatever the molecule. Thus, rituximab and tocilizumab may be used safely in patients with a history of cancer, and the use of other biologics should be discussed on a multidisciplinary meeting. However, for more recent biologics and for JAK-inhibitors, too few data are available, and additional studies with adequate methodology, longer duration of follow-up and a larger sample size are still needed.

## References


- Zintzaras E, Voulgarelis M, Moutsopoulos HM. The risk of lymphoma development in autoimmune diseases: a meta-analysis. *Arch Intern Med* 2005;165:2337-44.

- Hellgren K, Smedby KE, Backlin C, et al. Ankylosing spondylitis, psoriatic arthritis, and risk of malignant lymphoma: a cohort study based on nationwide prospectively recorded data from Sweden. *Arthritis Rheumatol* 2014;66:1282-90.

- Wang HL, Zhou YM, Zhu GZ, Yang Z, Hua BJ. Malignancy as a comorbidity in rheumatic diseases: a retrospective hospital-based study. *Clin Rheumatol*. 2018;37(1):81-85.

- Simon TA, Thompson A, Gandhi KK, et al. Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis. *Arthritis Res Ther* 2015;17:212.

- Kamel OW, van de Rijn M, Weiss LM, et al. Brief report: reversible lymphomas associated with Epstein-Barr virus occurring during methotrexate therapy for rheumatoid arthritis and dermatomyositis. *N Engl J Med* 1993;328:1317-21.

- Yamada T, Nakajima A, Inoue E, et al. Incidence of malignancy in Japanese patients with rheumatoid arthritis. *Rheumatol Int* 2011;31:1487-92.

- Kameda T, Dobashi H, Miyatake N, et al. Association of higher methotrexate dose with lymphoproliferative disease onset in rheumatoid arthritis patients. *Arthritis Care Res (Hoboken)* 2014;66:1302-9.

- Mariette X, Cazals-Hatem D, Warszawki J, et al. Lymphomas in

rheumatoid arthritis patients treated with methotrexate: a 3-year prospective study in France. *Blood* 2002;99:3909-15.

- Beaugerie L, Brousse N, Bouvier AM, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet* 2009;374:1617-25.

- Antoni S, Soerjomataram I, Møller B, Bray F, Ferlay J. An assessment of GLOBOCAN methods for deriving national estimates of cancer incidence. Bull World Health Organ. 2016;94(3):174-184.

- Solomon DH, Mercer E, Kavanaugh A. Observational studies on the risk of cancer associated with tumor necrosis factor inhibitors in rheumatoid arthritis: a review of their methodologies and results. *Arthritis Rheum* 2012;64:21-32.

- Bongartz T, Sutton AJ, Sweeting MJ, et al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *Jama* 2006;295:2275-85.

- Liu Y, Fan W, Chen H, et al. Risk of breast cancer and total malignancies in rheumatoid arthritis patients undergoing TNF-alpha antagonist therapy: a meta-analysis of randomized control trials. Asian Pac J Cancer Prev 2014;15:3403-10.

- Bongartz T, Warren FC, Mines D, et al. Etanercept therapy in rheumatoid arthritis and the risk of malignancies: a systematic review and individual patient data meta-analysis of randomised controlled trials. *Ann Rheum Dis* 2009;68:1177-83.

- Michaud TL, Rho YH, Shamliyan T, et al. The comparative safety of tumor necrosis factor inhibitors in rheumatoid arthritis: a meta-analysis update of 44 trials. *Am J Med* 2014;127:1208-32.

- Askling J, Fahrbach K, Nordstrom B, et al. Cancer risk with tumor necrosis factor alpha (TNF) inhibitors: meta-analysis of randomized controlled trials of adalimumab, etanercept, and infliximab using patient level data. Pharmacoepidemiol Drug Saf 2011;20:119-30.

- Lopez-Olivo MA, Tayar JH, Martinez-Lopez JA, et al. Risk of malignancies in patients with rheumatoid arthritis treated with biologic therapy: a meta-analysis. Jama 2012;308:898-908.

- Leombruno JP, Einarson TR, Keystone EC. The safety of anti-tumour necrosis factor treatments in rheumatoid arthritis: meta and exposure-adjusted pooled analyses of serious adverse events. Ann Rheum Dis 2009;68:1136-45.

- Le Blay P, Mouterde G, Barnetche T, et al. Short-term risk of total malignancy and nonmelanoma skin cancers with certolizumab and

golimumab in patients with rheumatoid arthritis: metaanalysis of randomized controlled trials. J Rheumatol 2012;39:712-5.

- Singh JA, Wells GA, Christensen R, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane Database Syst Rev 2011;CD008794.

- Thompson AE, Rieder SW, Pope JE. Tumor necrosis factor therapy and the risk of serious infection and malignancy in patients with early rheumatoid arthritis: a meta-analysis of randomized controlled trials. Arthritis Rheum 2011;63:1479-85.

- Mariette X, Matucci-Cerinic M, Pavelka K, et al. Malignancies associated with tumour necrosis factor inhibitors in registries and prospective observational studies: a systematic review and meta-analysis. *Ann Rheum Dis* 2011;70:1895-904.

- Mercer LK, Lunt M, Low AL, et al. Risk of solid cancer in patients exposed to anti-tumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. *Ann Rheum Dis* 2015;74:1087-93.

