Tuberculosis in Children with Rheumatic Diseases Treated with Biologic Disease-Modifying Anti-Rheumatic Drugs

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Mediterr J Rheumatol 2021;32(4):290-315

E-ISSN: 2529-198X

MEDITERRANEAN JOURNAL OF RHEUMATOLOGY | 32 4 2021

NARRATIVE REVIEW

Tuberculosis in Children with Rheumatic Diseases on Biologic Disease-Modifying Anti-Rheumatic Drugs: A Narrative Review

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ABSTRACT

Chronic rheumatic diseases entail the use of biologics in children. Immunosuppressive effects of drug therapy put children at risk of various infections including tuberculosis (TB). Even though TB is a major concern among individuals on biological DMARDs, the incidence and distribution among children on these drugs is not known. Hence, we performed a literature search to ascertain the prevalence of tuberculosis amongst children with rheumatic disorders treated with biological agents. Articles available on MEDLINE and SCOPUS published on or after January 1, 2010 to 1 October 2019 were reviewed and collated. We found that published data on TB infections in children with rheumatic disorders on biologics is scant even from regions with highest TB burden. Tuberculosis was reported on occasion (0-5 cases per country) in the developed world with most reports being from Turkey. While most of the retrospective studies suggest that TB risk is minimal in the paediatric rheumatology patients, prospective studies suffer from a short observation period. Most registries focus on response to therapy rather than complications. In this review we have then discussed about the variation in screening strategies for latent TB and the role of bacille Calmette-Guerin (BCG) vaccination. Based on the dearth of data and inconsistency in data collection, we propose a way forward in the form of establishing well-designed long-term prospective national registries from countries with high background prevalence of TB with focus not only on treatment efficacy but also on adverse events and infections.

Mediterr J Rheumatol 2021;32(4):290-315

https://doi.org/10.31138/mjr.32.4.290

Article Submitted: 19 Jun 2021; Revised Form: 17 Aug 2021; Article Accepted: 15 Sep 2021; Available Online: 27 Dec 2021

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Keywords: tuberculosis, biologics, rheumatology, paediatrics

INTRODUCTION

Despite the advent of glucocorticoids and immunosuppressive therapies, chronic rheumatic diseases of childhood such as Juvenile Idiopathic Arthritis (JIA), Systemic Lupus Erythematosus (SLE), Idiopathic Inflammatory Myositis (IIM), Auto-inflammatory Syndromes (AIS)and Paediatric Vasculitis (PV) result in significant morbidity, and, at times, even mortality.[1–3] In the developing world, infections are the leading con-

tributors to such morbidity. Tuberculosis (TB) is one such infection, which remains a particular challenge in these parts of the world.[4] The emergence of drug-resistant tubercular strains and polypharmacy, in the setting of chronic illnesses further compounds the problem.[5]

Recent estimates suggest the prevalence of TB in India to be 3.2 cases per thousand population.[4] The presence of rheumatic disorders (RDs) entails treatment with glucocorticoids and immunosuppressive drugs for prolonged periods, more so in cases of lupus, vasculitis and myositis. Some patients with JIA, lupus, vasculitis, and, rarely, IIM, also have underlying antibody deficiencies or complement pathway defects, further increasing their infection risk. Over the past years, there have been efforts towards decreasing usage of glucocorticoids in rheumatic disorders and advocating rational use of immunosuppressive agents. In addition to this, public health initiatives have attempted to address the issues of adequate treatment of TB.[2] The changing dynamics of therapeutic practices could have a bearing on the prevalence of TB in these diseases, and also influence the ways this problem can be addressed. Thus, it is important to understand the prevalence, risk factors, and outcomes of TB infection among children with RDs on biologics. In this review, we have performed a literature search on the prevalence, screening strategies, and global reporting patterns of TB across various studies among children with RDs on biological DMARDs. We have then summarised the available literature and discussed the possibilities that could explain our findings. Finally, we have suggested the way ahead to obtain more robust information from underrepresented countries.

REVIEW STRATEGY

The search strategy for writing review articles as proposed by Gasparyan et al. was followed.6 Articles available on MEDLINE and Scopus, published on or after January 1, 2010, until October 1, 2010 were reviewed using search words “juvenile” and “dermatomyositis” and “biologics” (n=71); “paediatric” AND “Lupus” AND “biologics” (n=81); “paediatrics” AND “Vasculitis” AND “Biologics” (n=55).

In addition, for the literature review on registry data in paediatric rheumatology, Scopus searches were conducted combining “registry” with each of the following: “paediatric” AND “Lupus” (n=100), “juvenile” and “myositis” (n=40); “juvenile” and “arthritis” (n=368); biologics” AND “Rheumatology” (n=359) and “Autoinflammatory” AND “syndromes” (n=50).

Also, select review articles on the subject were cross-referenced to obtain additional references. **Figure 1** summarises the search results.

Articles with data on outcomes in children of treatment with biologics were included. Review articles, systematic reviews, case reports, and articles without data in children, and those in languages other than English, and where full-text was not available were excluded. Congress abstracts did not feature in the searches. Studies which had TB where there was no clear separation between those receiving bDMARDS vs those on csDMARDs were excluded. Serious infections were defined as per the publishing author’s definitions. The Zotero software, an open-source tool, was used for references management and citations.

