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REVIEW RHEUMATOLOGY

Risk of cancer and conventional syntethic DMARDS: A narrative review

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ABSTRACT

Immunosuppressors and immunomodulators are widely used for the treatment of rheumatic diseases. Among them are the conventional Disease-Modifying Antirheumatic Drugs (DMARDs) such as methotrexate, azathioprine, antimalarials, cyclosporine, etc. These drugs can induce remission or control inflammation, improving patients' outcomes. Nevertheless, there is some concern that these drugs may have a carcinogenic potential, favoring the appearance of tumors. Herein, a narrative review of malignancy risk after using conventional DMARDs is done.

Keywords: Cancer; disease-modifying antirheumatic drugs; DMARDs; immunosuppressive drugs.

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The association of rheumatic diseases with cancer is well known. However, the mechanisms underlying this association are challenging to be studied as this link may be multifactorial. Immune-mediated rheumatic diseases may be associated with cancer due to shared environmental exposures, virus infections, or a shared genetic background [1]. In this instance, in rheumatoid arthritis (RA), tobacco exposure and Epstein Barr infection are common environmental triggers for both disorders: cancer and the rheumatic condition [2, 3]. Moreover, the dysfunctional immune surveillance seen in immune-mediated diseases may favor the cancer's appearance. The development of lymphoproliferative diseases in Sjogren's syndrome is a classic example of the increased risk of malignancy in this context. Excessive glandular B lymphocyte stimulation and impaired B cell apoptosis are considered to lead to tumorigenesis and B cell clonal expansion [1]. In RA, long-term inflammatory activity is also associated with increased tumor risk [1]. Another point to consider is that several rheumatic conditions may present as paraneoplastic syndromes. Inflammatory myositis, mostly dermatomyositis, has been characteristically identified in this setting, usually in lung, breast, ovarian, and nasopharyngeal cancer and lymphomas [4, 5]. Even some connective tissue diseases may have clinical manifestations associated with cancer appearance. This is the case of lung fibrosis associated with lung cancer [6] and esophagitis with Barrett's epithelium [7] in scleroderma.

The increased risk of malignant diseases driven by exposure to drugs used to treat rheumatic diseases is an area of concern. Several medications, such as azathioprine, methotrexate, cyclophosphamide, etc., have tumorigenic effects [1].

The association of cancer and conventional rheumatic disease-modifying drug treatment is the focus of this review.

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METHOTREXATE (MTX)

MTX is widely used in rheumatology; it is considered the gold standard treatment in RA and is used as a steroid-sparing agent in several other rheumatological conditions. Despite a favorable side-effect profile, it has been associated with the appearance of solid tumors and lymphomas. In patients with RA, the use of MTX is linked to the development of lymphoproliferative diseases (LPD), and the regression of the LPD after MTX withdrawal is considered strong evidence for the carcinogenic potential of this drug [8].

A study of 48 MTX-LPD, comparing them with non-MTX-LPD (n=28) and sporadic LPD (n=150), found that RA-LPD had similar clinicopathological characteristics regardless of MTX use but for spontaneous regression of LPD after removal of MTX in MTX-LPD and a shorter interval between the diagnosis of RA and LPD in MTX-LPD than in non-MTX-LPD. The 5-year overall survival rates in cases of MTX-LPD and non-MTX-LPD were 58.9% and 52.8%, respectively, significantly worse than that in sporadic LPD [8].

A study in the cancer risk among patients with several rheumatic diseases (RA, ankylosing spondylitis or AS and psoriatic arthritis or PsoA) and the possible association with treatment could not detect a significant increase in cancer risk with used medications including methotrexate [9].

The risk of breast cancer recurrence with methotrexate therapy was not significantly increased in a study that verified the recurrence of breast cancer 365 days after primary cancer surgery in RA and inflammatory bowel disease patients using MTX in the database from Medicare (US National Health Insurance) [10].

In a nested case-control study evaluating factors related to MTX-LPD among 38 patients that developed LPD on MTX (15 with lymphoma), regression was observed in 60.4% (n=29; 6 with lymphoma) following drug withdrawal. The development of MTX-LPD was associated with high lactate dehydrogenase (LDH) levels and elevated DAS (Disease Activity Score)-28 but not with the MTX dose [11].

