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Review article

Incidence of neoplasms in the most prevalent autoimmune rheumatic diseases: a systematic review☆

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ABSTRACT

This article is a systematic review of the literature about the coexistence of cancer and autoimmune rheumatic diseases, their main associations, cancers and possible risk factors associated, with emphasis on existing population-based studies, besides checking the relation of this occur with the use of the drugs used in the treatment of autoimmune diseases. A search was conducted of scientific articles indexed in the Cochrane / BVS, Pubmed / Medline and Scielo / Lilacs in the period from 2002 to 2012. Also consulted was the IBICT (Brazilian digital library of theses and Masters), with descriptors in Portuguese and English for "Systemic sclerosis", "Rheumatoid Arthritis", " Systemic Lupus Erythematosus" and "Sjögren's syndrome", correlating each one with the descriptor AND "neoplasms". The results showed that in the database IBICT a thesis and a dissertation for the descriptor SLE met the inclusion criteria, none met RA one thesis to SS. Lilacs in the database/Scielo found two articles on "Rheumatoid Arthritis" AND "neoplasms". In Pubmed/Medline the inicial search resulted in 118 articles, and 41 were selected. The review noted the relationship between cancer and autoimmune rheumatic diseases, as well as a risk factor for protection, although the pathophysiological mechanisms are not known.

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Incidência de neoplasias nas doenças reumatológicas autoimunes mais prevalentes: uma revisão sistemática

Palavras-chave:
Neoplasias
Lúpus eritematoso sistêmico
Artrite reumatoide
Síndrome de Sjögren
Esclerose sistêmica

RESUMO

O presente artigo é uma revisão sistemática da literatura que aborda a coexistência de neoplasias e doenças reumatológicas autoimunes, suas principais associações, tipos de cânceres e os possíveis fatores de riscos associados, com ênfase nos estudos de base populacional existentes, além de verificar a relação dessa ocorrência com o uso dos fármacos utilizados no tratamento de doenças autoimunes. Foi realizada uma busca de artigos científicos indexados na *Cochrane/BVS*, *Pubmed/Medline* e *Scielo/Lilacs* no período de 2002 a 2012. Também foi consultada a IBICT (biblioteca digital brasileira de teses e mestrados), com os descritores em português e inglês para as palavras: "Esclerose sistêmica", "Artrite reumatoide", "Lúpus Eritematoso Sistêmico" e "Síndrome de Sjögren", correlacionando cada um com o descritor AND "neoplasias". Os resultados mostraram que, na base de dados IBICT, preencheram os critérios de inclusão uma tese e uma dissertação para o descritor LES, nenhuma para AR e uma tese para SS. Na base de dados *Lilacs/Scielo* foram encontrados dois artigos sobre "Artrite Reumatoide" AND "neoplasias". No *Pubmed/Medline*, a busca inicial resultou em 118 artigos; destes, preencheram os critérios e foram secionados 41 artigos. Esta revisão observou relação entre neoplasias e as doenças reumatológicas autoimunes, tanto como fator de risco quanto de proteção, embora os mecanismos fisiopatológicos não estejam totalmente elucidados.

Introduction

The coexistence of rheumatic diseases with malignancies of various origins has been reported in the literature. Neoplastic changes can induce rheumatic paraneoplastic syndromes, which also may be late complications of a rheumatic disease.[1]

Rheumatologic paraneoplastic syndromes may occur during the course of neoplastic disease, manifesting simultaneously with the development of a neoplasia, may precede the diagnosis by several years or develop some time after a neoplasia diagnosis. It is often difficult to differentiate them from the idiopathic form and it is believed that the presence of such changes can be considered as predictor of malignancy and of adverse outcomes.[2-5]

According to Szekanecz,[6] neoplasms differ from paraneoplastic syndromes due to the fact that the latter are not related to direct invasion of the tumor or metastasis, but to a variety of biological mediators derived from it, such as hormones, peptides, antibodies, cytotoxic lymphocytes and autocrine and paracrine mediators.

