



Risk of cancer after long-term therapy of autoimmune disorders with glucocorticoids or DMARDs—a controversial issue

Jakob D. Rudzki

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Summary Most autoimmune diseases like RA (rheumatoid arthritis) are usually associated with lifelong treatment. The etiology of RA remains unclear, but it depends on a high-risk genetic background and an environmental trigger, which leads to autoimmune dysregulation and results in autoinflammation. This process preferentially affects joints but may spread to different organs and systems. Several studies have illustrated that patients with RA have an increased overall incidence of malignancy compared to the general population (risk of 5–10%). However, it remains unclear if biological agents like DMARDs (disease-modifying antirheumatic drugs) are associated with a potential increased risk of generating new neoplasms. Data indicate that it is unlikely that RA patients who have received biological agents have a much higher risk of developing lymphoproliferative disorder, other hematologic malignancies or solid tumors compared to MTX (methotrexate) users. In most cases, it also depends on the activity of the underlying rheumatic disease. Thus, clinical decision making must carefully weigh benefits and risks of both aspects of antirheumatic treatment and the risk of elevating the likelihood of developing cancer. The decision to treat with a DMARD must always be based on clinical features and reflect the risk pattern of the individual patient. Up to now, there is no clear evidence that proves the link between long-term DMARD or glucocorticoid use and the increased incidence of newly developed neoplasms. The pathophysiological context is still not well understood and

the underlying link between RA and lymphoma still needs to be addressed.

Keywords Disease-modifying antirheumatic drugs · Methotrexate · Neoplasms · Inflammation · Cancer

bDMARDs and sDMARDs—two big players in treatment of autoimmune diseases

Disease modifying antirheumatic drugs (DMARDs) comprise two large groups of diverse compounds: biological DMARDs (bDMARD) and synthetic DMARDs (sDMARD) (listed in detail in Table 1).

Several studies have presented data that strengthens the association between higher incidence of cancer in RA patients. A nationwide cohort in Taiwan assessed the risk for cancer among 23,644 patients with RA between 1996 and 2007 without any history of malignancies with SIR (standardized incidence rates) of 2.7 for all subtypes of lymphoma (Non-Hodgkin lymphoma [NHL] SIR 3.5; Hodgkin lymphoma [HL] SIR 1.76) [3]. From 2001 to 2005 a Japanese group demonstrated in an observational cohort study an increased SIR for lymphoma in RA patients with an SIR of 6.07 for all types of lymphoma. In this study the potential risk factors were defined as male gender and older age [4]. Setoguchi et al. conducted a cohort study to estimate the effect of biologic DMARDs on cancer. The primary endpoints were hematologic malignancies like multiple myeloma, lymphoma and leukemia as well as common solid cancer like colorectal, lung, stomach, breast, prostate, uterine, ovarian, urinary tract/bladder and finally melanoma. The pooled cohort included 1152 bDMARD users and 7306 MTX users. Comparing the two groups, the propensity score-adjusted pooled hazard ratio was 1.37 (CI 95% 0.71–2.65) for hematologic malignancies and 0.91 (CI 95% 0.65–1.26) for solid cancer and revealed 11 hema-

OA Dr. J. D. Rudzki (✉)
Medical University Innsbruck, Innsbruck, Austria
UKIM V—Tirol Kliniken, Landeskrankenhaus Innsbruck,
Anichstraße 35, 6020 Innsbruck, Austria
jakob.rudzki@tirol-kliniken.at

