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REVIEW

Biologics Versus JAK Inhibitors. Part I: Cancer Risk. A Narrative Review

Miguel Mansilla-Polo · Daniel Morgado-Carrasco

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ABSTRACT

***Introduction*:** Biological drugs (BD) and Janus kinase inhibitors (JAKi) have revolutionized the treatment of diverse dermatoses. However, there are concerns regarding their safety, especially the risk of cancer and opportunistic infections. Here, we discuss the risk of cancer associated with the BD and JAKi used in dermatology.

***Methods*:** A narrative review was carried out. All relevant articles evaluating the risk of cancer associated with BD or JAKi and published between January 2010 and February 2024 were selected.

***Results*:** Multiple large studies have evaluated the association between BD, JAKi and cancer risk. However, there is a lack of prospective, comparative studies. Overall, patients undergoing BD and JAKi present a cutaneous cancer incidence similar to that in the general population. The drugs more strongly associated with non-skin cancer risk were anti-tumor necrosis factor (anti-TNFs) agents and JAKi (especially tofacitinib and oral ruxolitinib). This risk appears to increase with age, the presence of other factors (such as chronic immunosuppression from previous drugs or other comorbidities), and specific diseases such as rheumatoid arthritis (RA) and myelodysplastic syndrome. Conversely, BD such as interleukin (IL)-17 and IL-23 inhibitors may even reduce the risk of some visceral and hematological malignancies. In patients with dermatological conditions such as psoriasis and atopic dermatitis, the risk of malignancies may be lower than in other subgroups, and probably comparable to the general population.

***Conclusions*:** The incidence of cancer in patients undergoing BD or JAKi is generally low. This incidence can be higher in elderly patients with RA or myelodysplastic syndrome, and in those undergoing prolonged therapy with tofacitinib or ruxolitinib (oral), or anti-TNF agents.

M. Mansilla-Polo
Department of Dermatology, Hospital Universitario y Politécnico La Fe, Valencia, Spain

M. Mansilla-Polo
Instituto de Investigación Sanitaria (IIS) La Fe, Valencia, Spain

M. Mansilla-Polo
Department of Dermatology, Faculty of Medicine, Universitat de València, Villarroel 170, 08036 Valencia, Spain

D. Morgado-Carrasco (✉)
Department of Dermatology, Hospital Clínic de Barcelona, Universitat de Barcelona, Barcelona, Spain
e-mail: morgado@clinic.cat

D. Morgado-Carrasco
Department of Dermatology, Hospital de Figueres, Fundació Alt Empurdà, Figueres, Spain

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Key Summary Points

In general, biological drugs and Janus kinase inhibitors (JAKi) are considered safe regarding the risk of cancer.

The incidence of cancer may be increased in patients undergoing prolonged treatment with with anti-tumor necrosis factor (anti-TNF) agents, tofacitinib and oral ruxolitinib (possibly more so with these latter two agents).

Cancer incidence may be increased in elderly patients or those with other factors, such as chronic immunosuppression from previously administered drugs.

Overall, the risk of cancer in patients with dermatological conditions (such as psoriasis, psoriatic arthritis, or atopic dermatitis) is low, and could be lower than in other subgroups (such as those with rheumatoid arthritis or myelodysplastic syndrome), and possibly comparable to the general population.

INTRODUCTION

Conventional immunosuppressants such as corticosteroids, cyclosporine, methotrexate, or azathioprine present a significant burden of side effects (AEs) [1], including cytopenias (methotrexate or azathioprine), renal dysfunction or hypertension (cyclosporine), and an elevated incidence of cutaneous and extracutaneous neoplasms and opportunistic infections in patients undergoing long-term therapy [2]. Biologic drugs (BD) have revolutionized the management of multiple dermatoses [3]. BD target specific protein receptors, and are typically administered subcutaneously or intravenously. They present a more selective action, and tend to have a more favorable safety profile [4]. Diverse BD are available in dermatology, including inhibitors of tumor necrosis factor alpha (anti-TNF), interleukin (IL)-4 (anti-IL-4), IL-17 (anti-IL-17), and IL-23 (anti-IL-23), among others. BD have been linked to AEs such as generic reactions at injection sites, flu-like symptoms, or respiratory, gastrointestinal, and genitourinary infections [5]. Anti-TNF drugs have been associated with severe reactivation of latent tuberculosis infection (LTBI), reactivation of the hepatitis B virus (HBV), and the occurrence of cutaneous and extracutaneous neoplasms [6].

More recently, Janus kinase inhibitors (JAKi) have emerged. JAKi are a series of proteins essential for intracellular signaling of various cytokines, and play a crucial role in regulating the immune system and inflammation [7]. Currently, six molecules have been approved for use in dermatology: upadacitinib, baricitinib, abrocitinib, ritlecitinib, deucravacitinib, and topical ruxolitinib. Off-label uses have been reported for multiple dermatoses, and the approval of these drugs for diverse inflammatory dermatoses is anticipated (Table 1) [8]. As JAKi block intracellular signaling, they could theoretically reduce systemic AEs, when compared to conventional immunosuppressants [7]. However, concerns have recently arisen about their safety profile. In September 2021, the Food and Drug Administration (FDA) reviewed the post-marketing safety trial results comparing tofacitinib with anti-TNF in rheumatoid arthritis (RA), and concluded that tofacitinib posed a higher risk of major cardiovascular events (MACE), thromboembolic events, malignant neoplasms, and death. Based on these results, a boxed warning was issued, which also extended to other JAKi [8, 9].

In the first part of this review, we will discuss the available evidence regarding the relationship between BD and JAKi used for dermatological disorders, and the risk of cancer.

METHODS

We conducted a narrative review of the literature. Searches were performed on MEDLINE and Google Scholar from January 2010 to February 2024 using the following key terms: "cancer," "malignancy," "skin cancer," "melanoma," "anti-TNF," "etanercept," "infliximab,"

Table 1 Approved indications in dermatology and mechanism of action of the main JAK inhibitors

Drug	Route of administration	Mechanism of action	FDA-approved indications in dermatology	EMA-approved indications in dermatology
Abrocitinib	Oral	Selective JAK1 inhibitor	Moderate-to-severe atopic dermatitis	Moderate-to-severe atopic dermatitis
Upadacitinib	Oral	Selective JAK1 inhibitor	Moderate-to-severe atopic dermatitis Active psoriatic arthritis	Moderate-to-severe atopic dermatitis Active psoriatic arthritis
Baricitinib	Oral	JAK1 and JAK2 inhibitor	Moderate-to-severe atopic dermatitis Alopecia areata in > 18 years	Moderate-to-severe atopic dermatitis Alopecia areata in > 18 years
Ruxolitinib	Topical	JAK1 and JAK2 inhibitor	Mild-to-moderate atopic dermatitis Non-segmental vitiligo	Non-segmental vitiligo
Ritlecitinib	Oral	Selective JAK3 inhibitor	Alopecia areata in > 12 years	Alopecia areata in > 12 years
Deucravacitinib	Oral	Selective TYK2 inhibitor	Moderate-to-severe plaque psoriasis	Moderate-to-severe plaque psoriasis

FDA Food and Drugs Administration; *EMA* European Medicines Agency; *JAK* Janus kinase; *TYK2* tyrosine kinase 2; *FML* FMS-like tyrosine kinase 3

"adalimumab," "certolizumab," "golimumab," "anti IL-17," "secukinumab," "ixekizumab," "brodalumab," "bimekizumab," "anti IL-23," "guselkumab," "tildrakizumab," "risankizumab," "anti IL-12/23," "ustekinumab," "anti IL-1," "anti CD-20," "rituximab," "anti IL-4/13," "dupilumab," "tralokinumab," "anti IgE," "omalizumab," "anti IL-31," "nemolizumab," "JAK inhibitors," "abrocitinib," "upadacitinib," baricitinib," "ruxolitinib," "tofacitinib," "deucravacitinib," "ritlecitinib."

The search was directed to articles written in Spanish and English. These articles were screened based on their abstracts, and selected according to their relevance after reading the studies. Observational studies, clinical trials, post-trial analysis studies, systematic reviews (SR), and meta-analyses (MA) were included. Two authors (MMP and DMC) carried out the search and article selection. The procedures followed here are in accordance with the standards of the committee on ethical human experimentation and with the Helsinki Declaration of 1975, as revised in 1983. We have not used patients' names, initials, or hospital numbers. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Anti-TNF and Cancer Risk (Table 2)

Anti-TNFs

We found 50 studies on anti-TNF agents and the risk of cancer. Among them, 34 include anti-TNF as a group (≥ 3 drugs of this class) [10–44], with four on etanercept (ETN) therapy [45–48], two on infliximab (IFX) [49, 50], six on adalimumab (ADA) [46, 51–55], three on certolizumab [56–58], and one on golimumab treatment [56]. Globally, the risk of cancer could be slightly increased with the use of anti-TNF agents, especially for non-melanoma skin cancer (NMSC)

Table 2 Main studies that assess the relationship between anti-TNF agents and cancer risk

Year, authors	*N*	Study type/design	Results
2011, Askling et al. [10]	15,418 patients with anti-TNF vs. 7486 controls	MA of RCT (dermatological and non-dermatological indications)	131 (0.84%) individuals under anti-TNF therapy were diagnosed with cancer, compared to 48 (0.64%) individuals randomized to comparators The only tumor associated with TNF inhibitors was NMSC [RR of 2.02 (95% CI: 1.11–3.95)] No difference in incidence among adalimumab, etanercept, and infliximab
2012, Mercer et al. [11]	1881 patients treated with anti-TNF agents compared with 3629 patients receiving DMARDs	Multicenter prospective study of patients with RA Includes adalimumab, etanercept, and infliximab	SIR for skin cancer was increased in both cohorts compared to the English population: SIR 1.72 (95% CI 1.43–2.04) for anti-TNF; 1.83 (95% CI 1.30–2.50) for DMARDs only In patients without previous skin cancer, basal cell carcinoma incidence per 100,000 patient-years was 342 (95% CI 290–402) after anti-TNF and 407 (95% CI 288–558) after DMARD HR after anti-TNF adjusted for treatment weighting was 0.95 (95% CI 0.53–1.71) Squamous cell carcinoma incidence per 100,000 patient-years: anti-TNF 53 (95% CI 33–79); DMARD 43 (95% CI 12–110); adjusted HR 1.16 (95% CI 0.35–3.84)

