LEADING ARTICLE

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Lymphoma in Patients with Rheumatoid Arthritis

What is the Evidence of a Link with Methotrexate?

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Abstract

An increasing number of instances of lymphoma in patients with rheumatoid arthritis who are treated with methotrexate continue to appear. The majority of patients with lymphoproliferation have features of immunosuppression-associated lymphoma. Rheumatoid arthritis itself and the actions of methotrexate concur in leading to a immunosuppressed state.

Possible oncogenic mechanisms and the risk factors for patients with rheumatoid arthritis to develop lymphoma while receiving methotrexate include: (i) intense immunosuppression and severe disease in combination with genetic predisposition and; (ii) an increased frequency of latent infection with pro-oncogenic viruses like Epstein-Barr virus.

The aetiological role of methotrexate in the development of these lymphomas is supported by the spontaneous remission of these malignancies in some of patients with rheumatoid arthritis after methotrexate has been stopped. The physicians caring for patients with rheumatoid arthritis receiving methotrexate should be vigilant about signs and symptoms suggestive of lymphoma, mostly in those patients with significant comorbidity, long standing and severe disease who are more likely to be immunosuppressed. If a lymphoma appears in these patients, methotrexate should be stopped.

Spontaneous remission may occur and a period of observation is advisable when clinically possible. If functional deterioration appears or there are signs of lymphoproliferative organ invasion after several months then specific antineoplastic treatment should be instituted.

Many rheumatologists use methotrexate early in the course of rheumatoid arthritis with the hope of arresting this aggressive, rapidly erosion-producing and life-shortening disease.[1] In general, methotrexate is considered to have a faster onset of action than gold and azathioprine in patients with rheumatoid arthritis, to be very effective and to lack the carcinogenesis associated with azathioprine use.[2-6]

There have been sporadic cases of malignancy in patients with psoriasis who were treated with methotrexate. However, the lack of oncogenicity

with methotrexate is supported by the absence of increased risk of secondary tumours seen in patients with psoriasis and choriocarcinoma who are undergoing long term treatment with the drug.[7-10]

In patients with rheumatoid arthritis, methotrexate oncogenicity is controversial. The already increased intrinsic risk of lymphoproliferation in these patients and the unknown number of patients taking methotrexate are complicating factors in assessing the real incidence of lymphoma in patients with rheumatoid arthritis receiving methotrexate. Case reports link methotrexate to different types of cancers.[10-13]

This paper reviews critically the facts and controversy surrounding the oncogenic role of methotrexate in patients with rheumatoid arthritis and presents mechanistic theories which may operate in methotrexate-induced lymphoma. A few practical points for the clinician are also highlighted.

1. Literature Review and Patients' Characteristics

We reviewed cases of lymphoma in patients receiving methotrexate that have been reported in the English literature. The details of 25 well documented cases of non-Hodgkin's lymphoma in rheumatoid arthritis patients treated with methotrexate, including 2 patients treated at our hospital (patients 1 and 2),[14-29] are shown in table I. Another case has been reported in a patient with rheumatoid arthritis who was treated with both methotrexate and cyclosporin.[30]

15 patients with rheumatoid arthritis and 3 patients with dermatomyositis who developed lymphoma were reported by Kamel et al.[20,25] None had Sjögren's syndrome. Of these 18 patients, 11 had been treated with methotrexate (8 of these patients had rheumatoid arthritis and 3 had dermatomyositis). Epstein-Barr virus–associated lymphomas occurred in 83% of patients receiving methotrexate. Epstein-Barr virus was found in the malignant cells of the 2 patients who had a spontaneous remission of the disease after methotrexate was stopped.

Other studies, medical record searches and reports found additional cases suggesting a possible small increase in lymphoma incidence.[31-33]

To date, the total number of lymphoma cases in patients with rheumatoid arthritis receiving methotrexate approaches 50 including 7 new cases of non-Hodgkin's lymphomas reported to a cancer registry at our institution.