Table 1 Listing up bDMARDS & sDMARDS

Compound	Trade name®	Description	Administration frequency
bDMARD			
Anakinra	Kineret	A human interleukin 1 receptor antagonist protein	SQ daily
Infliximab	Remicade	A chimeric (mouse/human) monoclonal anti-TNF-alpha antibody	IV every 4-8 wk
Etanercept	Enbrel	A soluble TNF-alpha receptor fusion protein	SQ weekly
Adalimumab	Humira	A fully human anti-TNF-alpha monoclonal antibody	SQ every 2 wk
Rituximab	Mabthera, Rituxan	A chimeric (mouse/human) monoclonal anti CD20 directed antibody	IV on d1 /d15, repeated every 24 wk
Abatacept	Orencia	Fusion protein composed of the Fc IgG1 region & fused to extracellular domain of CTLA-4	IV every 4 wk; or SQ weekly
Tocilizumab	Actemra	Humanized anti IL-6 receptor monoclonal antibody	IV every 4 wk; or SQ every 1-2 wk
Golimumab	Simponi	A fully human anti-TNF-alpha monoclonal antibody	IV every 8 wk; or SQ every 4 wk
Certolizumab-pegol	Cimzia	Fragment of a monoclonal antibody directed against TNF-alpha	SQ, every 2 wk
sDMARD			
<i>Conventional synthetic DMARDs</i>			
Methotrexate	Ebetrexat	Inhibitor of AICAR transformylase → increase of intracellular AMP and extracellular adenosine	Oral, weekly
Leflunomide	Arava	Inhibition of dihydroorotate dehydrogenase, needed for the de novo synthesis of pyrimidines	Oral, daily
Hydroxychloroquine	Hydroxychloroquin	Stabilization of lysosomes	Oral, daily
Sulfasalazine	Salazopyrin	Immune modulation of unclear mechanism	Oral, daily
Additional sDMARDs:		Gold/auranofine, azathioprine, chlorambucil, cyclosporine, cyclophosphamide, mycophenolate, minocycline, penicillamine, tacrolimus, tofacitinib	
<i>Targeted synthetic DMARDs</i>			
Tofacitinib	Xeljanz	Janus Kinase inhibitor	Oral, daily
<i>bDMARD biological Disease Modifying Antirheumatic Drug, sDMARD synthetic Disease Modifying Antirheumatic Drug; AICAR aminoimidazole carboxamide adenosine ribonucleotide, AMP adenosine monophosphate, IV intravenous, SQ subcutaneous, wk weeks</i>			

tologic malignancies and 46 solid tumors during 2940 person-years of bDMARDs use and 88 hematologic malignancies and 558 solid neoplasms during 30,300 person-years of MTX use. The authors concluded that it remains a challenge to study the effect of an infrequent exposure of bDMARDs on rare diseases like hematologic malignancies [5].

Systemic literature review (SLR) of observational studies, including the evidence of the safety of DMARDs and glucocorticoids in patients with rheumatoid arthritis, supported the formation of the recommendations for the management of RA. Patients on tumor necrosis factor inhibitors (TNFi) compared to patients treated with conventional sDMARDs showed a higher risk of dangerous infections (adjusted HR 1.1–1.8), a higher risk of tuberculosis and an increased risk of reactivating infectious diseases like herpes zoster. Interestingly, this group excluded a higher risk for malignancies in general, lymphoma or non-melanoma skin cancer, except the risk for melanoma, which was described to be elevated (aHR 1.5) [6].

Some compounds in detail

Methotrexate

The objective of an Australian study carried out in 2008 focused on assessment of cancer risk of a co-

hort of 459 RA patients treated with methotrexate in community practice. Standardized incidence ratios (SIRs) were calculated using state population cancer rates stratified by sex, age (in a 5-year group) and calendar year. Buchbinder et al. estimated a SIR of 1.5 (95%CI 1.2–1.9) for risk of malignancy among methotrexate-exposed RA patients relative to the general population split up as follows: 3-fold increase in melanoma SIR 3.0 (95%CI 1.2–6.2), a 5-fold increase in non-Hodgkin's lymphoma SIR 5.1 (95%CI 2.2–10.0) and finally an almost 3-fold increase in lung cancer SIR 2.9 (95%CI 1.6–4.8). A consequent and regular skin cancer screening for all RA patients particularly those treated with immunosuppressive agents is highly recommended by the authors [8]. A more recent Swedish study revealed a statistically significant risk increase ($p < 0.001$) in CMM (cutaneous malignant melanoma) observed in MTX-exposed patients compared with patients without MTX exposure. Interestingly, in a subgroup analysis, only women older than the age of 70 years at treatment start preserved the difference between the groups [9]. Hence, this just guides the clinician to take extra care to ensure cancer screening in patients with RA whether methotrexate is prescribed or not.