Table 2 continued

Year, authors	*N*	Study type/design	Results
2013, Raaschou et al. [12]	Patients with RA treated ($n = 10{,}878$) or not ($n = 42{,}198$) with TNF inhibitors and matched general population comparators ($n = 162{,}743$)	Multicenter prospective study Includes all TNF-inhibitors Includes patients with RA	RA patients not treated with biological drugs were not at significantly increased risk of melanoma compared with the general population (hazard ratio 1.2, 95% confidence interval 0.9–1.5) 38 invasive melanomas occurred in RA patients treated with TNF inhibitors; these patients had an increased risk of melanoma compared with RA patients not treated with biological drugs (hazard ratio 1.5, 1.0–2.2) (20 additional cases per 100,000 person-years) The risk of a second primary melanoma was nonsignificantly increased (hazard ratio 3.2, 0.8–13.1) in rheumatoid arthritis patients treated with TNF inhibitors compared to those not treated with biological drugs

Table 2 continued

Year, authors	*N*	Study type/design	Results
2014, Dulai et al. [14]	5528	SR with trials and observational studies with > 5 patients Includes patients with infliximab therapy for children with ulcerative colitis or CD, or adalimumab therapy for children with CD	Two patients presented with lymphoma (2.1/10,000 person-year follow up -PYF-), similar to the expected rate of lymphoid neoplasia in the entire pediatric population (5.8/100,000 PYF; SIR 3.5; 95% CI, 0.35–19.6), and lower than the population of pediatric patients receiving thiopurine monotherapy (4.5/10,000 PYF; SIR, 0.47; 95% CI, 0.03–6.44) and among adults treated with anti-TNF agents (6.1/10,000 PYF; SIR, 0.34; 95% CI, 0.04–1.51)
2015, Mercer et al. [16]	11,767 patients without history of cancer who received TNF inhibitors, compared to 3249 patients without prior cancer treated with DMARDs	Multicenter prospective study Includes all TNF- inhibitors Includes patients with RA	427 solid cancers were reported in 52,549 patient-year follow-up in the TNF inhibitors group [81 (95% CI 74–89) per 10,000 patient-years)] and 136 cancers were reported in 11,672 patient-years in the DMARDs cohort [117 (95% CI 98–138) per 10,000 patient-years] After adjusting for differences in baseline characteristics, there was no difference in risk of solid cancer for TNF inhibitors compared to DMARDs-treated patients: HR 0.83 (95% CI 0.64–1.07) There was no difference in the relative risk of cancer for any of the individual anti-TNF drugs

Table 2 continued

Year, authors	*N*	Study type/design	Results
2015, Aaltonen et al. [18]	3762	Multicentric retrospective study of patients with RA	92 malignancies were registered The crude rates of malignancies were highest among the users of DMARDs and RTX, and lowest among patients treated with IFX, with no differences in aIRR
2015, Kopylov et al. [19]	19,582	Single-center retrospective study of patients with IBD Includes adalimumab and infliximab	Neither immunomodulators nor anti-TNF-α agents were associated with an increased risk of melanoma or colorectal cancer
2016, Scott et al. [20]	9460 individuals (6841 with RA and 2788 with IBD)	Single-center retrospective study of patients with RA and IBD Includes all anti-TNF agents and rituximab	The risk of a second NMSC was increased in patients with RA and a history of NMSC, especially if they had taken or were taking concomitant treatment with methotrexate There was no association between a second NMSC and the use of anti-TNF for IBD

Table 2 continued

Year, authors	*N*	Study type/design	Results
2016, Hellgren et al. [21]	8703 patients with SpA who had started TNFi during 2001–2011 vs. an anti TNFi-naïve SpA cohort ($n = 28,164$) vs. a Swedish age-matched and sex-matched general population comparator cohort ($n = 131,687$)	Multicenter retrospective study Includes all TNF-inhibitors	Based on 1188 cancers among the TNFi-naïve patients with SpA, the RR of cancer overall was 1.1 (95% CI 1.0–1.2) Based on 147 cancers among TNFi initiators with SpA, RR versus TNFi-naïve was 0.8 (95% CI 0.7–1.0) and results were similar for ankylosing spondylitis and psoriatic arthritis when analyzed separately Site-specific cancer RRs: prostate 0.5 (95% CI 0.3–0.8), lung 0.6 (95% CI 0.3–1.3), colorectal 1.0 (95% CI 0.5–2.0), breast 1.3 (95% CI 0.9–2.0), lymphoma 0.8 (95% CI 0.4–1.8), and melanoma 1.4 (95% CI 0.7–2.6) In conclusion, in patients with SpA, treatment with TNFi was not associated with increased risks of cancer, either overall or for the six most common cancer types

Table 2 continued

Year, authors	*N*	Study type/design	Results
2016, Poullenot et al. [22]	Cohort of > 10,000 patients	Multicenter ambispective study Includes IBD patients	79 cases of IBD patients with previous malignancy diagnosed 17 months (median; range: 1–65) before inclusion were identified The most frequent cancer locations were breast ($n = 17$) and skin ($n = 15$) After a median follow-up of 21 (range: 1–119) months, 15 (19%) patients developed incident cancer (8 recurrent and 7 new cancers), including 5 basal-cell carcinomas
2017, Mercer et al. [24]	130,315 RA patients with 579,983 person-years of follow-up	Multicenter retrospective study of patients with RA Includes all TNF inhibitors	Pooled SIRs of melanoma for biologic-naïve and TNFi were 1.1 (95% CI 0.9–1.4) and 1.2 (0.99–1.6), respectively This study did not confirm an overall increased risk of melanoma following exposure to TNFi
2017, Mercer et al. [25]	11,931 TNF inhibitors-treated patients vs. 3367 biological-I patients	Multicenter prospective study Includes patients with RA	There was no difference in the risk of lymphoma for the TNF inhibitors versus the biological-I group: HR 1.00 (95% CI 0.56–1.80) in medium-term follow-up. No risk differences were observed for individual TNF inhibitors

Table 2 continued

Year, authors	*N*	Study type/design	Results
2017, Lemaitre et al. [26]	189,289	Multicenter retrospective study of patients with IBD	The risk of lymphoma was higher among those exposed to thiopurine monotherapy (aHR, 2.60; 95% CI, 1.96–3.44; $p < 0.001$), anti-TNF monotherapy (aHR, 2.41; 95% CI, 1.60–3.64; $p < 0.001$), or combination therapy (aHR, 6.11; 95% CI, 3.46–10.8; $p < 0.001$) The risk was higher in patients exposed to combination therapy vs. those exposed to thiopurine monotherapy (aHR, 2.35; 95% CI, 1.31–4.22; $p < 0.001$) or anti-TNF monotherapy (aHR, 2.53; 95% CI, 1.35–4.77; $p < 0.001$)
2018, Dreyer et al. [27]	15,286	Multicenter prospective study Includes patients with rheumatoid arthritis	The use of bDMARDs was associated with a HR of 1.11 (95% CI 0.74–1.67) for developing a SMN compared with non-use (cancer site adjusted) After further adjustment for the extent of the primary cancer, the HR for death was 1.20 (95% CI 0.88–1.63) for bDMARDs use before cancer, 1.36 (95% CI 0.78–2.39) for bDMARD use only after cancer, and 1.22 (95% CI 0.70–2.13) for use both before and after the cancer

Table 2 continued

Year, authors	*N*	Study type/design	Results
2019, Micic et al. [28]	3807 TNF inhibitor patients vs. 7972 controls	SR and MA of observational studies Only patients with a history of previous cancer were recorded Include all TNF inhibitors—dermatological and non-dermatological indications	The pooled RR of new or recurrent cancer among individuals with a history of cancer exposed to anti-TNF therapy was not significantly different compared to control therapies (IRR 0.90; 95% CI 0.59–1.37)
2020, Chupin et al. [29]	261,689	SR with MA Four observational studies Includes patients with IBD	Compared to patients not exposed to anti-TNF and thiopurines, those exposed to anti-TNF monotherapy, thiopurine monotherapy, or combination therapy had pooled IRR (per 1000 patient-years) of lymphoma of 1.52 (95% CI: 1.06–2.19; $p = 0.023$), 2.23 (95% CI: 1.79–2.79; $p < 0.001$), and 3.71 (95% CI: 2.30–6.00; $p \leq 0.01$), respectively The risk of lymphoma associated with combination therapy was higher than with thiopurines or anti-TNF alone, with pooled IRR of 1.70 (95% CI: 1.03–2.81; $p = 0.039$) and 2.49 (95% CI: 1.39–4.47; $p = 0.002$), respectively The risk did not differ between anti-TNF monotherapy and thiopurine monotherapy, with pooled IRR of 0.72 (95% CI: 0.48–1.07; $p = 0.107$)

