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RHEUMATOID ARTHRITIS (L MORELAND, SECTION EDITOR)

A Practical Approach to the Use of Conventional Synthetic, Biologic and Targeted Synthetic Disease Modifying Anti-Rheumatic Drugs for the Treatment of Inflammatory Arthritis in Patients with a History of Malignancy

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Abstract

Purpose of Review Conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) have been used in the treatment of inflammatory arthritis (IA) for many years. More recently, biologic (bDMARDs) and targeted synthetic (tsDMARDs) DMARDs have further improved treatment. Due to increased patient longevity and effective oncology treatment, rheumatologists often encounter patients with IA and previous malignancy. The immunosuppressive effect of DMARDs causes concern regarding impaired tumour surveillance with a potential increased risk of malignancy. We reviewed the literature regarding the risk of malignancy in patients on cs-/b-/tsDMARDS and sought to provide practical advice regarding use of these drugs in patients with previous malignancy.

Recent Findings Data from randomised controlled trials is limited as patients with pre-existing malignancy are often excluded. Reassuringly, an increasing range of "real world" data from various national b/tsDMARD registries has not provided a convincing signal that these drugs increase tumour recurrence. Nevertheless, awareness of, and adherence to, national screening guidelines for malignancy is important.

Summary Given the improvement in quality of life achieved with these novel and well-tolerated therapeutic agents, the benefit/risk profile remains overwhelmingly favourable in most patients.

Keywords Disease modifying anti-rheumatic drugs · csDMARDs · Biologics · bDMARDs · tsDMARDs · Malignancy · Cancer

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Introduction

Conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) have long been the mainstay of treatment for inflammatory arthritis (IA; Table 1). More recently, biologic (bDMARDs) and targeted synthetic (tsDMARDs) DMARDs have further improved treatment (Table 1) [1, 2].

Rheumatologists often encounter patients with IA and previous malignancy. In the Consortium of Rheumatology Researchers of North America (CORRONA) Registry, 9.7% of RA patients had a previous malignancy, excluding non-melanoma skin cancer (NMSC) [3], while 7.6% of bDMARD-naive and 3.3% of patients treated with a TNF inhibitor (TNFi) in the Australian Rheumatology Association Database (ARAD) had a previous malignancy [4].

Potential Mechanisms of Oncogenesis with csDMARDs and TNFi

The immunosuppressive effect of DMARDs causes concern regarding impaired tumour surveillance with a potential increased risk of malignancy. Conventional synthetic DMARDs, such as methotrexate (MTX) and leflunomide (LEF), inhibit T and B lymphocyte function and proliferation [5, 6]—both of which are essential for tumour surveillance [7]. In animal studies, recombination activation gene 2 (RAG2)-deficient mice, which lack B and T lymphocytes, have a high risk of intestinal and lung adenocarcinoma [8, 9]. In humans, immunodeficiency due to HIV/AIDS or post-transplant immunosuppression increases the risk of malignancy [10, 11]. Tumour necrosis factor (TNF) was named for its tumour-killing activity in animal models [12, 13]. This led to concern that inhibition of TNF or other pro-inflammatory cytokines might promote oncogenesis.

Table 1 Conventional synthetic, targeted synthetic and biologic disease modifying anti-rheumatic drugs (DMARDs) for treatment of inflammatory arthritis

Type of DMARD	Agent
Conventional synthetic DMARDs	Methotrexate Leflunomide Sulfasalazine Cyclosporin Azathioprine Hydroxychloroquine Sodium aurothiomalate (gold)
Biologic DMARDs	
Tumour necrosis factor inhibitors	Infliximab Adalimumab Etanercept Golimumab Certolizumab pegol
Interleukin-6 receptor inhibitor	Tocilizumab
T cell co-stimulation blockading agent	Abatacept
B cell-depleting agent	Rituximab
Interleukin 12/23 inhibitor	Ustekinumab
Interleukin 17A inhibitor	Secukinumab
Targeted synthetic DMARDs	
Janus kinase inhibitor	Tofacitinib Baricitinib

Limitations of DMARD Safety Data Regarding Risk of Malignancy

The contribution of DMARDs to malignancy in patients with IA is unclear because of multiple confounders. There is increased malignancy in patients with IA due to chronic systemic inflammation and higher rates of certain carcinogens, especially cigarette smoking [14]. Patients with chronic inflammation from psoriasis have an increased risk of NMSC and lymphoma, independent of immunosuppression [15, 16].

