Update on malignancies in children with juvenile idiopathic arthritis in the German BIKER Registry

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Abstract

Objective

While tumour necrosis factor (TNF)-α-inhibitor treatment improved outcome of juvenile idiopathic arthritis (JIA) management markedly, concerns have been raised about an association of TNF-α-inhibitor treatment and an increased risk for malignancies, especially lymphoma.

Methods

Cases of suspected malignancies documented in the German Biker Registry are reviewed in detail.

Results

Until Dec 31, 2015, 3695 JIA patients were prospectively followed with a total of more than 13,198 observation years. 12 cases of suspected malignancies, including 7 lymphoid neoplasms, have been reported in patients treated with methotrexate (MTX) , and /or TNF-α inhibitors. 11 patients had received MTX, two received cyclosporine A, single patients received sulfasalazine, azathioprine or leflunomide. 10 patients were exposed to biologics, 9 etanercept, two adalimumab, one infliximab and one case was consecutively treated with adalimumab, etanercept, infliximab and abatacept. A case of mild myelodysplasia, in which the patient recovered spontaneously, a case of lymphoproliferation without clonality and a case of cervical dysplasia were treated as suspected, but not confirmed malignancies. Cases in which a malignant disease was confirmed included two cases of Hodgkin's lymphoma, one case of non-Hodgkin's lymphoma, two cases of acute lymphatic leukaemia (ALL) and one patient with lymphoproliferative disorder, who recovered after discontinuation of immunosuppressive therapy. Single confirmed cases of thyroid carcinoma, yolk sac carcinoma and anaplastic ependymoma have also been described. One patient not exposed to biologics died of ALL, all other patients recovered.

Conclusion

In this large cohort of JIA patients, the occurrence of malignancies was higher than in the general population. Whether JIA patients had an increased risk for malignancies, either through their rheumatic disease, or through treatment remains in debate. Treatment with etanercept seems not to further increase the malignancy risk. Long-term observation of JIA patients treated with TNF-α inhibitors into adulthood remains an important task.

Key words

juvenile idiopathic arthritis, tumour necrosis factor-α inhibitors, methotrexate, malignancy, lymphoma

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Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic inflammatory rheumatic disease in childhood and can lead to severe disability (1-3). The introduction of biological therapies opened a new era for the treatment of JIA. Remission of disease is now a goal well in reach. Now, 15 years after the first biologic for treatment of paediatric rheumatic disease was approved, especially long-term effects are of great interest and long-term data are available. Description of cases of malignancies, especially lymphoma in young patients treated with tumour necrosis factor (TNF)-α inhibitors raised questions about long-term risks of these therapies (4). Observations in larger cohorts suggest an increased risk of developing lymphoma in JIA patients compared to the general population (5, 6). Whether treatment with TNF-α inhibitors enhances this risk, remains unclear. The safety information in children with JIA from clinical trials is still limited; the number of treated patients is relatively small and the long-term follow-up is relatively short. Most of the information concerns anti-TNF therapies and here especially patients treated with etanercept, which was the first biologic approved for JIA. Surveillance using registries can be useful to contribute in this field. National registries can provide far larger numbers of patient years and treatment courses. The German BIKER registry (Biologika in der Kinderrheumatologie) is currently the largest of the national registries. The first 5 cases of malignancies have been described earlier (7). This is an update providing information on 7 new cases of suspected malignancy and a risk calculation including the previously published cases.

Methods

The German "Biologika in der Kinderrheumatologie" (BIKER) Registry has been approved by the local ethics committee (8, 9). Written consent was obtained and the data were collected pseudonymised. Patients of the German JIA-BIKER registry newly starting treatment with a biologic between 2000 and 2015 were included in the registry if they had assessments at baseline and at least at one follow-up visit. Patients' characteristics included gender, age, diagnosis, disease duration, previous treatments and initial concomitant treatment and comorbidities. Clinical data included ANA-positivity, HLA-B27, morning stiffness, and the following disease activity parameters: number of tender, swollen, active joints and number of joints with limitation of motion, physician's global assessment of disease activity (visual analogue scale, VAS), patient's/parent's assessment of overall wellbeing and pain (both with VAS), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and the functional assessment by the Childhood Health Assessment Questionnaire (CHAQ) disability index (10). The Juvenile Arthritis Disease Activity Score (JADAS) was calculated as described (11).