Table 2 continued

Year, authors	*N*	Study type/design	Results
2021, Li et al. [30]	75,406	SR with MA 23 studies, all clinical trials Includes patients with RA psoriatic arthritis and ankylosing spondylitis	Exposure to anti-TNF-α agents was associated with an increased risk of cancer under the random-effects model (OR: 1.36, 95% CI: 1.20–1.53, $p < 0.00001$) Only three studies showed an increased risk of cancer development and were all conducted in patients with RA
2022, Charkaoui et al. [31]	32,403 patients with UC, and 15,542 (48%) of them were exposed to anti-TNF	Multicenter retrospective study Includes patients with UC	Whereas the risk of CRC associated with anti-TNF exposure was not decreased in the overall group of patients with UC (hazard ratio [HR], 0.85; 95% CI, 0.58–1.26), anti-TNF exposure was associated with a decreased risk of CRC in patients with long-standing colitis [disease duration ≥ 10 years] [HR, 0.41; 95% CI, 0.20–0.86]
2022, Choi et al. [33]	4592	Multicenter retrospective study Includes patients with RA	Treatment with TNF inhibitors was consistently associated with a lower risk of cancer than in the nbDMARD cohort (IR per 1000 person-years, 6.5 vs. 15.6; adjusted HR, 0.379; 95% CI, 0.255–0.563) The adjusted HR (95% CI) was significantly lower in the TNF inhibitor cohort than the nbDMARD cohort for gastrointestinal cancer (0.432; 0.235–0.797), breast cancer (0.146; 0.045–0.474), and genitourinary cancer (0.220; 0.059–0.820)

Table 2 continued

Year, authors	*N*	Study type/design	Results
2022, Ytterberg et al. [34]	1455 patients received tofacitinib 5 mg/12 h; 1456 received tofacitinib 10 mg/12 h; and 1451 received a TNFi	Randomized, open-label, non-inferiority, post authorization, safety endpoint trial Includes patients with RA	During a median follow-up of 4.0 years, the incidence of cancer was higher with the combined tofacitinib doses (4.2% [122 patients]) than with a TNF inhibitor (2.9% [42 patients]) The hazard ratio was 1.48 (95% CI, 1.04–2.09) for cancer
2022, Song et al. [35]	4929 patients (1064 JAK inhibitor-treated and 3865 TNFi-treated patients)	Retrospective multicenter study Includes patients with RA	The incidence rates of overall malignancy were 0.54 per 100 Pys (95% CI 0.26–1.14) in JAKi users and 0.85 per 100 Pys (95% CI 0.66–1.10) in TNFi users In an inverse probability of treatment weighting analysis with a balanced sample (4101 JAKi-treated and 5131 TNFi-treated patients), HR was 0.83 (95% CI 0.55–1.27) for overall malignancy: 0.77 (95% CI 0.50–1.19) for solid malignancy and 2.86 (95% CI 0.41–20.00) for hematological malignancy In conclusion, in this study malignancy risk in Korean patients with RA was not increased with JAKi use compared to TNFi use

Table 2 continued

Year, authors	*N*	Study type/design	Results
2022, Khosrow-Khavar et al. [36]	83,295	Real-life data from a cohort of patients with RA treated with tofacitinib or TNFi	The pooled weighted HR for the primary outcome of any malignancy associated with tofacitinib treatment compared to any malignancy associated with TNFi therapy was between 1.01 and 1.17 (95% CI 0.83, 1.62) (compared to the ORAL Surveillance trial HR of 1.48 [95% CI 1.04, 2.09] This study did not find evidence of an increased risk of malignancy development with tofacitinib therapy, in comparison with TNFi therapy, in RA patients treated in a real-world setting
2023, Yu et al. [37]	131,492	Multicenter retrospective study Includes patients with IBD	Although the risk of lymphoma in patients with IBD remains low, exposure to anti-TNF is one of the most common associated risk factors (standardized incidence ratios [SIR] 5.7; 95% CI 2.7–11.9)

Table 2 continued

Year, authors	*N*	Study type/design	Results
2023, Curtis et al. [38]	4362	Analysis of ORAL Surveillance clinical trial Includes patients with RA aged ≥ 50 years with ≥ 1 additional cardiovascular risk	Incidence for malignancies excluding NMSC was higher with tofacitinib (combined and individual doses) versus TNFi Risk of lung cancer (most common subtype with tofacitinib) was higher with tofacitinib 10 mg twice per day versus TNFi In the overall study population, the risk of malignancies excluding NMSC was similar between both tofacitinib doses and TNFi until month 18 but increased with tofacitinib after month 18
2023, Kim et al. [39]	40,322	40,322	IL-17 and TNFi users, both treatments conferred comparable risk of cancer
2023, Huss et al. [41]	14,890	Multicentric prospective study Includes patients with RA and psoriatic arthritis	In RA, based on 38 incident cancers other than NMSC with JAKi vs. 213 with TNFi, the overall HR was 0.94 (95% CI 0.65–1.38). At 2 or more years after treatment started, the HR for NMSC was 2.12 (95% CI 1.15–3.89) In clinical practice, the short-term risk of cancer other than NMSC in individuals initiating treatment with JAKi was not higher than for TNFi, but there was evidence of increased risk of NMSC

Table 2 continued

Year, authors	*N*	Study type/design	Results
2023, Min et al. [42]	Set 1: 1596 RA patients (JAKi group: 645; TNFi group: 951) Set 2: 11,765 RA patients (JAKi group: 2498; TNFi group: 9267)	Multicentric retrospective study Includes patients with RA Includes all JAKi	The HR for cancer in the JAKi groups and TNFi groups of sets 1 and 2 were similar [0.68 (95% CI, 0.25–1.88)]
2023, Ahn et al. [43]	101,816	Multicentric prospective study of patients with seropositive RA Includes patients with TNF-inhibitors, JAK-inhibitors (group 1), or nbDMARDs	Compared to patients treated only with nbDMARDs, the IRRs of overall cancers in patients administered JAKi/biologics was 0.88 0.91 (95% CI 0.90–0.92) Site-specific lung, liver, prostate, and skin cancers were more frequent in JAKi/biologics users The incidence of overall cancer was not increased in patients with seropositive RA treated with JAKi/biologics and was relatively lower than nbDMARD only users, underscoring optimal disease control for risk mitigation

Table 2 continued

Year, authors	*N*	Study type/design	Results
2023, Ahn et al. [43]	101,816	Multicentric prospective study Includes patients with seropositive RA Includes patients with TNFi and JAK-i (group 1) vs. nbDMARDs	Compared to patients treated only with nbDMARDs, the IRR of overall cancers in patients administered JAKi/biologics was 0.88 0.91 (95% CI 0.90–0.92) Site-specific lung, liver, prostate, and skin cancers were more frequent in JAKi/biologics users The incidence of overall cancer was not increased in patients with RA treated with JAKi/biologics and was relatively lower than nbDMARD-only users, underscoring optimal disease control for risk mitigation
2023, Russell et al. [44]	36,681	MA Includes 62 randomized clinical trials and 16 observational studies Includes adults with RA, psoriatic arthritis, psoriasis, axial spondyloarthritis, IBD, or atopic dermatitis	The incidence of all malignancies including NMSCs was not significantly different between JAKi and placebo (IRR 0.71; 95% CI 0.44–1.15) or between JAKi and methotrexate (IRR 0.77; 95% CI 0.35–1.68) Compared to TNFi, JAKi were associated with an increased incidence of malignancies (IRR 1.50; 95% CI 1.16–1.94)

IL interleukin; *TNF* tumor necrosis factor; *TNFi* TNF inhibitor (anti-TNF); *JAKi* JAK inhibitor; *R* receptor; *Ig* immunoglobulin; *Py* Person-year; *SR* systematic review; *MA* meta-analysis; *RCT* randomized clinical trial; *IRR* incidence rate ratio; *SIR* standardized incidence ratio; *aIRR* adjusted incidence rate ratio; *RR* relative risk; *HR* hazard ratio; *aHR* adjusted hazard ratio; *CI* confidence interval; *DMARD* disease-modifying antirheumatic drugs; *bDMARDs* biologic disease-modifying antirheumatic drugs; *nbDMARDS* non-biologic disease-modifying antirheumatic drugs; *IFX* infliximab; *ADA* adalimumab; *RTX* rituximab; *NMSC* non-melanoma skin cancer; *RA* rheumatoid arthritis; *AD* atopic dermatitis; *CD* Crohn's disease; *IBD* inflammatory bowel disease; *UC* ulcerative colitis; *SpA* spondyloarthritis

and in patients with other risk factors (increased age, comorbidities).

An MA of randomized controlled trials (RCTs) ($n > 15{,}000$) published in 2011, including patients treated with ADA, ETN, or IFX for diverse pathologies, showed that the only tumor associated with anti-TNF was non-melanoma skin cancer (NMSC) [relative risk (RR) of 2.02 (95% CI: 1.11–3.95)], with no differences among the three drugs [10]. This risk was especially relevant in patients with rheumatoid arthritis (RA). Anti-TNFs presented a significant risk when compared with non-biological disease-modifying antirheumatic drugs (nbDMARDs). In 2015, a multicenter prospective study ($n > 10{,}000$) compared the risk of solid organ malignancies in RA patients treated with anti-TNF to that in patients treated with nbDMARDs. After adjusting for differences in baseline characteristics, there was no significant difference between treatments: hazard ratio (HR) 0.83 (95% CI 0.64–1.07). Furthermore, there was no difference in the RR of cancer for any of the individual anti-TNF [16]. A multicenter retrospective study with 4500 patients suggested that individuals with RA undergoing anti-TNF treatment might even have a lower risk of cancer than those treated with nbDMARDs. The adjusted HR (95% CI) was significantly lower in the anti-TNF cohort than in the nbDMARD cohort for gastrointestinal cancer (0.432; 0.235–0.797), breast cancer (0.146; 0.045–0.474), and genitourinary cancer (0.220; 0.059–0.820) [33]. Regarding inflammatory bowel disease (IBD), in 2022, a multicenter retrospective study with > 30,000 patients showed that the risk of colorectal cancer could even be decreased in patients under anti-TNF treatment for ≥ 10 years (HR, 0.41; 95% CI, 0.20–0.86). [31] However, other studies have linked anti-TNF in IBD patients with the risk of lymphomas, especially when combined with other treatments [29, 37].

