Malignancy as a comorbidity in rheumatic diseases.

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Malignancy As A Co-Morbidity In Rheumatic Diseases

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Abstract:

Patients with systemic autoimmune rheumatic diseases, particularly rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, and idiopathic inflammatory myopathies, are at increased risk for developing malignancies. Cancer occurrence adds to the disease burden in these patients, adversely affecting quality of life and life expectancy. This risk is related to the pathobiology of the underlying rheumatic disease including the inflammatory burden, immunologic defects, personal and environmental exposures such as smoking and some viral infections. Immunomodulatory therapies, especially chemotherapeutic agents, are also associated with an increased risk of cancer in these conditions. The decision to use immunomodulating therapies in patients with rheumatic disease must take into account the disease severity, expectations for disease control, comorbidities, and host and environmental risk factors for cancer. Effective screening and monitoring strategies is important to reduce the risk of cancer in these patients.

Key messages

- The risk of malignancy, especially lymphoproliferative malignancy, is increased in several systemic rheumatic diseases
- The malignancy risk is related to the pathobiology of the underlying rheumatic disease, traditional cancer risk factors, and some rheumatic disease therapeutics
- Immunomodulating therapy decisions must take into account the disease severity, comorbidities, and host and environmental risk factors for cancer.

Introduction

Malignancy is an important part of the burden of comorbidities associated with rheumatic diseases. Patients with systemic inflammatory rheumatic disorders generally have an increased risk of developing malignancy, with certain malignant tumors being increased in particular subsets of patients (1, 2). This increased risk is the result both of fundamental underlying immunologic effects of autoimmunity on cancer risk as well as the risk of cancers associated with drug treatments of rheumatic diseases. In some cases, common environmental risk factors for chronic inflammatory diseases and malignancy contribute to increased comorbidity (3).

Cancer may also constitute a major diagnostic challenge in patients with rheumatic symptoms. Musculoskeletal complaints may be manifestations of paraneoplastic processes, and some patients with a tentative diagnosis of a chronic rheumatic disorder at presentation actually have an underlying malignancy (4). In patients with established rheumatic disease, it is sometimes difficult to distinguish symptoms related to the tumor from worsening of the rheumatic condition. In addition, the development of cancer, or a history of malignancy in the past, may have a major impact on long term management of rheumatic diseases (5).

The purpose of this review is to discuss what is currently known about comorbidity from malignancy in rheumatic diseases, including recent developments relevant to the management of patients with chronic inflammatory disease.

Concepts of autoimmunity and tumorogenesis

The accelerated growth of cancer cells in immunodeficient mice and the increased risk of cancer in heavily immunosuppressed transplant patients have shaped the perception of the immune system as a potent barrier against neoplasms (6, 7). It may be expected that immunosuppressive treatment would inevitably result in effects favoring malignant cell

growth. However, emerging evidence supports the seemingly paradoxical notion formulated perhaps first by Rudolph Virchow in 1863, that inflammation is a critical component in cancer initiation and progression, and that reduction of systemic inflammation may reduce cancer risk in these conditions (8).

The association between several systemic autoimmune diseases and lymphoproliferative malignancies is compatible with the concept of chronic activation of B cells and T cells as a driving force for the development of cancer comorbidity. The magnitude of this risk increase is particularly high in primary Sjögren's syndrome (9, 10), where B cells and autoantibodies are clearly implicated in the disease process, but also applies to systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) (9,10), where it is associated with disease severity (11, 12). Furthermore, the increased risk of lymphoma extends to other autoimmune disorders, such as idiopathic thrombocytopenic purpura and sarcoidosis (13).

Epidemiologic concepts

Assessment of cancer risk in rheumatic diseases must be placed against the lifetime risk of developing cancer, which is approximately 20 percent in Western Europe and North America, with about 5 percent of the general population having current cancer or a history of cancer (14). Approximately 1 in 10 women will develop breast cancer, and as many as 1 in 8 men will develop prostate cancer, 1 in 25, colorectal cancer, 1 in 40, lung cancer, and approximately 1 in 100, lymphoma or other lymphoproliferative malignancy (14).