There is limited data from randomised controlled trials (RCTs) regarding risk of malignancy with DMARDs. A history of malignancy (except for NMSC) is typically an exclusion criterion for study enrolment [17, 18]. The long latency of oncogenesis means RCTs generally lack sufficient follow-up to detect these events [17, 19]. Registry data from patients seen in routine clinical practice is more helpful, though possible biases exist. Registries such as CORRONA, Anti-Rheumatic Therapies in Sweden (ARTIS), British Society of Rheumatology Biologics Register (BSRBR) and the German Rheumatoid Arthritis Observation of Biologic Therapies (RABBIT) follow patients long-term, but there can be variability in procedures for detection of cancer recurrence and restriction of data collection to certain cancers. There can also be selection bias of patients at lower risk of malignancy for treatment with bDMARDs and more rigorous malignancy screening of patients on immunosuppression. Survivor bias may also be present, as patients with aggressive malignancy may die and be underrepresented. Furthermore, not all clinical centres submit data to the registries.

We will discuss current evidence regarding the risk of malignancy, especially malignancy recurrence in patients on DMARDs for IA, and provide a practical approach to DMARD use in patients with previous malignancy.

Methods

Medline (via PubMed) was searched from January 2000 to July 2017 by combining MeSH terms for “anti-rheumatic

agents", "DMARDS", "methotrexate", "sulphasalazine", "hydroxychloroquine", "leflunomide", "azathioprine", "cyclosporine", "gold", "etanercept", "adalimumab", "certolizumab", "infliximab", "golimumab", "abatacept", "tofacitinib" and "rituximab" and "malignancy" or "cancer". The search was limited to "English" language and "human" subjects. Other papers or conference abstracts considered relevant were used along with those found by citation tracking. Each rheumatologist (PW, HB, CB, PH, MM, JR, RW, LY) was responsible for researching and writing one to two topics and presenting results to the combined group. Recommendations were made by consensus. The manuscript was then circulated to a dermatologist (PS), oncologist (GC) and haematologist (MP) for review.

Methotrexate

Lymphoproliferative Malignancies

MTX Use in Those with No Previous Lymphoproliferative Malignancy (Table 2)

Patients with RA develop lymphoproliferative disorders (LPD) at a frequency 2.0–5.5 times higher than the general population [35]. While Epstein-Barr virus (EBV) reactivation has been implicated in the pathogenesis of some LPD, it is only found in 40% of MTX-LPD in RA patients [36]. The spontaneous regression that may occur in 50–60% of cases after MTX withdrawal supports a causative role for MTX [37, 38].

A French prospective study of almost 30,000 RA patients showed no excess risk of non-Hodgkin's lymphoma (NHL) compared to the general population (standardised mortality ratio, SMR 1.07, 95% CI 0.6–1.7) [39]. This contrasts with Hodgkin's lymphoma (HL), where the annual incidence in RA patients was higher compared to the general population (SMR 7.4, 95% CI 3.0–15.32) [39].

MTX Use in Those with Previous Lymphoproliferative Malignancy (Table 2)

A study of BSRBR-RA patients with prior malignancy found three of nine patients in the csDMARD cohort with a history of NHL had a recurrence [23•]. In the RABBIT database, only two of 55 patients in the csDMARD cohort had a prior lymphoma with no report of lymphoma recurrence [40].

The Canadian guidelines recommend that in RA patients with a history of LPD, the use of csDMARDs other than hydroxychloroquine (HCQ) and sulfasalazine (SSZ) should be done cautiously [21]. The American College of Rheumatology (ACR) recommend combination csDMARDs in preference to a TNFi [1], for patients with previous LPD.

Skin Cancer

Melanoma

MTX Use in Those with No Previous Melanoma (Table 2)

An Australian study of 803 bDMARD-naïve RA patients (76% ever treated with MTX) reported an increased risk of melanoma compared with the general population (SIR 2.72, 95% CI 1.13–6.53) [4]. However, a more recent report from the same registry did not find an elevated risk of melanoma in the csDMARD cohort [41].

A Swedish population-based cohort study of 49,136 RA patients found no increased risk of melanoma (HR 1.2, 95% CI 0.9–1.5) in csDMARD-treated patients compared with the general population [42].

Another Swedish study involving all patients (n = 101,966) dispensed MTX from pharmacies (2005–2014) reported a small increased risk of melanoma in MTX-exposed patients compared to those without MTX exposure (5-year risk 0.48% [95% CI 0·43–0·53] compared to 0.41% [95% CI 0·39–0·43], respectively) [43].

The largest study to date (130,315 RA patients from 11 biologic registers in nine European countries) found no significant increase in overall melanoma risk (SIR 1.1; 95% CI 0.9–1.4) in the csDMARD group [22•].

MTX Use in Those with Previous Melanoma

Published data are sparse. In the BSRBR csDMARD cohort, two of 15 patients with prior melanoma had a recurrence (Table 2) [23•].