Regarding dermatological indications, a single-center retrospective study ($n = 280$) demonstrated that the incidence of NMSC in psoriasis patients treated with anti-TNF was higher than in those with RA treated with anti-TNF [HR 6.0 (1.6–22.4 95% CI)]. This could be explained by different baseline characteristics between the groups (e.g., previous phototherapy in psoriasis patients) [15].

Regarding patients with a history of cancer, an SR and MA, including 3807 patients under anti-TNF therapy (with dermatological and non-dermatological disorders) versus 7972 controls, all those with a previous history of cancer, showed that the pooled RR of new or recurrent cancer was not significantly different between the groups (IRR 0.90; 95% CI 0.59–1.37) [28].

The risk of malignancies has also been evaluated in pediatric and young adult patients under anti-TNF therapy. Overall, the risk was low and comparable to the general population [48, 50].

Anti-TNF Versus JAK Inhibitors or Other Therapies

A multicenter retrospective study ($n > 3500$) revealed that the rates of malignancies were higher with rituximab than with infliximab [18]. Other comparative studies have suggested a higher incidence of cutaneous and extracutaneous cancers with JAKi (especially tofacitinib) when compared to anti-TNF agents [34, 38, 41, 43, 44]. An MA including 62 RCTs and 16 observational studies ($n > 35{,}000$) concluded that JAKi were associated with a higher incidence of malignancy (IRR 1.50; 95% CI 1.16–1.94), both NMSCs and non-NMSCs, than anti-TNFs [44]. However, other studies have shown a similar incidence of cancer with anti-TNF drugs and JAKi [35, 40, 47].

Anti IL-17 and Cancer Risk (Table 3)

We found six studies analyzing the relationship between anti-IL-17 drugs or IL-17 receptor (R) inhibitors (IL-17i) and the risk of cancer. Among them, four studies that simultaneously investigated various IL-17i [39, 59–61], including > 140,000 patients in total, showed that the incidence of neoplasms with these agents was very low, both cutaneous and non-cutaneous cancer. In fact, anti-IL-17 could even confer a decreased risk of certain neoplasms in patients with psoriasis, compared to the native population [61].

Table 3 Main studies that assess the relationship between anti IL-17, IL-23, and ustekinumab and cancer risk

Agent	Year, authors	N	Study design	Results
IL-17/IL-17 R inhibitors (group)	2023, Kim et al. [39]	40,322	Multicenter retrospective study of patients with PsA, PsO, and SpA	IL-17 and TNF-α inhibitor users, both treatments conferred comparable risk of cancer
	2023, Wu et al. [59]	43,087	SR with MA Includes 45 randomized placebo-controlled studies and 27 open-label extension studies	Short-term RR of malignancy was 0.83 (95% CI: 0.41–1.71) with IL-17 inhibitors and 0.87 (95% CI: 0.37–2.04) with IL-23 inhibitors Similar results were found in the long-term analysis
	2023, Krzysztofik et al. [60]	18,739	SR with MA Includes 19 studies reporting the IRs of melanoma and NMSC in patients with PsO and PsA	The overall IR of melanoma was 0.08 (95% CI, 0.05–0.15) events per 100 Pys and the overall IR of NMSC was 0.45 (95% CI, 0.33–0.61) events per 100 Pys The Irs of melanoma were comparable across patients treated with IL-17 inhibitors, IL-23 inhibitors, and JAKi, while the Irs of NMSC were higher in patients treated with JAK than in those treated with biologics

Table 3 continued

Agent	Year, authors	N	Study design	Results
	2024, Kridin et al. [61]	42,326	Global population-based prospective cohort Includes patients with psoriasis	Patients prescribed IL-17i experienced a decreased risk of NHL (HR, 0.58; 95% CI, 0.40–0.82; $p = 0.002$), colorectal cancer (HR, 0.68; 95% CI, 0.49–0.95; $p = 0.024$), hepatobiliary cancer (HR, 0.68; 95% CI, 0.58–0.80; $p < 0.001$), ovarian cancer (HR, 0.48; 95% CI, 0.29–0.81; $p = 0.005$), melanoma (HR, 0.52; 95% CI, 0.37–0.73; $p < 0.001$), and BCC (HR, 0.57; 95% CI, 0.48–0.67; $p < 0.001$) IL-23 inhibitors were associated with a reduced risk of NHL (HR, 0.39; 95% CI, 0.19–0.78; $p = 0.006$), hepatobiliary cancer (HR, 0.44; 95% CI, 0.31–0.62; $p < 0.001$), and BCC (HR, 0.76; 95% CI, 0.57–0.99; $p = 0.046$)

Table 3 continued

Agent	Year, authors	N	Study design	Results
Secukinumab (IL-17A inhibitor)	2021, Lebwoh et al. [62]	15,019	Analysis of clinical trial and post-marketing surveillance data Includes 49 trials Includes patients with psoriasis, PsA, and AS	Over a 5-year period, the EAIR of malignancy was 0.85 per 100 PTY [95% (CI) 0.74–0.98] in secukinumab-treated patients Overall, the observed vs. expected number of malignancies from secukinumab clinical trial data were comparable, as indicated by an SIR of 0.99 (95% CI 0.82–1.19) across indications The estimated crude cumulative incidence reporting rate per 100 PTY for malignancy was 0.27 in the post-marketing surveillance data across indications, with a cumulative exposure of 285,811 PTY In summary, the risk of malignancy was low for up to 5 years of secukinumab treatment

Table 3 continued

Agent	Year, authors	N	Study design	Results
Ixekizumab (IL-17A inhibitor)	2023, Smith et al. [63]	6892	Analysis of clinical trial and post-marketing surveillance data Includes 17 trials Includes patients with psoriasis	NMSC was the most common event (IR 0.3) affecting 55 patients; of those, 44 had BCC (IR 0.2) and 16 had SCC (IR 0.1) Two treatment-emergent melanoma events were identified In summary, the risk of malignancy was low in ixekizumab treatment
IL-23 inhibitors (group)	2023, Wu et al. [59]	43,087	SR with MA Includes 45 randomized placebo-controlled studies and 27 open-label extension studies	Short-term RRs of malignancy were 0.83 (95% CI: 0.41–1.71) with IL-17 inhibitors and 0.87 (95% CI: 0.37–2.04) with IL-23 inhibitors Similar results were found in the long-term analysis

Table 3 continued

Agent	Year, authors	N	Study design	Results
	2023, Krzysztofik et al. [60]	18,739	SR with MA Includes 19 studies reporting the IR of melanoma and NMSC in patients with PsO and PsA	The overall IR of melanoma was 0.08 (95% CI, 0.05–0.15) events per 100 Pys, and the overall IR of NMSC was 0.45 (95% CI, 0.33–0.61) events per 100 Pys The Irs of melanoma were comparable across patients treated with IL-17 inhibitors, IL-23 inhibitors, and JAK inhibitors, while the Irs of NMSC were higher in patients treated with JAK inhibitors than in those treated with biologics

Table 3 continued

Agent	Year, authors	N	Study design	Results
	2024, Kridin et al. [61]	42,326	Global population-based prospective cohort Includes patients with psoriasis	Patients prescribed IL-17i experienced a decreased risk of NHL (HR, 0.58; 95% CI, 0.40–0.82; $p = 0.002$), colorectal cancer (HR, 0.68; 95% CI, 0.49–0.95; $p = 0.024$), hepatobiliary cancer (HR, 0.68; 95% CI, 0.58–0.80; $p < 0.001$), ovarian cancer (HR, 0.48; 95% CI, 0.29–0.81; $p = 0.005$), melanoma (HR, 0.52; 95% CI, 0.37–0.73; $p < 0.001$), and BCC (HR, 0.57; 95% CI, 0.48–0.67; $p < 0.001$) IL-23 inhibitors were associated with a reduced risk of NHL (HR, 0.39; 95% CI, 0.19–0.78; $p = 0.006$), hepatobiliary cancer (HR, 0.44; 95% CI, 0.31–0.62; $p < 0.001$), and BCC (HR, 0.76; 95% CI, 0.57–0.99; $p = 0.046$)

Table 3 continued

Agent	Year, authors	N	Study design	Results
Guselkumab (IL-23 inhibitor)	2023, Blauvelt et al. [64]	1721	Pooled results from the VOYAGE 1 and VOYAGE 2 trials of guselkumab Includes patients with psoriasis	24/1,721 had NMSC (0.34/100 Pys; basal; squamous cell carcinoma ratio, 2.2:1), and 32 had malignancies excluding NMSC (0.45/100 Pys) For comparison, the malignancy rate excluding NMSC was 0.68/100 Pys in the Psoriasis Longitudinal Assessment and Registry Malignancy rates (excluding NMSC/cervical cancer in situ) in guselkumab-treated patients were consistent with those expected in the general US population (standardized incidence ratio = 0.93)
	2023, Lebwohl et al. [65]	2891	SR of RCTs Includes 7 RCTs	Rates of serious adverse events (6.3/100 Pys vs. 6.7/100 Pys), adverse events leading to discontinuation (5.0/100 Pys vs. 9.7/100 Pys), and malignancy (0.5 patients/100 Pys vs. 0.0 patients/100 Pys) were low and comparable between guselkumab and placebo

