Biologic agents represent a major advance in the treatment of JIA. In 2008 a US Food and Drug Administration (FDA) warning raised the hypothesis that anti-TNF therapies may be associated with an increased incidence of malignancies in children. More recent data seem to suggest that JIA itself, as in the case of RA, is associated with an increased risk of malignancy and that this risk is not further increased with anti-TNF treatment. However, only long-term prospective data on a very large number of patients will provide a definite answer. This article summarizes the current evidence in order to help health professionals properly advise patients and their families about the possible risk of malignancies in JIA treated with biologic agents.

Key words: juvenile idiopathic arthritis, anti-TNF therapy, etanercept, abatacept, infliximab, malignancy, lymphoma, adverse events.
For the registries, usually limited in national settings, comparison is normally done with groups of patients treated with MTX alone or in combination with biologic agents, with data from the literature including the incidence of specific adverse events (AEs) or serious AEs (SAEs) such as cancer in normal child populations [22–29].

More recently, safety data were derived from nationwide cohort studies such as in Sweden, [30] or from administrative claims records such as Medicaid or PharMetrics [31, 32].

An excellent review of the overall safety of biologic therapies in JIA patients with particular emphasis on SAEs was published in 2010 by Hashkes et al. [33].

**Anti-TNF, cancer and JIA**

The 2008 FDA black box warning [34] results were published in 2010 by Diak et al. [35], who searched the FDA’s AE Reporting System (AERS) to identify malignancies associated with the use of infliximab, etanercept and adalimumab (information related to adalimumab was limited since it was the latest anti-TNF agent to be marketed) in children that had started therapy between 0 and 18 years of age. The reporting rates for infliximab and etanercept were compared with the background rate of malignancy in the general paediatric population. Forty-eight cases of malignancy were identified: 31 following infliximab use, 15 following etanercept use and 2 following adalimumab use. Half of the malignancies reported were lymphomas (both Hodgkin’s and non-Hodgkin’s lymphoma), while the remaining reported cases involved a variety of different malignancies, including leukaemia, melanoma and solid organ cancers. In the majority of the reported cases (88%) anti-TNF blockers were used concomitantly with other immunosuppressants.

Compared with a background cancer rate of 16.8 per 100 000 in the general paediatric population, the reporting rates for all malignancies were 66 and 22 per 100 000 patients using infliximab and etanercept, respectively. When the analysis was restricted to lymphomas, the equivalent reporting rates were 44 and 11 for patients receiving infliximab and etanercept, respectively, compared with 2.4 in the general paediatric population. Of the patients who had malignancies, 25 had IBD (mostly Crohn’s disease), 19 had JIA and 4 had other diseases. Most patients treated with infliximab had IBD and concomitantly received immunosuppressive therapy (6-mercaptopurine, AZA and MTX alone or in combination). A large number of patients treated with etanercept had JIA and were concomitantly treated with MTX.

Diak et al. [35] recognized that several biases confounded and limited the interpretation of their findings, including

(i) the known under-reporting rate of spontaneous communication to the AERS database
(ii) the fact that different diseases (with different natural associations with cancer occurrence) were combined in the analysis and (iii) previous or concomitant treatment with other immunosuppressive drugs suspected to be associated with an increased risk of cancer.

Moreover, possible diagnostic errors in the case of leukaemia occurring a few months after the diagnosis of JIA could not be excluded. Indeed, leukaemia, the most common childhood malignancy, may cause arthritic complaints and may be initially misdiagnosed as JIA.

The conclusions by Diak et al. [35] were that although TNF blockers might increase the risk of malignancy, a clear causal relationship could not be established. In other words, as pointed out by Lehman [36] in an accompanying editorial, although the hypothesis that TNF blockers may be associated with an increased risk of malignancy could not be excluded, there was still no convincing evidence that the use of anti-TNF drugs in children with JIA is associated with an increased risk of malignancy beyond that due to the disease alone or the disease when treated with MTX.