- Wadström H, Frisell T, Askling J. Anti-Rheumatic Therapy in Sweden (ARTIS) Study Group. Malignant Neoplasms in Patients With Rheumatoid Arthritis Treated With Tumor Necrosis Factor Inhibitors, Tocilizumab, Abatacept, or Rituximab in Clinical Practice: A Nationwide Cohort Study From Sweden. *JAMA Intern Med*. 2017;177(11):1605-1612.

- Buchbinder R, Van Doornum S, Staples M, Lassere M, March L. Malignancy risk in Australian rheumatoid arthritis patients treated with anti-tumour necrosis factor therapy: analysis of the Australian Rheumatology Association Database (ARAD) prospective cohort study. *BMC Musculoskelet Disord*. 2015;16:309.

- Wu CY, Chen DY, Shen JL, et al. The risk of cancer in patients with rheumatoid arthritis taking tumor necrosis factor antagonists: a nationwide cohort study. Arthritis Res Ther 2014;16:449.

- Haynes K, Beukelman T, Curtis JR, et al. Tumor necrosis factor alpha inhibitor therapy and cancer risk in chronic immune-mediated diseases. Arthritis Rheum 2013;65:48-58.

- Wolfe F, Michaud K. Biologic treatment of rheumatoid arthritis and the risk of malignancy: analyses from a large US observational study. Arthritis Rheum. 2007 Sep;56(9):2886-95.

- Harigai M, Nanki T, Koike R, et al. Risk for malignancy in rheumatoid arthritis patients treated with biological disease-modifying antirheumatic drugs compared to the general population: A nationwide cohort study in Japan. *Mod Rheumatol* 2016;1-9.

- Lan JL, Tseng CH, Chen JH, Cheng CF, Liang WM, Tsay GJ. Reduced risk of all-cancer and solid cancer in Taiwanese patients with rheumatoid arthritis treated with etanercept, a TNF-α inhibitor. Medicine (Baltimore). 2017;96(7):e6055.
- Hellgren K, Dreyer L, Arkema EV, et al. Cancer risk in patients with spondyloarthritis treated with TNF inhibitors: a collaborative study from the ARTIS and DANBIO registers. *Ann Rheum Dis* 2017 Jan;76(1):105-111.
- Nyboe Andersen N, Pasternak B, Basit S, et al. Association between tumor necrosis factor-alpha antagonists and risk of cancer in patients with inflammatory bowel disease. *Jama* 2014;311:2406-13.
- Pundole, X., Zamora, N.V., Siddhanamatha, H. *et al.* Overall survival in patients with rheumatoid arthritis and solid malignancies receiving biologic disease-modifying antirheumatic therapy. *Clin Rheumatol*. 2020;39:2943-2950.
- Pappas DA, Rebello S, Liu M, Schenfeld J, Li YF, Collier DH et al. Therapy With Biologic Agents After Diagnosis of Solid Malignancies: Results From the Corrona Registry. The Journal of Rheumatology Apr 2019, jrheum.171457.
- Burmester GR, Panaccione R, Gordon KB, et al. Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. *Ann Rheum Dis* 2013;72:517-24.
- Dreyer L, Mellemkjaer L, Andersen AR, et al. Incidences of overall and site specific cancers in TNFalpha inhibitor treated patients with rheumatoid arthritis and other arthritides - a follow-up study from the DANBIO Registry. *Ann Rheum Dis* 2013;72:79-82.
- Scott FI, Mamtani R, Brensinger CM, et al. Risk of Nonmelanoma Skin Cancer Associated With the Use of Immunosuppressant and Biologic Agents in Patients With a History of Autoimmune Disease and Nonmelanoma Skin Cancer. *JAMA Dermatol*. 2016;152(2):164-172.
- Raaschou P, Simard JF, Asker Hagelberg C, et al. Rheumatoid arthritis, anti-tumour necrosis factor treatment, and risk of squamous cell and basal cell skin cancer: cohort study based on nationwide prospectively recorded data from Sweden. *Bmj* 2016;352:i262.
- Fagerli KM, Kearsley-Fleet L, Mercer LK, et al. Malignancy and mortality rates in patients with severe psoriatic arthritis requiring tumour-necrosis factor alpha inhibition: results from the British Society for Rheumatology Biologics Register. *Rheumatology (Oxford)*. 2019;58(1):80-85.
- Raaschou P, Simard JF, Holmqvist M, et al. Rheumatoid arthritis, anti-tumour necrosis factor therapy, and risk of malignant melanoma: nationwide population based prospective cohort study from Sweden.

*Bmj* 2013;346:f1939.

- Mercer LK, Askling J, Raaschou P, et al. Risk of invasive melanoma in patients with rheumatoid arthritis treated with biologics: results from a collaborative project of 11 European biologic registers. *Ann Rheum Dis 2017;76:386–391.*
- Damento GM, Pulido JS, Abbott BA, Hodge DO, Dalvin LA. TNF-Alpha Inhibition and Other Immunosuppressants in the Development of Uveal and Cutaneous Melanoma. *Mayo Clin Proc*. 2019;94(7):1287-1295.
- Esse S, Mason KJ, Green AC, Warren RB. Melanoma Risk in Patients Treated With Biologic Therapy for Common Inflammatory Diseases: A Systematic Review and Meta-analysis. JAMA Dermatol. Jul 2020;156(7):787-794
- Lee J, Clarke K. Anti-TNF agents in patients with inflammatory bowel disease