The combination of increased risk for some, and decreased risks for other types of cancers in different rheumatic diseases, may result in a neutral effect for malignancies in general. Correct study methodology is essential to examination of these risks. The statistical approach for capturing differences in sparse event data, particularly when malignancy is not a

prespecified study outcome, and assumptions of proportional hazards models and stable frequencies of events over time for a non-linear risk such as cancer, can result in major analytical flaws (15).

The occurrence of cancer has a profound effect on the already compromised quality of life of patients with rheumatic diseases and may affect survivorship. A population-based study of cancer survival in patients with inflammatory arthritis from Great Britain suggests a decreased survival compared to the general population (16).

Malignancies associated with various rheumatic diseases are listed in Table 1.

Malignancy and rheumatoid arthritis

The risk of cancer has been more extensively studied in patients with RA than in most other rheumatic disorders. In a large study utilizing statewide discharge records from California linking RA to Cancer Registry data for 1991 – 2002, including patients observed for a total of approximately 400,000 person years, an increased risk of developing lymphoproliferative cancers was found among both women and men with RA (17). Males had significantly higher risk for lung, liver, and esophageal cancer, although a lower risk for prostate cancer was noted. Females were at decreased risk for several cancers including cancers of the breast, ovary, uterus, cervix, and melanoma, with risk reduction ranging 15 to 57 percent, compared to the general population.

A link between lymphoma and RA was first reported from a medical record linkage study in 1978 (18). Subsequently, a considerable body of evidence has emerged that supports the link between RA as a pathogenic factor in the development of lymphoma. An SIR of 2.4

for lymphoma was described in a population of over 20,000 Danish patients, and an increased risk of 1.9 in 1,852 US patients (19, 20).

In a meta-analysis of 21 publications from 1990 – 2007 on the risk of malignancy in patients with RA, the risk of lymphoma was increased approximately two-fold [standardized incidence ratio (SIR) 2.08, 95% confidence interval (CI)1.8 to 2.39], with a greater risk of both Hodgkin's and non-Hodgkin's lymphoma (2). The risk of lung cancer was increased with an SIR of 1.63. There was a decreased risk for colorectal cancer (SIR 0.77, 95% CI 0.65 to 0.90), and, as in the study from California, a decreased risk for breast cancer (SIR 0.84). The overall SIR for malignancy was slightly increased at 1.05. The overall increased risk of cancer in patients with RA was largely driven by the increased risks for lymphoproliferative cancers.

Patients with RA may be at a particularly high risk for the diffuse large B-cell type of non-Hodgkin's lymphoma (21). Large B-cell lymphomas have been reported to represent up to two-thirds of the non-Hodgkin's lymphomas in patients with RA (13, 16), about twice the rate of diffuse large B-cell lymphoma as a proportion of overall non-Hodgkin's lymphoma in the general population, although there are some conflicting results on these patterns (22).

The risk of non-Hodgkin's lymphoma appears to be higher in patients who have severe RA with persistently high disease activity over time, and among those who have positive rheumatoid factor (11, 16). In particular, a high cumulative disease activity has a major impact. The unadjusted odds ratio (OR) for average disease activity comparing highest versus lowest quartile was 71.3 (95% CI 24.1 to 211.4), and the OR for cumulative disease activity of the 10^{th} decile versus 1^{st} decile was 61.6 (95% CI 21.0 to 181.0) in a case control registry study from Sweden (11). Lymphoproliferative malignant disease is also particularly increased in patients with extra-articular manifestations such as Felty's syndrome (23) and

secondary Sjögren's syndrome (24), again suggesting a role of disease associated lymphoproliferation (in this case splenomegaly and autoimmune sialoadenitis, respectively). A rare form of leukemia which can occur in RA is large granular T cell lymphocyte leukemia (T-LGL) (25). It is usually chronic and rarely becomes aggressive.

An increased risk of lung cancer has been reported in individual studies (26) as well as in the meta-analysis mentioned above (2). This may be secondary to an increased risk of RA in smokers, described in population based prospective cohort studies (27, 28). On the other hand, in a study of patients with RA in the United States veteran's population, the risk of lung cancer was increased by 43 percent compared to the general population even after adjustment for tobacco and asbestos exposure (29). However, since data on the intensity and duration of smoking was not available in this study, the impact of such factors on the risk increase could not be determined.