An analysis of the risk of high-grade cervical dysplasia and cervical cancer in systemic lupus erythematosus patients (SLE) according to treatment with immunosuppressors using commercial health plans and Medicaid databases compared immunosuppressor drug users with those using antimalarials. Methotrexate users in the Medicaid sample (n=19,861) had an IR=2.55/1000 persons-years (95% CI=1.4–4.5) of cervical dysplasia and cancer-related to antimalarial users. In the example of a commercial health plan (n=7,223), an IR=4.25/1000 persons-year (95% CI=1.77–10.2) was found [12].

Highlight key points

- Disease-Modifying Antirheumatic Drugs (DMARDs) are largely used for the treatment of rheumatic diseases.
- These drugs have a carcinogenic potential, favoring the appearance of tumors

A Swedish study, using data of dispensed MTX from Swedish pharmacies during 2005–2014 (n=101,966) compared with 509,279 controls, found a small but statistically significant increase in cutaneous melanoma in those exposed to MTX [13].

Looking for the association of several DMARDs with non-melanoma skin cancer (NMSC) in RA, it was found that MTX in a cumulative dose from 1–3 g had an OR 2.5 (95% CI=2.2–5.8) and in a cumulative dose higher than 3 g had OR=4.6 (95% CI in 1.7–12.4) in individuals under 65 years of age and 17.9 (95% CI=2.3–44.2) in those ≥65 years of age for this sort of cancer [14].

An analysis comparing the risk of several malignancies in RA patients receiving MTX and MTX plus biological disease-modifying drugs, using the database from the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS), found that MTX alone increased the risk of leukemia (OR=2.9; 95% CI=2.3–3.7), stomach cancer (OR=3.9; 95% CI=2.8–5.5), breast (OR=2.3; 95% CI=2.0–2.6), colorectal (OR=3.0; 95% CI=2.5–3.6), pancreatic (OR=2.5; 95% CI=1.7–3.5), prostate (OR=2.1; 95% CI=1.6–2.8), kidney (OR=3.9;95% CI=2.9–5.3), ovarian (OR=3.1; 95% CI=2.3–4.2), lung malignancies (OR=2.7;95% CI=2.4–3.1) and melanoma (OR=2.2; 95% CI=1.7–2.7) but not liver cancer. Association with biological DMARDs further amplified the risk of breast (OR=1.54; 95% CI=1.2–1.9), ovarian (OR=2.4; 95% CI=1.2–4.6), and lung cancer (OR=1.52; 95% CI=1.2–1.9) in RA patients receiving MTX [15].

The comparison of hematologic malignancies in RA Japanese patients receiving MTX alone (n=2,052) with those receiving MTX in combination with biologics (n=782) showed a higher risk of malignant lymphoma in the combination compared to MTX alone (OR=4.2; 95% CI=1.6 to 11.1). The median time between MTX prescription and

the onset of lymphoma was 3.58 years for MTX alone and 3.42 years for the combination therapy [16].

A study with 986 RA patients treated with MTX identified 95 new malignancies in 90 patients; LPD was the most common. The cumulative incidence of LPD was 1.3% in 5 years and 4.7% after 10 years of MTX use. Accordingly, approximately 1 in 20 patients with RA developed MTX-LPD over the 10 years of MTX treatment. Cancer regression after MTX discontinuation was observed in 2/3 and 7/13 of Epstein-Barr-negative and -positive cases, respectively. The incidence of MTX-LPD was significantly increased if the patients used concomitant tacrolimus. The RA patient's survival was not affected by the malignancy [17].

A study on the occurrence of skin cancer, including malignant melanoma and NMS after treatment initiation with methotrexate versus antimalarials in patients older than 65 with RA, and using Medicare fee-for-service claims data in the USA, found that 2.74 % of patients developed skin cancer during this period without differences between the group using MTX and antimalarials. However, the subgroup analysis showed a 37% higher risk for basocellular carcinoma and a 21% lower risk for squamous cell carcinoma in the MTX group. This study comprised data from 11 years (2006 to 2017), including 38,842 new users of MTX and 25,291 new users of antimalarials [18].

AZATHIOPRINE (AZA)

AZA is an immunosuppressive agent that acts as an antagonist of purine metabolism, causing a reduction of circulating B and T lymphocytes, [19, 20] diminishing immunoglobulin synthesis and interleukin (IL)-2 secretion [21]. It is frequently used to manage rheumatic diseases and other immune-mediated disorders. AZA's most common side effects include gastrointestinal intolerance, bone marrow suppression, infection, and risks of malignancy [22]. AZA is thought to favor malignant transformation by nonrepaired DNA double-strand breaks that form highly mutagenic DNA bases [23].