Non-melanoma Skin Cancer

MTX Use in Those with No Previous NMSC (Table 2)

Studies indicate a 20–80% increased risk of NMSC in bDMARD-naive RA patients compared with the general population [24•]. A Swedish cohort study of bDMARD-naïve RA patients (n = 46,409, 1998–2012) reported an increased risk of basal cell cancer (BCC; HR 1.22; 95% CI 1.07–1.41) compared with the general population [24•]. The rate of squamous cell cancer (SCC) in bDMARD-naive RA patients was nearly double that of the general population (HR1.88; 95% CI 1.74–2.03) [24•]. In contrast, a nationwide Taiwanese study reported a decreased risk of NMSC in RA patients [44].

MTX Use in Those with Previous NMSC (Table 2)

In a US retrospective cohort study of RA patients (n = 6841), 910 developed a second NMSC—an incidence rate of 58.2 (95% CI 54.5–62.1) per 1000 person-years (p-y). When

Table 2 Summary of evidence for risk of malignancy with conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs)

csDMARD				
MTX	**No previous LPD**	**Key references**	**Previous LPD**	**Key references**
	No increased risk.	[20]	Limited data. Consider on case-by- case basis. Consider Rituximab.	[1, 21]
MTX	**No previous melanoma**		**Previous melanoma**	
	Probably no increased risk.	[22•]	Limited data. Consider on case-by- case basis. Baseline and at least annual skin check recommended.	[23•]
MTX	**No previous NMSC**		**Previous NMSC**	
	Data unclear. Baseline and annual skin check recommended.	[24•]	Increased risk of subsequent NMSC. Baseline and at least annual skin check recommended.	[25]
MTX	**No previous sol malignancy**		**Previous solid malignancy**	
	Data unclear.	[26, 27•]	No increased risk of recurrence. Prior solid malignancy not a contraindication to MTX. Patients should undergo regular cancer screening as per national guidelines.	[1, 21, 28]
LEF	**No previous malignancy**		**Previous malignancy**	
	No increase in LPD or solid cancers.	[29]	No data. May be used in previous NMSC and solid tumours. Use with caution in LPD.	[1, 21]
SSZ	**No previous malignancy**		**Previous malignancy**	
	No increased risk.	[1, 21]	No increased risk.	[1, 21]
AZA	**No previous malignancy**		**Previous malignancy**	
	Increased risk of LPD and lung cancer. Increased risk of melanoma and NMSC. Advise sun protection and annual skin check.	[30, 31]	May be used if previous solid malignancy. Possible increased risk of NMSC recurrence. Advise sun protection and annual skin check.	[28, 30, 31, 32, 33]
HCQ	**No previous malignancy**		**Previous malignancy**	
	No increased risk.	[1, 21]	No increased risk.	[1, 21]
Gold	**No previous malignancy**		**Previous malignancy**	
	No increased risk.	[33]	Prior LPD, skin or solid malignancy not contraindication to gold. Can be continued during treatment of malignancy.	[21]
Cy A	**No previous malignancy**		**Previous malignancy**	
	Probable increased risk of melanoma and NMSC. Possible increased risk of lymphoma and lung cancer.	[30, 34]	No published data on cancer recurrence. Use with caution in consultation with haematologist/oncologist.	

MTX methotrexate, *LEF* leflunomide, *SSZ* sulfasalazine/salazopyrine, *AZA* azathioprine, *HCQ* hydroxychloroquine, *Cy A* cyclosporin A, *LPD* lymphoproliferative disorders, *NMSC* non-melanoma skin cancer

adjusted for other medications, the risk of NMSC increased in those with ≥ 1 year of MTX use (HR 1.24; 95% CI 1.04–1.48). This translated to a number-needed-to-treat of 29.4 to cause one additional NMSC per year with MTX monotherapy [25].

However, both the Canadian [21] and American [1] guidelines recommend a csDMARD rather than a bDMARD or tsDMARD in RA patients with previous melanoma or NMSC. While MTX may increase the risk of NMSC in RA patients, in Australia where approximately two in three of the population will have a skin cancer by the age of 70 years, avoiding MTX is impractical.

Solid Tumours

MTX Use in Those with No Previous Solid Malignancy (Table 2)

A retrospective cohort study (2001–2010) using CORRONA data compared cancer incidence rates in RA patients exposed to cs- and bDMARDs [26]. The incidence rate of solid tumours per 1000 p-y in the MTX group ($n = 1566$) was 3.84 (95% CI 0.78–6.90) compared to 0.53 (95% CI 0–2.02) for other csDMARDs ($n = 904$) and 1.94 (95% CI 0.53–3.35) for TNFi ($n = 3761$). Although there was overlap between the 95% CI's, these findings suggested MTX was associated with a higher risk of solid malignancy than other csDMARDs or a TNFi. The authors considered the possibility of channelling bias, limitations of an observational study and the relatively small number of malignancy cases.