Adverse events (AEs) were collected throughout the observation and specially requested on each routine follow-up visit. Follow-up visit reports were collected after 1, 3 and 6 months and 6 monthly thereafter. After enrolment all medication use was documented, if a patient stopped treatment with a biologic or methotrexate (MTX), AEs were collected 6 monthly. Missing and outstanding reports were sent reminders. Patients reaching their 18th birthday were followed-up in the JUMBO registry for adult JIA patients (12). Data from JUMBO have not been included in this analysis.

In the case of AEs the investigator assessed and recorded the AE in detail on the AE form including the date and time of onset, description, severity, time course, duration and outcome, relationship of the AE to study drug, and alternative aetiology for events not considered 'probably related' to all drugs exposed. To collect detailed data special forms for AE of special interest were used, including those for malignancies and suspected malignancies. Outcome of the event was documented as well. Observation time was calculated from the baseline visit until the last visit reported, which usually happened around the patient's 18th birthday. For the AE of malignancies an ever exposed analysis was also used.

As comparator group 1517 patients newly starting treatment with MTX were recruited from Nov. 2005 until Nov. 2011. Documentation was equal to the biologics registry. If in this group patients started on TNF-inhibitor or other biologics, they were switched to the biologics registry cohort.
Reported cases of malignancies were reviewed by four paediatric oncologists and rated either as confirmed malignancies or suspected but unconfirmed malignancies.

Results
The German BIKER registry (Biologika in der Kinderrheumatologie) is currently the largest of the national registries. Since 2001 in total 3695 patients have been documented, including 2197 patients exposed to etanercept, 670 patients exposed to adalimumab, 189 patients exposed to tocilizumab and further patients receiving other biologic therapies for treatment of JIA. Single patients received successively up to 6 different biologics. 1077 patients not exposed to biologics but to MTX were recruited as a control cohort. During the observation period of 15 years, 12 cases of suspected malignant disease have been reported to the German Biker Registry. Of these, 5 cases have been previously described in 2011 (7). The 7 new cases identified since then (cases 6–12) are described in detail in this report. Summarising data of all 12 patients are shown in Table I.

Case 6
This female patient was diagnosed with systemic onset JIA at the age of 5 ½ years. Due to several years of treatment with corticosteroids she suffered from Cushing's syndrome. The patient was treated with MTX for 12 years, etanercept for 26 months and azathioprine (cumulative exposure 14 months) until at the age of 17 years when diagnosis of myelodysplasia, presenting with pancytopenia was given. She had also received cyclosporine A for 2 and a half years until 3 years prior to diagnosis of myelodysplasia. Antirheumatic treatment was stopped and 3 days of high dose corticosteroids were given for flare of arthritis. Thereafter, the blood cell counts had returned within normal range. At the last follow-up at the patient's 18th birthday, she had recovered from pancytopenia. Etanercept treatment was not discontinued and is still ongoing as of last follow-up. Also MTX was restarted 3 weeks after diagnosis of myelodysplasia. After review of the case report by the oncologist panel the case was rated as unconfirmed malignancy.

Case 7
The diagnosis of JIA (enthesitis-related arthritis [ERA] category) was given at the age of 10 years to a female patient who thereafter was treated with MTX for nearly 8 months. At the age of 12, acute lymphatic leukaemia (ALL) was diagnosed. The leukaemia progressed aggressively despite treatment according to the COALL protocol and the patient died of this malignancy 6 months later. After a review of the case report by the oncologist panel the case was rated as confirmed malignancy.

