SOCIEDADE BRASILEIRA DE REUMATOLOGIA

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Review article

Biological therapy and development of neoplastic disease in patients with juvenile rheumatic disease: a systematic review

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ARTICLE INFO

Article history:
Received 6 February 2016
Accepted 8 September 2016
Available online 5 December 2016

Keywords:
Rheumatic disease
Children
Teenager
Biological factors
Neoplasms

ABSTRACT

Juvenile rheumatic diseases affect the musculoskeletal system and begin before the age of 18. These conditions have varied, identifiable or unknown etiologies, but those of an autoimmune inflammatory nature have been associated with an increased risk of development of cancer, regardless of treatment. This study aims to assess, through a systematic review of the literature according to Prisma (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) quality criteria, the risk of cancer in patients with juvenile rheumatic disease, and its association with biological agents. The criteria described by the Strengthening the Reporting of Observational Studies in Epidemiology initiative were used in order to assess the methodological quality of those individual items selected in this study. We analyzed nine publications, from a total of 251 papers initially selected. There was an increase in cancer risk in the population with juvenile rheumatic disease *versus* the general population. Most specified cancers were of a lymphoproliferative nature. Seven studies did not specify the treatment or not defined an association between treatment and cancer risk. Only one study has suggested this association; in it, their authors observed high risk in patients diagnosed in the last 20 years, a period of the advent of new therapies. One study found an increased risk in a population not treated with biological agents, suggesting a disease in its natural course, and not an adverse effect of therapy. Studies have shown an increased risk of malignancy associated with juvenile rheumatic disease, and this may be related to disease activity and not specifically to the treatment with biological agents.

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http://dx.doi.org/10.1016/j.rbre.2016.11.008

Uso de imunobiológicos e desenvolvimento de doenças neoplásicas em pacientes com doenças reumáticas juvenis: revisão sistemática

Palavras-chave:
Doenças reumáticas
Criança
Adolescente
Fatores biológicos
Neoplasias

RESUMO

As doenças reumáticas juvenis afetam o sistema musculoesquelético e se iniciam antes dos 18 anos. Apresentam etiologia variada, identificável ou desconhecida, porém as de natureza inflamatória autoimune têm sido associadas ao maior risco de desenvolvimento de neoplasias, independentemente do tratamento. Este artigo propõe avaliar, por meio de revisão sistemática da literatura de acordo com os critérios de qualidade *Prisma* (*Preferred Reporting Items for Systematic Reviews and Meta- Analyses*), o risco de câncer em pacientes com doenças reumáticas juvenis e sua associação com imunobiológicos. Os critérios descritos pela iniciativa *Strengthening the Reporting of Observational Studies in Epidemiology* foram usados para avaliar a qualidade metodológica individual dos artigos selecionados no presente estudo. Foram analisadas nove publicações, de 251 incialmente selecionadas. Houve aumento no risco de câncer na população com doença reumática juvenil comparada com a população em geral. A maioria dos cânceres especificados foi de natureza linfoproliferativa. Sete estudos não especificaram a terapêutica ou não definiram associação entre ela e o risco de câncer. Apenas um estudo sugeriu essa associação e observou maior risco em pacientes diagnosticados nos últimos 20 anos, período de advento de novas terapias. Um estudo constatou maior risco em uma população não tratada com imunobiológicos, sugeriu tratar-se da evolução natural da doença, e não do efeito adverso da terapêutica. Os estudos demonstram aumento no risco de malignidade associada a doenças reumáticas juvenis que pode estar relacionada à atividade da doença, e não especificamente ao tratamento com imunobiológicos.

Introduction

The term juvenile rheumatic disease encompasses a variety of conditions affecting primarily or secondarily the musculoskeletal system and that have their onset in patients below the age of 18 years. These conditions show varied, identifiable or unknown etiologies, among which stand out those resulting from a dysregulation of the immune system and that are associated with chronic inflammation. Thus, the majority of patients with rheumatic diseases are treated with immunosuppressive therapeutic agents.[1]