Autoimmune rheumatic diseases are chronic diseases, more common in females. Among these, the most prevalent include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren's syndrome (SS) and systemic sclerosis (SSc).[7,8] Such autoimmune disorders are associated with the activation of autoreactive T and B lymphocytes and with the release of proinflammatory cytokines that can possibly increase the risk of cancer.[9] Taking into account that autoimmune diseases are chronic disorders and prevalent in the population, one can expect that patients with such diseases are most likely to develop neoplasias.[10]

The participation of immunosuppressive drugs in the treatment of autoimmune rheumatic diseases has also been described in the pathogenesis of malignancy. The potential mechanisms described include interruption of immunological surveillance and destruction of malignant cells, increased susceptibility to contamination with oncogenic infectious agents, for instance, viral agents, pharmacological effects of the alkylating agents or antimetabolites on deoxyribonucleic acid (DNA), and the specific effects on the immune system, which can increase or decrease the chances of a transformed cell to survive and proliferate.[11]

In the literature, data related to this topic is scarce, especially in Brazil. This paper aims to conduct a systematic review of literature on the subject, because of its importance in clinical practice, and verify the main associations between the most prevalent autoimmune rheumatic diseases and the types of cancer present, in addition to addressing the possible implications of using drugs in these circumstances.

Methodology

Search criteria

For this study, a systematic review technique was chosen. The search for scientific articles indexed in Cochrane/VHL, Pubmed/Medline and SciELO/Lilacs databases from 2002 to 2012. The IBICT (Brazilian digital library of theses and Masters programs) was also consulted, using the descriptors in portuguese and their corresponding in english: "Rheumatoid arthritis", "SLE", "Systemic sclerosis" and "Sjögren's syndrome", correlating each with the descriptor AND "neoplasms".

Inclusion and exclusion criteria

Full articles published in english and portuguese from 2002 to 2012,which addressed the neoplasia occurrence in the

above autoimmune rheumatic diseases were included in the study. Articles describing the association of cancer and the main drugs used in the treatment of these autoimmune rheumatic diseases (methotrexate, azathioprine, cyclophosphamide, and immunobiological agents) were also selected.

In the present review, case reports or articles that related neoplasms and dermatomyositis and/or polymyositis were not included to avoid confusion, since there is a strong association of these conditions with paraneoplastic syndromes. We also excluded studies associating the occurrence of neoplasms with vasculitis, due to important differences in the pathogenesis of these diseases with the autoimmune diseases selected, and also to the fact that these are uncommon syndromes, not meeting the purposes of this study.

Selection of studies

The analysis of titles and abstracts, according to the eligibility criteria, was performed by two independent reviewers. In cases of disagreement, they were analyzed by a third reviewer.

Presentation of results

After the election of articles, a reading and analysis of the association among cancer and selected rheumatic diseases was made. Population studies were described according to the author, year, studied population, observation on the occurrence of neoplasia in patients with autoimmune diseases, main malignancies observed in each disease and standardized incidence ratio in the 95% confidence interval (CI). of Studies relating the main drugs used in the therapy of these diseases and their possible associations with oncogenesis were also analyzed.

Results

In the IBICT database, the following results concerning the initial search were obtained: no thesis for “Systemic sclerosis" AND “neoplasms”, one thesis/dissertation on “Systemic sclerosis” AND “neoplasms”, one thesis on “rheumatoid arthritis” AND “neoplasms”, four theses/dissertations on “Systemic Lupus Erythematosus” AND “neoplasms”, and also four theses for “Sjögren's syndrome” AND “neoplasms”. One thesis and one dissertation for the descriptor SLE, one dissertation for the descriptor LES, none for AR and one thesis for SS met the inclusion criteria. In the Lilacs/Scielo database, two articles were found for “Rheumatoid Arthritis” AND “neoplasms”, but only one of them approached the studied matter .

In Pubmed/Medline database, the initial search yielded 118 articles. Reports of paraneoplastic syndromes and articles about cancer treatments in patients with the assessed rheumatic diseases were excluded from the study. Thus, we selected 41 articles that met the inclusion criteria described above (Fig. 1). The articles obtained, organized by author and year, neoplasia and standardized incidence ratio (SIR) in the 95% confidence interval (CI) are shown in Table 1, and the main population studies by author and year are shown in Table 2.