Many patients with rheumatoid arthritis developing lymphoma while receiving methotrexate have features typical of lymphoma found in patients who are immunosuppressed. Extra-nodal involvement appeared in the majority of the patients (69%) listed in table I. Brain involvement was not found in this series of patients even though it is reported at a higher frequency in transplant (28%)[34] and AIDS patients (22%)[35] than in the general population (1%). The predominant type of lymphoma is large, B cell non-Hodgkin's lymphoma, the type seen in 90% of AIDS and transplant patients with lymphoma but less common (65%) in the general population with lymphoma.[34-40] In patients with rheumatoid arthritis with lymphoma who were not treated with methotrexate, the histological characteristics are similar to patients in the general population with lymphoma.[41,42] Epstein-Barr virus is present with much less frequency in general population lymphoma cells (4%)[43] than in lymphoma cells of AIDS (50%)[39] or post-transplant patients (80%).[40] Epstein-Barr virus was found in 41% of the lymphoma patients treated with methotrexate for rheumatoid arthritis.[14] Finally, a common feature for immunosuppression-related lymphoproliferation in post-transplant and these rheumatoid arthritis patients is the spontaneous remission which occurs after stopping the immunosuppressive drugs.[44]

The strongest causal link between methotrexate and lymphoma in patients with rheumatoid arthritis is demonstrated by such a spontaneous tumour remission after stopping methotrexate. Documented

spontaneous remission after stopping methotrexate has been reported in the literature for 8 patients.[16,20,26-28,31,33] Of these 8 patients, 4 had Epstein-Barr virus positive lymphomas. All the other patients who developed lymphoma following the use of methotrexate underwent chemo- and/or radiation therapy, indicating that not all the other patients had total or partial remission coincident with stopping methotrexate. It is also possible that some of the patients were treated too early with chemo- and radiation therapy, without being allowed the grace spontaneous remission period. Five patients died as a result of their lymphoma. This represents a high mortality rate compared with that for lymphomas complicating transplantation (1%).[34,37] The aggressiveness of the lymphomas, the advanced age at which lymphoma appeared (average 64 years), the exposure to chemotherapy in the majority of patients, and the comorbidity of rheumatoid arthritis itself, or the drugs used to treat it, may explain the high mortality of these patients. Sjögren's syndrome, itself a potent risk factor for lymphoma development, was usually not present.[45]

2. The Role of Methotrexate in Oncogenicity

Patients with rheumatoid arthritis are at an increased risk for lymphoma independent of drug therapy. The mechanisms leading to malignancy in patients with rheumatoid arthritis include a common, latent clone of lymphocytes that can cause either rheumatoid arthritis or lymphoma, depending on the genetic and environmental factors as well as intensity of immunological activity in a particular individual. CD5+ clonal expansion, known to be present in patients with rheumatoid arthritis, may lead to a neoplastic process.[46,47] The decreased counts[48] and function[49-51] of T suppressor lymphocytes and natural killer cells[52-54] are also contributing factors.

The T suppressor lymphocyte function against pro-oncogenic Epstein-Barr virus infections is also defective in patients with rheumatoid arthritis.[55-57]

Oncogenicity of methotrexate is supported by *in vitro* and *in vivo* studies as well as by increasing numbers of case reports linking it to the development of predominantly B cell non-Hodgkin's lymphomas in patients with rheumatoid arthritis, mainly the patients who experience spontaneous remission.

Table II summarises the possible mechanisms for disease itself and methotrexate-induced oncogenicity in patients with rheumatoid arthritis. The exact mechanisms by which methotrexate induces its therapeutic effect remains controversial. The rapid onset of action of methotrexate would favour an anti-inflammatory effect, either through its inhibition of cytokines like interleukin (IL)-1 and IL-6 and leukotrienes and/or via an increase in adenosine at the sites of inflammation.[58,59] Enhanced adenosine release may be responsible for some of the adverse effects of methotrexate, for example, accelerated nodulosis.[59] Even though methotrexate has immunomodulating or immunosuppressive effects,[60] this might not be the mechanism through which methotrexate brings about its efficacy.