In agreement with the study from California (17), a reduced risk of colon, rectal and endometrial cancer was also found in a Swedish national register study of 42,262 patients hospitalized with RA from between 1980 and 2004 indexed to the Swedish national cancer register (30). The decreased risk of colorectal cancer may be attributable to long-term non-steroidal anti-inflammatory drug use in patients with RA (31).

Malignancy and systemic lupus erythematosus

Several studies have suggested a moderately increased risk of cancer in patients with SLE), with particularly increased rates of both Hodgkin's and non-Hodgkin's lymphoma (32). The risk is especially high for diffuse large B-cell lymphoma, often of aggressive subtypes (33, 34).

A large multicenter international cohort of 9,547 patients with an average follow-up of 8 years confirmed an increased overall risk of cancer in patients with SLE, with the risk increase mainly driven by increased risk of lymphoproliferative cancer. For all cancers combined, the SIR estimate was 1.15 (95% CI 1.05 to 1.27); for all hematologic malignancies, it was 2.75; and for non-Hodgkin's lymphoma, it was 3.65. The data also suggested a significantly increased risk of lung cancer (SIR = 1.37) and hepatobiliary cancer (SIR = 2.60) (1).

A study using a California statewide patient hospital discharge database from 1991 to 2001 and Cancer Register data for comparison with the background population revealed an overall significantly increased cancer risk in 30,478 SLE patients followed for 157,969 person years (35). Again, the risk of liver cancer was increased, as well as the risk of cancer in the vagina/vulva.

Other studies have also reported possibly increased risk for malignancies other than lymphoproliferative cancers in SLE, including thyroid cancer (36) and squamous cell skin cancer (37). The risk for breast cancer may be increased by about 1.5 to 2 fold compared to the general population, even after consideration of age, parity, family history, and exogenous estrogens (32, 38). The underlying mechanisms are incompletely understood, but one study suggested that patients with SLE are less likely to undergo breast cancer screening than healthy women (39). They also appear to be less likely to undergo routine cervical cancer testing, which may explain the increased risk of abnormal Pap smears and cervical dysplasia in women with SLE (40), although the risk for invasive cervical cancer was not increased (1).

Women with SLE may be at higher risk for lung cancer (41). Since smoking is a major predictor of lung cancer, this may, as in the case of RA, be partly explained by an

observed association between smoking and SLE, reflecting a complex interplay of disease susceptibility factors (42).

Risk factors for the major cause of excess cancer morbidity in SLE, hematologic malignancies, may relate to inflammatory burden and disease activity, immunologic defects and overexpression of *Bcl*-2 oncogenes as well as viruses, especially EBV (41). Leukopenia, independent of immunosuppressive treatment, has been shown to be a risk factor for leukemia in patients with SLE, suggesting that bone marrow investigation may be indicated in SLE patients with longstanding leukopenia and anemia (43). Longer disease duration and disease activity with moderately severe end organ damage predict the development of non-Hodgkin's lymphoma in patients with SLE (11).

Malignancy and Sjögren's syndrome

The association between primary Sjögren's syndrome and lymphoproliferative disorders has been estimated to correspond to a relative risk compared to the general population ranging from 6 to 44 in individual studies; a meta-analysis of cohort studies reported a pooled SIR of 18.8 (10). The life time risk of non-Hodgkin's lymphoma in patients with primary Sjögren's syndrome has been reported to be 5-10 % (9), although one study with long term follow-up demonstrated a cumulative incidence of 18 % (44). In one prospective cohort study, premature mortality in patients with primary Sjögren's syndrome was exclusively associated with the development on non-Hodgkin's lymphoma (45).