Case 8
This female patient, 4 years, 9 months old, was diagnosed with persistent oligoarthritis JIA, for which she received intraarticular steroids. Due to aggressive uveitis treatment first with MTX and 3 months later, infliximab was initiated. After 7 months, hypertrophy of pharyngeal tonsils was noted, followed by tonsillectomy. Histologic analysis showed polymorphic lymphoproliferative alterations, but molecular pathologic analyses could not detect clonality. Test for EBV showed negative results. After discontinuation of MTX and infliximab the patient never showed further signs of lymphoproliferative disease, but uveitis did flare, leading to bilateral lens replacement. After a review of the case report by the oncologist panel the case was rated as unconfirmed malignancy.

Case 9
At the age of 6, this female patient was given the diagnosis rheumatoid factor negative polyarthritic JIA with synovitis and effusions of the shoulder joint in magnetic resonance imaging. She was treated with MTX, low dose steroids and intraarticular steroids. The patient was diagnosed with acute lymphatic leukaemia 3 months later. Reviewing the case, before the start of treatment, anaemia and mild neutropenia were present at diagnosis but temporarily absolute neutrophil counts regained normal values (leucocytes 5,200/ ml, neutrophils 1,600/µl). With the initial anomalies in blood count it is possible that ALL was present before starting MTX therapy. After chemotherapy, the patient is now in complete remission for 6 years and has not shown any signs of active arthritis since. After a review of the case report by the oncologist panel the case was rated as confirmed malignancy. Although exsudative polyarthritis was present at presentation, diagnosis of JIA remains doubtful in this patient. ALL might have been present before starting MTX and masked by treatment with low dose systemic steroids. However, this case constitutes a malignancy observed and reported under anti-rheumatic treatment with MTX.

Case 10
Since the age of 5 years, 9 months, this male patient suffered from rheumatoid factor negative polyarthritic JIA and was initially treated with diclofenac, corticosteroid pulse therapy and MTX treatment for 2 years, followed by a combination therapy with etanercept and MTX for 2 years and a monotherapy with etanercept for a further 3 years. The total exposure time with MTX was calculated as 4 years, those with etanercept as 5 years. The patient was diagnosed with anaplastic ependymoma (WHO grade 3) 14 months after discontinuation of etanercept treatment and about 4 years after discontinuation of MTX. The tumour was completely removed surgically. The patient received additional subsequent radiochemotherapy and recovered with neuroendocrine sequelae. After review of the case report by the oncologist panel the case was rated as confirmed malignancy.

Case 11
In this case a male patient suffered from JIA (enthesitis-related arthritis [ERA] category) from the age of 11 years on-

Table I. Patients' details from the German BIKER registry with reported malignancy.

Year	Age at diagnosis# (years)	m/f	JIA category	Type of malignancy	Drugs ever exposed	Medical treatment at diagnosis#	Outcome	JADAS10 at baseline
				Confirmed malignancies				
2003*	18	m	ERA	Thyroid carcinoma	MTX, ETA	MTX, ETA	rec	8.5
2005*	16	m	ERA	Yolk sac carcinoma	MTX, ETA	MTX, ETA	rec	24.5
2007*	14	m	RF-Poly	NHL	MTX, ETA, ADA, AZA, CSA	MTX, ETA	rec	24.7
2007	12	f	ERA	ALL	MTX	MTX	dead	9.8
2009*	5	m	sJIA	HL	MTX, ETA	None	rec	9.5
2009	7	f	RF-Poly	ALL	MTX	None	rec	31
2012	14	m	RF-Poly	Anaplastic ependymoma	MTX, ETA	None	rec seq	16.6
2013	18	m	ERA	HL	ETA, Sulfa	ETA	rec	15.3
2015	16	f	RF-Poly	LPD	MTX, ETA	MTX, ETA	rec	n.a.
				Suspected, but not confirmed malignancies				
2007	17	f	sJIA	Myelodysplasia	MTX, ETA, AZA, CSA	MTX, ETA	rec	14.8
2007	6	f	P Oligo	LPD	MTX	MTX	rec	11.9
2009*	20	f	P Oligo	Cervical dysplasia	MTX, ETA, ADA, INF, LEF, ABA	MTX, INF	rec	n.a.