A Swedish register-based cohort study (1999–2012) of bDMARD-naive women with RA ($n = 34{,}984$ patients) and general population comparators showed a greater risk of cervical intraepithelial neoplasia (CIN) 1 (HR 1.53; 95% CI 1.23–1.89) and CIN 2–3 (HR 1.39; 95% CI 1.16–1.66), but not of invasive cervical cancer (HR 1.09; 95% CI 0.71–1.65) compared with the general population [27•].

MTX Use in Those with Previous Solid Malignancy (Table 2)

A BSRBR study found that in the csDMARD cohort ($n = 3235$ patients), nine of the 96 patients with a history of previous solid malignancy had a recurrence or new primary malignancy [45].

There was no increased risk of breast cancer recurrence in RA patients who were then treated with MTX ($n = 892$ patients in each arm; adjusted HR 1.07, 95% CI 0.67–1.69) [46•].

A meta-analysis of RA patients with prior malignancy ($n = 7985$, 1159 new/recurrent cancers, 20,926 p-y of follow-up) found similar rates of cancer recurrence in those treated with csDMARDs (MTX or azathioprine, AZA; 36.2 per 1000 p-y) and those on no immunosuppression (37.5 per 1000 p-y) [28].

The Canadian guidelines recommend csDMARDs may be used in RA patients with a history of solid malignancy [21]. The ACR [1] recommend DMARD treatment be selected as if the patient had no prior malignancy.

Leflunomide

LEF Use in Those with No Previous Malignancy

Post-marketing data suggest no increase in LPD compared to the expected rate for RA and no increase in solid malignancy [29].

LEF Use in Those with Previous Malignancy

There is no published data to inform LEF use in these patients. Canadian guidelines suggest LEF be avoided in patients with pre-existing LPD within the preceding 5 years (Table 2) [21].

Sulfasalazine

Sulfasalazine has been used in patients with IBD and RA for decades without any evidence of increased malignancy (Table 2) [1, 21].

Azathioprine

AZA Use in Those with No Previous Malignancy (Table 2)

A prospective study of 1634 non-transplant patients given AZA or cyclophosphamide (CYC) found a 13-fold increased risk of NHL in the 643 RA patients in the cohort [47]. A BSRBR prospective cohort study of bDMARD-naïve RA patients (3771 patients, 13,325 p-y of follow-up) identified 182 new cancers. Malignancy risk in the pooled group of 365 patients who received AZA, cyclosporin A (CSA) or CYC was increased (relative risk, RR 1.63, 95% CI 1.05–2.52) [30]. Previous cancer was not an exclusion criterion in this study. Haematologic malignancy occurred at more than twice the expected rate (SIR 2.43, 95% CI 1.58–3.55), with a marked increase in risk of lymphoma—SIR for Hodgkin's disease 12.82 (95% CI 4.16–29.92) and NHL 3.12 (95% CI 1.79–5.07). Lung cancers were also increased (SIR 2.39, 95% CI 1.75–3.19) [30]. Data from BSRBR suggests an increased risk of BCC, but not SCC in RA patients ever exposed to AZA (HR 1.53, 95% CI 1.11–2.11) [48].

AZA Use in Those with Previous Malignancy (Table 2)

Most data comes from the transplant literature and are difficult to interpret as combination immunosuppression is used. There is little published safety data regarding AZA use in patients with IA.

A retrospective cohort study examined the risk of NMSC with cs- or bDMARDs in 9460 patients with RA or inflammatory bowel disease (IBD) [25]. There was no increased risk of a second NMSC after 1 year of AZA or other thiopurine (TP) therapy (HR 1.49, 95% CI 0.98–2.27) [25].

A meta-analysis of 3706 IBD patients (10,332 p-y) and 7985 RA patients (20,926 p-y) found no difference in rates of incident or recurrent cancer in TP or MTX users [28]. However, TP use was associated with a higher risk of new or second NMSC (71.6/100-patient-years, 95% CI 58.9–84.2, $p = 0.035$) compared to non-immunosuppressed patients or those on a TNFi. No studies have shown increased relapse rates for melanoma in RA patients on AZA [49].

Hydroxychloroquine

HCQ Use in Those with No Previous Malignancy

Hydroxychloroquine appears to have anti-neoplastic effects in pre-clinical models [50].

HCQ Use in Those with Previous Malignancy

The ACR [1] and Canadian guidelines [21] recommend HCQ for RA patients with previous melanoma or NMSC and previously treated LPD or solid malignancy (Table 2).

Gold and Cyclosporin A

The published evidence is summarised in Table 2.

Tumour Necrosis Factor Inhibitors

TNFi Use in Those with No Previous Malignancy (Table 3)

A study from the Danish DANBIO database (2000–2008) of 10,436 patients with IA showed no increase in overall cancer risk in TNFi-treated compared to TNFi-naïve patients (HR 1.02, 95% CI 0.80–1.3) [65]. However, an increased risk of colon cancer (HR 3.52, 95% CI 1.11–11.15) in the TNFi group was noted.