Table 3 continued

Agent	Year, authors	N	Study design	Results
	2024, Strober et al. [66]	1061 patients received placebo vs. 2257 under guselkumab	Integrated analysis of 11 phase II/III clinical studies in PsO (7 studies) and PsA (4 studies)	The rates of malignancy were 0.59 vs. 0.25 patients/100 Pys, between guselkumab and placebo During the placebo-controlled period, one patient in the placebo group (renal clear cell carcinoma) and five guselkumab-treated patients presented with malignancies (one NMSC, one rectal adenocarcinoma, one prostate cancer, one plasma cell myeloma, and one melanoma in situ) During long-term treatment, 32 patients (0.30/100 Pys) had a total of 41 NMSC events and 41 patients had a malignancy other than NMSC (0.38/100 Pys). Malignancies other than NMSC reported in more than one patient included breast ($n = 7$), colorectal ($n = 7$), melanoma ($n = 6$ [including three cases of melanoma in situ]), prostate ($n = 5$), head and neck ($n = 4$), bladder ($n = 2$), and lymphoma ($n = 2$)

Table 3 continued

Agent	Year, authors	N	Study design	Results
Tildrakizumab (IL-23 inhibitor)	2020, Reich et al. [67]	1862	Pooled analyses of two RCT phase III (reSURFACE 1 and reSURFACE 2) through 148 weeks	Rate of malignancies was 0.6 per 100 Pys
Risankizumab (IL-23 inhibitor)	2022, Gordon et al. [70]	1606	SR of RCTs Included data from 17 phase I–III trials	With long-term risankizumab treatment, the rate of NMSC was 0.7 per 100 Pys and malignant tumors excluding NMSC was 0.5 per 100 Pys
Ustekinumab (IL12/23 inhibitor)	2012, Gordon et al. [72]	3117	Analyses of phase II and III clinical trials Includes four studies Includes patients with psoriasis	Rates of malignancies during the placebo-controlled periods were comparable between groups (placebo: 1.70; 45 mg: 0.99; 90 mg: 0.98) and remained stable over time in ustekinumab groups Rates of malignancies, excluding NMSC, were comparable to rates expected in the general US population based on the Surveillance, Epidemiology, and End Results database

Table 3 continued

Agent	Year, authors	N	Study design	Results
	2023, Krzysztofik et al. [60]	18,739	SR with MA Includes 19 studies reporting the IR of melanoma and NMSC in patients with psoriasis and psoriatic arthritis	The overall IR of melanoma was 0.08 (95% CI, 0.05–0.15) events per 100 Pys and the overall IR of NMSC was 0.45 (95% CI, 0.33–0.61) events per 100 Pys The Irs of melanoma were comparable across patients treated with IL-17 inhibitors, IL-23 inhibitors, and JAKi, while the Irs of NMSC were higher in patients treated with JAKi than in those treated with biologics

IL interleukin; *TNF* tumor necrosis factor; *TNFi* TNF inhibitor (anti-TNF); *JAKi* JAK inhibitor; *R* receptor; *Ig* immunoglobulin; *Py* person-year; *PTY* patient treatment-years; *SR* systematic review; *MA* meta-analysis; *RCT* randomized clinical trial; *IRR* incidence rate ratio; *SIR* standardized incidence ratio; *aIRR* adjusted incidence rate ratio; *RR* relative risk; *HR* hazard ratio; *aHR* adjusted hazard ratio; *EAIR* exposure-adjusted incidence rates; *CI* confidence interval; *DMARD* disease-modifying antirheumatic drugs; *bDMARDs* biologic disease-modifying antirheumatic drugs; *nbDMARDS* non-biologic disease-modifying antirheumatic drugs; *IFX* infliximab; *ADA* adalimumab; *RTX* rituximab; *NMSC* non-melanoma skin cancer; *RA* rheumatoid arthritis; *AD* atopic dermatitis; *CD* Crohn's disease; *IBD* inflammatory bowel disease; *UC* ulcerative colitis; *SpA* spondyloarthritis; *AS* ankylosing spondylitis; *PsO* psoriasis; *PsA* psoriatic arthritis; *BCC* basal cell carcinoma; *SCC* squamous cell carcinoma; *NHL* non-Hodgkin lymphoma

Regarding secukinumab, in 2021, an analysis of 49 RCTs and post-marketing surveillance data, including > 15,000 patients with psoriasis, PsA, and/or ankylosing spondylitis (AS), reported an exposure-adjusted incidence rate (EAIR) of malignancy of 0.85 per 100 persons treated per year [95% CI 0.74–0.98] in secukinumab-treated patients, a relatively low incidence at 5 years of follow-up [62]. Similar results were observed with ixekizumab [63].

Anti IL-17 Versus Anti-TNF

A population-based study published in 2024 ($n > 40,000$) revealed that patients undergoing anti-TNF treatment had an increased risk of cancer compared to those receiving anti-IL-17 and IL-23 drugs. Anti-IL17 could even decrease the risk of malignancies, especially non-Hodgkin lymphoma (NHL), colorectal cancer, ovarian cancer, hepatobiliary cancer, melanoma, and basal cell carcinoma [61].

Anti IL-23 and Cancer Risk (Table 3)

We found 11 studies that evaluated the risk of cancer in patients treated with IL-23 inhibitors (IL-23i): three studies simultaneously investigated various drugs [59–61], three focused on guselkumab [64–66], two on tildrakizumab [67, 68], and three on risankizumab [69–71].

The majority of studies indicate a very low incidence of neoplasms, comparable or even lower than the general population [59–61]. Similar findings were shown individually for guselkumab [64–66], tildrakizumab [67, 68], and risankizumab [69–71]. The previously mentioned population-based study by Kidrin et al. [61] showed that patients under IL-23i experienced a decreased risk of NHL (HR, 0.39; 95% CI, 0.19–0.78; $p = 0.006$) and hepatobiliary cancer (HR, 0.44; 95% CI, 0.31–0.62; $p < 0.001$). A recent SR and MA, including 19 observational studies and > 18,000 individuals, compared the incidence of malignancies among patients undergoing anti IL-17, anti IL-23, ustekinumab, or JAKi, and showed that the incidence of NMSC was higher in patients undergoing JAKi when compared to those receiving anti IL-17, ustekinumab, or anti IL-23, but was similar for other types of tumors [60].

Ustekinumab (Anti IL-12/23) and Cancer Risk (Table 3)

We found three studies evaluating ustekinumab and the risk of malignancies. They revealed a very low risk [32, 60, 72]. An analysis of four clinical trials (> 3000 individuals) showed that the rate of cancer was similar in patients receiving a placebo [32, 72].

Anti CD-20 and Cancer Risk (Table 4)

We found five studies that evaluated the relationship between rituximab (RTX) and neoplastic risk [18, 20, 24, 73, 74]. A multicentric retrospective study with 3762 individuals with RA showed that the crude rates of malignancies were highest among the users of RTX and nbDMARD, and lowest among patients treated with IFX [18]. A multicenter retrospective study on 130,315 RA patients did not revealed an overall increased risk of melanoma following exposure to rituximab [24]. Similar results were observed in a global company safety database that included 409,706 patients, where data showed no evidence of an increased risk of malignancy of any type following rituximab treatment in patients with RA [74].

Anti IL-4/13 and Anti IL-13 and Cancer Risk (Table 4)

We found four studies that evaluated the risk of malignancies with dupilumab [75–78] and three with tralokinumab [79–81] An SR and MA including 22 observational studies in patients with AD under dupilumab (anti-IL-4/13) revealed that no cases of malignancy were reported [75]. Strikingly, Mota et al., using worldwide real data in safety databases (VigiBase®) ($n > 10,000,000$), linked dupilumab to cases of cutaneous T-cell lymphoma [relative odds ratio (ROR) = 11.11] [78]. This association was not found in other studies [75–77].

Regarding tralokinumab (anti-IL-13), a post hoc analysis of clinical trials on 1174 patients

Table 4 Main studies that assess the relationship between rituximab, anti IL-4/13 agents, omalizumab, and cancer risk

Agent	Year, authors	*N*	Study design	Results
Rituximab (CD-20 inhibitor)	2015, Aaltonen et al. [18]	3762	Multicentric retrospective study Include patients with RA	The crude rates of malignancies were highest among the users of cDMARD and RTX, and lowest among patients treated with IFX, with no differences in aIRR
	2016, Scott F et al. [20]	9460 individuals (6841 with RA and 2788 with IBD	Single-center retrospective study Includes all anti-TNF agents and rituximab Includes patients with RA and IBD	There is no association between a second NMSC and the use of rituximab for IBD or RA
	2016, Fleury et al. [73]	4621	SR with MA Includes nine clinical trials Patients with NHL	A total of 169 SPMs were observed in patients randomized to rituximab compared with 165 SPMs in patients not randomized to rituximab (OR = 0.88; 95% CI 0.66–1.19) In summary, this study suggested no SPM predisposition among NHL survivors exposed to rituximab at a median follow-up of 6 years

Table 4 continued

Agent	Year, authors	*N*	Study design	Results
	2017, Mercer L [24]	130,315 rheumatoid arthritis patients with 579,983 person-years of follow-up	Multicenter retrospective study Includes patients with RA	Pooled SIRs for biologic-naïve and rituximab were 1.1 (95% CI 0.9–1.4) and 1.3 (0.6–2.6), respectively Incidence rate ratios vs. biologic-naïve patients with rituximab was 1.2 (0.5–2.9) This study did not confirm an overall increased risk of melanoma following exposure to rituximab
	2020, Emery et al. [74]	409,706	Global company safety database for adverse event reporting and from the rituximab global clinical trial program for RA consisting of 8 RCT, 2 long-term open-label extensions, and 1 open-label prospective study	Overall malignancy reporting rate of approximately 4.2 events per 1000 patients No evidence of increased risk of malignancy, of any organ-specific type, was found following rituximab treatment
Dupilumab (IL4/13 inhibitor)	2021, Halling et al. [75]	3303	SR and MA Includes 22 observational studies in patients with AD	No cases of malignancy were reported