ERA: enthesitis-related arthritis; RF- Poly: rheumatoid factor negative polyarthritis; sJIA: systemic arthritis JIA; p Oligo: persistent oligoarthritis; NHL: Non-Hodgkin's lymphoma, HL: Hodgkin's lymphoma; ALL: acute lymphatic leukaemia; LPD: lympho-proliferative disorder; MTX: methotrexate; ETA: etanercept; ADA: adalimumab; INF: infliximab; AZA: azathioprine; CSA: Cyclosporine A; LEF: leflunomide; ABA: abatacept; Rec: recovered; seq: sequelae, *cases previously published (7), #at diagnosis of malignancy.

wards. Initially he was treated with sulfasalazine for 2 years; etanercept was added after 5 months for the next 3 years and discontinued in remission. After about 3 years, etanercept was restarted and given for another 21 months before being discontinued at the age of 16 and a half years, while at this time an enlarged cervical lymph node was noted and followed up for a further 8 months when the decision for a biopsy was made. The biopsy revealed lymphocyte-predominate Hodgkin's lymphoma, stage IIA. Treatment according to ABVD protocol led to remission, lasting for 2 years now. After a review of the case report by the oncologist panel, the case was rated as confirmed malignancy.

Case 12

In this case a female patient was nearly 4 years old when she was diagnosed with rheumatoid factor negative polyarthritic JIA. Additionally, she suffers from multiple other diseases (complex congenital heart disease, multicystic kidney, thrombophilia, retardation, bone anomalies), suggestive of an underlying genetic disorder. The patient was treated with MTX for 10 months 10 years ago and then again for 2 and a half years by a combination of MTX and etanercept until she presented with multiple subcutaneous nodules accompanied by elevation of lactate dehydrogenase (maximum level 323 U/l [<230 U/l]. Histological examination revealed infiltration of subcutaneous tissue with EBV-positive clonal B-cell lymphoproliferation, areas consistent with lymphomatoid granulomatosis grade 3, and areas with the criteria of EBV-positive diffuse large cell B cell lymphoma. The patient was classified as clinical stage IIIA due to a mediastinal node detected by thoracic computer tomography.

However, after discontinuation of MTX and etanercept, nodules, including the mediastinal node, decreased in size or disappeared and LDH normalised. Reviewing this clinical course lead to the assessment of the neoplasm as lymphoproliferative disorder (LPD) associated with iatrogenic immunosuppression rather than manifest lymphoma. After review of the case report by the oncologist panel the case was rated as confirmed malignancy.

In summary, 12 patients were reported to the BIKER registry from 2000 to 2015, who developed a malignancy during childhood and adolescence. Observation times collected from the baseline report until the last report of the patients revealed 13,198 years. 2 patients had never been exposed to biologics. Ten patients received biologics, 9 of those were exposed to etanercept, of which 2 successively received adalimumab and infliximab and one was additionally treated with abatacept. One patient received infliximab for treatment of uveitis.

Of the 9 patients treated as confirmed malignancies 7 were ever treated with biologics, and 5 received etanercept at the time of diagnosis of malignancy. Also 8 patients had ever been treated with MTX, 1 with sulfasalazine. Six patients received MTX at the time of diagnosis of malignancy.

The total number of 12 suspected malignancies observed in the registry led to a calculated incidence of 0.91/1000 years. A case of ALL, which might have been present before start of MTX therapy was rated a confirmed malignancy, if this particular malignancy occurred after start of treatment with MTX remains debateable. A case of mild myelodysplasia, in which the patient recovered spontaneously, a case of lymphoproliferation without clonality and a case of cervical dysplasia were treated as suspected, but not confirmed malignancy. The calculated incidence did not differ markedly, if these unconfirmed malignancies were excluded from the analysis (9/13198 observation years, incidence 0.68/1000 years). Both rates, including or excluding unconfirmed malignancies, found in the

Table II. Risk ratios (RR) and 95% Confidence intervals (95%CI) for confirmed malignancies compared with rates taken from the German Childhood Cancer Registry report 2015 (13) (1657/2056 cancers in children <15/<18 years of age in 10.5/12.9 x 10^6 children).