The BSRBR compared 11,766 RA patients without prior cancer who received a TNFi, with 3246 similar patients treated with csDMARDs. Addition of a TNFi to csDMARDs did not increase the risk of malignancy (HR 0.83, 95% CI 0.64–1.07) compared to those on a csDMARD alone [51•].

The ARTIS group reviewed data on over 43,000 RA patients and found that RA patients had an increased risk of cervical dysplasia, CIN1 (HR 1.53, 95% CI 1.23–1.89) and CIN2 (HR1.39, 95% CI 1.16–1.66)] relative to the general population [27•]. Patients with RA treated with a TNFi had an increased risk of invasive cervical cancer compared to bDMARD-naïve RA patients (HR 2.1, 95% CI 1.04–4.23). However, causality could not be clearly attributed as patients who received a TNFi had greater exposure to DMARDs and cytotoxics [27•].

A recent ARAD study found an increased risk of malignancy in TNFi-naive RA patients with no previous malignancy—SIR for invasive cancers 1.69 (95% CI 1.05–2.02), lung cancer 2.69 (95% CI 1.43–5.68) and prostate cancer 2.10 (95% CI 1.18–4.1) [41]. However, treatment with a TNFi did not increase this risk.

A study of spondyloarthritis (SpA) patients from the ARTIS and DANBIO registries identified 147 cancers in 8703 patients treated with a TNFi and compared these with data from a Swedish TNFi-naïve SpA cohort ($n = 28{,}164$ patients) and a population comparator cohort ($n = 131{,}687$). There was no increase in overall cancer risk in patients treated with a TNFi compared to TNFi-naïve patients (RR 0.8, 95% CI 0.7–1.0) [52•].

Recent work from ARTIS showed no increased risk of invasive solid or haematologic malignancy in 15,129 RA patients commenced on a TNFi as first (HR 0.93, 95% CI 0.85–1.01) or second (HR 0.89, 95% CI 0.76–1.04) bDMARD when compared to 46,610 RA patients on csDMARDs [53].

TNFi Use in Those with Previous Malignancy (Table 3)

Data in this patient group are sparse. Most biologics registries have not found an increased risk of malignancy recurrence in RA patients treated with a TNFi [40, 45, 51•].

The BSRBR identified 425 prior malignancies in over 18,000 RA patients. One hundred and one of these 425 patients developed a new cancer. The recurrence rate of malignancy was lower in TNFi-treated RA patients (age- and gender-adjusted HR 0.55, 95% CI 0.35–0.86) [23•]. Another BSRBR study involving 11,738 RA patients identified 238 patients with cervical CIN3. Although numbers were small, no new female genital cancers occurred in 190 patients treated with a TNFi compared to two in 48 patients receiving csDMARDs [66].

The United States Medicare data (2000–2012) suggested the risk of breast cancer recurrence in patients with RA and IBD was not increased in those who received a TNFi (HR 1.13, 95% CI 0.65–1.97) [46•].

A meta-analysis of 16 studies, including nine with RA patients, showed a similar rate of cancer recurrence in RA patients with a prior cancer who received no immunosuppressive drugs, a TNFi and immunomodulators or various combination therapies [28].

Table 3 Summary of evidence for biologic disease modifying anti-rheumatic drugs (bDMARDs) and targeted synthetic (ts-) DMARDS

bDMARDs/tsDMARD				
TNFi	**Use in those with no previous malignancy**	**Key refs**	**Use in those with previous malignancy**	**Key refs**
	Overall, no increased risk compared to TNFi-naïve RA & SpA patients. Possible increased risk of invasive cervical cancer and colon cancer compared to bDMARD-naïve RA patients.	[27•, 51•, 52•, 53]	No increased risk in RA.	[23•, 28, 51•]
TNFi	**Use in those with no previous NMSC**		**Use in those with previous NMSC**	
	No increased risk of malignancy compared to csDMARDs, but increased risk of malignancy compared to general population. Possible increased risk of invasive SCC. Regular skin checks every six to 12 months, depending on geographical location, recommended.	[24•, 48, 53]	Addition of TNFi to MTX in RA increases risk of second NMSC. Regular skin checks every six to 12 months, depending on geographical location, recommended.	[25]
TNFi	**Use in those with no previous melanoma**		**Use in those with previous melanoma**	
	Most studies show no increased risk of melanoma in TNFi-treated RA. One conflicting study.	[41, 53, 54]	Insufficient published data. Skin checks every six months advised.	[42]
TCZ	**Use in those with no previ malignancy**		**Use in those with previous malignancy**	
	No increased risk.	[55, 56]	No increased risk but limited data.	[57]
ABA	**Use in those with no previ malignancy**		**Use in those with previous malignancy**	
	Most studies show no increased risk. One study suggested increased risk of NMSC but small numbers.	[26, 58]	No increased risk but limited data.	[25]
RTX	**Use in those with no previ malignancy**		**Use in those with previous malignancy**	
	No increased risk.	[59, 60]	No increased risk.	[1, 21, 23•]
Secukinumab	**Use in those with no previ malignancy**		**Use in those with previous malignancy**	
	No increased risk but limited data.	[61, 62]	No published data.	
Ustekinumab	**Use in those with no previ malignancy**		**Use in those with previous malignancy**	
	No increased risk but limited data.	[63]	No published data.	
TFN	**Use in those with no previ malignancy**		**Use in those with previous malignancy**	
	No increased risk.	[59, 64]	No published data.	