  and malignant melanoma—challenges in management. Int J Colorectal Dis. 2015 Dec;30(12):1595-602.
- Mercer LK, Low AS, Galloway JB, et al. Anti-TNF therapy in women with rheumatoid arthritis with a history of carcinoma in situ of the cervix. Ann Rheum Dis 2013;72:143-4.
- Cordtz R, Mellemkjaer L, Glintborg B, et al. Malignant progression of precancerous lesions of the uterine cervix following biological DMARD therapy in patients with arthritis. Ann Rheum Dis 2015;74:1479-80.
- Wadstrom H, Frisell T, Sparen P, et al. Do RA or TNF inhibitors increase the risk of cervical neoplasia or of recurrence of previous neoplasia? A nationwide study from Sweden. Ann Rheum Dis 2016;75(7):1272-8.
- Weinblatt ME, Bathon JM, Kremer JM, et al. Safety and efficacy of etanercept beyond 10 years of therapy in North American patients with early and longstanding rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2011;63:373-82.
- Bykerk VP, Cush J, Winthrop K, et al. Update on the safety profile of certolizumab pegol in rheumatoid arthritis: an integrated analysis from clinical trials. *Ann Rheum Dis* 2015;74:96-103.
- Kay J, Fleischmann R, Keystone E, et al. Golimumab 3-year safety update: an analysis of pooled data from the long-term extensions of randomised, double-blind, placebo-controlled trials conducted in patients with rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis. *Ann Rheum Dis* 2015;74:538-46.
- Mariette X, Tubach F, Bagheri H, et al. Lymphoma in patients treated with anti-TNF: results of the 3-year prospective French RATIO registry. *Ann Rheum Dis* 2010;69:400-8.
- Mercer LK, Regierer AC, Mariette X, Dixon WG, Baecklund E, Hellgren K et al. Spectrum of lymphomas across different drug treatment groups

in rheumatoid arthritis: a European registries collaborative project. Ann Rheum Dis 2017;76:2025–2030.

- Hellgren K, Di Giuseppe D, Smedby KE, Sundström C, Askling J, Baecklund A, for the ARTIS study group, Lymphoma risks in patients with rheumatoid arthritis treated with biological drugs—a Swedish cohort study of risks by time, drug and lymphoma subtype, *Rheumatology (Oxford) 2020*, keaa330.
- Lemaitre M, Kirchgesner J, Rudnichi A, et al. Association Between Use of Thiopurines or Tumor Necrosis Factor Antagonists Alone or in Combination and Risk of Lymphoma in Patients With Inflammatory Bowel Disease. *JAMA*. 2017;318(17):1679-1686.
- Raaschou P, Söderling J, Turesson C, Askling J; ARTIS Study Group. Tumor Necrosis Factor Inhibitors and Cancer Recurrence in Swedish Patients With Rheumatoid Arthritis: A Nationwide Population-Based Cohort Study. *Ann Intern Med*. 2018;169(5):291-299.
- Micic D, Komaki Y, Alavanja A, Rubin DT, Sakuraba A. Risk of Cancer Recurrence Among Individuals Exposed to Antitumor Necrosis Factor Therapy: A Systematic Review and Meta-Analysis of Observational Studies. *J Clin Gastroenterol*. 2019;53(1):e1-e11.
- Lesage C, Longvert C, Prey S, Maanaoui S, Dréno B, Machet L et al. Incidence and Clinical Impact of Anti-TNFα Treatment of Severe Immune Checkpoint Inhibitor-induced Colitis in Advanced Melanoma: The Mecolit Survey. J Immunother. 2019 Jun;42(5):175-179.
- Okihiro A, Hasija R, Fung L, et al. Development of neoplasms in pediatric patients with rheumatic disease exposed to anti-tumor necrosis factor therapies: a single Centre retrospective study. *Pediatr Rheumatol Online J*. 2018;16(1):17.
- Hooper M, Wenkert D, Bitman B, et al. Malignancies in children and young adults on etanercept: summary of cases from clinical trials and post marketing reports. *Pediatr Rheumatol Online J* 2013;11:35.
- Beukelman T, Xie F, Chen L, Horton D, Lewis JD, Mamtani R, et al. Risk of malignancy associated with paediatric use of tumour necrosis factor inhibitors. Ann Rheum Dis. 2018 Jul;77(7):1012-1016.
- van Vollenhoven RF, Fleischmann RM, Furst DE, et al. Longterm Safety of Rituximab: Final Report of the Rheumatoid Arthritis Global Clinical Trial Program over 11 Years. *J Rheumatol* 2015;42:1761-6.
- Emery P, Furst DE, Kirchner P, Melega S, Lacey S, Lehane PB. Risk of Malignancies in Patients with Rheumatoid Arthritis Treated with Rituximab: Analyses of Global Postmarketing Safety Data and Long-Term Clinical Trial Data. *Rheumatol Ther*. 2020;7(1):121-131.
- Lopez-Olivo, Colmegna I, Karpes Matusevich AR, Qi SR, Zamora NV, Sharma R et al. Systematic Review of Recommendations on the Use of Disease-Modifying Antirheumatic Drugs in Patients With Rheumatoid Arthritis and Cancer. Arthritis Care Res. 2020;72: 309-318