A case-control study with 202 RA patients using azathioprine and 202 RA without this medication followed for 20 years found that RA patients without azathioprine had a 4–8-fold increase of lymphomas, and RA treated with azathioprine had a 10-fold increase of this neoplasm. In this cohort, azathioprine was used in the 5 mg/kg/day dose. The authors concluded that the risk from azathioprine treatment was small compared to the risk of background RA [24]. However, an analysis of 16 patients with non-Hodgkin lymphoma and SLE, compared with 26 controls found that every use of azathioprine did not increase the risk of this malignancy (RR=0.9; 95% CI=0.5–2.5) [25].

Another case-control study with 619 RA patients who developed hematologic malignancies and 6,190 controls, followed during 23 years, found that individuals with azathioprine exposure had a rate ratio of 1.44 (95% CI=1.01–2.03) to develop malignancy [26].

Eleven cancer cases in a series of 451 patients with Behçet's disease were detected and the use of azathioprine significantly decreased cancer risk. The authors proposed that suppression of inflammation was the underlying mechanism [27]. This finding was corroborated by another study in Behçet's disease comparing 22 patients with cancer (myelodysplastic syndrome was the most common) and 44 cancer-free controls. This study found that azathioprine did not increase cancer chances (OR=4.0, 95% CI: 0.8 to 21.4) [28].

ANTIMALARIALS (ATM)

ATM (chloroquine and hydroxychloroquine) are 4-aminoquinoline derivatives with numerous biological effects, including immunomodulatory actions used in rheumatology, mainly in treating RA and SLE [29]. Despite the appearance of new treatment modalities, ATM still has a place in SLE treatment where it plays a disease-modifying role. It also has anti-lipidemic and antithrombotic effects [29].

A meta-analysis including nine other studies found that antimalarials may reduce the risk of cancer in SLE (RR=0.68; 95% CI=0.55–0.85). The subgroup analysis of 4 nested case-control and 3 case-cohort studies confirmed this finding, but in the 3 cohort studies, no differences between users and non-users of antimalarial were found [30].

A retrospective case-controlled study of 72 SLE patients with hematological malignancies found that hydroxychloroquine had a protective role in patient mortality (RR=0.28;95% IC=0.09–0.84) [31].

A prospective cohort study of 5,077 RA patients from Korea with a median disease duration of 6 years found that malignancy risk was reduced in the RA cohort when compared to the general population (IR=0.40; 95% CI=0.31 to 0.51), and that the use of hydroxychloroquine played a protective role [32].

CYCLOPHOSPHAMIDE (CYC)

CYC is an alkylating agent considered one of the most potent immunosuppressive therapies. It has been used to treat organ-threatening manifestations of various autoimmune and inflammatory diseases. It can be used orally or intravenously. Despite its remarkable effectiveness, it has many toxic side effects. Malignancy is one of them. The mechanisms underlying the increased cancer risk in this context are poorly understood. CYC might interfere with mitosis and induce DNA damage by forming DNA adducts [33]. Some neoplasms may appear many years after the drug discontinuation [34].

A study with 1065 patients with Wegener's granulomatosis from the nationwide Swedish Inpatients Register (from 1969 to 1995) looking for bladder cancer diagnoses found 23 cases of malignancy. The risk of bladder cancer doubled for every 10 g increment in cyclophosphamide, and the treatment duration longer than 1 year was associated with an eight-fold increased risk. The authors pointed to a dose-response relationship between cyclophosphamide and the risk of bladder cancer [35].

An analysis of the cancer incidence in 914 SLE patients in a Korean hospital from 1997 to 2007, and compared with a matched cohort from the National Cancer Registry, found that 16 cancer cases occurred (mainly cervix, non-Hodgkin lymphoma, and bladder cancer). A cumulative cyclophosphamide dose over 6 g was associated with cancer appearence [36].

Another study, using the French Vasculitis Study Group database, found that among the 805 patients observed for 4,230 patients-years, 22 hemorrhagic cystitis and 7 cancers from the urinary tract were identified. Patients with small necrotizing vasculitis had a 5-fold higher risk of urinary tract cancer. They also found that 10g increments in cumulative CYC dose, any use of oral CYC, and the diagnosis of Wegener independently predicted cancer and/or hemorrhagic cystitis [37].

In granulomatosis with polyangiitis, the risk of cancer with cyclophosphamide was studied in 293 patients (156 males and 137 females with a mean age of 59 years, median follow-up of 9.7 years, and median cumulative CYC dose of 24 g) and found an overall increase in cancer (SIR=1.9; 95% CI=1.5 to 2.4) mainly in NMSC and bladder cancer. If the cumulative CYC dose was 1–36 g, the only type of malignancy to occur in excess was NMSC; if >36 g, there was an overall increase in cancer, mainly bladder cancer, myeloid leukemia, and NMSC. No significant increase in malignancies was observed among those CYC-naïve [38].