Table 4 continued

Agent	Year, authors	*N*	Study design	Results
	2023, Owji et al. [76]	1627 patients with dupilumab (exposed) vs. 8080 patients not treated with dupilumab (unexposed)	Retrospective multicentric study Includes patients with AD	721 primary malignancies were observed during the study period (477 keratinocyte, 244 non-keratinocyte): 42 in the exposed and 679 in the unexposed group (IR 12.88 and 15.04, respectively; adjusted HR 1.010, $p = 0.946$) Subset analyses of keratinocyte and non-keratinocyte cancers each lacked statistical significance ($p = 0.973$ and $p = 0.645$, respectively) 40 recurrent cancers were observed during the study period in patients with a history of malignancy: 3 in the exposed and 37 in the unexposed setting (IR 0.92 and 0.82, respectively; adjusted HR 0.828, $p = 0.758$)

Table 4 continued

Agent	Year, authors	*N*	Study design	Results
	2023, Mota et al. [78]	> 10,000,000	Worldwide real data in safety bases (VigiBase®) All diagnoses	Dupilumab had the most reported cases, with a total of 363, followed by mepolizumab with 233, benralizumab with 62, and reslizumab with 8 The most frequently reported malignancies for each biologic drug included breast cancer and lung cancer Overall, no signal of cancer was detected for any biological drug, as relative odds ratio (ROR) was < 1 for the total number of neoplasms Cutaneous T-cell lymphoma cases associated with dupilumab showed the most significant positive signal (ROR = 11.11)
Tralokinumab (IL-13 inhibitor)	2022, Blauvelt et al. [79]	1174	Post hoc analysis of clinical trials Includes patients with AD	There were (excluding NMSC and carcinoma in situ of the cervix) 9 malignancies: breast cancer, invasive ductal breast carcinoma, prostate cancer, Hodgkin disease, malignant melanoma, and squamous cell carcinoma of skin

Table 4 continued

Agent	Year, authors	*N*	Study design	Results
Omalizumab (R Ig-E inhibitor)	2012, Busse et al. [84]	7789	SR Includes data from 67 phase I to IV RCTs All diagnoses	The primary analysis identified malignancies in 25 patients (RDBPC trials): 14 in 4254 omalizumab-treated patients and 11 in 3178 placebo-treated patients Incidence rates per 1000 patient-years of observation time for omalizumab- and placebo-treated patients were 4.14 (95% CI, 2.26–6.94) and 4.45 (95% CI, 2.22–7.94), respectively; the corresponding rate ratio was 0.93 (95% CI, 0.39–2.27)
	2015, Lai et al. [85]	2749	SR with MA Includes six RCTs Includes patients with allergic asthma	There were no cases of malignancies related to omalizumab treatment
	2019, Rubini et al. [86]	> 2000	SR with MA Includes 13 studies (in the RS) and six studies (in the MA) in patients with CSU	There were no malignancy cases
	2020, Jia et al. [87]	2863	SR with MA Includes nine RCTs in patients with CSU	Adverse effects were dose-dependent There were no higher rates of malignancies than in the placebo control group

Table 4 continued

Agent	Year, authors	*N*	Study design	Results
	2022, Ali et al. [88]	> 5000	Retrospective multicentric study All diagnoses	Cancer rates among patients exposed to omalizumab were not higher than the general population. It is concluded that omalizumab is safe in real clinical practice
Nemolizumab (IL-31 inhibitor)	2022, Liang et al. [82]	809	SR with MA Includes 8 RCTs Includes patients with AD with pruritus	No significant difference was observed in the occurrence of any AEs (RR = 1.03, 95% CI: 0.93–1.13, $p = 0.593$; $I^2 = 0\%$) between the intervention and control groups There was no increased malignancy rate in the nemolizumab-treated group

IL interleukin; *TNF* tumor necrosis factor; *TNFi* TNF inhibitor (anti-TNF); *JAKi* JAK inhibitor; *Py* Person-year; *PTY* patient treatment-years; *SR* systematic review; *MA* meta-analysis; *RCT* randomized clinical trial; *SIR* standardized incidence ratio; *aIRR* adjusted incidence ratio; *RR* relative risk; *HR* hazard ratio; *aHR* adjusted hazard ratio; *OR* odds ratio; *ROR* relative odds ratio; *EAIR* exposure-adjusted incidence rate; *CI* confidence interval; *IFX* infliximab; *RTX* rituximab; *NMSC* non-melanoma skin cancer; *RA* rheumatoid arthritis; *AD* atopic dermatitis; *PsO* psoriasis; *PsA* psoriatic arthritis; *BCC* basal cell carcinoma; *SCC* squamous cell carcinoma; *NHL* non-Hodgkin lymphoma; *SPM* secondary malignancies; *CSU* chronic spontaneous urticaria; *AE* adverse event

with AD found nine neoplasms in the group under biologic treatment [79].

Anti IL-31 and Cancer Risk (Table 4)

We found two studies that assessed the relationship between nemolizumab and cancer [82, 83]. An SR with MA, including eight RCTs (809 patients with AD), did not reveal an increased risk of cancer in individuals under nemolizumab therapy [82].

Anti Ig-E and Cancer Risk (Table 4)

We found five studies (four of them were SR) evaluating the relationship between neoplasms and omalizumab. In all the included studies, cancer rates among patients exposed to omalizumab were not higher than in the general population [84–88].

Anti IL-1 (Anakinra, Canakinumab, Rilonacept) and Cancer Risk

We found five studies on anti-IL-1 agents and the risk of cancer: two analyzing various anti-IL-1 [89, 90], two on canakinumab [91, 92] and one on rilonacept [93]. All of the studies, including an SR with > 10,000 patients with cryopyrin-associated periodic syndromes (CAPS) treated with anti-IL-1 therapy, showed that these drugs did not increase the rate of neoplasms compared to the general population [90].

JAK Inhibitors and Cancer Risk (Table 5)

JAK Inhibitors (ALL) and Cancer Risk

We found 46 studies on JAKi agents and the risk of cancer. Among them, 11 included JAKi as a group (≥ 2 drugs of this class) [35, 40–44, 60, 94–98]. An SR and MA from 2020, encompassing 82 RCTs with over 66,000 RA patients, revealed that the incidence rates of malignancies (excluding NMSC) were 0.89 per 100 person-years, which is slightly higher than would be expected in the general population (0.5–0.6 per 100 person-years) [95]. Jalles et al., utilizing data from VigiBase®, a French pharmacovigilance database that reports skin cancers (> 100,000 registered cases), revealed a disproportionality signal for squamous cell carcinoma (SCC) with ruxolitinib and tofacitinib, for melanoma with ruxolitinib and tofacitinib, and Merkel cell carcinoma with ruxolitinib and tofacitinib, and only for Merkel cell carcinoma with baricitinib [96].

Anti-JAKi Versus Biologics

A retrospective study involving nearly 5000 patients reported that the incidence of malignancies in RA patients was not increased with JAKi use compared with anti-TNF therapy [35]. This finding has been supported by other studies [42, 43]. However, some studies have reported a higher incidence of neoplasms in patients undergoing JAKi treatment compared to anti-TNF [41, 44], including a recent multicenter retrospective study (n > 36,000) which concluded that compared to anti-TNF, JAKi were associated with an increased incidence of cancer (incidence rate ratio 1.50; 95% CI 1.16–1.94), both NMSCs and non-skin cancer [44].

JAK-1 Inhibitors (Abrocitinib, Upadacitinib) and Cancer Risk

We found nine studies on the risk of neoplasms with selective JAK 1 (JAK-1) inhibitors: three focusing on abrocitinib [77, 99, 100] and six on upadacitinib [55, 101–105]. In the three studies with abrocitinib, including 787 patients with AD, no cases of cancer were reported [77, 99, 100]. Regarding upadacitinib, a recent SR including 25 RCTs (> 10,000 patients) reported that most of the RCTs did not find a significant increase in the rate of malignancies with upadacitinib therapy when compared to placebo or to anti-TNFs [101, 103, 105]. However, an extended study of a phase 3 RCT (493 patients with RA) showed a higher rate of neoplasia in the 12 mg/day group, mainly at the expense of NMSC [102]. An SR with 11 RCTs and > 50,000 patients (including patients with RA, PsA, and spondyloarthritis) revealed a dose-dependent increase in the incidence of NMSC in RA

Table 5 Main studies that assess the relationship between JAK inhibitors employed in dermatology and cancer risk

Agent	Year, authors	*N*	Study type/Design	Results
All JAK inhibitors	2020, Olivera et al. [95]	66,159	SR with MA Includes 82 studies (trials and observational studies) in patients with tofacitinib, upadacitinib, filgotinib, and baricitinib in patients with RA, IBD, PsO, or AS	The incidence rate of AEs was 42.65 per 100 person-years and of serious AEs was 9.88 per 100 Pys Incidence rate of malignancy (other than NMSC) was 0.89 per 100 Pys
	2022, Jalles et al. [96]	All reports of skin cancers from the French Pharmacovigilance database occurring since 1978 up to 31	Data from cases/non-cases analysis in VigiBase® (the World Health Organization international database of suspected adverse drug reaction) Includes ruxolitinib, tofacitinib, and baricitinib	A disproportionality signal was found to be positive for SCC with oral ruxolitinib (IC025 = 3.92) and tofacitinib (IC025 = 0.82); for melanoma with ruxolitinib (IC025 = 0.81) and tofacitinib (IC025 = 0.74); and Merkel cell carcinoma with ruxolitinib (IC025 = 4) and tofactinib (IC025 = 1.01); and only for Merkel cell carcinoma with baricitinib (IC025 = 0.53)