The majority of lymphomas seen in these patients are either mucosa-associated lymphoid tissue (MALT) lymphomas (46), or large B-cell lymphomas (47). Less commonly seen lymphoproliferative diseases include lymphocytic leukemia, Waldenström's macroglobulinemia, and multiple myeloma (48). Risk factors for non-Hodgkin's lymphoma

include hypocomplementemia, persistent or recurrent salivary gland swelling, and cutaneous vasculitis, palpable purpura and low complement factor C4 levels (47, 49, 50). In a recent prospective study, the detection of germinal-center like structures in salivary gland biopsies obtained at diagnosis of primary Sjögren's syndrome were highly predictive of future development of lymphoma (51). Taken together, the evidence strongly suggests that the increased risk of lymphoproliferative cancer is due to chronic B cell activation in these patients. For MALT lymphomas, infection with *Helicobacter pylori* may play a role (46). The risk of other cancers than lymphoproliferative malignancies does not appear to be particularly high in patients with Sjögren's syndrome (48).

Malignancy and other rheumatic diseases

The risk of malignancy in patients with systemic sclerosis (scleroderma) appears to be increased, although reports are conflicting (52, 53). Estimated SIRs vary from 1.5 to 5.1, compared to the general population, with the most markedly increased risks for individual cancers reported for lung cancer and non-Hodgkin's lymphoma (54, 55). The risk of oropharyngeal and esophageal cancer has also been reported to be increased in patients with scleroderma (54). Esophageal disease related to systemic sclerosis is the likely reason for the increased incidence of Barrett's esophagus, which has been reported to be present in 12.7 percent of patients with scleroderma (55) and may explain the increased risk of esophageal cancer in this population. Risk factors for development of other types of tumors in patients with scleroderma may be related to inflammation and fibrosis of affected organs. The role of smoking (53), and the presence of scleroderma-specific antibodies, particularly topoisomerase-I (Scl-70) (52) in this context is unclear. In contrast to systemic sclerosis, localized scleroderma, including morphea and linear scleroderma, has not been associated with increased risk of cancer (56).

Among idiopathic inflammatory myopathies occurring in adults, dermatomyositis, and, to a lesser extent, polymyositis, have been associated with malignancies (57-59). The etiology of these associations is not well understood, and the assessment of risk is complicated by the temporal relationship between development of malignancy and the myositis. In particular, some cancers pre-date the onset of inflammatory myopathy so that the inflammatory myopathy can be better considered a paraneoplastic syndrome, whereas it is also likely that the presence of inflammatory myopathies represents a risk factor for the subsequent development of malignancy (57). The most common malignancies in populations of patient with inflammatory myopathies of Northern European descent are adenocarcinomas of the cervix, lungs, ovaries, pancreas, bladder, and stomach, which account for over two-thirds of these cancers (60, 61). In patients from Southeast Asia, a higher proportion of nasopharyngeal cancers are found, followed by lung cancer (60).

Myositis specific antigens develop during the process of regeneration in patients who have myositis and are the same antigens expressed in some cancers known to be associated with the development of inflammatory myopathies (62), suggesting that such mechanisms may be directly involved in tumor development. This contrasts sharply from the pattern of increased malignancy in patients with RA or primary Sjögren's syndrome, which is apparent only after several years and associated with persistently active disease (11, 49).

Vasculitis may be a manifestation of a paraneoplastic syndrome, but there is no major evidence to support an association between primary systemic vasculitis and cancer overall, although one study using the Danish Cancer Registry suggested an increased risk of non-melanoma within two years of the vasculitis diagnosis in granulomatosis with polyangiitis (OR = 4.0; 95% CI 1.4 to 12) (63). The risk of malignancy among patients with giant cell arteritis was not increased in a population-based study of 204 patients with giant cell arteritis and 407 age- and sex-matched controls (64).

The risk of cancer among patients with spondyloarthropathies is less well studied than that of patients with RA and other connective tissue diseases. There does not seem to be any association with cancer overall in psoriatic arthritis (65) or ankylosing spondylitis (66, 67), and patients with ankylosing spondylitis do not appear to be at increased risk of malignant lymphoma (68).

Pharmacologic treatment and malignancy in patients with rheumatic diseases

The assessment of malignancy risk associated with both non-biologic and biologic disease-modifying anti-rheumatic drugs (DMARDS) is challenging because of the overall general high burden of cancer in the population, the variable rheumatic disease related cancer risk, and the potential risks of cancer associated with agents used to treat them. Disease severity may be a risk factor for developing cancer, introducing confounding or channeling bias if patients with severe rheumatic disease are treated more intensively with immunomodulatory agents. The sequential use and combined use of immunomodulatory agents further complicates the assessment of risk related to individual agents. A further concern, as with all immunosuppressive drugs, is the oncogenic potential of immunosuppressive therapies in patients who have a pre-existent or concurrent cancer, and whether such patients should be treated with DMARDs, and, if so, which DMARDs.