Discussion

Systemic lupus erythematosus and neoplasia

SLE is a heterogeneous systemic disease manifesting in mild, moderate or severe clinical form that can escalate with multiple organs and/or systems involvement. Due to the modernization of its therapy and to the improvements in the prognosis of the disease in general, the survival rates of patients increased and in consequence chronic organ damage and late complications (such as malignancy) became decisive for the morbidity and mortality of these patients.[12]

The common pathogenic pathways for LES and neoplasms have been described, and reinforced by the following concepts: a high frequency of malignancies in patients with autoimmune diseases; neoplastic disorders in autoimmune diseases may occur as paraneoplastic syndromes; and the fact that immunosuppressive therapy may increase the risk of

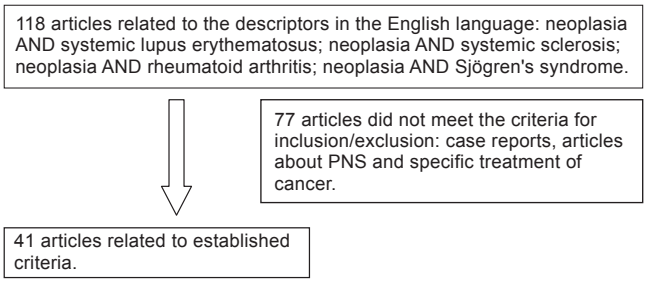

Fig. 1 – Algorithm of the methodology of selection of papers found in Pubmed/Medline. PNS, paraneoplastic syndromes.

Table 1 – Main cancers in each autoimmune disease and their standardized incidence ratio (SIR) in a confidence interval (CI) of 95%.

Autoimmune disease	Standardized incidence ratio (SIR)/Confidence interval (CI) of 95%/References
Systemic lupus erythematosus	
General risk	1.25[19] / 1.15[23]/1.14[21]
Blood cancer	2.75[23]
Non-Hodkgin’s lymphoma	2.86[19]/ 3.64[23]
Lung cancer	1.73[19] /1.37[23]
Hepatobiliary cancer	2.6[23]/ 2.7[21]
Vulvovaginal cancer	3.27[21]
Prostate cancer	0.72[22]
Sjogren's syndrome	
Overall risk	3.25[27]
Non lymphoid overall risk	1.5[26]
Lymphoma	37.5[26] / 48.1[27]
Systemic sclerosis	
Overall risk	1.5[33]
Lung cancer	1.6[33]
Blood cancer	2.5[33]
Rheumatoid arthritis	
Overall risk	1.05[41]
Blood cancer	2.74[27]
Non-Hodgkin’s lymphoma	3.54[27]
Lung cancer	1.63[41]
Colorectal cancer	0.77[41]
Breast cancer	0.84[41]

Table 2 – Population studies according to author/ year/country and observations about emergence of malignancies in patients with autoimmune diseases.

Authors/year	Population basis/year of research	Observation
Bjornadal et al., 2002[20]	5.715 LES patients; Sweden (1964-1995)	443 cases of neoplasia
Bernatsky et al., 2006[23]	9.547 LES patients; international multicentric (1970-2001)	431 cases of neoplasia observed; 114 deaths
Parikh-Patel et al., 2008[21]	30.478 LES patients; USA (1991-2002)	1.273 cases of neoplasia
Bernatsky et al., 2011[22]	6.068 men with LES; follow-up for 6.3 years; Canada	Prostate cancer considered as a protective factor
Lazarus et al., 2006[26]	112 patients with SS; London (1979-2006)	25 cases of neoplasia
Zhang et al., 2010[27]	1.320 patients with SS; Peking (1990-2005)	Follow-up for 4.4 years: 29 cases of neoplasia
Olesen et al., 2010[33]	2.040 patients with SSc; Denmark (1977-2006)	Follow-up for 6.4 years: 222 cases of neoplasia.
Chen et al., 2011[37]	23.644 patients with RA; Taiwan (1996-2007)	935 cases of cancer

SLE, systemic erithematous lupus; SS, Sjögren syndrome; SSc, systemic sclerosis; RA, rheumatoid arthritis.