From the time that biological therapies such as etanercept, adalimumab and infliximab were introduced in the pediatric population (over 10 years), in order to inhibit tumor necrosis factor alpha (TNF-α), a cytokine with a wide range of proinflammatory actions, these remarkable drugs have proven to be extremely effective for the treatment of a wide variety of rheumatic and inflammatory conditions.[2,3] But in 2008 the Food and Drug Administration (FDA), the US government agency responsible for the control of drugs in that country, reported an increase in the malignancy rate among pediatric users of these agents, which occurred after a mean of 30 months of treatment.[1,3] Forty-eight cases of malignancy (31 cases involving infliximab, two cases involving adalimumab, and 15 cases involving etanercept) were identified. This resulted in an investigation that required, since November 2009, more stern warnings, for instance, by applying a "black label" in the box of all TNF-α inhibitor agents (as a way to warn that these drugs can cause serious or even fatal adverse effects), which raised concern about the relationship between malignancy and juvenile rheumatic disease,[1,3,4] which had been initially based on the increased risk observed in adults with rheumatic disease.[5–8]

The FDA report was criticized for methodological reasons, and was followed by several studies that have investigated the association between malignancy, JIA, and other juvenile rheumatic diseases.

The authors aimed to determine, through a systematic review, the risk of cancer in patients with juvenile rheumatic disease compared to the general population and if biological agents are associated with malignancy in children and adolescents with rheumatic disease.

Methods

A systematic literature review was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) quality criteria. PRISMA consists of a list of 27 items that are considered essential in order to carry out a systematic review or meta-analysis which can gather scientific evidence in a clear and reliable manner.[9] The electronic databases MEDLINE/PubMed (http://www.ncbi.nlm.nih.gov/pubmed), LILACS (http://lilacs.bvsalud.org), Scielo (http://www.scielo.br) and Cochrane Library/Bireme (http://cochrane.bireme.br/portal/php/index.php) were consulted.

For searching the MEDLINE/PubMed database, a search of the literature guided by a question in PPR[10] (Problem/Predictor/Result) context was performed. The clinical question formulated was: "In patients with juvenile rheumatic

Table 1 – Descriptors used for issue in a PPR (Problem/Predictor/Result) context-driven literature research using MEDLINE/PubMed database.

Question: In patients with juvenile rheumatic diseases [P], the use of biological agents [P] is related to the development of neoplastic disease [R]?

(P) PROBLEM	(P) PREDICTOR	(R) RESULT
Juvenile rheumatic diseases	Biological agents	Neoplastic disease
Descriptors	Descriptors	Descriptors
"child", "childhood", "adolescence", "adolescent", "young", "juvenile", "pediatric", "rheumatic diseases", "idiopathic arthritis", "lupus", "idiopathic uveitis", "polyarteritis nodosa"	*"biologics agents", "biological therapy", "tumor necrosis factor alpha blockers", "TNF alpha blockers", "tumor necrosis factor alpha inhibitors", "TNF alpha inhibitors", "Anti-TNF-a", "infliximab", "etanercept", "adalimumab", "MTX"*	*"malignancy", "malignancies", "neoplastic disease", "neoplasia", "cancer", "lymphoma"*

disease (P – problem), the use of biological agents (P – Predictor) is related to the development of neoplastic diseases (R – Result)? Table 1 sets out the descriptors related to each of the PPR items. For the search in Scielo, LILACS and Cochrane Library/Bireme databases, the same descriptors were introduced in Boolean combination.

Observational original articles (cohort studies, retrospective studies, and case series) to assess the development of neoplastic disease in patients with juvenile rheumatic diseases were included. There were no restrictions with regard to language, place of conduction of the study, or year of publication.

Duplicate articles, literature reviews, case reports with fewer than five cases, editorials, and abstracts were excluded.

The selection of the studies found in the databases was performed independently by two reviewers using title and summary evaluation and full article reading when one was identified as a potentially eligible paper. Disagreements were dealt with after a conference.

The criteria described by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) initiative[11] were applied in order to assess individually the methodological quality of the articles. This initiative brings a checklist with 22 items of recommendations on what should be included in a more precise and complete description of observational studies. The studies are rated as satisfactory when more than 66% of the explained items are included; as intermediate when 33–65% of the items are included; or unsatisfactory, when less than 32% of the items are included. The classification of an original study as an intermediary or unsatisfactory one is related to a greater likelihood of this study in presenting different biases.

All items included in the review were approved by the respective ethics committees of data collection sites. For the present study, and in accordance with the resolution of the National Health Council – Ministry of Health, number 196 from 1996, an analysis by the Research Ethics Committee (REC) is not required.