Age group	Drug cohort	Type of malignancy	Number	Incidence/ 1000 PY (95% CI)	RR (95%CI)*	*p* (Wald test)
<15 years	Methotrexate (3224 PY)	All	2	0.62 (0.16-2.48)	3.93 (0.98-15.73)	0.053
		Lymphoma & Leukaemia	2	0.62 (0.16-2.48)	9.16 (2.29-36.70)	0.002
	Etanercept # (5333 PY)	All	3	0.56 (0.18-1.74)	3.56 (1.15-11.1)	0.028
		Lymphoma & Leukaemia	2	0.38 (0.09-1.5)	5.54 (1.38-22.2)	0.016
<18 years	Methotrexate (4182 PY)	All	2	0.48 (0.12-1.91)	3.0 (0.75-12.0)	0.12
		Lymphoma & Leukaemia	2	0.48 (0.12-1.91)	6.7 (1.67-26.82)	0.007
	Etanercept # (6998 PY)	All	7	1.0 (0.48-2.1)	6.3 (3.0-13.2)	<0.0001
		Lymphoma & Leukaemia	4	0.57 (0.21-1.52)	8.0 (2.99-21.38)	<0.0001

py: patient years. #no difference was found between methotrexate and etanercept cohorts.

German Biker Registry exceed the rate expected according to data of the German childhood cancer registry significantly (0.16/1000 years, $p<0.001$). (13) Incidence of definite malignancies was compared to the cancer registry incidence; the calculated risk-ratio in the MTX cohort (2 acute lymphatic leukaemia) was not significantly increased for all malignancies (RR 3.00; 95% CI 0.75–12.00, $p=0.12$), but for haemato-lymphatic malignancies (RR 6.7; 95% CI 1.67–26.82, p 0.007). The risk ratio in the biologics cohort also was significantly increased (RR for all malignancies 6.3; 95% CI 3.0–13.2, $p<0.0001$; RR for leukaemia/lymphoma 8.0 (95%CI 2.99–21.38, $p<0.0001$). No difference was found between the incidence rate of malignancies within the biologics cohort compared to the non-biologics cohort ($p=0.36$).

Interestingly, 4 of the 6 confirmed haemato-lymphatic malignancies occurred in patients before the age of 15 years. Due to a high number of patients in the TNF-inhibitor cohort and a higher total number of observation years, the calculated incidence was numerically higher in the MTX cohort (0.62/1000 PY; 95%CI 0.16–2.48) than in the TNF-inhibitor cohort (0.38/1000 PY; 95% CI 0.09–1.5) for patients under the age of 15 years. All 3 confirmed solid tumours occurred in the TNF-inhibitor cohort, 2 of them after the age of 15.

Furthermore, we tried to assess the activity/severity of JIA in our patients affected by a malignancy to analyse if this patient cohort represents a more susceptibly cohort because of higher disease activity. The JADAS10 score in the 12 patients affected by a malignancy (Median 16.7, Mean ± SD 15.0±7.6) and the JADAS10 of those 7 patients affected by lymphoma/ALL (Median 17, Mean ± SD 13.6±8.9) were in range with that of the total BIKER-registry cohort (Median 15.2, Mean ± SD 14.6±7.6).

Discussion

Over the last 15 years, 3695 patients were included in the German Biker Registry. Follow-up until adulthood covered 13,198 years of observation. The total number of patients with suspected malignancy was 12 until the age of 18 with equal numbers of male and female patients. Non-haematological malignancies were single cases from very different entities involving the brain, the thyroidal gland, the uterus and the testis. While the number of patients is too low to support reliable statistical analysis, it seems remarkable, that calculated incidence rates are significantly higher than incidence rates observed by the German Childhood Cancer Registry (13). Of course low patient numbers do not allow adjustment for age and gender. Hence, the comparison with the overall incidence of malignancies in Germany should be interpreted carefully.