Later, Simard et al. [30] evaluated the risk of cancer occurrence in a nationwide Swedish population-based cohort of 9020 JIA patients matched with five general-population comparators (n = 44 858). While the incident malignancies were not higher in the whole JIA cohort (since 1969), when the analysis was restricted to the JIA cases diagnosed in 1987 or later, the relative risk increased to 2.3 (95% CI 1.2, 4.4) for all malignancies and to 4.2 for lymphoproliferative malignancies and this increased risk could not be explained by the introduction of biologic therapies because the association was similar in the analyses that ended in 1999. No firm conclusions were possible because of the low numbers of malignancies observed and the short follow-up time. Simard et al. [30] concluded that there was an elevated risk of malignancy among biologic therapy-naive patients with JIA identified during the last 20 years and that this association had to be taken into account for the interpretation of cancer risk in JIA treated with newer therapies. It should be noted that 1986 was the year in which the first report for the use of MTX in JIA was published [37, 38].

All reports of malignancy in paediatric patients (including subjects who received etanercept before age 18 years and developed a malignancy before age 22 years) were collected by the sponsor companies [Amgen and Wyeth (Pfizer)] from the etanercept clinical trials database and global safety database using the Medical Dictionary for Regulatory Activities (MedDRA, version 12.0) standardized MedDRA query ‘Malignancies’ from 1998 to August 2009 [39]. All cases were included regardless of exposure to other TNF blockers or other biologics and whether the other exposure was before or after etanercept. The data did not suggest any increased overall risk of malignancy with the use of etanercept, although the reported rate of lymphoma was higher in paediatric patients treated with etanercept than in normal children. However, as also pointed out in the editorial by Cron et al. [40], the risk was difficult to assess mainly because of the absence of knowledge of the underlying frequency of leukaemia and lymphoma in
JIA and the confounding use of concomitant immunosuppressive medications.

Information coming from national registries did not further clarify the issue. In the German JIA registry, five malignancies (one each non-Hodgkin’s lymphoma, Hodgkin’s lymphoma, thyroid carcinoma, yolk sac carcinoma and cervical dysplasia) were reported out of 1260 patients on biologic therapy, with all patients having received other immunosuppressive agents prior to the biologic [28]. One case (a Hodgkin’s lymphoma) was reported in the Canadian registry (1834 patients) [29]. No malignancies were reported in the Dutch registry (146 patients) [23].

More recently Beukelman et al. [31] identified, using Medicaid claims, 7812 children with JIA treated with MTX and/or an anti-TNF (primarily etanercept) and compared their malignancy standardized incidence ratios (SIRs) with those of 321821 children with attention deficit hyperactivity disorder or other paediatric conditions. For all children the SIR was 4.4 (95% CI 1.8, 9.0) for probable and highly probable malignancies when compared with the control group, but this risk did not seem to be further increased by the concomitant use of MTX or TNF inhibitor [31, 41, 42]. They concluded that children with JIA appear to have an increased rate of incident malignancy compared with children without JIA and that the treatment for JIA, including TNF inhibitors, did not appear to be significantly associated with the development of malignancy; however, larger and longer-term studies are needed to confirm these conclusions. The authors, as well as the accompanying editorial [41], recognized that the study had some limitations, including the small number of patients analysed, especially in the group treated with TNF inhibitors, the wide CIs and the short follow-up (24 months for the entire cohort and 1.5 years of TNF inhibitor exposure).

Similar conclusions were reached by Nordstrom et al. [32], who assembled, from the PharMetrics Patient-Centric Database, a cohort of biologics-naive patients diagnosed with JIA between 1998 and 2007 and a matched cohort of comparators without JIA. The JIA and non-JIA cohorts included 3605 and 37689 patients, respectively, with a mean age of 11 years. The incidence rates of cancer were 67.0 cases per 100 000 person-years for JIA and 23.2 cases per 100 000 person-years for non-JIA. The risk of cancer associated with biologics-naive JIA was elevated (hazard ratio 2.8). The JIA cohort had a significantly elevated standardized incidence ratio of 4.0, while that in the non-JIA cohort (1.4) was not significantly greater than the mean values observed in the USA.

In summary, more recent investigations seem to suggest that JIA itself is associated with malignancy and that treatment with TNF blockers does not increase this risk. However, since both cancer and JIA in childhood are rare, a very large group of patients needs to be analysed for a long period of time before any sound conclusion can be reached.

Safety information regarding drugs different from anti-TNF are very limited. In the phase III abatacept withdrawal trial, which enrolled 190 patients in the open-label phase, a case of acute lymphoblastic leukaemia was reported. No cases of malignancy were reported in the double-blind phase [9] or in a long-term open-label follow-up study of the participants in the trial (n = 153) [43].