Table 5 continued

Agent	Year, authors	*N*	Study type/Design	Results
	2022, Song et al. [35]	4929 patients (1064 JAK inhibitor-treated and 3865 TNF inhibitor-treated patients)	Retrospective multicenter study Includes patients with RA	The incidence rates of overall malignancy were 0.54 per 100 Pys (95% CI 0.26–1.14) in JAKi users and 0.85 per 100 Pys (95% CI 0.66–1.10) in TNFi users In this study, malignancy risk in Korean patients with RA was not increased with JAKi use compared with TNFi use
	2023, Krzysztofik et al. [60]	18,739	SR with MA Includes 19 studies reporting IR of melanoma and NMSC in patients with PsO and PsA	The overall IR of melanoma was 0.08 (95% CI 0.05–0.15) events per 100 Pys, and the overall IR of NMSC was 0.45 (95% CI 0.33–0.61) events per 100 Pys The Irs of melanoma were comparable across patients treated with IL-17 inhibitors, IL-23 inhibitors, and JAKi, while the Irs of NMSC were higher in patients treated with JAKi than in those treated with biologics

Table 5 continued

Agent	Year, authors	*N*	Study type/Design	Results
	2023, Huss et al. [41]	14,890	Multicentric prospective study Includes patients with RA and PsA	In RA, based on 38 incident cancers other than NMSC with JAKi vs. 213 with TNFi, the overall HR was 0.94 (95% CI 0.65–1.38). Based on 59 vs. 189 incidents of NMSC, the HR was 1.39 (95% CI 1.01–1.91). At 2 or more years after treatment started, the HR for NMSC was 2.12 (95% CI 1.15–3.89) In PsA, based on 5 vs. 73 incident cancers other than NMSC, and 8 vs. 73 incident NMSC, the HRs were 1.9 (95% CI 0.7–5.2) and 2.1 (95% CI 0.8–5.3) In summary, in clinical practice, the short-term risk of cancer other than NMSC in individuals initiating treatment with JAKi was not higher than for TNFi

Table 5 continued

Agent	Year, authors	*N*	Study type/Design	Results
	2023, Ahn et al. [43]	101,816	Multicentric prospective study Includes patients with seropositive RA Includes patients with TNFi and JAKi. vs. DMARDs	Compared to patients treated only with nbDMARDs, the IRRs of overall cancers in patients administered JAKi/biologics was 0.88, 0.91 (95% CI 0.90–0.92) The incidence of overall cancer was not increased in patients with seropositive RA treated with JAKi/biologics and was relatively lower than nbDMARD-only users, underscoring optimal disease control for risk mitigation
	2023, Min et al. [42]	Set 1: 1596 RA patients (JAKi group: 645; TNFi group: 951) Set 2: 11,765 RA patients (JAKi group: 2498; TNFi group: 9267)	Multicentric retrospective study Includes patients with RA in Korea Includes all JAKi	The HR for cancer in the JAKi groups and TNFi groups of sets 1 and 2 were similar between the two groups [0.68 (95% CI 0.25–1.88)]

Table 5 continued

Agent	Year, authors	*N*	Study type/Design	Results
	2023, Russell et al. [44]	36,681	MA Includes 62 RCTs and 16 observational studies Includes adults with RA, PsA, PsO, AS, IBD, or AD	The incidence of all malignancies including NMSCs was not significantly different between JAKi and placebo (IRR 0.71; 95% CI 0.44–1.15) or between JAKi and methotrexate (IRR 0.77; 95% CI 0.35–1.68) Compared with TNFi, however, JAKi were associated with an increased incidence of malignancy (IRR 1.50; 95% CI 1.16–1.94), both NMSCs and non-NMSCs
	2024, Westermann et al. [97]	875 and 4247 RA patients treated with JAK inhibitors (JAKi) and biologic DMARDs, respectively	Multicentric retrospective study Includes patients with rheumatoid arthritis (RA)	Comparing the two groups using weighted cause-specific Cox models, an HR of 1.41 (95% CI 0.76, 2.37, 95% Cis) was seen for JAKi vs. bDMARD-treated patients with RA
	2024, Yoon et al. [98]	7341	SR and MA Includes 14 RCTs Includes patients with AD with the following drugs: abrocitinib (10, 30, 100, and 200 mg), baricitinib (1, 2, and 4 mg) and upadacitinib (7.5, 15, and 30 mg)	The risk of NMSC and malignancies other than NMSC [0.97 (0.25–3.81, $I^2 = 0\%$), 0.58 (0.14–2.33, $I^2 = 0\%$); respectively] was not increased

Table 5 continued

Agent	Year, authors	*N*	Study type/Design	Results
Abrocitinib (selective JAK1 inhibitor)	2023, Simpson et al. [77]	643	Post hoc analysis of the JADE COMPARE trial Includes patients with AD	No cases of malignancy were recorded in either of the two groups
Upadacitinib (selective JAK1 inhibitor)	2022, Burmester et al. [55]	2257	Post-trial analysis focalized into safety Includes patients with active psoriatic arthritis (PsA) Includes patients with upadacitinib and adalimumab	Rates of malignancies were similar across treatment groups
	2023, Guttman-Yassky et al. [101]	2485	Integrated analysis of phase 3 studies Includes data of patients AD of phase 3 RCT	The malignancy rate was very low and comparable to the general population, both in NMSC and in other types of cancer
	2024, Mysler et al. [103]	> 10,000	SR Includes 25 randomized clinical trials Includes patients with RA, PsA, and AD	Most of the reported studies did not find a higher rate of infections or malignancy with upadacitinib compared to other comparators (especially anti-TNF)

Table 5 continued

Agent	Year, authors	*N*	Study type/Design	Results
	2024, Rubbert-Roth et al. [104]	> 50,000	SR Include 11 trials Includes patients with RA, PsA, AS, or nr-axSpA	In RA, rates of malignancy excluding NMSC were generally similar between UPA 15 mg, UPA 30 mg, ADA, and MTX In RA, NMSC rates were higher with UPA 30 mg than UPA 15 mg; both UPA 15 mg and UPA 30 mg were higher than ADA and MTX In PsA, rates of malignancy excluding NMSC and NMSC were generally similar between UPA 15 mg, UPA 30 mg, and ADA. In AS and nr-axSpA, malignancies were reported infrequently In summary, rates of malignancy excluding NMSC were generally similar between UPA 15 mg, UPA 30 mg, ADA, and MTX, and were consistent across RA, PsA, AS, and nr-axSpA. A dose-dependent increased rate of NMSC was observed with UPA in RA

Table 5 continued

Agent	Year, authors	*N*	Study type/Design	Results
Baricitinib (JAK1 and JAK2 inhibitor)	2022, Taylor et al. [107]	3770	Long-term data in safety of clinical trial Includes patients with RA	The IR for malignancy (excluding NMSC) during the first 48 weeks was 0.6 and remained stable thereafter (IR 1.0) There were 198 (1.3%) cases of malignancy. Among them, 9 lymphomas (0.06%) and 50 NMSC (0.3%) The SIR for malignancies excluding NMSC was 1.07 (95% CI 0.90–1.26) No clear dose differences were noted for exposure-adjusted Irs (per 100 PYE) for malignancies
	2023, Bieber et al. [108]	2636	Long-term data in safety of clinical trials Includes patients with AD	There were 14 malignancies excluding NMSC (IR = 0.3) In this study, baricitinib maintained a similar safety profile to earlier analyses
	2023, Mahmoud et al. [110]	1282	SR with MA Includes 3 RCTs of patients with AA	No higher rates of malignancies were found than in the general population
Deucravacitinib (selective TYK2 inhibitor)	2023, Armstrong et al. [125]	666	Randomized, double-blinded, placebo-controlled phase 3 POETYK PSO-1 trial Includes patients with PsO	No second malignancies were recorded with deucravacitinib

Table 5 continued

Agent	Year, authors	*N*	Study type/Design	Results
	2024, Lebwohl et al. [126]	1519	POETYK PSO-1 trial extension Includes patients with PsO	Exposure-adjusted incidence rates (EAIRs) per 100 person-years were similar at 1 year and 2 years, respectively, for malignancies (1.0 vs. 0.9)
Ritlecitinib (selective JAK3 inhibitor and TYK inhibitor)	2024, King et al. [127]	1269	SR of ritlecitinib trials Includes 4 trials in phase 2a/2b/III Includes patients with AA	Proportions (incidence rates -Irs-) were < 0.1% (0.05/100 PY) for malignancies (excluding non-melanoma skin cancer) The safety profile was maintained in adolescents (12–18 years)

IL interleukin; *TNF* tumor necrosis factor; *TNFi* TNF inhibitor (anti-TNF); *JAKi* JAK inhibitor; *R* receptor; *Ig* immunoglobulin; *Py* person-year; *PTY* patient treatment-years; *SR* systematic review; *MA* meta-analysis; *RCT* randomized clinical trial; *IRR* incidence rate ratio; *SIR* standardized incidence ratio; *aIRR* adjusted incidence ratio; *RR* relative risk; *HR* hazard ratio; *aHR* adjusted hazard ratio; *EAIR* exposure-adjusted incidence rates; *CI* confidence interval; *DMARD* disease-modifying antirheumatic drugs; *bDMARDs* biologic disease-modifying antirheumatic drugs; *nbDMARDS* non-biologic disease-modifying antirheumatic drugs; *IFX* infliximab; *ADA* adalimumab; *RTX* rituximab; *UPA* upadacitinib; *NMSC* non-melanoma skin cancer; *RA* rheumatoid arthritis; *AD* atopic dermatitis; *CD* Crohn's disease; *IBD* inflammatory bowel disease; *UC* ulcerative colitis; *SpA* spondyloarthritis; *AS* ankylosing spondylitis; *PsO* psoriasis; *PsA* psoriatic arthritis; *BCC* basal cell carcinoma; *SCC* squamous cell carcinoma; *NHL* non-Hodgkin lymphoma; *Nr-axSpA* non-radiographic axial spondyloarthritis; *MTX* methotrexate; *AA* alopecia areata

patients treated with upadacitinib, but not in patients with spondyloarthritis or PsA. The incidence of other types of cancer was not increased [104].