Results

Fig. 1 displays the selection process of papers.

At the end of the search in PubMed database, from the 65 pre-selected papers, 61 articles were excluded after examination of their title and/or summary, for not having relation with the proposed theme, and four articles were included for a full reading. Of the 186 scientific articles returned to our research in other databases through Boolean combinations, 181 articles were excluded after reviewing the titles and abstracts because of duplication (compared with the papers obtained in the previous search), for not representing the original articles, or by presenting irrelevant topics for the purpose of this research; five potentially eligible papers were included.

After reading the nine selected papers, secondary references cited in the articles obtained were sought, but the relevant references to this work had already been selected through database searches. Thus, this search method was irrelevant to our research.

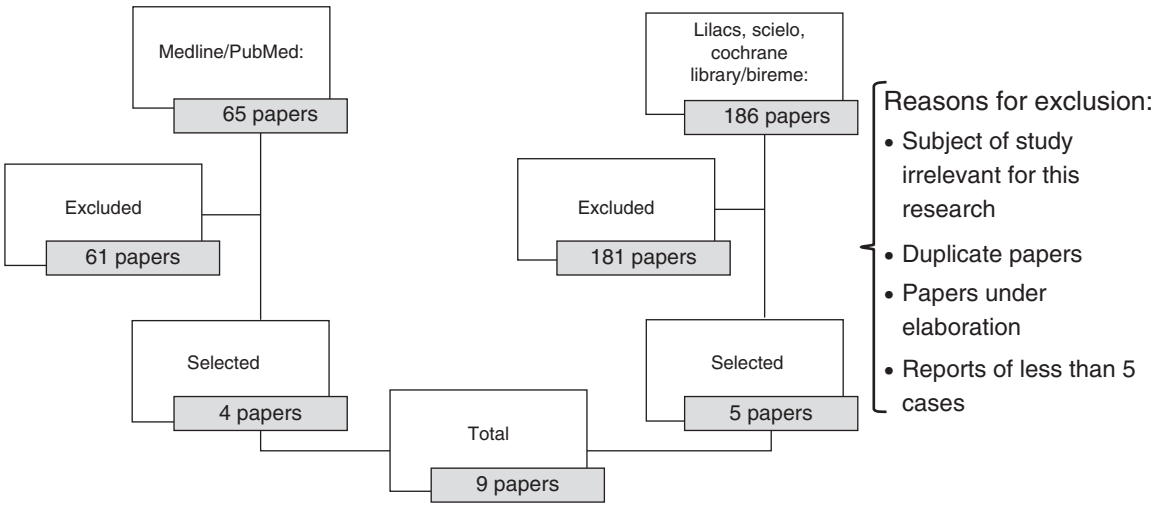

Fig. 1 – Selection process of papers for the systematic review.

Table 2 – General characteristics of the papers included in the systematic review.

Authorship/year	Origin	Study design/control	Number of participants (in the study)	Objective	Diseases	Age group	Biological agents	Rate ratio (CI = 95%)	Cancer type	Conclusions
Simard et al., 2010[12]	Stockholm/Sweden	Retrospective analytical observational cohort/control group study with comparators of the general population for each case	9027	To determine the risk of cancer in patients with JIA *versus* the general population.	JIA	Up to 16 years old	–	RR for cancer in all numbers: 1.1 (CI 0.9–1.5); RR for MLD in JIA after 1987: 4.2 (CI 1.7–10.7); RR for general cancer in JIA after 1987: 2.3 (CI 1.2–4.4).	Cancer in general, MLD	High risk in patients with a less than 20 years JIA Dx; it may be associated with current therapies.
Horneff, 2010[13]	Sankt Augustin/Germany [German language study]	Case report	5	Report of 5 cases documented in the German register of cancer in patients with JIA treated with TNF-α inhibitor agents.	JIA	Up to 16 years old	MTX; TNF blockers (etanercept; adalimumab; infliximab)	–	NHL; HL; thyroid cancer; yolk sac cancer; cervical dysplasia	Consider and report risks and benefits of using biological agents; long-term observation of patients.
Bernatsky et al., 2011[15]	Montreal, Quebec/Canada	Retrospective analytical observational cohort/control group study with comparators of the general population for each case	1834	To present preliminary data on the incidence of malignancy in JIA, compared with the rates in the general population.	JIA	Mean of 8.6 years (standard deviation, 5.1)	–	SIR for cancer in general: 0.12 (CI 0.0–0.70); SIR for hematologic cancer: 0.76 (CI 0.02–4.21)	HL	Soon after a Dx of JIA, the overall risk of cancer is not increased; it is possible an increased risk of MLD.
Horneff et al., 2011[14]	Sankt Augustin/Germany	Observational analytical retrospective cohort study	1260	To review German registers of cancer in children exposed to TNF blockers and verify if there is a higher risk, especially for lymphoma.	JIA	Up to 16 years old	MTX; TNF blockers (etanercept; adalimumab; infliximab)	–	NHL; HL; thyroid carcinoma; yolk sac carcinoma; cervical dysplasia	Patients with JIA exposed to biological agents or cytotoxic drugs should have a long-term follow-up, even in adulthood.