2.1 Cytogenetic Actions

The activity of methotrexate is mediated through its action on different enzymes. The most sensitive of these is dihydrofolate reductase, which causes dose-dependent inhibition of purine and pyrimidine synthesis. Related to these actions, methotrexate may have untoward cytogenetic effects.

In 1 study of patients with lymphoma associated with methotrexate treatment 5q- and Philadelphia chromosomes were found.[31]

A high correlation was demonstrated between the mutagenicity and oncogenic transformation induced by chemotherapeutic agents in *vitro* studies on the one hand, and their carcinogenicity *in vivo* on the other.[61,62]

Table I. A literature review of B and T cell non-Hodgkin's lymphoma occurring in patients with rheumatoid arthritis (RA) treated with methotrexate (MTX)

Case no.	Reference no.	Age/ gender	Length of diagnosis of RA (y)	Total MTX dose (mg)	Lymphoma presentation	Cell type	Treatment	Outcome	Presence of Sjögren's/ Epstein-Barr virus
1	14	54F	18	1040	Cough, chest pain, shortness of breath, chest mass on CT	Large B cell non-Hodgkin's lymphoma. Monoclonal	Chemotherapy, MTX withheld	Remission	No/no
2	14	76F	17	1360	Upper GI bleeding	MALT B cell non-Hodgkin's lymphoma	Chemotherapy, MTX withheld	Remission	No/no
3	15	NA	NA	180	NA	Non-Hodgkin's lymphoma	MTX continued	NA	NA
4	15	NA	NA	380	NA	Non-Hodgkin's lymphoma	MTX discontinued	NA	NA
5	16	83F	23	3600-5500[a]	Progressive fatigue and bodyweight loss, with diffuse adenopathy on examination. Left upper abdominal wall mass	Small, cleaved T cell non-Hodgkin's lymphoma. Monoclonality not confirmed	No therapy (MTX withheld)	Spontaneous remission	Yes/no[b]
6	17	50F	8	990	Large submandibular mass	Diffuse, large, follicular B cell non-Hodgkin's lymphoma	Chemotherapy, MTX withheld	Remission	No/no
7	18	44M	7	748	Bodyweight loss and left upper quadrant abdominal pain. Diagnosis by biopsy of perisplenic mass	Diffuse large cell non-Hodgkin's lymphoma. Monoclonal	Chemotherapy, MTX withheld	NA	No/NA
8	18	48M	11	538	Night fevers, groin and buttock pain, gross haematuria	Diffuse large cell non-Hodgkin's lymphoma. Monoclonal	Chemotherapy, MTX withheld	Died	No/NA
9	19	70M	31	470	Supraclavicular mass	Follicular centrocytic B cell lymphoma	Chemotherapy, MTX withheld soon after diagnosis	Stable disease	No/NA
10	20	86F	18	1400	Rapidly expanding mass on thenar eminence	Diffuse large B cell, immunoblasts, plasmacytoid	No therapy (MTX withheld)	Spontaneous remission	No/yes
11	21	55F	9	760-1500	High fevers, sweats, hepatosplenomegaly and adenopathy	Polymorphous diffuse non-Hodgkin's lymphoma of T cell phenotype	Chemotherapy, MTX withheld	Died	No/NA
12	22	72M	20	330	Axillary mass	Diffuse large cell non-Hodgkin's lymphoma	Localised radiotherapy (MTX continued initially)	Remission	NA/NA
13	23	47F	23	990	NA	Non-Hodgkin's lymphoma–B cell, diffuse, large cell	Chemotherapy. MTX withdrawn	Complete remission	No/NA
14	24	64F	3-4	560	Blurred vision and choroidal thickening on ophthalmological examination. Later shortness of breath, malaise, fevers, sore throat, adenopathy. Diagnosis by axillary node biopsy	Large B cell non-Hodgkin's lymphoma	Prednisone (as empirical treatment for scleritis)	Died shortly after diagnosis	No/NA
15	25	80F	NA	1500	Salivary gland	Diffuse mixed lymphoma, B cell phenotype	Chemotherapy/radiotherapy	Remission	No/yes
16	25	60F	NA	920	Lymph node	Diffuse large cell. B cell phenotype	Chemotherapy	Alive with disease	No/no
17	25	62F	NA	1600	Skin	Diffuse large cell. B cell phenotype	Radiotherapy	Remission	No/no