JAK-1 and JAK-2 Inhibitors (Baricitinib, Ruxolitinib) and Cancer Risk

We found 11 studies: one on ruxolitinib and baricitinib [106], four studies on baricitinib [107–110], and six studies on ruxolitinib [111–116]. Regarding baricitinib, the incidence of cancer was low, and there was no higher rate of malignancies when compared to the reference population in studies involving RA [107] ($n=3770$), AD [108] ($n=2636$), or alopecia areata (AA) ($n>1300$) [109, 110].

Concerning oral ruxolitinib, an agent traditionally used in hematological disorders such as myelofibrosis and polycythemia vera, diverse studies have demonstrated an increased incidence of secondary neoplasms [111, 112]: a multicentric retrospective study on 700 patients with myelofibrosis revealed that 11.4% of cases developed a neoplasm after starting ruxolitinib and 50% were NMSC [112]. Other studies have also shown an increased incidence of NMSC, especially SCC [113–115]. NMSCs have also been reported with the use of topical ruxolitinib in RCTs on patients with vitiligo, although all cases were considered unrelated to the treatment [116]. A recent study that reviewed nearly 14,000 patient-years of post-marketing safety data from the first year following market approval of ruxolitinib cream found four NMSC in two patients [116].

PAN-JAK Inhibitors (Tofacitinib) and Cancer Risk

Twelve studies were found that assessed the risk of cancer with the administration of the JAK-1, JAK-2, JAK-3, and TYK-2 inhibitor tofacitinib [34, 36, 38, 47, 117–124]. Diverse studies reported that the incidence of neoplasms with tofacitinib was low and similar to the general population, including NMSC [117–121, 123, 124]. A recent SR and MA including 26 controlled studies (22 RCTs) showed that the RR for any cancer with tofacitinib therapy compared to any control treatment was 1.06 (95% CI, 0.86–1.31; $p=0.95$). When comparing tofacitinib to either placebo or biological therapy, no difference was found in the overall cancer risk (versus placebo, RR = 1.04; 95% CI, 0.44–2.48; $p=0.95$; versus biological drugs, RR = 1.06; 95% CI, 0.86–1.31; $p=0.58$). However, when tofacitinib was compared to anti-TNF, the overall cancer RR was 1.40 (95% CI, 1.06–2.08; $p=0.02$). For skin cancer, the RR was 1.30 (95% CI, 0.22–5.83; $p=0.88$). In conclusion, a slightly higher risk was found in patients treated with tofacitinib than in those treated with anti-TNF agents [122]. Similar findings were reported in a randomized, open-label, non-inferiority, post-authorization, safety endpoint trial with 1455 RA patients comparing tofacitinib to anti-TNF [HR 1.48 (95% CI, 1.04–2.09)] [34], and in a study that reviewed data from real practice (>80,000 patients) [36].

TYK-2 Inhibitors (Deucravacitinib) and Cancer Risk

We found two studies ($n=666$ and $n=1519$) on the association of cancer and deucravacitinib in patients with psoriasis. Neither article reported a higher incidence of malignancies with this drug than in the general population [125, 126].

JAK-3 and TYK Inhibitors (Ritlecitinib) and Cancer Risk

An SR including four RCTs and >1000 patients with AA revealed no higher rate of cancer with ritlecitinib in individuals aged ≥ 12 years. In this study, the risk of NMSC was not specifically analyzed [127].

DISCUSSION

Biologics and Cancer Risk

TNF-α is a cytokine with pleiotropic activity, and plays a crucial role in inflammation, exhibiting pro-inflammatory characteristics and influencing various aspects of inflammation and immune regulation. Concerns have arisen

about the potential induction of immunotolerance by anti-TNF treatment, leading to the development of malignancies [128]. However, we found a low risk of cancer with these agents, higher in RA patients with other comorbidities such as advanced age, exposure to other immunosuppressants, and/or hematological disorders [10, 11]. When comparing anti-TNF with other BD, evidence suggested that treatment with anti-IL-17 or anti-IL-23 may have a lower cancer risk than anti-TNF, potentially even lower than the general population [61]. This could be attributed to a pro-tumor role of IL-17 or IL-23, as suggested by some studies [129]. Regarding other BD such as IL-4/13 (dupilumab), IL-13 (tralokinumab), CD-20 (rituximab), IgE R (omalizumab), IL-12/23 (ustekinumab), and IL-31 (nemolizumab) inhibitors, as well as anti-IL-1, IL-5, and IL-6, no higher risk of cancer was found compared to the general population or to other biologics.

Regarding anti IL-4/13, concerns have been raised about the association of dupilumab with certain lymphoproliferative processes. This was initially based on cases of patients treated with dupilumab and subsequently diagnosed with cutaneous T-cell lymphomas (LCCT). However, recent studies have indicated no clear association, with most cases likely being diagnostic errors, initially diagnosed as AD but later confirmed as LCCT [130].

JAK Inhibitors and Cancer Risk

JAKi block multiple cytokines and intracellular pathways of immunosurveillance. The disruption of immunosurveillance could increase the risk of cancer [8]. In our review, some studies demonstrated a higher incidence of cancer, particularly of NMSC, in patients undergoing JAKi, especially with tofacitinib and ruxolitinib, [96]. This may be secondary to the less selective inhibition of tofacitinib (JAK-1, JAK-2, JAK-3, and TYK-2) and ruxolitinib (JAK-1 and JAK-2). However, the patients receiving these drugs may have clinical characteristics (elderly with myelodysplastic syndrome for ruxolitinib and RA patients for tofacitinib) rendering them prone to the development of malignancies. The association of oral ruxolitinib with SCC is noteworthy and has been shown in several case series, often involving high-risk and poor-prognosis tumors [114]. This should be considered in patients undergoing ruxolitinib and presenting with other risk factors for cutaneous cancer [113–115].

For the rest of JAKi, the overall association with cancer was limited and comparable to the general population, although a slightly higher rate of NMSC has been reported with upadacitinib, which is dose-dependent and only in RA [104].

Cancer Risk: Biologics Versus JAK Inhibitors

Multiple studies have attempted to compare the incidence of cancer in patients undergoing BD (especially anti-TNF) and JAKi. Although some have demonstrated a similar incidence [35, 42, 55], most have revealed a higher cancer incidence in patients treated with JAKi than those with anti-TNF or other BD [34, 38, 40, 41, 44, 47, 60]. This risk seems higher particularly for NMSC [41], in patients under prolonged therapy [38], in RA individuals [34, 38, 47], and in patients using tofacitinib [34, 47] or ruxolitinib [114]. However, it is important to emphasize that the overall safety profile of JAKi is favorable and generally superior to other classic immunosuppressants (systemic corticosteroids, azathioprine, methotrexate, cyclophosphamide) [8]. Additionally, the higher incidence of neoplasms has been mainly observed in patients with extra-dermatological disorders (RA and myelodysplastic syndrome), who tend to be older, with more comorbidities, and have undergone prior therapy with multiple immunosuppressants [8]. Nevertheless, new guidelines evaluating the safety of JAKi and certain BD are needed. Recently, the Pharmacovigilance Risk Assessment Committee proposed measures to address severe side effects linked to JAKi in immune-mediated inflammatory diseases [131]. These and other measures may provide a more comprehensive understanding of JAKi and other BD.

Limitations

Our study has several limitations. First, it is a narrative review rather than a systematic one. Second, not all JAKi and BD available were

included. The risk of sonidegib, vismodegib, and immunotherapy was not assessed. However, efforts were made to include as many drugs as possible. Third, a significant portion of the included studies evaluated rheumatological conditions (such as RA, PsA, or spondyloarthropathies), digestive disorders (IBD), or hematological conditions (such as myelodysplastic syndromes), and these patients may present comorbidities or an intrinsic cancer risk that may differ from that of dermatologic patients. Fourth, there is limited literature on newer drugs (e.g., abrocitinib) and a reduced follow-up interval with these agents. Lastly, many studies globally assessed cancer incidence without specific mention of cutaneous cancer, as most reported studies focused on non-dermatological conditions. All these factors make the generalization of reported findings and their conclusions difficult.

CONCLUSIONS

The drugs most strongly associated with cancer risk are anti-TNF agents and JAKi (specifically tofacitinib and ruxolitinib). BD and JAKi tend to represent an incidence of cutaneous cancer similar to the general population.

When comparing BD with JAKi, the latter seem to be associated with a higher risk of malignancies. This risk appears to increase with age, with the presence of other factors such as chronic immunosuppression from previous drugs or other comorbidities, and with specific diseases such as RA and myelodysplastic syndrome. In patients with dermatological conditions (such as psoriasis, PsA, AD), this risk may be lower than in other subgroups and possibly comparable to the general population.

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Declarations

Conflict of Interest. Miguel Mansilla-Polo and Daniel Morgado-Carrasco have no conflicts of interest to declare.

Ethical Approval. The procedures followed here are in accordance with the standards of the committee on ethical human experimentation and with the Helsinki Declaration of 1975, as revised in 1983. We have not used patients' names, initials, or hospital numbers. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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