No cases of malignancy have been reported in the clinical trials with anti-IL-1 or anti-IL-6 inhibitors [10–14, 44].

TNF, cancer and RA

Concern about the potential increase in malignancies in patients treated with anti-TNF agents derives from the role played by TNF in the protection against tumours. The term TNF was coined to describe an activity, reportedly produced by endotoxin-stimulated macrophages, leading to necrosis of both mouse and human tumours [45]. Several years later the TNF protein was identified and the gene cloned. It was then confirmed that high doses of human recombinant TNF induce necrosis of both syngeneic and xenografted tumours; further studies have shown that anti-tumour effects of TNF are due to destruction of the tumour vasculature and that TNF is an important effector molecule in the killing of immunogenic tumour cells by CDB+ T cell and natural killer cells [46].

On the other hand, it is now well known that inflammation itself can favour the occurrence of tumours. Current estimates suggest that ~25% of cancers are associated with chronic inflammation [47]. Examples include microbial infections (Helicobacter pylori infection is associated with gastric cancer and gastric mucosal lymphoma), viral infections (HBV and HCV are associated with hepatocellular carcinoma) and chronic inflammatory diseases (IBD is associated with colon cancer). Moreover, an oncogenic change may itself induce an inflammatory microenvironment that promotes the development of tumours. Inflammatory cells, chemokines and cytokines are present in the microenvironment of tumours in experimental animal models and humans from the earliest stages of development and have been shown to have many tumour-promoting effects [47]. In this context, TNF-α has been shown to favour tumour development and growth [46, 47]. For example [46, 47], (i) unlike their normal counterparts, many malignant cells constitutively produce small amounts of TNF-α and there is evidence from animal models that this malignant cell–derived TNF-α enhances the growth and spread of several tumours; (ii) treatment of tumour cells or mice with TNF increases the metastatic activity of transplanted tumour cells and (iii) TNF−/− mice treated with a skin carcinogen develop fewer, not more, tumours. Most of these pro-tumour actions of TNF-α appear to be mediated via TNFR1.

An increased risk of lymphoma has been observed among adults with RA, [48] particularly among those with a high burden of inflammatory activity [49].

Studies in adults with RA have demonstrated no increased risk of malignancy in association with TNF blocker treatment compared with the risk in RA patients.
who did not receive TNF inhibitors, with the possible exception of skin cancer, including melanoma [50–54].

Pharmacovigilance initiative in the European Union and beyond

In 2012 a new pharmacovigilance regulation was implemented [55] in the European Union (EU). The practical implementation of the legislation has been demanded to the European Medicines Agency (EMA) starting in July 2012. The objectives are to strengthen the current system for monitoring the safety of drugs on the European market in order to make it more robust and transparent; to facilitate better detection, assessment, understanding and prevention of AEs; to minimize duplication of effort and to free up resources by rationalizing and simplifying adverse drug reaction (ADR) reports and periodic safety update reports required of marketing authorization holders. More information can be found at the EMA website [55].

A new scientific committee has been established at the EMA called the Pharmacovigilance Risk Assessment Committee (PRAC). The PRAC’s role is to advise the Committee on Medicinal Products for Human Use (CHMP) and the Coordination Group for Mutual Recognition and Decentralised Procedures (CMDh) on safety issues in relation to medicines in the EU. The PRAC members include patient organizations and healthcare professionals, as well as experts from the EU member states appointed on the basis of their relevant expertise in pharmacovigilance and risk assessment.

While involvement of individual health professions is foreseen, the EMA will not directly accept ADR reports from healthcare professionals, patients or consumers.

The EMA launched the website ‘European database of suspected ADR reports’ (http://www.adreports.eu/) providing public access, in 22 languages, to all reports of suspected side effects that have been submitted to EudraVigilance. EudraVigilance is a database designed for the collection of reports of suspected ADRs by competent national authorities and by the pharmaceutical companies that hold the marketing authorizations (licences) for the drugs. Research organizations are supposed to be able to access EudraVigilance in 2015–16.

It is unclear at this stage if the EMA will take advantage of the numerous academic initiatives in the field of pharmacovigilance, such as the existing national and international registries.