TNFi tumour necrosis factor inhibitor, *TCZ* tocilizumab, *ABA* abatacept, *RTX* rituximab, *TFN* tofacitinib, *NMSC* non-melanoma skin cancer, *RA* rheumatoid arthritis, *SpA* spondyloarthropathy

Tumour Necrosis Factor Inhibitors and NMSC

TNFi Use in Those with No Previous NMSC (Table 3)

A BSRBR study of 11,881 RA patients treated with a TNFi compared to 3629 RA patients treated with csDMARDs found an increased risk of skin cancer (BCC and SCC) in both groups compared with the general population [SIR of 1.72 (95% CI 1.43–2.04) and 1.83 (95% CI 1.30–2.50) for TNFi and csDMARDs, respectively [48]. There was no increased risk of BCC or SCC with a TNFi compared to csDMARD alone—adjusted HR 0.95 (95% CI 0.53–1.71) and HR 0.93 (95% CI 0.32–2.76), respectively.

A Swedish study of RA patients (46,409 bDMARD-naïve and 12,588 treated with a TNFi) matched with a general population cohort found an increased risk of BCCs in bDMARD-naïve RA patients (HR 1.22, 95% CI 1.07–1.41) with no further increase following a TNFi (HR 1.14, 95% CI 0.98–1.33) [24•]. However, the risk of SCC was almost doubled in bDMARD-naïve RA patients compared to the general population (HR 1.88, 95% CI 1.74 to 2.03) and increased by a further 30% in those treated with a TNFi (HR 1.30, 95% CI 1.10 to 1.55).

Recent ARTIS data did not detect an increased risk of invasive SCC when a TNFi was used as the first (HR 1.09, 95% CI 0.84–1.42) or second (HR 0.86, 95% CI 0.54–1.39) bDMARD [53].

TNFi Use in Those with Previous NMSC (Table 3)

A retrospective study of 9460 US RA patients (2006–2012) found an increased risk of a second NMSC in RA patients treated with MTX and a TNFi compared to MTX alone (HR 1.49, 95% CI 1.03–2.16) (Table 3) [67•].

Tumour Necrosis Factor Inhibitors and Melanoma

TNFi Use in Those with No Previous Melanoma (Table 3)

Recent Australian work found melanoma risk was not elevated in bDMARD-naïve RA patients (SIR 1.51, 95% CI 0.57–5.53) with no difference in risk between TNFi- and bDMARD-naïve participants (RR 0.71, 95% CI 0.46–1.08) [41].

In contrast to an earlier study [42], recent ARTIS data did not show an increased risk of invasive melanoma in RA patients treated with a TNFi as the first (HR 0.84, 95% CI 0.60–1.18) or second (HR 0.94, 95% CI 0.53–1.66) bDMARD [53]. The authors speculated that lower cumulative inflammation levels and less immunosuppression might have altered melanoma risk.

Analysis of data from 11 European Biologics Registers involving over 130,000 RA patients did not find an increased risk of invasive melanoma in RA patients following TNFi exposure compared to the country-specific general population risk (SIR 1.2, 95% CI 0.99–1.6) [68•].

TNFi Use in Those with Previous Melanoma (Table 3)

In the ARTIS database, 5.6% (3/54) of TNFi-treated patients with prior melanoma (in situ or invasive) had an in situ recurrence compared with a 3.4% (10/295) recurrence rate in non-bDMARD-treated RA patients [42]. Although numbers were too small to allow a firm conclusion, the authors advised increased vigilance to detect early melanoma.

Tocilizumab

TCZ Use in Those with No Previous Malignancy (Table 3)

Analysis of long-term extension (LTE) studies of RA patients treated with tocilizumab (TCZ) (4009 patients, mean treatment duration 4 years) found an increased risk of all malignancies, excluding NMSC, for both the US (SIR 1.36; 95% CI 1.01–1.80) and non-US population (SIR 1.81; 95% CI 1.44–2.23) [55]. However, these rates were not higher than expected for patients with RA [55].