Non-steroidal anti-inflammatory drugs and glucocorticosteroids do not appear to be associated with increased risk of malignancy in patients with RA or other rheumatic diseases (11, 69). In a large population-based cohort study of patients with RA from Sweden, a total duration of oral steroid treatment of less than two years was not associated with lymphoma risk, whereas treatment going on for longer than two years was associated with a lower lymphoma risk (71). RA duration at the initiation of oral corticosteroids did not affect

lymphoma risk. Whether this observed reduced lymphoma risk may be due to decreased disease activity, is a generic effect of steroids, or is specific to RA is uncertain (70).

Non-biologic DMARDs

The non-biologic (nb-) DMARDs sulfasalazine and hydroxychloroquine, gold and penicillamine do not appear to be associated with an increased risk of cancer. There is a paucity of data regarding the long-term risks of malignancies occurring with leflunomide. The risk of cancer is increased with chemotherapeutic nb-DMARDs, particularly cyclophosphamide, with substantially elevated risks of lymphoma, leukemia and bladder cancers (71). The increased risk of hemorrhagic cystitis of the urinary bladder and development of bladder cancer is due to cyclophosphamide metabolites, especially acrolein. For this reason, current recommendations are to attempt to restrict the use of cyclophosphamide to six months or less and use it only in life-threatening or organ-threatening disease. The risk of bladder cancer may be less with the use of pulse intravenous cyclophosphamide than with daily oral administration. Some authors advocate the concurrent intravenous administration of mesna, which inactivates acrolein in the urine.

The use of azathioprine may be associated with an increased risk for lymphoproliferative disorders. Studies of patients with RA have consistently shown an increased risk of malignant lymphoma (11, 72, 73), whereas the available data are limited in patients with SLE (74). The risk in patients with RA remained significantly increased in analyses adjusted for disease activity (11).

The overall malignancy risk attributable to methotrexate treatment in patients with rheumatic diseases does not appear to be increased, although there are numerous reports which suggest that the risk of lymphoproliferative diseases may be increased. A specific effect of methotrexate on malignancy risk may be difficult to sort out from an association with

disease activity. Most cases of methotrexate associated lymphomas reported in the literature are B-cell lymphomas, often with extranodal involvement (75). The concept of a direct role of methotrexate in potentiating the development of lymphoma is strengthened by observations of spontaneous remission of B-cell lymphomas after discontinuation of methotrexate in 8 of 50 reported cases, including 4 who were positive for Epstein-Barr virus (75).

Biologic response modifiers

Biologic response modifiers target specific pathways involved in the pathogenesis of some rheumatic diseases such as RA and spondyloarthritis. The term "targeted" should not imply absolute selectivity between physiologic and pathologic processes with these drugs.

Anti-tumor necrosis factor (TNF) agents are used for a wide range of indications, and such drugs are now the cornerstone of therapy for patients with severe or refractory RA and spondyloarthropathies. TNF inhibitors are potent modulators of inflammation, apoptosis and other processes, and, from a mechanistic standpoint, they could either enhance or inhibit the development of cancer (76-78). Table 2 lists meta-analyses and cohort studies exploring the impact of such treatment on the risk of malignancy in RA.

Some meta-analyses of randomized clinical trials (RCTs) have suggested a possibly increased risk of cancer in patients with RA early after starting treatment with adalimumab or infliximab (79), or etanercept (80), respectively (Table 2). In a pooled analysis using RCTs of etanercept, infliximab, or adalimumab, the exposure-adjusted analysis revealed an OR of 1.21 (95% CI 0.79, 4.28) and 3.04 (95% CI 0.05, 9.68) for malignancy, excluding non-melanoma skin cancers (NMSCs) in patients treated with recommended and high doses of anti-TNF agents, respectively (81). As NMSC was not an exclusion criteria for anti TNF therapy, the data on the increased risk for this condition may be influenced by a selection bias. A recent

meta-analysis, including patients with RA from 74 RCTs, reported the relative risk associated with all TNF-inhibitors as 0.99 (95 % CI 0.61 to 1.60) excluding NMSCs, and 2.02 (95 % CI 1.11 to 3.95) for NMSCs (82). A study of patients with early RA included in adalimumab trials did not reveal any significant increase in cancer risk (83). Finally, a meta-analysis of RCTs of certolizumab or golimumab in RA showed no increased risk of malignancies overall or NMSC compared to controls (84).