Solomon et al. carried out a large RA cohort-based study in the US to estimate the comparative risk of cancer across different DMARD groups compared to

methotrexate, the cornerstone of current RA treatment. Actually, this was the first study done defining MTX as a comparator group. The final study sample comprised 6806 patients, whereas 179 of those patients developed a definite or probable cancer. Finally, the authors concluded that there was no significant increase in cancer risk for the different biologic DMARDs compared with MTX. Rather, they found a reduced risk of cancer among users of TNF antagonists and non-biologic DMARDs users compared with MTX [10].

Tumor necrosis factor inhibitors

Systemic reviews were performed to estimate the risk ratios (RR) of mortality, cardiovascular events, cancer including hematologic neoplasms like lymphoma but also solid cancer or melanoma and finally even of the association with severe infectious events under treatment with TNFi (tumor necrosis factor inhibitors). As expected primarily serious infections were significantly increased during treatment with TNFi compared to other DMARDs (adjusted HR [aHR] = 1.1–1.8) [6]. They also confirmed the safety of administration of existing sDMARDs and bDMARDs for the treatment of RA, but DMARDs administration is not without risk. The authors stated that there is a significantly higher risk for upcoming infections like tuberculosis or serious infections of herpes zoster. Finally, Ramiro et al. concluded that the risk of all types of malignancies was not elevated but need to be confirmed and TNFi usage should be considered with reserve [6].

Of particular interest, the administration of TNFi and MTX together as an additional compound compared to MTX alone does not seem to increase the lymphoma risk when using TNFi in the most common way (TNFi plus MTX) (OR 1.1 [95%CI 0.6–2.0]). Separately analyzed data for infliximab and etanercept reflects similar results and excludes associations between TNFi and lymphoma in a study of lymphomas in 19,562 patients over 89,710 person-years of follow-up covering anti-TNF exposure in 10,815 patients. The authors concluded that there was no link between an increase in lymphoma with anti-TNF treatment [11].

Glucocorticoids and long-term effects related to elevated risk for malignancies

Rheumatoid arthritis patients frequently take glucocorticoids as part of their daily regimen. Therefore, glucocorticoids still have a prominent position in the treatment algorithm of RA. However, this is not without fear of their safety profile. During a total duration of less than 2 years of treatment with glucocorticoids, no association was found with lymphoma risk (OR=0.87; 95%CI 0.51 to 1.5), whereas interestingly treatment over 2 years and beyond was associated to a low lymphoma risk (OR=0.43; 95%CI 0.26–0.72). Importantly, the authors highlighted that the dura-

tion of RA disease at the initiation time point of oral steroids did not affect lymphoma risk at all. Intra-articular steroids were linked to a reduced lymphoma risk but only when used as swift flare treatment (OR=0.22 [95%CI 0.13–0.37]) and if there is a link to lymphoma then in particular to DLBCL [12]. Additionally, chronic usage of corticosteroids is associated with wound- and bone-healing disorders and surgical site infections [13].

Discussion

Risk evaluation is difficult because both the autoimmune disease and the chosen treatment option may be associated with an overall increased risk of malignancy or at least some distinct subtypes of malignancies. Interestingly, the overall malignancy risk in patients suffering from RA is quite similar to that of the general population as illustrated in a great meta-analysis published in 2015 [14].

In general, there are some confounders that finally make it impossible to clearly determine whether the potential risk of developing cancer increases after or under the treatment of DMARDs or long-term glucocorticoid usage. There exists a preponderance of evidence that TNFi do not increase the development of most solid tumors with the exception of skin cancer. However, uncertainty remains because of the fact that even recent studies (prospective trials and population-based trials) failed to confirm a strict correlation with increased risk for malignancies [1, 7]. Another confounding factor is defined by increased disease activity that strongly correlates with lymphoma risk [15] especially in case of RA. A group of Korean researchers tried to estimate the incidence of malignancy in early RA patients and to evaluate the relative risk of malignancy by using the Korean National Claims Database comprising a total of 14,081 identified patients. Using a multivariable logistic regression analysis Cho et al. revealed that bDMARDs treatment of early RA patients decreases the overall risk of developing malignancies and this group highlights that it may not affect the risk of developing hematologic malignancies. They also stressed the well-recognized association between RA and malignancies [16].