A Japanese study of 5573 patients who commenced IV TCZ for RA and were observed for 3 years found the risk of malignancy was lower than that reported in a large cohort of Japanese patients with RA (SIR 0.79; 95% CI 0.66–0.95) [56]. There was a higher incidence of lymphoma compared with the general Japanese population (SIR 3.13, 95% CI 1.82–5.39), but the SIR was not higher than that reported in bDMARD-experienced Japanese RA patients [56].

A recent analysis of 7093 RA patients treated with TCZ in clinical trials from 2005 to 2015 identified four cases of melanoma. The risk of melanoma was comparable to that in the source population (SIR 0.71; 95% CI 0.19–1.81) [69].

TCZ Use in Those with Previous Malignancy (Table 3)

No increased risk of recurrent malignancy with TCZ was found using data from the RABBIT registry. However, few patients with prior malignancy were treated with TCZ [57].

Abatacept

Abatacept (ABA) is a fusion protein of cytotoxic T lymphocyte-associated antigen-4 and IgG1 which selectively modulates the CD80/CD86—CD28 co-stimulatory signal

required for full T lymphocyte activation [70]. Upregulation of T lymphocyte co-stimulation with agents such as ipilimumab has revolutionised the treatment of melanoma and other malignancies [71]. This raises concern ABA might be oncogenic.

ABA Use in Those with No Previous Malignancy

A meta-analysis of the risk of malignancy in patients treated with bDMARDs and tofacitinib (TFN) in both RCTs and LTE studies showed no increased risk of malignancy with ABA compared to csDMARDs or placebo [59]. Comparison of 4134 RA patients treated with ABA in seven clinical trials and 41,529 csDMARD-treated RA patients from five observational cohorts found no increased risk of malignancy or lymphoma with ABA [58].

A CORRONA study showed no increased risk of cancer with ABA compared to MTX (HR 1.55, 95% CI 0.40–5.97). However, this study found a reduced risk of cancer in those on csDMARDs compared to MTX (HR 0.17, 95% CI 0.05–0.65) and a similar reduction in cancer risk in patients on a TNFi compared to those on MTX (HR 0.29, 95% CI 0.05–0.65). The risk of NMSC was increased (HR 15.3; 95% CI 2.05–114) in ABA-treated patients [26]. However, the small number of NMSC cases (five) resulted in wide confidence intervals.

ABA Use in Those with Previous Malignancy (Table 3)

A retrospective study of 9460 patients with RA or IBD who commenced MTX or bDMARDs after a NMSC showed that ABA (HR 1.40, 95% CI 0.48–4.03) was not associated with an increased risk of another NMSC [25].

Rituximab

RTX Use in Those with No Previous Malignancy

Finnish data revealed 92 malignancies from 10,994 p-y with no difference in adjusted incidence rate ratios between rituximab (RTX) 1.1 (95% CI 0.59–1.9; $n = 438$ patients) and csDMARDs 1.2 (95% CI 0.63–2.3; $n =$ 1400 patients) [72]. A meta-analysis found no increased risk of malignancy with RTX [OR 0.54 (95% CI 0.20–1.50)] compared to several reference populations [59]. An analysis of 11 European biologic registries also found no difference in melanoma incidence between the general population and patients exposed to RTX compared with bDMARD-naïve patients (SIR 1.4; 95% CI 0.6–3.2; $n =$ 9431 patients on RTX; 28,705 p-y of follow-up) [68•].

The RTX clinical trial programme (8 RCTs, 2 LTEs, 1 open label trial) involving 3595 RA patients who received a mean of four courses of RTX over 11 years (14,816 p-y) found no increased risk of malignancy [60]. In particular, the age- and sex-matched incidence of malignancy in those who received RTX was similar to the general US population and in adults with RA (SIR 1.07; 95% CI 0.88–1.29). (All patients received MTX with RTX.)

RTX Use in Those with Previous Malignancy (Table 3)

Data from BSRBR showed those with prior malignancy who received RTX did not demonstrate an increased risk of cancer [age- and gender-adjusted HR 0.43 (95% CI 0.10-1.80)] [23•]. However, patient numbers were low (19 with prior solid malignancy and four with LPD). A US retrospective cohort study of 9460 individuals with RA or IBD enrolled in Medicare from January 1, 2006 through December 31, 2012 found that compared with MTX monotherapy, RTX was not associated with an increased risk of recurrence of NMSC in those with a previous NMSC (HR 1.44, 95% CI 0.26–8.08) [67•].

Both the Canadian and American guidelines support the use of RTX for RA treatment in patients with previous lymphoma [1, 21]. The ACR recommendation is to use RTX in preference to a TNFi in the context of previous LPD based on the established use of RTX as treatment for LPD/lymphoma and the possibility of an increased risk of lymphoma with TNFi.