Table 2 – (*Continued*)

Authorship/year	Origin	Study design/control	Number of participants (in the study)	Objective	Diseases	Age group	Biological agents	Rate ratio (CI = 95%)	Cancer type	Conclusions
Nordstrom et al., 2012[17]	Lexington, Massachusetts/USA	Retrospective analytical observational cohort/control group study with 20 comparators of the general population for each case	3605	To estimate the relative risk of diagnosis of cancer among patients with JIA, compared with patients without JIA.	JIA	Mean of 11 years	–	HR: 2.8 (CI 0.9–8.3); SIR for JIA cohort: 4.0 (CI 2.6–6.0); SIR for non-JIA cohort: 1.4 (CI 0.6–2.6)	Lymphoma; soft tissue cancer	A significant risk of cancer (nearly 3 times greater) was found in patients with JIA not treated with biological agents.
Beukelman et al., 2012[18]	Alabama/USA	Observational analytical retrospective cohort/controlled study with two cohorts of children with Dx of chronic disease without JIA	7812	To determine the incidence of malignancy related to the treatment of children with JIA, compared with children without JIA.	JIA	Up to 16 years old	MTX; TNF blockers	SIR for cancer in general: 4.4 (CI 1.8–9.0); SIR for biological agents: 6.9 (CI 2.3–16); SIR for MTX: 3.9 (CI 0.4–14); SIR for TNF blockers: 0,0 (CI 0–9.7)	Brain cancer; leukemia; soft tissue cancer; GIT cancer	The cancer risk seems to be higher in children with JIA, but it is not associated with the use of TNF blockers.
Bernatsky et al., 2013[16]	Montreal, Quebec/Canada	Retrospective analytical observational cohort/control group study with comparators of the general population for each case	1020	To evaluate the incidence of cancer in JSLE.	JSLE	Up to 18 years old; mean of 12.6 years (standard deviation, 3.6)	–	SIR for invasive cancer: 4.7 (CI 2.6–7.8); SIR for hematologic cancer: 5.2 (CI 1.1–15.2)	NHL/leukemia	There is an increased risk of cancer in JSLE that can arise only after the patient has reached adulthood.
Hasija et al., 2014[19]	Toronto/Canada	Observational analytical retrospective cohort study	357	To determine the rate and also risk factors for the occurrence of cancer in patients with JIA treated with biological agents.	JIA/IU/PAN	Onset of rheumatic disease: 1.7–7.3; Dx of neoplasm; 15.3–17.9 years	MTX; infliximab; etanercept	–	NPC e renal carcinoma; MLD; PMT; sarcoma	Patients with refractory disease in use of drugs should have a routine surveillance for onset of cancer.

Table 2 – (Continued)

Authorship/year	Origin	Study design/control	Number of participants (in the study)	Objective	Diseases	Age group	Biological agents	Rate ratio (CI = 95%)	Cancer type	Conclusions
Kok et al., 2014[20]	Linkou/Taiwan	Retrospective analytical observational cohort/control group study with four comparators of the general population for each case	2892	To investigate the magnitude of risk associated with JIA and its treatment to the development of cancer in children in Taiwan.	JIA	Up to 16 years old	MTX; TNF blockers	HR: 3.14 (CI 1.98–4.98), RR: 2.75 (CI 1.75–4.32) and IRR: 3.21 (CI 2.01–5.05) for cancer; IRR: 7.38 for leukemia, 8.3 for lymphoma, 11.07 for sarcoma, 2.08 for others.	Leukemia; lymphoma; soft tissue sarcoma; other	Children with JIA have a 3-time higher cancer risk East Asia; biological agents do not increase this risk.