malignancies occurrence.[13] Added to this, in a recent publication the presence of antiphospholipid antibodies was considered a risk factor for the occurrence of thrombotic events and for the development of cancer.[14]

Regarding etiopathogeny, LES as well as various other malignancies have in common a genetic predisposition to environmental factors (such as ultraviolet radiation, infection by viruses such as Epstein-Barr virus [EBV], smoking and obesity), and hormonal changes related to these two conditions (prolactin, estrogen and growth hormones, among others).[15]

Disproportionate humoral responses are considered fundamental in the pathogenesis of systemic autoimmune diseases such as SLE and SS. Among these, an abnormal regulation of the cell cycle is observed, which interferes with cell proliferation, differentiation and apoptosis, causing B cell longevity. In these processes, cytokines such as interleukin-6 (IL-6), 10 (IL-10) and B-cell activating factor (BAFF) have played an important role.[16,17]

It is believed that because of chronic antigenic stimulation, B cells contribute to the increased circulating levels of BAFF, and the impaired autoregulation of these cytokines may trigger a vicious cycle in which high levels of proliferation and induction of BAFF or its ligand enhance the activation of the humoral immune system. A similar pathogenic mechanism has been described in B-cells related malignancies.[12,18]

For several authors, there has been an increased incidence of malignancies in patients with SLE.[13,19-22]

A population-based cohort evaluated 5,715 patients hospitalized for SLE between 1964 and 1995, according to the National Swedish Cancer Registry. Altogether, 443 cases of malignancies were assessed. The overall risk was increased by 25% (Standardized incidence rate [SIR] = 1.25, CI 95% = 1.14-1.37). Non-Hodgkin lymphoma risk increased almost three times (SIR = 2.86, CI 95% = 1.96-4.04), thus providing a greater incidence for neoplasia in patients with SLE. There was also an increased risk of lung (SIR = 1.73, CI 95% = 1.25-2.32) and squamous cell skin (SIR = 1.53, CI 95% = 0.98 -2.28) cancer, which was more pronounced in cases with more than 15 years of follow-up.[19]

In 2006, Bernatsky et al. conducted an international multicenter study that included patients with SLE from 23 registered centers, to analyze the causes of mortality of this disease; a major cause analyzed was the presence of cancer. Patients at each center were linked to regional cancer registries that provided epidemiological data and 9,547 patients were observed for an average period of eight years.

Within the observation time, 431 cases of cancer were registered. The data confirmed an increased risk of cancer among patients with SLE. For all cancers combined, the estimated SIR was 1.15 (CI 95% = 1.05-1.27); for all hematological malignancies, 2.75 (95 % CI = 2.13-3,49), and for non-Hodgkin lymphoma, 3.64 (CI 95% CI = 2.63-4.93). The findings also suggested an increased risk of lung (SIR = 1.37, CI 95% = 1.05-1.76) and hepatobiliary (SIR = 2.60, CI 95 % = 1.25-4,78) cancer.[23]

In another cohort including individuals with SLE from the state of California (USA) from 1991 to 2002, the risk of occurrence of malignancies was studied. From the 30,478 patients diagnosed with SLE, 1,273 had a form of cancer. The overall cancer risk was significantly elevated (SIR = 1.14, CI 95% = 1.07-1.20). This study demonstrated an increased risk of malignancies of the genital tract, including vaginal and vulvar (SIR = 3.27, CI 95% = 2.41-4.31), as well as liver (SIR = 2.70, CI 95% = 1.54-4.24) cancer.[21]

In 2011, Bernatsky et al. analyzed 6,068 men suffering from SLE. The development of prostate cancer in this sample was lower than expected for the general population, with an estimated incidence rate for risk of prostate cancer development in this population of 0.72 (CI 95% = 0.57-89). Thus, according to the findings of this study, LES was a protective factor against this type of cancer. One of the hypotheses proposed to explain these results is the occurrence of low levels of adrenal hormones in these patients.[22]

Sjögren's syndrome and neoplasia

Sjögren's syndrome (SS) is an autoimmune disease characterized by lymphocytic infiltration of exocrine glands and persistent dysregulation of the immune system. SS is associated with a 44-fold risk increase for non-Hodgkin development, and Masaki and Sugai[24] in 2004 estimated in their review that about 5% of cases of primary SS could develop this complication.