Secukinumab

Secukinumab Use in Those with No Previous Malignancy

The balance of in vitro evidence suggests inhibition of this cytokine family (IL-17A-F) has anti-tumour effects [73, 74].

As secukinumab was first used to treat psoriasis, most published data are from this patient group. While patients with psoriasis have an increased risk of SCC (SIR 5.3; 95% CI 2.63–10.71) and BCC (SIR 2.00; 95% CI 1.83–2.20), but not melanoma (SIR 1.07; 95% CI 0.85–1.35) [75], there was no evidence using pooled data from 10 studies (four phase II and six phase III RCTs) [61] that secukinumab increased malignancy risk above this [62] (Table 3).

Secukinumab Use in Those with Previous Malignancy (Table 3)

There are no published data.

Ustekinumab

Ustekinumab Use in Those with No Previous Malignancy (Table 3)

Both PSUMMIT1 [76] and PSUMMIT2 [77] excluded patients with current or previous malignancy (with the exception of BCC, skin SCC in situ, or cervical carcinoma in situ that had been treated with no recurrence, or skin SCC that had been treated with no recurrence) within 5 years of study commencement.

Data from the German Psoriasis Registry (PsoBest) found no increased risk of malignancy in patients with psoriasis treated with ustekinumab compared to conventional immunosuppressants [63]. Although only 2.6% of patients had a previous oncologic history apart from skin cancers, similar reassuring findings were reported from the Psoriasis Longitudinal Assessment and Registry (PSOLAR) [78].

Ustekinumab Use in Those with Previous Malignancy (Table 3)

There are no published data.

Tofacitinib

TFN Use in Those with No Previous Malignancy (Table 3)

Patients with prior malignancy (except for BCCs, SCCs and CIN) were excluded from the RCTs. No increased risk of malignancy was reported in any of the published studies (5671 patients, 12 studies) [64]. A recent meta-analysis found no increased risk of malignancy in patients receiving TFN (OR 1.15, 95% CI 0.24–5.47) [59].

TFN Use in Those with Previous Malignancy (Table 3)

There are no published data.

Conclusions

Although there has been concern csDMARDs, and more recently, bDMARDs and tsDMARDs, may impair tumour surveillance due to their immunosuppressive effect, there has been no convincing evidence these drugs significantly increase tumour recurrence. However, awareness of, and adherence to, national screening guidelines for malignancy is important. While RCTs usually exclude patients with pre-existing malignancy, the various national b/tsDMARD registries provide useful "real world" data which should be regularly updated and analysed. Given the improvement in quality of life achieved with these novel therapeutic agents, the benefit/risk profile is favourable in most patients.

Author Contributions All authors read and approved the final manuscript (see the "Methods" section for explanation).

Compliance with Ethical Standards

Conflict of Interest Dr. Kodali reports non-financial support from Bristol-Myers Squibb Australia (BMSA), non-financial support from Amgen, personal fees and non-financial support from Janssen-Cilag, non-financial support from Abbvie, non-financial support from Pfizer, non-financial support from Roche, outside the submitted work.

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Abbreviations *ABA,* abatacept; *ACR,* American College of Rheumatology; *ARAD,* Australian Rheumatology Association Database; *ARTIS,* Anti-Rheumatic Therapies in Sweden; *AZA,* azathioprine; *BCC,* basal cell cancer; *bDMARDs,* biologic disease modifying anti-rheumatic drugs; *BSRBR,* British Society of Rheumatology Biologics Register; *CI,* confidence interval; *CORRONA,* Consortium of Rheumatology Researchers of North America; *CIN,* cervical intraepithelial neoplasia; *CSA,* cyclosporin A; *csDMARDs,* conventional synthetic disease modifying anti-rheumatic drugs; *CYC,* cyclophosphamide; *HL,* Hodgkin's lymphoma; *HCQ,* hydroxychloroquine; *HR,* hazard ratio; *IA,* inflammatory arthritis; *IBD,* inflammatory bowel disease; *IV,* intravenous; *LEF,* leflunomide; *LPD,* lymphoproliferative disorders; *LTE,* long-term extension; *MTX,* methotrexate; *NHL,* non-Hodgkin's lymphoma; *NMSC,* non-melanomatous skin cancer; *p-y,* patient-years; *RABBIT,* Rheumatoid Arthritis Observation of Biologic Therapies; *RCT,* randomised controlled trial; *RR,* relative risk; *RTX,* rituximab; *SCC,* squamous cell cancer; *SIR,* standardised incidence ratio; *SMR,* standardised mortality ratio; *SpA,* spondyloarthritis; *SSZ,* sulfasalazine; *TCZ,* tocilizumab; *TFN,* tofacitinib; *TNFi,* tumour necrosis factor inhibitor; *TP,* thiopurine; *tsDMARD,* targeted synthetic disease modifying anti-rheumatic drugs; *US,* United States

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