JIA, Juvenile Idiopathic Arthritis; CI, confidence interval; NPC, nasopharyngeal carcinoma; MLD, malignant lymphoproliferative disease; Dx, diagnosis; HR, hazard ratio; IRR, incidence rate ratio; JSLE Juvenile Systemic Lupus Erythematosus; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; MTX, methotrexate; PAN, polyarteritis nodosa; PMT, pilomatrixoma; RR, relative risk; SIR, standardized incidence ratio; GIT, gastrointestinal tract; TNF-α, tumor necrosis factor alpha; IU, idiopathic uveitis.

The general characteristics of the papers included in the systematic review can be seen in Table 2, in their chronological order of publication. Therefore, the final product of this systematic review is a descriptive analysis of the data collected. Meta-analyses were not performed.

Of the nine selected articles,[12–20] three were conducted in Canada,[15,16,19] two in the US,[17,18] two in Germany,[13,14] one in Taiwan[20] and one in Sweden.[12] Although this review has not made restriction on the year of publication for the inclusion of articles, all the papers were written in the past five years, showing the up-to-dateness of this research. Of the nine papers, eight were retrospective observational cohort studies[12,14–20] rated as satisfactory by the STROBE Initiative, and one was a five-case report.[13]

The total number of patients with juvenile rheumatic disease evaluated in the studies with or without progression to neoplastic disease was about 27,800 children and adolescents. Of this population, approximately 0.5% had a neoplastic disease (in absolute numbers there was an incidence of 133 cases), which was considered as a statistically significant increased risk for patients in this condition (compared to the general population referred in these studies, where the incidence of malignancy was about 0.03%). Only one study did not support this result.[15]

Although the search has covered rheumatic diseases in general, the results obtained only involved studies dealing with autoimmune rheumatic diseases. Most of the papers studied populations with JIA (7 out of 9 articles,[12–15,17,18,20] whose participants comprised about 95% of the total number of children and adolescents with rheumatic diseases). One of these studies[16] addressed a population with JSLE (whose participants comprised almost 3.7% of the total number of children and adolescents with rheumatic diseases). And another study[19] addressed rheumatic diseases in general (whose participants comprised about 1.3% of the total number of children and adolescents with rheumatic diseases). This last study specified that JIA was the most common diagnosis.

Approximately 22% of cancers were specified as being of a hematologic and lymphoproliferative nature. Most studies did not specify the nature of all neoplasms found and various solid tumors were cited (thyroid gland carcinoma, yolk sac carcinoma, cervical dysplasia, soft tissue carcinoma, brain tumor, gastrointestinal tract tumor, nasopharyngeal carcinoma, kidney carcinoma, pilomatrixoma, among others).

Two[15,16] of the nine papers analyzed did not specify the therapies used by the participants. One study[12] found a higher risk of developing cancer in patients with juvenile rheumatic disease diagnosed in the past 20 years, raising the possibility that the new therapies adopted since 1999, involving biological agents, would be related. Three papers[13,14,19] failed to set an association between the treatment of juvenile rheumatic disease and cancer risk. Two studies[18,20] found a non-statistically significant increased risk of cancer development in the subgroups treated with TNF-α inhibitors when compared to the subgroup not exposed to these drugs. Finally, a statistically significant increased risk of neoplastic disease was found in a study[17] which aimed to assess this problem in a population who had not received treatment with biological agents.

Discussion

Epidemiological studies have shown an increase in the rate of malignancy incidence in association with juvenile rheumatic disease. Only the study of Bernatsky et al.[15] published in 2011 in Canada produced different results *versus* other studies, for reasons that are not clear. These authors investigated a population diagnosed with juvenile idiopathic arthritis (JIA) and concluded that in the first years after diagnosis the overall risk of cancer was not higher. But the results related to the risk of specific cancers were not clear and one could not rule out the possibility of an increased risk of hematologic malignancies.