Similarly to what occurs in SLE, in SS the participation of environmental factors (EBV, cytomegalovirus, retroviruses, hepatitis C virus or ultraviolet radiation) and the genetic predisposition (histocompatibility antigen [HLA] of B8, DR2, DR3 and DQ types) change of the immune system are described; particularly at populations of CD4+ T cells or humoral production of antibodies production (anti-SSA/Ro, anti-SSB/La and anti-muscarinic receptor type 3 antibody), as well as cytokines present such as interferon-gamma. In some cases,

monoclonal B-cell proliferation occurs and this may lead to lymphomas.[18,25]

In 2006, Lazarus et al.[26] performed a retrospective analysis of 112 patients from the outpatient services at the University College London Hospital during 1979. The patients were followed for a mean period of 10.8 years since the diagnosis of primary SS (pSS). The appearance of neoplasia was reported in 25 patients, with 11 cases of lymphoma (eight of mucosa-associated lymphoid tissue/MALT type, one well-differentiatied high-grade non-Hodgkin lymphoma, and two with unknown subtypes). Therefore, a significantly increased incidence of lymphoma in patients with pSS compared with the general population (SIR = 37.5, CI 95% = 20.7-67.6) was demonstrated. For cancers not originated in the lymphoid tissue, the observed increase in incidence was small and not statistically significant (SIR = 1.5, CI 95% = 0.9-2.6).[26]

A retrospective analysis at Peking Union Medical College Hospital from 1990 to 2005 recruited 1,320 SS patients that were followed for a mean of 4.4 years. Among them, 29 patients (2.2%) developed neoplasms during follow-up. The total SIR and SIR value for lymphomas were 3.25 and 48.1, respectively. In this study, different types of malignancies were observed: eight lymphomas, two myelomas and 19 solid tumors (invasive thymoma, breast cancer, lung cancer, gastrointestinal adenocarcinoma, hepatoma, squamous cell carcinoma of the tongue, cervical cancer, renal cell carcinoma, thyroid carcinoma and mucoepidermoid carcinoma of the parotid gland). At the risk factor analysis, it was observed that hyperplasia of the parotid glands, monoclonal immunoglobulins and the presence of hypergammaglobulinemia were identified as the main mechanisms involved in the pathogenesis of SS, compared with neoplasias.[27]

Systemic sclerosis and neoplasia

Systemic sclerosis (SSc) is a complex immune connective tissue disorder that leads to vascular damage and overproduction of extracellular matrix via activated fibroblasts. Its pathogenesis involves the interaction between endothelial cells, lymphocytes, macrophages, fibroblasts and the activation of several cytokines and growth factors important in the development of fibrosis. Immunological reactions involved in SSc have been associated with the development of malignancies, and high concentrations of pro-fibrotic cytokines such as transforming growth factor beta (TGF-β) were found in some types of cancer (breast, ovary and kidney).[28,29]

Another possible hypothesis for such association is the presence of SSc antigens expressed in tumoral cells. Most of SSc autoantigens are nucleolar and play a key role in ribosome synthesis and in mitogenesis. Probably these proteins are related to the rapid proliferation of malignant cells. Genetic mutations or post-translational modifications can produce protein products with conformational changes that accumulate in malignant tissue and create new epitopes.[30]

The association between cancer and SSc with fibrotic lung involvement was first described in 1953.[31] During 2005, Daniels and Jett found an increased risk of lung cancer in patients with disorders associated with pulmonary fibrosis, including systemic scleroderma. In this scenario, the suggested pathogenesis is that recurring injury and chronic inflammation result in genetic mutations and possible malignancy; however, this hypothesis needs further studying.[32]