- Daien C, Hua C, Gaujoux-Viala C, Cantagrel A, Dubremetz M, Dougados M, et al. Update of French society for rheumatology recommendations for managing rheumatoid arthritis. Joint Bone Spine 2019;86:135-50.
- Schiff MH, Kremer JM, Jahreis A, et al. Integrated safety in tocilizumab clinical trials. *Arthritis Res Ther* 2011;13:R141.
- Rubbert-Roth A, Sebba A, Brockwell L, et al. Malignancy rates in patients with rheumatoid arthritis treated with tocilizumab. *RMD Open* 2016;2 e000213.
- Yamamoto K, Goto H, Hirao K, et al. Longterm Safety of Tocilizumab: Results from 3 Years of Followup Postmarketing Surveillance of 5573 Patients with Rheumatoid Arthritis in Japan. *J Rheumatol* 2015;42:1368-75.
- Kim SC, Pawar A, Desai RJ, et al. Risk of malignancy associated with use of tocilizumab versus other biologics in patients with rheumatoid arthritis: A multi-database cohort study. *Semin Arthritis Rheum*. 2019;49(2):222-228.
- Peleva E, Exton LS, Kelley K, Kleyn CE, Mason KJ, Smith CH. Risk of cancer in patients with psoriasis on biological therapies: a systematic review. *Br J Dermatol*. 2018;178(1):103-113.
- Weinblatt ME, Moreland LW, Westhovens R, et al. Safety of abatacept administered intravenously in treatment of rheumatoid arthritis: integrated analyses of up to 8 years of treatment from the abatacept clinical trial program. *J Rheumatol* 2013;40:787-97.
- Montastruc F, Renoux C, Dell'Aniello S, et al. Abatacept initiation in rheumatoid arthritis and the risk of cancer: a population-based comparative cohort study. *Rheumatology. 2019;58(4):683-691.*
- de Germay S, Bagheri H, Despas F, Rousseau V, Montastruc F. Abatacept in rheumatoid arthritis and the risk of cancer: a world observational post-marketing study [published online ahead of print, 2019 Dec 27]. *Rheumatology (Oxford)*. 2019;kez604.
- Ozen G, Pedro S, Schumacher R, Simon TA, Michaud K. Safety of abatacept compared with other biologic and conventional synthetic disease-modifying antirheumatic drugs in patients with rheumatoid arthritis: data from an observational study. *Arthritis Res Ther*. 2019;21(1):141.
- Harigai M. Growing evidence of the safety of JAK inhibitors in patients with rheumatoid arthritis. *Rheumatology (Oxford)*. 2019;58(Suppl 1):i34-i42.
- Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. Science. 2011 Mar 25;331(6024):1565-70.

- Maneiro JR, Souto A, Gomez-Reino JJ. Risks of malignancies related to tofacitinib and biological drugs in rheumatoid arthritis: Systematic review, meta-analysis, and network meta-analysis. *Semin Arthritis Rheum*. 2017;47(2):149-156. doi:10.1016/j.semarthrit.2017.02.007

- Olivera PA, Lasa JS, Bonovas S, Danese S, Peyrin-Biroulet L. Safety of Janus Kinase Inhibitors in Patients With Inflammatory Bowel Diseases or Other Immune-mediated Diseases: A Systematic Review and Meta-Analysis. *Gastroenterology*. 2020;158(6):1554-1573.e12.
- Pfizer shares co-primary endpoint results from post-marketing required safety study of XELJANZ® (tofacitinib) in subjects with rheumatoid arthritis. Available online at: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-shares-co-primary-endpoint-results-post-marketing [Consulted 2021/02/18]


## Tables and figures

### Table 1. Comparison of cancer risk assessment methods in rheumatic diseases

| Study design | Advantages | Limits |
|---|---|---|
| **Randomized controlled trials (RCTs)** | High level of evidence for treatments efficacy and safety.<br>Control of the treatment exposure | Short durati<br>Selection bi<br>Limited sam |
| **Meta-analyses of RCTs** | Same than RCTs + larger sample size | Short durati<br>Selection bi |
| **Long term extension studies** | Same than RCTs +<br>longer duration of follow-up | Selection bi<br>Limited sam |
| **Cohort and registry studies** | Large sample size.<br>Unselected population.<br>Detailed data on the underlying disease, treatment, and co-morbidities. | Risk of rem<br>Possible lac<br>events. |
| **Health insurance database studies** | Larger sample size than cohort and registry.<br>Representativeness. | Less inform<br>potential co |

### Table 2. Meta-analyses and large observational studies assessing the risk of overall malignancies in anti-TNF patients compared to biologic-naïve patients

| Meta-analyses of Randomized controlled trials | Indication | Number of studies | Drugs | Risk of overall malign<br>Risk (OR, RR or HR) ( |
|---|---|---|---|---|
| Bongartz 2006 (16) | RA | 7<br>9 | Infliximab<br>adalimumab | OR= 3.29 (1.19-9.08)<br>Revised: OR=2.4 (1.2 |
| Bongartz, 2009 (18) | RA | 9 | Etanercept | OR=1.8 (0.8-4.3) |