Other examples for increased risk of specific lymphoma subtypes were primary Sjögren's syndrome associated with mucosal associated lymphoid tissue (MALT) lymphoma [17] and celiac disease which is linked to enteropathic T cell lymphoma. [18]. DLBCL (diffuse large B cell lymphoma) is reported as the most frequent neoplasm in SLE (systemic lupus erythematoses) which accounts for 37–62% and is consistent with a role of antigenic drive in autoimmunity-related lymphomagenesis [19]. Regarding the role of immunosuppressive therapy used (cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, antimalaria drugs and glucocorticoids), the authors could not find an exclusive explanation. It was possi-

ble to detect a trend between cyclophosphamide and cumulative steroid use and the appearance of lymphoma disease but without statistical significance. Notably, most of the SLE patients who had lymphoma were free of prior cyclophosphamide therapy [19].

A milestone in understanding the position of DMARDs in the treatment algorithms of rheumatoid arthritis has been the development of registries with well conducted analyses to evaluate safety and effectiveness in direct comparison to RCTs (randomized controlled trials) [6].

Patients suffering from active RA seem to be at a higher risk of lymphoma and lung cancer and a potentially decreased risk for colorectal and breast cancer compared with the general population [1]. Data reported in this paper suggest that a fair estimation of the risk of developing cancer under DMARDs and active RA is not possible. An overall twofold risk was associated with RA and lymphoma compared to general population SIRs 2.08 (95%CI 1.80–2.39). A considerable higher risk was observed in Hodgkin lymphoma than for non-Hodgkin lymphoma with SIRs of 3.29 (95%CI 2.56–4.22) and 1.95 (95%CI 1.7–2.24), respectively [1]. Klein et al. [2, 20] worked out the incidence, pathogenesis and biology of SLE and lymphoma. This review article of 2018 examined the largest and most significant studies published in recent years including all available systemic reviews and meta-analysis as well as large observational cohort studies covering the incidence and risk of lymphoma in SLE. In the end the authors concluded that there are three potential theories to understand the link between SLE and lymphoma. One underlying point involved in lymphomagenesis in SLE bear upon the continuous ongoing lupus activity. Inflammation and autoimmune disease imply an inherent role in triggering chronic immune stimulation which subsequently results in an increased risk for malignancy. Some cytokines and proteins are known to be associated with cell survival and proliferation like BAFF, APRIL, IL-6 and BCL-2 and are also frequently found in both SLE and lymphoma. In contrast to RA, persistent disease activity and SLE could not be linked to development of lymphoma nor was there a robust link to immunosuppressive therapy administered for this disease. Thus, some questions remain regarding the pathogenesis and the link between SLE and lymphoma [20].

Conclusion

Several crucial questions still remain like what happens to patients with a previous malignancy? Is it still safe to start with bDMARDs in patients with previous malignancies or is it rational or safe to change the bDMARD to a biologic with a different mode of action in case of malignancy occurring during or even after bDMARDs? In this context, registries seem to form a powerful tool to provide relevant information regarding safety concerns. Future trials (randomized

clinical trials) addressing those questions may help to gain more relevant information.

Some studies illustrated an increased risk for solid cancer like lung cancer and lymphoma compared to the general population. But there is an unmet need to set up further studies examining specific aspects like lifestyle factors or exposition to toxic substances by smoking to investigate the underlying mechanisms for an increased or decreased risk for cancer in patients with RA or SLE compared to the general population. This way it will be possible to advise and monitor patients accordingly to the generated results [14].

In striking contrast to the mentioned meta-analysis, a French group suggested that by dramatically reducing chronic inflammation in RA patients, TNFi are able to significantly reduce overall mortality and cardiovascular events without increasing the risk of cancer [14].

Despite all limitations an absolute clear statement cannot be given at this point. Only further studies evaluating specific risk factors including RA management strategies, lifestyle factors and the presence or absence of an active inflammatory process might be supportive to shed new light on these open questions.

The administration and treatment with DMARDs are by far safe but some limitations should be considered: age of patients at the start of treatment as well as active inflammatory processes are important factors to assess the risk of future malignancies under or after treatment with DMARDs. Another aspect of promoting opportunistic infections is a critical issue and should be kept in mind during the evaluation process of patients for DMARD therapy approaches.

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