In Behçet's disease, a case-control study with 22 patients with cancer (most hematological) and 44 controls found that CYC favored the cancer appearance with OR=7.8, 95% CI=1.9–39.6) [28].

MOFETIL MYCOPHENOLATE (MMF)

MMF is a prodrug of mycophenolic acid selective inhibitor of inosine monophosphate dehydrogenase, a rate-limiting enzyme essential for leukocyte production. [39] MPA prevents the proliferation of human T- and B-lymphocytes, being more selective for activated T-lymphocytes [39]. It is frequently used in treating lupus nephritis and interstitial lung involvement in connective tissue diseases, among others [40, 41].

The studies on the association of MMF with drug-induced cancer in rheumatic diseases are scarce. Case reports [42–45] and studies in transplanted patients reported an increased rate of lymphoproliferative disease, including those in the central nervous system [42–46], and squamous cell carcinoma, particularly in those using the drug for more than 5 years [46].

A study on the occurrence of therapy-related secondary myeloid neoplasms with several drugs used for the treatment of autoimmune diseases found that MMF was a safe drug with OR=0.66; 95% CI=0.21–2.03). However, in this study with 86 cases of myeloid neoplasm, only 5 individuals were using MMF [23].

CALCINEURIN INHIBITORS (CYCLOSPORINE OR CSA AND TACROLIMUS OR TAC)

CsA and TAC inhibit the calcineurin activity in immune cells, thereby preventing the activation and nuclear translocation of nuclear factor of activated T-cells (NFAT), leading to inhibition of Interleukin-2 (IL-2) production in T cells [47]. There is limited information about its use and malignancy risk in rheumatological conditions. Most existing evidence is from transplant cohorts in which CsA and TAC increase the risk of skin and lymphoid tissue malignancies [48]. The level of immunosuppression is the leading risk factor for malignancies with these drugs. There is a description that the reduction or discontinuation of this treatment caused regression of lymphoma and other lymphoproliferative lesions [49]. Animal studies suggest that CsA may have another mechanism. This drug promotes cancer invasiveness due to the

production of transforming growth factor (TGF)-beta; anti-TGF-beta monoclonal antibodies appear to prevent the CsA-induced increase in metastases [50].

An observation in CsA-treated RA individuals showed that they had a higher incidence of cancer in general (RR=3.6; 95% CI=2.2–5.8) when compared with patients treated with glucocorticoid alone. No differences were found when CsA was compared with other DMARDs [51].

A higher incidence of skin cancer (RR=2.6; 95% CI=1.3–4.5) and lymphoproliferative diseases (RR=10.7; 95% CI=2.2–31.3) was found in RA patients treated with cyclosporine when compared to the general population [52].

On the other side, an evaluation of the risk of malignancies in a retrospective cohort with 208 RA-treated patients using CsA and 415 RA controls followed for the median time of 5 years, found that CsA did not increase the cancer risk (RR=0.67; 95% CI=0.19–0.84) [53].

A large prospective multicenter study investigating malignancies in psoriasis patients treated with cyclosporine with 1,252 patients (7% with arthropathy) followed for 5 years found a 6-fold higher incidence of skin malignancy, most of them squamous cell carcinoma. Patients treated for more than 2 years had higher risk. The incidence of non-skin cancer was similar to the general population [54].

A retrospective study using the Taiwan National Health Insurance Research Database found that patients with RA using cyclosporine compared to non-RA had OR=5.7; 95% CI=2.2–14.8 para NMSC [14].

The effect of treatment withdrawal in iatrogenic immunodeficiency-associated lymphoproliferative disorders studying 59 patients with LPD (50 receiving MTX, 4 receiving TAC, and 5 receiving the combination of MTX and TAC; most with RA) observed that the treatment withdrawal leads to regression without relapse in 22 (38%) and relapse after regression in 12 (21%). In the cases of diffuse large B-cell lymphoma, the regression was associated with Epstein–Barr virus positivity [55].

Conclusion

The analysis of the drug effect on malignancy risk is complex due to the significant heterogeneity of the studies: different rheumatic diseases in the background, diverse therapeutic regimes, and study designs may offer difficulties in interpreting results. Nevertheless, the awareness of this possibility should be present in all physicians prescribing this form of treatment.

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