The mutagenicity of methotrexate has been well demonstrated in various studies.[61,63-65] *In vivo* and *in vitro*, methotrexate produced a high number of chromosomal aberrations,[66,67] chromatid and chromosomal breaks, gaps and chromatid exchanges in addition to dicentrics and morphological transformation *in vitro*. These effects appeared even at methotrexate doses not too dissimilar from those used in rheumatoid arthritis (12.5 to 50mg). The cell populations that survive methotrexate treatment demonstrate heritable genetic damage.[68] Increase in sister chromatid exchanges, a powerful predictive test, was demonstrated in *vitro* studies even at lower doses.[69] In 1 study, chromosome and chromatid breaks as well as erythroblast micronuclei, another sensitive measure of DNA damage, have been found with increased frequency in bone marrow cell isolates from 18 methotrexate-treated patients with psoriasis.[64] Other studies have detected aneuploidy in bone marrow aspirates,[12] arrest in metaphase,[70] decrease in S-phase peripheral blood lymphocytes[71] and fragile chromosomes.[72] Fragile sites are weak points in the chromosomes that are prone to breakage and rearrangements under certain conditions, including folate deprivation. Such abnormalities facilitate somatic mutations that might be associated with certain cancers.

The cumulative effect of cytogenetic abnormalities, even though they may be small in the beginning, should be also considered with a treatment such as methotrexate which is used long term.

2.2 Immunological Abnormalities and Decreased Oncogenic Surveillance

Spontaneous tumour remission after methotrexate is stopped may be due to a regeneration of the immune system, and may be associated with the recovery of oncogenic surveillance and the subsequent elimination of a malignant clone. The cell-mediated immune system is important in oncogenic surveillance. Alterations in such activities

18	25	82F	NA	240-360	Skin	Diffuse large cell. B cell phenotype	Chemotherapy	Died	No/no
19	25	50M	NA	1400-1800	Salivary gland	Follicular large cell lymphoma. B cell phenotype	Chemotherapy	Remission	No/no
20	26	57F	24	2400-3600	Diffuse lymphadenopathy splenomegaly, fever	Non-Hodgkin's lymphoma–B cell, diffuse, large cell	MTX withdrawn. No chemotherapy	Spontaneous remission	No/yes
21	27	NA	21	5460	NA	Non-Hodgkin's lymphoma large/small cell	No therapy	Spontaneous remission; maintained at 5y	No/no
22	27	NA	20	120	NA	Non-Hodgkin's lymphoma large cell	Chemotherapy	Remission; maintained at 1y	No/no
23	28	65M	25	2981	Inguinal mass, bodyweight loss	Non-Hodgkin's lymphoma–B cell, diffuse, large cell, monoclonal	MTX withdrawn. Low dose prednisone	Spontaneous remission	NA/yes
24	28	66F	21	4137	Nodular masses and feet	Non-Hodgkin's lymphoma–B cell, diffuse, large cell, monoclonal	MTX withdrawn	Spontaneous remission	NA/yes
25	29	59F	12	3180	Soft tissue mass on left forearm and right lower extremity, 7kg bodyweight loss	Non-Hodgkin's lymphoma–B cell, diffuse, large cell, monoclonal	MTX withdrawn. Chemotherapy	Complete remission	NA/yes

a 10-15 mg/wk for 7y.

b Cytomegalovirus positive.