The assessment of incidence rates is difficult. Several studies suggest an increased risk for adult RA patients to develop malignancy or certain types of cancer. Data from adults with RA indicate an increased risk of lymphoma while the incidence of some other malignancies may be lower than in the general population (14, 15). The same may be true in the paediatric patients but numbers of patients with rheumatic diagnoses are low, as is the general cancer risk.

Nordstrom *et al*. found a nearly 3-fold increased risk of cancer in biologic-naïve patients with JIA (16), and Beukelman described an increased rate of malignancy for children with JIA, which did not further increase on therapy with either MTX or TNF-α inhibitors (5). Thus, a higher frequency of malignancies is to be expected in JIA patients. In a large US database analysis Wolfe and Michaud found an association between a higher rate for melanoma and non-melanotic skin cancer (NMSC) and treatment with biologics in adult RA patients (17). These entities are rather rare in childhood; if at all NMSC is known as a typical but rare secondary malignancy in paediatric cancer patients. No case has been reported to the Biker Registry.

A large cohort study from the US implied a 1.5-fold increased risk for cervical dysplasia and cancer among adult RA patients compared to a control group (18). There are scarce data available, whether treatment with biologics or MTX enhances this risk. Cervical dysplasia of the uterus is associated with HPV infection in the majority of cases. Whether reactivation of HPV during treatment with TNF-α inhibitors or MTX occurs more frequently has not been studied. One case was reported to BIKER. Vaccination against the human papilloma virus should be recommended to all female JIA patients.

Simard *et al*. (6) evaluated the occurrence of cancer in JIA patients in a nationwide Swedish population-based cohort of 9020 JIA patients compared to a matched general population of 44, 858 individuals. While the malignancy rate was not higher in the whole JIA cohort, an analysis restricted to the JIA cases diagnosed after 1987 revealed a 2.3 (95% CI 1.2, 4.4) fold increased relative risk for all malignancies and a 4.2-fold risk for lymphoproliferative malignancies. These increased risks could not be explained by the introduction of biologic therapies because the association was similar in the analyses that ended in 1999. Simard *et al*. (6) concluded that there was an elevated risk of malignancy among biologic therapy naive patients with JIA. This association had to be taken into account for the interpretation of cancer risk in JIA treated with newer therapies (19). It should be noted that 1986 was the year in which the first report for the use of MTX in JIA was published (20, 21).

A collection of 48 cases of cancer over a 10-year period in children and young adults who had been treated with TNF inhibitors before the age of 18 years, published by the US Food and Drug Administration (FDA) raised concerns about the safety of these drugs worldwide (4). This 2008 FDA black box warning identified malignancies associated with the use of infliximab, etanercept and adalimumab in children with rheumatic diseases but also with colitis and Crohn's disease. The majority of cases occurred with infliximab and in chronic inflammatory bowel disease patients but not in JIA patients who in the majority received etanercept instead of anti-TNF antibodies.

In a recent review, Ruperto and Martini (19) pointed out that several investigations suggest that JIA itself is associated with an increased malignancy risk and that treatment with TNF blockers does not increase this risk. However, since both cancer and JIA in childhood are rare, larger patient groups need to be analysed for a longer period of time. Therefore, a number of national registries have been set up including those from the United Kingdom, The Netherlands, Canada, Poland, Hungary, and from very early on in Germany.

One case (Hodgkin's lymphoma) was reported in the Canadian registry (1834 patients) (22). No malignancies were reported in the Dutch registry [214 patients] (23) British [483 patients] (24), Polish registry [188] (25) or Hungarian registry [n=72] (26). Thus, the German BIKER is by far the largest of the national registries. It remains unknown, why the number of malignancies collected exceeds the number found in other registries since the combined patient number is comparable. Differences in the manner or the strength or the duration of surveillance have to be proposed with advantage towards the German registry.