Olesen et al.[33] assessed patients with an initial diagnosis of SSc selected from the Danish National Registry that included inpatients and outpatients during the period from 1977 to 2006. About 2,040 patients were evaluated and followed for a mean period of 6.4 years. Among these patients, 222 cancer cases were identified. The general SIR for cancer was 1.5 (CI 95% = 1.3-1.7); for men, SIR = 2.2 (CI 95% = 1.7-2.8) and for women, SIR = 1.3 (CI 95% = 1.1-1.6). The most common cancers were lung (SIR = 1.6, CI 95% = 1.2-2.0) and hematologic (SIR = 2.5, CI 95% = 1.5-4.0) cancer.[33]

Rheumatoid arthritis and neoplasia

Rheumatoid arthritis (RA) is a disease that affects primarily joints and cartilage through the development of pannus, a product of inflammatory cells and cytokins that transform synoviocytes into locally invasive and destructive cells. Although predominantly joint affecting, RA can evolve with extra-articular manifestations affecting the skin, vessels, heart, lungs and peripheral nerves, as well as a significant association with focal and systemic malignancy.[34]

The possible mechanisms for the increased risk of hematological cancers in this pathology include: persistent immune stimulation (which can lead to clonal selection and predispose CD5+ B cells to malignant transformation), decreased number and function of suppressor T cells (including those directed against prooncogenic Epstein-Barr virus) and decreased activity of natural killer cells in the synovial fluid, tissue, blood and lymph.[35]

According to Askling et al.,[36] who examined the risk of cancer in a cohort study comparing RA patients *versus* the general population, there was little evidence of an increased cancer risk for most types of non-hematological cancers, but there was a moderate increase in the risk of developing lung cancer. In contrast, this study showed an approximate two-fold higher risk of lymphoma in patients with RA compared to the general population. However, these authors stated that the determinants of this association between RA and lymphoma remain unknown.

A cohort evaluated the association between RA and malignancy in Asian populations. The study included 23,644 patients with RA who had no previous history of malignancies, obtained through National Health Insurance Administration of Taiwan database between 1996 and 2007. Among patients with RA, 935 cancer cases were observed. This group showed an increased risk, especially for hematological cancers (SIR = 2.74, 95 % CI = 2.68-2.81). The relative risk of cancer was higher among young people.

Most cases of cancer were detected at the first year after RA diagnosis. The relative risk for cancer decreased with an increasing duration of the study and between hematological cancers, non-Hodgkin's lymphoma had the highest risk of development (SIR = 3.54, CI 95% = 3.45-3.63). Among solid tumors, the risk of kidney, vaginal and vulvar cancer were the greatest. A decreased risk of cervix and nonmelanoma skin cancer in patients with RA was also observed.[37]

Thompson, Rider and Poper (2011) conducted a meta-analysis on the risk of infection and malignancies in patients with

RA treated with anti-TNFα. Regarding the analysis for association of malignancy, the survey of literature data from six randomized clinical trials showed that malignancies occurred in 19 of 2,183 patients (0.87%) who received at least one dose of a TNFα inhibitor, and in 10 of 1,236 patients (0.81%) in the control group. The risk of malignancy did not increase in patients treated with a TNFα inhibitor, compared to control patients treated with methotrexate (SIR = 1.08, CI 95% = 0.50-2.32).

The results of this meta-analysis provide continuous support to the existing data showing that the overall increased risk for malignancies was not observed with anti-TNFα.[38]

The study by Dixon et al.[39] corroborated the hypothesis of a null association of cancer with the use of anti-TNFα, even in patients with a history of neoplasia. An analysis was conducted on patients enrolled by the British Society of Rheumatology Biologics Registers (RSRBR) diagnosed with RA and who were starting an anti-TNFα drug as their first biological agent. Patients enrolled within six months after the start of biologic therapy were excluded. Rates of malignancy for 177 patients treated with anti-TNFα and for 117 patients with active RA treated with disease-modifying antirheumatic drugs (DMARDs) were compared, all of them with a history of prior malignancy.