CT = computerised transaxial tomography; **GI** = gastrointestinal; **MALT** = mucosa-associated lymphoid tissue; **NA** = not available.

may be associated with the development of malignancies.[73,74] As shown previously, studies demonstrate independent abnormalities of T cell surveillance and function in patients with rheumatoid arthritis, mostly deficiencies of Epstein-Barr virus–specific immunity.[55-57] This results in poor handling of Epstein-Barr virus infection which may lead to latent infection, immunodeficiency and malignant transformation.[75-78] The Epstein-Barr virus may induce some of its effects through a decrease in B lymphocyte apoptosis.[79] Methotrexate also has immunosuppressive effects[60] and may accentuate the immune abnormalities already present in patients with rheumatoid arthritis. The inhibition of folate-dependent methionine regeneration from homocysteine by methotrexate, and its inhibition of methyl donors s-adenosyl methionine and polyamines, may also inhibit T cell function.[80] Inhibition of polyamines have the following consequences.

- Decreased ability of lymphocytes to respond to IL-2 and mitogens[81] which might explain the antiproliferative effect of methotrexate on lymphocytes and inhibition of immunoglobulin and rheumatoid factor synthesis.[71,82,83]
- Substantial reduction of lymphocyte DNA synthesis.[80]
- Decreased cytolytic activity of lymphocytes *in vivo*.[84]
- A beneficial effect seen in lupus-prone mice.[85]
- Inhibition of primary delayed-type hypersensitivity in mice.[86]

Methotrexate has proven to have an apoptotic action on activated T cells. When phytohemagglutinin-stimulated peripheral blood mononuclear cells were treated with methotrexate, proliferation of activated T cells was inhibited. It is likely that this effect was due to induction of apoptosis in T cells.[87]

Aside from the above inhibitory effects on T cell function, increased T helper counts, decreased T suppressor/T helper cell ratio and total lymphocyte count were seen in long term studies of methotrexate therapy in patients with rheumatoid arthritis and

Table II. Possible mechanisms of oncogenicity in rheumatoid arthritis caused by disease state and methotrexate treatment

Rheumatoid arthritis-related oncogenicity
CD5+ clonal expansion and selection due to severe disease and intense immunological activity
Epstein-Barr virus latent infection
Genetic predisposition
Methotrexate-related oncogenicity
Cytogenetic actions
Immunological actions and decreased oncogenic surveillance
Co-carcinogenic actions

in children with acute lymphatic leukaemia.[88-90] Even though low dose methotrexate appears to have immunosuppressive effects at least in a subset of treated patients, it is likely that important immunosuppression is not the case in the majority of patients with rheumatoid arthritis.

In addition to these basic data and long term clinical studies in patients with rheumatoid arthritis and other disorders, other clinical evidence supports methotrexate-induced immunosuppression when the drug is used in low doses.

In a comprehensive review, Boerbooms at al.[91] found that, when treated with methotrexate, patients with severe rheumatoid arthritis have a higher frequency of infections than patients with moderate rheumatoid arthritis. Opportunistic infections are more frequently reported in patients with rheumatoid arthritis treated with methotrexate and more rarely reported in those rheumatoid arthritis patients treated with azathioprine, cyclosporin or cyclophosphamide and in patients with psoriasis and psoriatic arthropathy treated with methotrexate.

Similarly, patients who developed lymphoma when receiving methotrexate had a long-standing disease that was at a well advanced clinical stage with important functional disability, erosions, deformities and nodularity. Rheumatoid arthritis duration from its onset until lymphoma development may be variable (between 8 and 30 years), but many patients have a disease duration of more than

10 years (more than 20 in several patients) [table I]. The duration of treatment may also be variable (3 months to 84 months) leading to a variable cumulative dose of methotrexate, from 180 to 5500mg (mean 1.4g). The majority of the patients received a cumulative methotrexate dose of more than 500mg and more than 1000mg in about half of them.