| | | | | |
|---|---|---|---|---|
| Leombruno, 2009 (22) | RA | 18 | Infliximab<br>Adalimumab<br>Etanercept | Recommended doses:<br>High dose: OR= 2.49 (<br>Including skin cancer a |
| Askling, 2011 (20) | All inflammatory diseases | 74 | Infliximab<br>Adalimumab<br>Etanercept | HR=0.99 (0.61-1.68)<br>Excluding NMSC |
| Lopez-Olivo, 2012 (21) | RA | 63 | Infliximab, Adalimumab, Etanercept, certolizumab, Golimumab | OR=1.31 (0.78-2.20)<br>(20 trials)<br>Solid tumors (excluding malignancies) |
| Thompson, 2011 (25) | Early RA | 6 | Infliximab<br>Adalimumab<br>Etanercept | OR=1.08 (0.50-2.32) |
| Le Blay, 2012 (23) | RA | 6 | Certolizumab<br>Golimumab | OR=1.06 (0.39-2.85)<br>Excluding NMSC |
| Liu, 2014 (17) | RA | 34 | Infliximab, Adalimumab, Etanercept, certolizumab, Golimumab | All doses: RR (ITT): 1.3<br>High dose: RR (ITT: 2<br>Approved dose: RR (IT<br>Low dose: RR (ITT): 0. |
| Michaud, 2014 (19) | RA | 44 | Infliximab, Adalimumab, Etanercept, certolizumab, Golimumab | OR= 1.29 (0.85-1.97) |
| Singh, 2016 (24)<br>Cochrane | n | 79<br>Including 19 reporting cancer data | | All anti-TNF = 9 trials<br>OR 1.21(0.63 to 2.38)<br>All biologics: 16 trials<br>OR of 1.07 (0.68 to 1.6 |
| **Pooled analyses of observational studies or large database** | **Indication** | **Number of studies or number of patients** | **Drugs** | **Risk of overall malign**<br>**Risk (OR, RR or HR) (** |
| Mariette, 2011 (26) | RA, AS | 29 studies of 12 registries | Infliximab<br>Adalimumab<br>Etanercept | 0.95 (0.85-1.05) |

| | | | | |
|---|---|---|---|---|
| Nyboe Andersen, 2014 (41) | IBD | 4 databases<br>4553 pts /56146 pts | Infliximab<br>Adalimumab<br>Certolizumab | RR=1.07 (0.85-1.36) |
| Haynes, 2013 (32)<br>SABER | RA | anti-TNF= 19,750 pts,<br>not-exposed= 9,805 pts | Infliximab, Adalimumab, Etanercept, | During exposure<br>HR=0.80 (0.59–1.08)<br>Until start of an alterna<br>HR=0.94 (0.79–1.12) |
| Wu, 2014 (31) | RA | anti-TNF= 4,426 pts<br>not-exposed= 17,704 pts | All anti-TNF | aHR: 0.63 (0.49 to 0.8<br>SIR= 0.83 (0.65, 1.04)<br>Anti-TNF vs. taiwanese |
| Buchbinder, 2015 (30)<br>ARAD registry | RA | 5,752 person-years exposed to TNFi | Infliximab, etanercept, adalimumab | SIR=0.77 (0.58, 1.04) c population<br>SIR=0.65 (0.37, 1.17) c patients |
| Harigai, 2016 (38)<br>SECURE database | RA | Biologic exposed: 14,440 pts | infliximab, etanercept,<br>adalimumab, golimumab, tocilizumab, or abatacept | SIR= 0.75 (0.67–0.83)<br>All biologics vs. Japan reference |
| Wadström, 2017 (28)<br>ARTIS registry | RA | Biologic exposed: 15,129 TNFi users, 7,405 other bDMARDs users | TNFi, abatacept, tocilizumab, rituximab | For TNFi as 1st bDMAR<br>For TNFi as 2nd bDMA |

AS: ankylosing spondylitis; IBD: inflammatory bowel diseases; PsA: psoriatic arthritis; RA: rheumatoid arthritis

**Table 3. Meta-analyses and large observational studies assessing the risk of organ specific solid cancers (breast, colorectal, lung or prostate cancer) in patients with bDMARD**

| Meta-analyses of Randomized controlled trials | Indication | Number of studies or number of patients | Drugs | Risk of specific solid<br>Risk (OR, RR or HR) |
|---|---|---|---|---|
| Liu 2014 (17) | RA | 28 RCTs, 11,741 pts | TNFi | For TNFi vs bionaive p<br>Breast cancer: OR= 0 |
| Wolfe 2007 (36)<br>NDBRB registry | RA | 13,001 pts (5,257 bDMARD-treated, 7,744 bionaive pts) | Adalimumab, Anakinra, Etanercept, Infliximab | For bDMARD vs biona<br>Breast cancer: OR= 0<br>Colorectal cancer: OR<br>Lung cancer: OR= 1.1<br>Prostate cancer: OR= |
| Haynes 2013 (32)<br>SABER | RA, IBD, psoriasis, PsA | 13,102 PR for RA; 1,508 PY for IBD; 371 PY for psoriasis; 618 PY for PsA | TNFi | For TNFi vs bionaive p<br>Breast cancer: HR= 0<br>Colorectal cancer: HR<br>Lung cancer: HR= 0.7<br>Prostate cancer: HR= |
| Nyboe Andersen 2014 (41)<br>Danish Civil Registration System, National Patient Registry & Danish Cancer Registry | IBD | 489,433 PY | TNFi | For TNFi vs bionaive p<br>Breast Cancer: RR= 0<br>Colorectal cancer: RR<br>Lung cancer: RR= 1.1 |
| Buchbinder 2015 (30)<br>ARAD | RA | 5,752 PY for TNFi; 1682 PY for bionaive pts | TNFi | For TNFi vs bionaive p<br>Breast cancer: RR= 0<br>Colorectal cancer: RR<br>Lung cancer: RR= 0.2<br>Prostate cancer: RR= |
| Mercer 2015 (27)<br>BSRBR registry | RA | 52,549 PY for TNFi; 11,672 for bionaive pts | TNFi | For TNFi vs bionaive p<br>Breast cancer: HR=0.<br>Colorectal cancer: HR<br>Lung cancer: HR=0.85 |