In BIKER, especially the total number of 6 (3 male and 3 female patients) confirmed haematological malignancies seems relatively high. However, acute lymphatic leukaemia and lymphoma are the most frequent malignancies in this age group in general. A retrospective cohort study in Taiwanese children using the National Health Insurance Research Database, reported a 7–8-fold risk for developing leukaemia or lymphoma in MTX and biologic naïve JIA patients (27).

Of interest are the 2 patients with lymphoproliferative disorder (LPD), both receiving MTX and TNF-inhibitor (one etanercept, one infliximab) at the time of diagnosis of LPD. One case was not a confirmed malignancy due to missing clonality. Both showed spontaneous regression, one even remission of LPD after discontinuation of antirheumatic agents, without further oncologic treatment. In one patient EBV was detected in tumour tissue via in-situ hybridisation in the malignant cells. In adult patients with rheumatoid arthritis and long-term MTX treatment several cases have been described, where discontinuation of MTX led to spontaneous regression or remission of LPD (28-30). In a Japanese analysis of 76 cases of lymphoproliferative disorders in adult RA patients with or without MTX therapy were compared with patients with sporadic LPD. In this cohort 11 patients were identified, who showed spontaneous regression of their LPD after MTX discontinuation. Of those, 5 patients remained in remission, 1 patient died of intercurrent disease and 5 patients had a recurrence of LPD and received chemotherapy (31). Interestingly the rate of EBV positive LPD was significantly higher than in the control group, whether the patients had MTX or not. In a retrospective review of 37 cases of LPD in RA patients receiving MTX, 16 patients were initially observed after MTX withdrawal without additional antitumour therapy. Six achieved a spontaneous complete remission (CR), three had a partial response (PR), one had a minimal response, and six had no response to MTX withdrawal. In 8 of the 10 responding patients, EBV was detected (32). This implies a causal role of MTX treatment in the two LPD cases discussed here. Furthermore, the immunogenic role of EBV in the context of an LPD evolved under immunosuppressive therapy will need further focus and studies. Regular assessment of MTX toxicity is advisable (33).

Two patients were diagnosed with acute lymphatic leukaemia. One of the leukaemia patients possibly had unrecognised ALL at start of MTX treatment. Certain malignancies, particularly leukaemia may present with musculoskeletal symptoms similar to JIA initially (34).

Hodgkin's lymphoma was documented twice, and one case with non-Hodgkin's lymphoma was reported. Despite a single case with ALL, all patients recovered.

Also in patients with JIA several authors found a higher incidence of haematologic cancers and lymphoma. (6, 35) A summary of reported cases of malignancies from clinical trials and post marketing reports suggest a higher frequency of Hodgkin's lymphoma in JIA patients from 0–17 years of age treated with etanercept. However, the number of patients was relatively low and no analysis of background risk of lymphoma was included (36). Until now no further increase in risk for lymphoma due to treatment with TNF-α inhibitors in JIA patients could be detected (5).

An increased background risk in adult RA patients for developing lymphoma has been described repeatedly (37, 38).

TNF-α inhibitor treatment did not further influence this risk substantially (38, 39) RA patients with higher disease activity risk are described to be at higher risk for malignancies (39). We analysed disease activity in our small cohort in comparison to the total BIKER registry cohort, but did not find an increased disease activity using the baseline JADAS. JADAS score at a single time point may not reflect the overall disease activity over the course of a patient's disease. As in some patients, the malignancy diagnosis was given after discontinuation of anti-rheumatic drugs in remission, continuous high disease activity is unlikely to have markedly contributed to the frequent occurrence of malignancies in our cohort.

Conclusion

In this large cohort of JIA patients the occurrence of malignancies was found to be increased compared to the general population. Lymphoid neoplasms were the most frequently observed malignancies. Non-lymphoid solid tumours were observed in single cases only. Whether JIA patients had an increased risk for malignancies, either through their rheumatic disease or through treatment, remains unclear. Treatment with etanercept seems not to further increase the malignancy risk since no difference was found in the incidence rate of malignancies compared to a non-biologics cohort. However, the numbers were too small to draw definite conclusions. Long-term observation of JIA patients treated with TNF-α inhibitors into adulthood remains an important task.

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