Another initiative worth notice is the Yellow Card in the UK. The system is run by the Medicine and Healthcare Products Regulatory Agency (MHRA) and the Commission on Human Medicines, collecting data from both health professionals and the general public on suspected side effects (https://yellowcard.mhra.gov.uk).

Pharmacovigilance initiatives are also run by the FDA, leading to revisions of drug labels and black box warnings whenever safety concerns arise.

Future perspectives

Despite an advance in our understanding of the possible link between disease, treatment and medium long-term safety, including an increased risk of malignancy, several problems still remain. Currently several national registries exist that have provided important insights into the efficacy and safety of these compounds, but taken individually, the related sample of patients is still relatively small (61–1260 patients), hampering the possibility of forming a statistically significant conclusion about safety events [22–29, 56, 57]. Also, the use of claims data is hampered by several limitations [30, 31, 41, 42]. As pointed out in the editorial by Onel et al. [41], the number of patients analysed is usually relatively small, ICD-9 codes may have no relation to the current JIA ILAR criteria and its categories, [58, 59] children with the mildest form of disease may have been excluded, disease duration or medication exposure is not calculated and the mean follow-up is usually short (e.g. 24 months).

To answer these limitations a proper active pharmacovigilance system with a very large sample size and an adequate follow-up of incident and prevalent cases is needed to better understand if safety concerns are due to medication, to the underlying inflammation of the disease or to both factors [38].

Currently, thanks to start-up support from the EU, the Paediatric Rheumatology European Society (PRES; principal investigator N. Wulffraat), with technical help from the Paediatric Rheumatology International Trials Organization (PRINTO) [60], has set up a project with the goal to collect worldwide prevalent (all patients under treatment or previously treated with MTX ± biologics) and incident cases (all cases newly treated with MTX ± biologics) of JIA children. Three main groups of patients will be identified, each one serving as a control group for the remaining group: (i) JIA treated with MTX alone, (ii) JIA treated with a combination of MTX and other drugs including but not limited to biologic agents and (iii) JIA treated only with NSAIDs and/or steroid injections only. Funding from the EU is supposed to cover the start-up activities for the initial 3 years and for the collection of safety data related to biologic drugs for a project that should be self-maintained thereafter through the involvement of other sources of funding (e.g. pharmaceutical companies).

Conclusions

In the last 10 years the advent of biologic therapies has revolutionized the treatment of JIA. The FDA warnings of a potential association between anti-TNF therapy and malignancy have not been confirmed by more recent data, which suggest that JIA itself, as in the case of RA, is associated with an increased risk of malignancy and that this risk is not increased by anti-TNF treatment. However, only long-term data on a large number of patients will provide a definite answer. Health professionals should be aware of the potential risk of malignancy associated
with JIA itself or with TNF inhibitor therapy in order to properly advise patients and their families.

**Rheumatology key messages**

- The FDA warned that anti-TNF therapies may increase the risk of malignancies in JIA.
- Recent data suggest that JIA itself is associated with an increased risk of malignancies not augmented by treatment.

**Disclosure statement**: A.M. declares receipt of honoraria from the following pharmaceutical companies for speakers’ bureaus and consultancy activity in the past 2 years: Abbott, Bristol Myers Squibb, Astellas, Boehringer, Italfarmaco, MedImmune, Novartis, NovoNordisk, Pfizer Roche and Sanofi Aventis. N.R. declares receipt of honoraria from the following pharmaceutical companies for speakers’ bureaus and consultancy activity in the past 2 years: Abbott, Abbvie, Alter, Boehringer, Bristol Myers Squibb, CD Pharma, Janssen Biologics B.V., Medac, MedImmune, Novartis, NovoNordisk, Astellas, Italfarmaco, Pfizer, Roche, Sanofi Aventis and Vertex Pharmaceuticals. A.M. and N.R. are full-time employees of the public GASLINI Hospital, which has received contributions from the pharmaceutical companies listed below in the past 2 years to support the research activities of the network of the Paediatric Rheumatology International Trials Organization (PRINTO): Bristol Myers Squibb, Centocor Research & Development, Glaxo Smith Kline, Italfarmaco, Novartis, Pfizer Inc., Roche, Sanofi Aventis, Schwarz Biosciences GmbH, Sobi and Wyeth Pharmaceuticals Inc.

**References**