| | | | | |
|---|---|---|---|---|
| Hellgren 2017 (40)<br>ARTIS & DANBIO registries | AS, PsA | 8,703 pts with TNFi; 28,164 bionaive pts with AS or PsA; | TNFi | For TNFi vs bionaive p<br>Breast cancer: RR=1.<br>Colorectal cancer: RR<br>Lung cancer: RR=0.6<br>Prostate cancer: RR= |
| Montastruc 2019 (74)<br>Truvet MarketScan & Medicare | RA | 64,188 patients (4,328 on abatacept vs 59,860 on other bDMARDs) | Abatacept, other bDMARDs (Adalimumab, Anakinra, Certolizumab Pegol, Etanercept, Golimumab, Infliximab, Rituximab, Tocilizumab, Tofacitinib) | For abatacept compar<br>Breast cancer: HR=1.<br>Lung cancer: HR=1.25 |
| Ozen 2019 (76)<br>MarketScan, PharMetrics, and Optum | RA | 146,900 pts (37,000 on abatacept vs 109,900 on other bDMARDs | Abatacept, other bDMARDs (Adalimumab, Anakinra, Certolizumab Pegol, Etanercept, Golimumab, Infliximab, Rituximab, Tocilizumab, Tofacitinib) | For abatacept compar<br>Breast cancer: HR=1.<br>Lung cancer: HR=1.1 |

AS: ankylosing spondyloarthritis; bDMARDs: biologic disease modifying anti-rheumatic drugs; IBD: inflammatory bowel disease; PsA: psoriatic arthritis; RA; rheumatoid arthritis; TNFi: TNF inhibitor

## Table 4. Studies analyzing the risk of non-melanoma skin cancer and melanoma with TNFi

| **Study** | **Indication** | **Number of studies** | **Drugs** | **Risk of non-melanoma skin cancer<br>Risk (OR, RR or HR) (95%CI)** |
|---|---|---|---|---|
| **Meta-analyses of Randomized controlled trials** | | | | |

| | | | | |
|---|---|---|---|---|
| Leombruno, 2009 (22) | RA, AS | 18 | Infliximab<br>Adalimumab<br>Etanercept | Recommended dose<br>OR=1.27 (0.67 to 2.42)<br>High dose<br>0.93 (0.27 to 3.15) |
| Askling, 2011 (20) | All | 74 | Infliximab<br>Adalimumab<br>Etanercept | HR= 2.02 (1.11 to 3.95) |
| Lopez-Olivo, 2012 (21) | RA | 63 | Infliximab,<br>Adalimumab,<br>Etanercept,<br>certolizumab,<br>Golimumab | OR=1.37 (0.59-3.19)<br>12 studies |
| Le Blay, 2012 (23) | RA | 6 | Certolizumab<br>Golimumab | OR=0.69 (95% CI 0.23–2.11) |
| **Long term extension of RCT** | | | | |
| Burmester, 2013 (35) | RA<br>AS<br>PsA<br>Ps<br>CD | 71<br>(23 458 pts) | Adalimumab | In RA: SIR= 1.39 (1.19 to 1.60)<br>In PsA: SIR= 1.76 (1.26 to 2.39)<br>In CD:SIR= 2.29 (1.44 to 4.47)<br>Not increased in AS and PsA patients<br>Anti-TNF vs. general population (SEER as reference) |
| **Pooled analyses of Observational studies** | | | | |
| Mariette, 2011 (26) | RA | 29 studies of 12 registries | Infliximab<br>Adalimumab<br>Etanercept | RR : 1.33 (95% CI 1.06, 1.60). |
| Nyboe Andersen, 2014 (41) | IBD | 4 databases<br>Anti-TNF :4553 pts<br>Not exposed: 56146 | Infliximab<br>Adalimumab<br>Certolizumab | |
| **Observational studies** | | **Number of patients** | | |
| Mercer, 2012<br>BSRBR (15) | RA | Anti-TNF=<br>11881<br>Not-exposed=<br>3629 | | Overall<br>HR= 0.95 (0.53 to 1.71)<br>Basal cell cancer<br>HR= 1.2 (0.8 to 1.7)<br>Squamous cell cancer<br>HR= 1.8 (0.6 to 5.4)<br>Anti-TNF vs. biologic naïve |
| Haynes, 2013<br>SABER (32) | RA | anti-TNF= 19750<br>not-exposed= 9805 | Infliximab,<br>Adalimumab,<br>Etanercept, | During exposure<br>HR=0.83 (0.49–1.42)<br>Until start of an alternative treatment<br>HR=1.07 (0.79-1.46) |
| Dreyer, 2013<br>DANBIO (44) | RA<br>AS<br>PsA | anti- TNF= 5345<br>not-exposed= 4351 | | HR= 1.10 (0.69 to 1.76)<br>Anti-TNF vs. biologic naïve<br>SIR= 1.92 (1.42 to 2.59)<br>Anti-TNF vs. general population |