Co-morbidity, genetic and environmental factors as well as concomitant use of other drugs may explain such variations. Methotrexate effects as an immunosuppressive are probably powerful enough only in this subset of patients with rheumatoid arthritis in whom the immunity is already severely altered in its functions, compared with the patients with mild or moderate rheumatoid arthritis and patients with psoriasis. Probably in other patients, like patients with psoriasis, this effect is not significant enough to induce malignancy, because of less immunological abnormalities and/or less Epstein-Barr virus latent infection. Different genetic backgrounds in these groups may play a role. Moreover, the clinical, histological and microbiological presentation in methotrexate-associated lymphoma in patients with rheumatoid arthritis is similar to presentation of lymphoma associated with immunosuppression.

The decreased T cell surveillance of Epstein-Barr virus infection with its oncogenic effect, inherent in patients with severe rheumatoid arthritis, is facilitated by the above effects of methotrexate on T lymphocytes function. The antibody response to Epstein-Barr virus early antigens (BHRF1, the viral homologue of Bcl-2, and BMRF1, a DNA-binding protein) was found to be increased in patients with rheumatic diseases and lymphoma, especially those with Sjögren's syndrome.[92] This may represent the presence of reactivated virus. The BHRF1 protein may induce lymphoproliferation by inhibition of apoptosis. Even though these findings may be important for clinical research, we do not believe them to be of practical relevance in the routine determination of the early antigens or their corresponding antibodies in the management of patients with rheumatoid arthritis.

In conclusion, oncogenic process linked to methotrexate as well other immunosuppressive drugs is similar to that found in cyclosporin-treated transplant patients, and involves immunosuppression in the presence of Epstein-Barr virus latent infection as a basic mechanism.

2.3 Methotrexate as a Co-Carcinogen

The co-carcinogenic action of methotrexate has been demonstrated in some animal studies[93] but not all.[94] Administered in combination with the skin carcinogenic agent methylcholanthrene for short periods of time, methotrexate has demonstrated anti-tumour activity. When administered for long periods of time, methotrexate acted as a co-carcinogen, with the development of skin cancer.[93]

As in animal studies, methotrexate may act as a co-carcinogen to procarcinogenic factors discussed in section 2.2 encountered in a subset of patients with rheumatoid arthritis: severe disease leading to immunosuppression, mainly directed towards Epstein-Barr virus infection and its prooncogenic effects on 1 hand, and intense immune activity on the other. Other important factors are genetic and environmental predisposition.

All the above mechanisms embrace a common basic pattern, consistent with a model of lymphoma in rheumatoid arthritis: initially a polyclonal reactive proliferation occurs, presumably in response to an inciting virus like Epstein-Barr virus or other injury. Later, during chronic lymphoproliferation, on a background of immunological abnormalities, a clone is selected and transformed preferentially resulting in monoclonality. Different mechanisms may act concomitantly.

Methotrexate, acting at different concentrations, may be the last straw that turns a benign state in to malignant one (fig. 1).