In general, larger observational studies have not shown an increased risk of malignancies associated with anti-TNF treatment for RA. In the Swedish Biologics Registry, the overall cancer risk was similar in anti-TNF treated patients with RA compared with three different control cohorts (85). In this database, there was no trend toward increased cancer incidence with longer duration of TNF exposures. Studies from other databases including the German and British Biologic Registries and a large North American cohort have not detected any significant safety signals with respect to overall cancer risk (86-89). A recent meta-analyses of published observational studies of patients with RA did not find any increased risk of cancer overall or of lymphoma in patients treated with TNF inhibitors (90). There was, however, an increased risk of non-melanoma skin cancer (OR 1.45; 95 % CI 1.15 to 1.76), and possibly, also an increased risk of melanoma (OR 1.92; 95 % CI 0.92 to 2.67). A recent review of the methodologies and results of such observational studies concluded that methods varied greatly across studies, but that overall, the available data are not compatible with a major increase in the risk of cancer in patients treated with TNF inhibitors (91).

A crucial clinical question is whether patients with pre-existent cancers should be exposed to anti-TNF or other immunomodulatory therapies. Patients with pre-existent malignancies are generally excluded from clinical trials, and, in clinical practice, clinicians may be reluctant to treat such patients with anti-TNF therapy, resulting in a channeling of treatment with these agents toward low risk cohorts. Analyses from the British Biologics

Register and the German Biologic Registry detected no increased risk of recurrent cancer in patients with pre-existing malignancy treated with anti-TNF agents (88, 89). However, there were very few events in these analyses, so definite conclusions about the overall or cancer specific risks in individual patients cannot be drawn.

Pooled analysis of safety data from patients with RA treated with rituximab in randomized control trials with over 5,000 patient years of exposure did not reveal any increase in the incidence of malignancy excluding non-melanoma skin cancer (92). The incidence appeared to be stable over multiple courses of rituximab, and no unusual of pattern of malignancy type was observed. Rituximab has been suggested as a preferred biologic for patients with RA who have had a history of cancer other than nonmelanotic skin cancer (93).

There is considerably less experience with long term treatment with abatacept and tocilizumab. Although immunosuppression with these drugs could theoretically facilitate tumor development, so far there have been no signals for increased malignancies in patients treated with these agents (94, 95). For patients with RA treated with the interleukin-1 receptor antagonist anakinra, the overall incidence of malignancies has been consistent with the expected rates reported in the US National Cancer Database (96).

Physicians caring for patients with rheumatic diseases must have heightened awareness of the increased risk for cancer, particularly lymphoproliferative malignancy, in their patients. Hence, effective management and risk reduction includes achieving optimal disease control, optimizing use of known carcinogenic therapies, and undertaking routine cancer screening that is appropriate to patient age, sex, familial cancer burden and risk factors such as smoking. Results from reports from clinical experience and clinical trials suggest that up to one quarter of malignancies occurring in patients in whom anti-TNF therapy is initiated may occur within the first 12 weeks of therapy, so that physicians should undertake more

thorough cancer screening, including full skin examination, in patients initiating DMARD and biologics therapy (97). Patients should be closely questioned and examined for signs and symptoms of malignancy throughout the course of their disease.

CONFLICT OF INTEREST

The authors declare no conflicts of interest with respect to this manuscript.