| | | | | |
|---|---|---|---|---|
| Raaschou, 2013<br>ARTIS (48) | RA | Anti-TNF =<br>10 878<br>not-exposed=<br>42 198 | | |
| Raaschou, 2016<br>ARTIS (46) | RA | anti-TNF (n=12558)<br>not-exposed (n=46409) | | Basal cell cancer<br>HR= 1.22 (1.07 to 1.41)<br>Biologic-naive vs. Swedish general population<br>HR= 1.14 (0.98 to 1.33)<br>Anti-TNF vs. biologic-naive<br>Squamous cell cancer<br>HR= 1.88 (1.74 to 2.03)<br>Biologic-naive vs. Swedish general population<br>HR=1.30 (1.10 to 1.55)<br>Anti-TNF vs. biologic-naive |
| Wu, 2014 (31) | RA | anti-TNF= 4426<br>not-exposed=17704 | All anti-TNF | SIR= 2.05 (0.66, 4.79)<br><br>Anti-TNF vs. Taiwanese genera population as reference |
| Harigai, 2016 (38)<br>SECURE database | RA | Biologic exposed:<br>14440 | infliximab, etanercept, adalimumab, golimumab, tocilizumab, abatacept | All skin cancer<br>SIR= 1.190 (0.340–2.210)<br>All biologics vs. japanese general population as reference |
| Scott, 2016 (45)<br>Medicare | RA, IBD | TNFi exposed: 2,805 pts | infliximab, adalimumab, certolizumab, golimumab, or etanercept | Total study group: HR=1.49 (95% CI 1.03–2.16) for TNFi compared to methotrexate alon<br>RA group: HR= 1.49 (1.03–2.16 for TNFi compared to methotrexate alone<br>IBD group: HR= 1.23 (0.78–1.94) for thiopurine vs TNFi |

| | | | | |
|---|---|---|---|---|
| Mercer, 2017 (49)<br>EULAR RODS study group | RA | Total study population: 130,315 pts<br>TNFi exposed: 48,304 pts | infliximab, adalimumab, certolizumab, golimumab, or etanercept<br><br>rituximab, tocilizumab, abatacept | |
| Damento, 2019 (50) | AS, IBD, PsA, RA, psoriasis | 1221 cases of melanoma | infliximab, adalimumab, certolizumab, golimumab, or etanercept | |
| Fagerli, 2019 (47)<br>BSRBR | PsA | TNFi exposed: 709 pts | Infliximab, adalimumab, etanercept | SIR 2.12 (95% CI: 1.19, 3.50) compared with the general population |

AS: ankylosing spondylitis; IBD: inflammatory bowel diseases; PsA: psoriatic arthritis; RA: rheumatoid arthritis;

## Table 5. Studies analyzing the risk of lymphoma with TNFi in Rheumatic diseases

| **Study** | **Indication** | **Number of studies** | **Drugs** | **Risk of lymphoma compared to RA controls<br>Risk (OR, RR or HR) (95%CI)** |
|---|---|---|---|---|
| **Meta-analyses of Randomized controlled trials** | | | | |
| Leombruno, 2009 (22) | RA | 18 | Infliximab<br>Adalimumab<br>Etanercept | Standard doses : OR=1.26 (0.52 to 3.06)<br>High doses : OR=1.14 (0.28 to 4.61) |
| Lopez-Olivo, 2012 (21) | RA | 63 | Infliximab,<br>Adalimumab,<br>Etanercept,<br>certolizumab,<br>Golimumab | 2.14 (0.55-8.38)<br>10 studies |
| **Long-term extension studies** | | | | |
| Weinblatt, 2011 (48) | RA | 9 | Etanercept | |
| Bykerk, 2013 (49) | RA | 10 | Certolizumab | |

| | | | | |
|---|---|---|---|---|
| Burmester, 2013 (35) | RA<br>AS<br>PsA | 71<br>(23 458 pts) | Adalimumab | |
| Kay, 2015 (50) | RA<br>AS<br>PsA | 6 | Golimumab | |
| **Pooled analyses of observational studies** | | | | |
| Mariette, 2011 (26) | RA and AS | 29 studies of 12 registries | Infliximab<br>Adalimumab<br>Etanercept | RR: 1.11 (0.70-1.51) |
| Nyboe Andersen, 2014 (41) | IBD | 4 databases<br>Anti-TNF :4553 pts<br>Not exposed: 56146 | Infliximab<br>Adalimumab<br>Certolizumab | All hematologic malignancies:<br>RR=1.36 (0.67-2.76)<br>RR=0.90 (0.42-1.91) adjusted for azathioprim use |
| **Observational studies*** | | | | |
| Mariette, 2010 (56)<br>RATIO | All indication | 38 cases of lymphoma | Infliximab<br>Adalimumab<br>Etanercept | Etanercept as reference<br>Infliximab :<br>OR= 4.73 (1.27-17.65)<br>Adalimumab :<br>OR= 4.12 (1.36-12.49) |
| Haynes, 2013 (32)<br>SABER | RA | anti-TNF 19,750,<br>not-exposed 9,805 | Infliximab,<br>Adalimumab,<br>Etanercept, | During exposure<br>HR= 0.83 (0.33–2.05)<br>Until start of an alternative treatment<br>HR= 1.25 (0.71–2.20) |
| Wu, 2014 (31) | RA | anti-TNF 4426<br>not-exposed 17704 | All anti-TNF | |
| Harigai, 2016 (38)<br>SECURE database | RA | Biologic exposed: 14440 | infliximab,<br>etanercept,<br>adalimumab,<br>golimumab,<br>tocilizumab, or<br>abatacept | |
| Mercer, 2017 (57)<br>EULAR RODS study group | RA | Total study group: 124,997 pts<br>TNFi users: 47,864 pts | infliximab,<br>etanercept,<br>certolizumab,<br>adalimumab,<br>golimumab,<br>tocilizumab, or<br>abatacept | Incidence in TNFi pts: 81/100,000 pyrs<br><br>Incidence in bionaive pts: 89/100,000 pyrs |