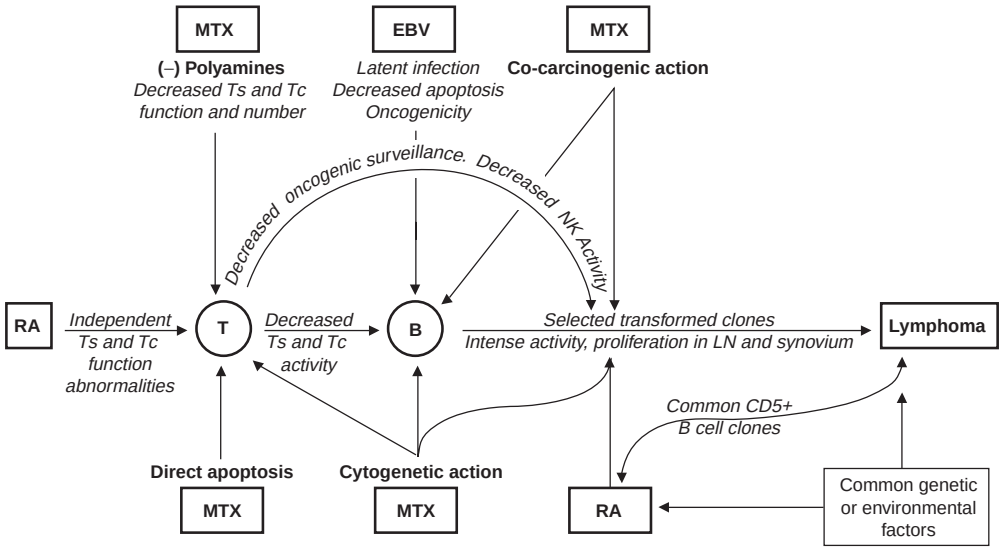

Fig. 1. Mechanisms of methotrexate (MTX) oncogenicity. B cells are transformed into premalignant or malignant clones by Epstein-Barr virus (EBV) and/or the cytogenetic actions of methotrexate. This process is facilitated by the decreased suppressor lymphocytes (Ts)/cytotoxic T lymphocyte (Tc) and natural killer (NK) cell function found in patients with rheumatoid arthritis (RA). Methotrexate accentuates Ts/Tc dysfunction through inhibition of polyamines and direct apoptosis. The very active B cell clones may undergo lymphomatous transformation in lymph nodes and synovium. A common CD5+ B cell clone which is expanded in rheumatoid arthritis may be induced by methotrexate to become malignant. Finally, common genetic or environmental factors that predispose to both rheumatoid arthritis and lymphoma may be influenced by methotrexate in a co-carcinogenic manner. **B** = B lymphocyte; **LN** = lymph nodes; **NK** = natural killer cell; **T** = T lymphocyte; **(–)** = inhibition.

3. Epidemiological Considerations

A definitive cause and effect relationship between methotrexate and lymphoma in rheumatoid arthritis is difficult to establish for a number of reasons. Most prominent of these is the intrinsic, increased risk of lymphoma attributed to rheumatoid arthritis itself. Comorbid associations, (i.e. Sjögren's syndrome and Hashimoto's thyroiditis),[45,95] the confounding effect of concomitant drug use, and the fact that patients requiring methotrexate may be part of a subpopulation that is more cancer-prone, must all be considered.

Recent detailed reviews conclude that while the risk of all cancers in patients with rheumatoid arthritis is probably not elevated, the risk of particular haematological malignancies, especially that of non-Hodgkin's lymphoma, probably is moderately increased.[96,97] Multiple myeloma was also found to have a high incidence.[96,98] The largest study involved over 46 000 Finnish patients with rheumatoid arthritis cross-referenced from the nation's comprehensive cancer and social insurance registries. The study revealed a relative risk of 2 for haematological malignancies (130 observed compared with 60 expected) with about equal risk for overall malignancy (1202 observed, 1138 expected). Non-Hodgkin's lymphoma had a relative risk of 2.7.[96] A risk of 1.9 [95% confidence interval (CI) 1.5 to 2.6] for non-Hodgkin's lymphoma was also found in a Swedish study.[97] While a study of 489 patients from Birmingham, England, conducted over a mean of 12.2 years concluded that the relative risk of non-Hodgkin's lymphoma in patients with rheumatoid arthritis patients was 24.1 (7 observed, 0.029 expected),[42,99] other studies from the US failed to reveal any increase in risk of haematological malignancy for patients with rheumatoid arthritis.[100,101]

In a study of 862 patients with rheumatoid arthritis conducted over a mean period of 17.4 years,[102] there were only 3 cases of non-Hodgkin's lymphoma (5.5 expected), with a standardised incidence ratio (SIR) of 0.5 (95% CI 0.11 to 1.60). The leukaemia was significantly over-represented [SIR 2.47, p = 0.026 (95% CI 1.12 to 4.69)] while there were no cases of Hodgkin's lymphoma [SIR 0.00 (95% CI 0.00-8.53)]. The risk of colorectal cancer was reduced [SIR 0.52, p = 0.037 (95% CI 0.25 to 0.96)]. No statistically significant difference was observed for the other types of malignancies. Factors such as Sjögren's syndrome, Felty's syndrome[103] and concomitant drug use, some of them cytotoxic, may have an effect upon the differences in these figures. Aside from the effects of cofactors and study design flaws, the true definition of the prevalence of lymphoma in methotrexate-treated patients with rheumatoid arthritis awaits the determination of precise epidemiological data.