Table 1. Rheumatic diseases associated with malignancy

Rheumatic Disease	Associated Malignancy	Risk Factors	Clinical Alert
Rheumatoid arthritis	Lymphoproliferative disease - Non-Hodgkin's lymphoma - Hodgkin's lymphoma	Greater disease severity, longer disease duration, immunosuppression, Felty's syndrome Secondary Sjögren's syndrome	Rapidly progressive, refractory flare in longstanding RA may suggest an underlying malignancy
Systemic lupus erythematosus	Lymphoproliferative disease - Non-Hodgkin's lymphoma - Hodgkin's lymphoma (+ breast cancer, liver cancer?)	Greater disease severity, longer disease duration, immunosuppression	Leukopenia Adenoma, splenic mass
Primary Sjögren's syndrome	Lymphoproliferative disease - large B-cell lymphoma -MALT lymphoma	Glandular features – Lymphadenopathy, parotid or salivary enlargement, germinal centers Extraglandular features – purpura, vasculitis, splenomegaly, lymphopenia, low C4 cryoglobulins	Clues to progression from pseudolymphoma to lymphoma include worsening of clinical features, disappearance of rheumatoid factor, and decline of IgM
Systemic sclerosis (scleroderma)	Alveolar cell carcinoma	Pulmonary fibrosis, interstitial lung disease	New changes on follow-up chest radiographs

	Non-melanoma skin cancer Adenocarcinoma of the esophagus	Areas of scleroderma and fibrosis in the skin Barrett's metaplasia	Changes in skin features or poorly healing lesions Longstanding problems with swallowing or gastrointestinal reflux
Idiopathic inflammatory myopathies	Ovarian, lung, and gastric cancer in Western populations; nasopharyngeal carcinoma in Asian populations	Older in age, normal creatinine kinase levels, presence of cutaneous vasculitis; less likely in setting of myositis-specific antibodies	All symptoms and signs that are not readily explained by myopathy

Table 2. Meta-analyses and cohort studies exploring anti-TNF treatment and overall risk of malignancies in rheumatoid arthritis

Author; year (reference)	Study design	Anti-TNF agent studied	No. of patients	Risk estimate (all anti-TNF agents vs RA control unless stated otherwise)
Bongartz et al. 2006 (79)	Meta-analysis of RCTs	Infliximab Adalimumab	5014	OR 3.3; 95 % CI 1.2 to 9.1
Bongartz et al. 2009 (80)	Meta-analysis of RCTs	Etanercept	5788	OR 2.4; 95% CI 1.2 to 4.8
Setoguchi et al. 2006 (86)	Cohort (3 health care utilization databases)	Infliximab Etanercept Adalimumab	7830 subjects ≥ age 65	HR 0.98; 95 % CI 0.73 to 1.31 excluding NMSC
Wolfe et al. 2007 (87)	Cohort (NDB)	Infliximab Etanercept Adalimumab	13689	OR 1.0; 95 % CI 0.8 to 1.2
Leombruno et al. 2009 (81)	Meta-analysis of RCTs	Infliximab Etanercept Adalimumab	8808	OR 1.31; 95 % CI 0.69 to 2.48 excluding NMSC
Askling et al. 2009 (85)	Cohort (ARTIS)	Infliximab Etanercept Adalimumab	6366	RR 1.00; 95 % CI 0.86 to 1.15 excluding NMSC
Strangfeld et al. 2010 (88)	Nested case control (RABBIT)	Infliximab Etanercept Adalimumab	Cases:74 Cohort overall: 5120	No difference in anti-TNF exposure
Askling et al.	Meta-analysis	Infliximab	22904	RR 1.30; 95 % CI 0.89 to1.95

2011 (82)	of RCTs	Etanercept Adalimumab		
Mariette et al. 2011 (89)	Meta-analysis of observational studies	Infliximab Etanercept Adalimumab	34072	RR 0.95; 95 % CI 0.85 to 1.05
Le Blay et al. 2012 (84)	Meta-analysis of RCTs	Certolizumab Golimumab	2710	OR 1.06; 95 % CI 0.39 to 2.85

RCTs=randomized controlled trials; OR=odds ratio; CI=confidence interval; NMSC=Non-melanoma skin cancer; NDB=National data bank; ARTIS=Arthritis treatment in Sweden (Swedish national biologics register); RABBIT=Rheumatoid arthritis – observation of biologic therapy (German acronym for the German national biologics register)

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