| | | | | |
|---|---|---|---|---|
| Hellgren, 2020 (58)<br>SRQ | RA | 107,638 pyrs for bDMARD users | adalimumab, certolizumab pegol, etanercept, golimumab and infliximab<br>rituximab, anakinra, abatacept, tocilizumab | HR=1.11 (0.23-5.37) for TNFi users vs other bDMARD users |

*Published after the 2011 meta-analysis of Mariette *et al*., or providing additional information

AS: ankylosing spondylitis; IBD: inflammatory bowel diseases; PsA: psoriatic arthritis; RA: rheumatoid arthritis

## Table 6. Risk of malignancies associated with biologics other than TNFi: Randomized controlled trial and longterm extension studies data

| Study | Indication | Number of studies | Drugs | Risk of overall malignancies | Risk of lymphoma |
|---|---|---|---|---|---|
| **Meta-analyses of Randomized controlled trials** | | | | **Compared to RA controls** | |
| Lopez-Olivo, 2012 (21) | RA | 63 | All anti TNF<br>Abatacept<br>Rituximab<br>Tocilizumab | Abatacept (4 trials)<br>OR= 0.82<br>(0.22-3.01)<br>Rituximab (4 trials)<br>OR= 2.28<br>(0.72-7.25)<br>Tocilizumab (4 trials)<br>OR= 2.22<br>(0.79-6.20)<br>Solid tumors (excluding skin cancer and hematologic malignancies) | Abatacept (1 tria<br>OR=4.51<br>(0.07-285.89)<br>Tocilizumab (1 trial)<br>OR= 0.05<br>(0.00-3.19) |
| Singh, 2016 (24) Cochrane | RA | 79 | | Non-anti-TNF biologic= OR 0.99 (0.58 to 1.78))<br>(7 trials) | |
| **Long-term extension studies** | | **Number of patients** | | **Compared to general population** | |
| Van Vollenhoven, 2015 (61) | RA | 11 studies: 3595 | Rituximab | SIR: 1.07<br>(0.88–1.29) SEER as reference | |
| Weinblatt, 2013 (70) | RA | 7 studies: 4134 | Abatacept | SIR: 0.99 (0.80, 1.22) SEER as reference | SIR: 2.49 (1.14, 4.73) SEER as reference |
| Rubbert-Roth, 2016 (70) | RA | 4009 | Tocilizumab | SIR=1.36<br>(1.01-1.80) SEER as reference<br>ence<br>SIR=1.81<br>(1.44-2.23)<br>GLOBOCAN as refer | non-Hodgkin lymphoma<br>SIR= 3.98<br>[1.07-10.18] SE<br>as reference |

| | | | | | |
|---|---|---|---|---|---|
| Yamamoto, 2015 (71) | RA | 5573 | Tocilizumab | Japanese general population as reference<br>SIR: 0.79 (0.66 to 0.95) | SIR: 3.13 (1.82 t<br>5.39)<br>Japanese gener<br>population as reference |
| Emery, 2020 (66) | RA | 409,706 patients exposed to rituximab | Rituximab | SEER population as reference: SIR= 1.1 (0.9–1.3)<br>RA pts as reference: SIR=1.07 (0.88–1.29) | |
| De Germay, 2020 (75)<br>VigiBase | RA | 306,414 RA ptswith a bDMARD (15,846 with abatacept and 290,568 with other bDMARDs) | Abatacept, Other bDMARDs (all TNFi, rituximab, tocilizumab, anakinra, sarilumab, tofacitinib) | ROR=0.98 (0.91, 1.05) for abatacept vs other bDMARDs | |
| **Observational studies** | | | | | |
| Peleva, 2017 (73) | psoriasis | 280 to 4410 pts 8 prospective cohort studies | Ustekinumab, etanercept, infliximab, adalimumab | Any cancer: SIR 0.98 (0.74–1.29) for ustekinumab users | SIR 0.80 (0.10 –2.91) for ustekinumab users |
| Montastruc, 2019 (74)<br>Medicare, Marketscan | RA | 4,328 abatacept users<br>59,860 other bDMARD users | Abatacept, other bDMARDs | aHR= 1.17 (1.06, 1.30) for abatacept vs other bDMARDs | |
| Kim, 2019 (72)<br>Medicare, IMS, Marketscan | RA | 13,102 tocilizumab users<br>26,727 TNFi users | Tocilizumab, TNFi | HR = 0.98 (95%CI 0.80-1.19) for tocilizumab vs TNFi | |
| Ozen, 2019 (76)<br>FORWARD | RA | 1,429 abatacept users, 3,490 other bDMARD users | Abatacept, other bDMARDs (adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab and tocilizumab) | HR=1.89 (0.93, 3.84) for abatacept vs other bDMARDs<br>HR= 0.93 (0.20, 4.27) for abatacept vs csDMARDs | |

AS: ankylosing spondylitis; IBD: inflammatory bowel diseases; PsA: psoriatic arthritis; RA: rheumatoid arthritis