Simard et al.[12] were the first authors to publish on the association between JIA and incidence of malignancy. These authors conducted a retrospective study in Sweden with a follow-up period from 1969 until 2007. This cohort was stratified into two subgroups of about 20 years of follow-up each. In the most recent cohort, evidence of an increase in the relative risk of cancer in general in JIA patients was found. Although data on the use of specific medications were not available for most of the study years, the authors speculate that the time difference observed in malignancy risk could be a result of the widespread use of methotrexate (MTX) in their most recent cohort of patients. In England, Cleary et al.[21] published in 2002 a series of cases with JIA who were treated with MTX and who later developed lymphoma, a finding that gives some support to this potential explanation, but this initial report was not followed by a controlled study.

Little is known about the incidence of malignancy in patients with JSLE. The Bernatsky et al.[16] report was the only publication found on the subject. Although the use of medications has not been evaluated, the data obtained suggest that the risk of incidence of malignancy in patients with JSLE can be increased, similar to what occurs in adult patients with SLE.

The study by Beukelman et al.,[18] published in 2012 and involving a population with JIA in the USA, evaluated more specifically the effects of the use of medications, but its authors found strong associations between the use of MTX or TNF-α inhibitors and the incidence of malignancy. The study subsequently performed by Kok et al.[20] in 2014 in Taiwan supports this result, but the sample size, the limited number of outcomes, and the follow-up periods (in the first study, 5 years; and in the second study, 8 years) were insufficient to allow any definitive conclusion.

Nordstrom et al.[17] in 2012 conducted a US study that found a statistically significant increased risk of cancer in people with JIA not treated with biological agents (up to three times higher *versus* the general population). These data raised the hypothesis that the incidence of cancer would be part of the natural history of the disease, and would not be a potential adverse effect of its treatment. It is unclear whether the degree of inflammatory activity of juvenile rheumatic disease would be the determining factor for the development of malignancy, but this would be consistent with previous studies in adults[5–8] with more consolidated results and, in that case, if it would be possible that biological agents could instead reduce the risk of incidence of malignancy through a better control of the disease and less tissue damage.

It is critical to be aware of the possibility of the plurality in the etiology of cancer in patients with juvenile rheumatic diseases, with the addition of other influences besides the chronic use of medications and the role of chronic inflammation, such as the individual genetic predisposition and perhaps environmental influences such as air pollution, nutrition and stress. The role of the environment, despite being a still poor-described topic in the literature, has been studied as a potential contributing factor to the triggering and reactivation of juvenile autoimmune diseases such as systemic lupus erythematosus, dermatomyositis, and juvenile idiopathic arthritis; and considering the importance of environmental influence in the etiology of neoplasms, future studies may reveal the relevance of this factor in the etiology of cancer and rheumatic diseases.[18,22]

On the other hand, never it will be too repetitive to underline the great importance of the watchful eye of rheumatologists, clinicians and pediatricians for the diagnosis of malignant diseases in children and adolescents with osteoarticular complaints, especially when the clinical picture does not include a specific rheumatic disease. Many children and adolescents with leukemia have complaints that mimic rheumatic diseases and that are misdiagnosed, resulting in a delay in proper treatment and diagnosis.[23]

The perception of the risk of malignancy in children with rheumatic disease due to the use of TNF-α inhibitors is obscured by the lack of knowledge regarding the risk that derives from the own natural course and from the chronic inflammatory process of this disease in its subtypes and severities, an aspect that has already been investigated in studies with adults; but so far the reports are reassuring.

The association between the use of biological agents and cancer suggested by the FDA in 2008[4] has not been confirmed; however, there is a scarcity of studies on the risk of neoplastic diseases in the population suffering from juvenile rheumatic disease. Thus, the limited number of endpoints in the literature is insufficient for the extraction of any definitive conclusion. Studies with longer follow-up and more patients are needed, so one can answer more consistently the question posed in this study.

Conclusion

Patients with juvenile rheumatic disease appear to be at increased risk of developing cancer. In children and adolescents with JIA, the most observed diagnosis in the populations studied, the risk is up to three times higher when compared to the general population, and most cancers are of hematological and lymphoproliferative nature. The greatest risk of incidence of malignant disease associated with juvenile rheumatic disease is not entirely attributable to treatment with biological agents.

Conflicts of interest

The authors declare no conflicts of interest.

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