The rates of malignancy incidence were of 25.3 events/1000 person per year in anti-TNFα group and 38.3/1,000 person per year in the DMARD cohort, generating a relationship of age and standardized incidence ratio of 0.58 (95 % CI = 0.23-1.43) for the cohort using anti-TNFα *versus* DMARD's. Of the patients previously afflicted with melanoma, 3 (18%) out of 17 in the cohort of anti-TNFα developed a malignant event, compared with 0 out of 10 in the DMARD cohort.[39]

According to the British Society for Rheumatology guidelines for the use of anti-TNFα, instruct that "caution should be exercised with the use of anti-TNFα therapies in patients with previous malignancy; however, the potential benefits of this treatment should be considered against the potential risk of recurrence of a particular malignancy. If the patient was recurrence free of any malignant tumor for the last 10 years, there is no evidence of a contraindication to anti-TNFα therapy."[40]

Smitten et al. (2008)[41] conducted a meta-analysis that evaluated 21 publications found on Medline from 1990 to 2007, from which 13 articles reported an increased SIR for general malignancies; 14 for lymphoma, 12 for lung cancer, 10 for colorectal cancer, and nine for breast cancer. Compared to the general population, global estimates suggest that RA patients have an increase of approximately twice the risk of lymphoma (SIR = 2.08, CI 95% = 1.80-2.39) and a higher risk of Hodgkin's lymphoma as well as non-Hodgkin's lymphoma. The risk of lung cancer also increased (SIR = 1.63, CI 95% = 1.43-1.87). In contrast, a decreased risk was observed for colorectal (SIR = 0.77, CI 95% = 0.65-0.90) and breast (SIR = 0.84, CI 95% = 0.79 -0.90) cancer. For general malignancy, SIR rate was 1.05 (CI 95% = 1.01-1.09).[41]

Therapy and the risk of malignancies

Besides pathogenic mechanisms that suggest an increased susceptibility of patients for cancer occurrence (impaired immune surveillance and destruction of cancerous cells, possible association of infection and uncontrolled lymphocyte proliferation by oncogenes), the therapy used in autoimmune rheumatic diseases has been described as a potentially carcinogenic factor (Table 3).[11]

The principal DMARDs classes used in rheumatology and for the therapy of the above-mentioned diseases include immunosuppressive and/or alkylating agents. Among the immunosuppressive agents commonly used as DMARDs in autoimmune diseases, methotrexate (MTX) and azathioprine are the most commonly prescribed, and the development of malignancies associated with their long-term use has been previously studied.

MTX is a dihydrofolate reductase antagonist, when present it inhibits DNA synthesis and inhibits the proliferation of B and T lymphocytes. In 1997, Bologna et al.[42] analyzed the possible relationship of an increased incidence of tumors and treatment with MTX in patients with rheumatoid arthritis. The study included 426 patients treated with MTX, from which eight cases of neoplasia were detected. In the other hand, in the control group with 420 patients who had never been treated with MTX, it was observed a development of six cases of neoplasia. The authors concluded that there was no statistically significant difference between groups and that further studies were required, since the drug could be a precipitating factor for tumorigenesis in predisposed patients.

According to Sobral (2006),[43] neoplasias that requirse treatment with MTX are rare. However, Wolfe and Michaud (2004)[44] and Franklin et al.[45] have found a higher incidence of malignancies, particularly lymphomas, in RA patients treated with immunosuppressants. Although it is not possible to differentiate the cause, it is usually associated with intense lymphocytic inflammatory activity or the use of immunosuppressive drugs to control severe active disease.[44,45]

Azathioprine is an immunosuppressive antimetabolite that acts by inhibiting the biosynthesis of adenine and gua-

Table 3 – Medication and its possible oncogenic mechanism.

Drug	Pathogenic paths
Methotrexate[42]	Antagonizes dihydrofolate reductase, inhibits DNA synthesis and proliferation of B and T cells Exhibits no increased risk[42]
Azathioprine[43.46]	Inhibits the biosynthesis of adenine and guanine, interfering with cell multiplication Inactivate body immunosurveillance. Possible increased risk of lymphoproliferative disorders[43,46]
Cyclophosphamide[43.46-48]	Crosslinkage with DNA strands prevent replication Increased risk of cervical intraepithelial neoplasm[48]
Biological agents[50-54]	Immunomodulation Infliximab and adalimumab with an increased risk of cancer, especially lymphoma and rectal, breast and lung cancer[51] Abatacept: no increased risk of malignancies was found[53,54]

nine, interfering with cell multiplication. The risk for oncogenesis is described as a limiting factor for its use on a large scale. The oncogenic risk is related to the inactivation of body immunosurveillance, combined with immunological changes in patients with autoimmune diseases. The main risk is associated with lymphoproliferative diseases and premalignant cervical atypia.[43,46]