A recent retrospective study at the Mayo Clinic from 1976 to 1992 studying 16 263 patients with rheumatoid arthritis cross-referenced with 21 270 patients with haematological malignancies found that 39 patients who had both. Out of this number, 12 had been treated with methotrexate; non-Hodgkin's lymphoma was the most common tumour. The authors concluded that if there is any association between methotrexate and lymphoma, it is vanishingly small.[31] Weaknesses of the study include the retrospective design, non–population-based recruitment and varied follow-up period. Furthermore, the study covered a period when methotrexate was much less popular as a treatment, while the use of cytotoxic disease-modifying antirheumatic drugs known to have elevated risks for lymphoma was more common.

The Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS) study,[32] revealed an odds ratio of 1.7 (95% CI 0.3 to 32.2) and of 4.0 (95% CI 0.4 to 197.0) for lymphoproliferation in patients with rheumatoid arthritis treated with methotrexate and azathioprine, respectively. The authors concluded that patients receiving methotrexate are at an increased risk for developing lymphoma, but this risk would be small considering the already high risk of lymphoma in rheumatoid arthritis which is independent of drug therapy.[32]

However, there are increasing reports of methotrexate-related malignancies over the past 5 years and cases are under-reported.

While the number of patients with rheumatoid arthritis taking methotrexate is uncertain, the number probably approaches 100 000. If we consider the largest population-based studies of lymphoma in rheumatoid arthritis, such as the Finnish and Swedish ones,[96,97] which found a relative risk of about 2, and knowing that in the general population there are about 14 cases of non-Hodgkin's lymphoma per 100 000 individuals per year,[104] we may expect to see about 28 new cases of non-Hodgkin's lymphoma annually in patients with rheumatoid arthritis receiving methotrexate. A registry is one option which may be employed to assess this incidence. Of course an ideal approach would be a prospective cohort study that would control for all of the variables discussed.

4. Conclusion

Even though, in an epidemiological sense, the link between lymphoma and methotrexate in patients with rheumatoid arthritis treated with methotrexate is not definitive, one cannot ignore the clinical facts of increasing case reports of this association (around 50 cases at present). The spontaneous remission of some lymphomas after methotrexate was stopped is the most compelling clinical fact which directly links methotrexate to the development of the lymphoma in these patients. Furthermore, an additive malignancy risk may be seen in the rheumatoid arthritis population given recent reports supporting the combination therapy employing both methotrexate and cyclosporin.[105]

Basic science data, although not perfect, support the oncogenicity of methotrexate in association with rheumatoid arthritis.

Because of the inherently increased lymphoma risk in rheumatoid arthritis, it is difficult to state the magnitude of this relationship with methotrexate. It is our belief that not all patients with rheumatoid arthritis are at risk of developing lymphoma while receiving methotrexate. We believe that only a subset of patients with rheumatoid arthritis and severe abnormalities like those discussed in section 2.2 are at risk. In this respect, this subset of patients would be different from other patients with rheumatoid arthritis patients and patients with psoriasis.

Physicians treating patients with rheumatoid arthritis with methotrexate should reconsider the clinical and medico-legal ramifications of their informed consent discussions with patients. They should maintain surveillance not only for liver, haematological and pulmonary toxicity, but also for the varied presentations of lymphoma (table I). These include new onset of constitutional symptoms and adenopathy, as well as pulmonary, or neurological abnormalities. We encourage clinicians to report cases of lymphoma in patients with rheumatoid arthritis receiving methotrexate and to search for the presence of Epstein-Barr virus and other herpes viruses in their patients' neoplastic cells. If the clinical situation permits, a period of observation for spontaneous remission is warranted.

Given the number of case reports so far and the evidence of lymphomas that resolve when methotrexate is withdrawn, it would be very helpful to undertake further controlled studies of this issue.

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