Alkylating agents have as primary target the cell cycle; these pharmaceuticals interrupt or disturb key steps in cell proliferation and consequently lead to replicating cells death.[43] According to Almeida et al.,[46] alkylating agents cross-link with DNA strands preventing its replication and thereby destroying the cells at rest or in active cell division. Consequently, cytotoxicity occurs by cross-reactivity with the other DNA strand.

In autoimmune rheumatic diseases, the most widely used alkylating agent is cyclophosphamide. Silva et al.[47] reported that the treatment with alkylating agents may induce secondary hematologic malignancies, including acute leukemias. In patients with SLE, Ognenovski et al.[48] reported a higher incidence of cervical intraepithelial neoplasias in patients taking cyclophosphamide.

In this context, biological agents are mainly used in RA therapy. These include antagonists of tumor necrosis factor α (anti-TNF-α), interleukin-1 receptor, IL-6 receptor and B cell surface markers (anti-CD20) as well as lymphocyte costimulation modulators.[49] In Brazil there are five types of anti-TNF-α agents: Etanercept, Infliximab, Adalimumab, Certolizumab pegol and Golimumab. The latter two were recently released for use in this country.

In a meta-analysis published in 2012, Solomon, Mercer and Kavanaugh[50] analyzed publications related to the use of biological agents and on the development of malignancies.

The drugs studied were abatacept, atanercept, adalimumab, infliximab, anakinra and rituximab in the treatment of RA. In most studies analyzed, an increased incidence of cancer in patients treated with anti-TNF agents was not demonstrated. However, in a meta-analysis of clinical trials Bongartz et al.[51] have demonstrated an association between infliximab and adalimumab with increased risk of cancer, especially lymphoma, colorectal, breast and lung types.

It has been shown that IL-6 is involved in the pathophysiology and prognosis of prostate cancer, hence anti-IL-6, a biological agent, appears to be involved in its prevention. However, there are no studies on the use of this drug as a protective factor for this neoplasia yet.[52]

Simon et al.[53] catalogued a total of 4,134 RA patients treated with abatacept evaluated in seven trials, and 41,529 RA patients treated with non-biologic DMARDs in five observational cohorts. From the patients treated with abatacept, 51 malignancies were detected, however these findings were not higher than the expected from the five cohorts of RA control cases. The values of SIR comparing RA patients against the general population were consistent with those reported in the literature. The overall incidence of malignancies (excluding nonmelanoma skin cancer), and of breast cancer, colorectal cancer, lung cancer and lymphoma in the abatacept group was the expected in a comparable population with RA. These data suggest that there are no new safety signs regarding malignancies; therefore, this issue should be monitored.

Corroborating the above hypothesis, Genovesel et al.[54] studied 1,167 RA patients treated with abatacept for a period of five years, without identifying an increased SIR among users of this agent.

Final considerations

The development of this review revealed a shortage of articles addressing the subject, in particular Brazilian studies, as well as epidemiological studies about the topic. Despite this limitation, this study found a relationship between neoplasias and the autoimmune rheumatic diseases analyzed, both as risk factors and as protective factors, although the pathophysiological mechanisms involved are not well understood. Hematologic cancers were observed in all conditions studied, especially lymphoma. In the particularities of each disease, lung cancer was strongly associated with SLE, SSc and RA, followed by colorectal and liver cancers. SLE represented a possible protective factor against prostate cancer, which was explained due to hormonal aspects of the disease in SLE patients.

The principal neoplasias were analyzed according to their incidence in each group of rheumatic diseases, and the carcinogenic potential of drugs used in the therapy of rheumatic diseases cannot be ignored, especially azathioprine and cyclophosphamide in RA and/or SLE patients. The authors also highlight the lack of Brazilian epidemiological studies addressing this association.

Conflicts of interest

The authors declare no conflicts of interest.

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