Figure 1. Number of articles obtained after searching through MEDLINE and Scopus.

SELECTION OF ARTICLES

Screening by title

The Scopus searches were imported into Zotero, and articles were first screened by title by one author, and those without relevance, systematic reviews, meta-analysis, narratives, and in languages other than English were removed (**Figure 1**). The exact process of data extraction is elaborated in the supplementary material.

Juvenile Idiopathic Arthritis and Tuberculosis

Juvenile idiopathic arthritis is a chronic rheumatic disorder consisting of polyarticular (rheumatoid factor positive and negative), oligoarticular, systemic-onset JIA, enthesitis-related-arthritis, psoriatic and undifferentiated subtypes. The occurrence of infections is known and associated with poor outcomes.[7] Tuberculosis is a chronic infection that can result in significant morbidity and mortality in children with JIA.[8]

Data in JIA consists of mixed cohorts of various subtypes of arthritis. Interestingly, most series report no occurrence of Tuberculosis (**Tables 1, 2 and 3**). Tuberculosis has been reported in four prospective studies, involving 2 each from Turkey and Portugal, and 1 each from Brazil and a multicentre trial. The follow-up duration in these studies ranged over 1-5 years. Of the various biologic registries screened, the only two cases of Tuberculosis reported are from Turkey. This is in contrast to minimal or no reports of Tuberculosis from UK, most European countries (France, Germany, Italy, and Greece) and Canada. The general prevalence of tuberculosis in Turkey is26/100,000 (2005). Brazil has one of the highest TB burdens with over 70,000 incident cases per year (**Figure 2D**). Portugal has the highest TB prevalence in Western Europe at 23 per 10,000 population, which resonates with the 2 cases reported of two studies in 232 patients.[9]

Interestingly, a study from India which has one of the highest background prevalence of Tuberculosis in the world, reported no Tuberculosis though the follow-up duration was 11 months. Plotting data available from various studies in paediatric rheumatology on a world map reveals the distribution is primarily limited to regions with low TB prevalence (**Figure 2A**). There is sizeable risk of confirmation biases regarding the safety of biologics resulting from absence of data from high TB incident parts of the world (**Figure 2 C**).

On the contrary, in adults, there are reports of greater tuberculosis on anti-TNFs, with the risk being highest with IFX(cumulative incidence 0.5% within the first 500 days of registration) as compared with ETA (0.2%).[10,11] It is worthwhile considering if BCG vaccination practices in children could explain differences between children and adults. Usage of biologics also induces an immunosuppressant state, and there is known risk of higher extra-pulmonary forms of TB in such a setting.[12] Diagnosing these could be a challenge, particularly so in the absence of a robust biomarker for extrapulmonary forms of tuberculosis.[13]

Juvenile Lupus and Tuberculosis

Data on tuberculosis in paediatric lupus is scant, being limited to 7 retrospective and 2 prospective studies (**Supplementary Table S1**). While most described the use of Rituximab, one prospective study on Belimumab featured 39 cases over 6 months of follow-up. The maximum duration of follow-up was 3 years and the largest series of 104 was from the United States in 2015. Whilst none of the series reported any tuberculosis, the largest series had overall 22 infections, of which 20 were major infections. Of note, most patients were on concomitant immunosuppressants or steroids during the study period. However, literature is replete with case reports of tuberculosis in lupus.[14] We have previously found TB in 6% of children with LN.[5] Thus, poor tuberculosis reporting could be from use of biologics in patients with less severe disease (minor organ manifestations), early mortality or underreporting. Previously use of high-dose cyclophosphamide (CYC) has been identified as a risk factor for infections in lupus.(15)The risk of infections could possibly be lower with biologics such as belimumab and RTX but this needs to be confirmed in larger studies.(16)

Juvenile inflammatory myositis and tuberculosis

Out of the various studies on inflammatory myositis, none looked at data on Tuberculosis specifically (**Supplementary Table S2**) suggesting dire need to collect information relevant to this in future studies. On the other hand, we have 4 papers previously describing high prevalence of tuberculosis in myositis, suggesting the need for careful assessment of this aspect in prospective cohorts with longer term follow-up.[17-20] We have described TB in 17.1% children from India with myositis (n=35, unpublished data). Unfortunately, biologics use is limited in this part of the world due to insurance policies and consequent financial constraints further leading to dearth of data.

Juvenile Vasculitis and Tuberculosis

Data on paediatric vasculitis is scant, being limited to 5 retrospective series, most being on Behcet's disease, Takayasu's arteritis, and Polyarteritis nodosa from Turkey, UK and Canada, overall reporting 35 cases (**Supplementary Table S3**). No serious infections were reported over the longest study period of 2.1 years.

Autoinflammatory syndromes and Tuberculosis

Although there is emerging data from registries including the Eurofever registry on various auto-inflammatory syndromes, most focus on treatment regimens and response to therapy with dearth of data on infections. In the limited studies available (**Supplementary Table 4**), no Tuberculosis was reported.[21-23]

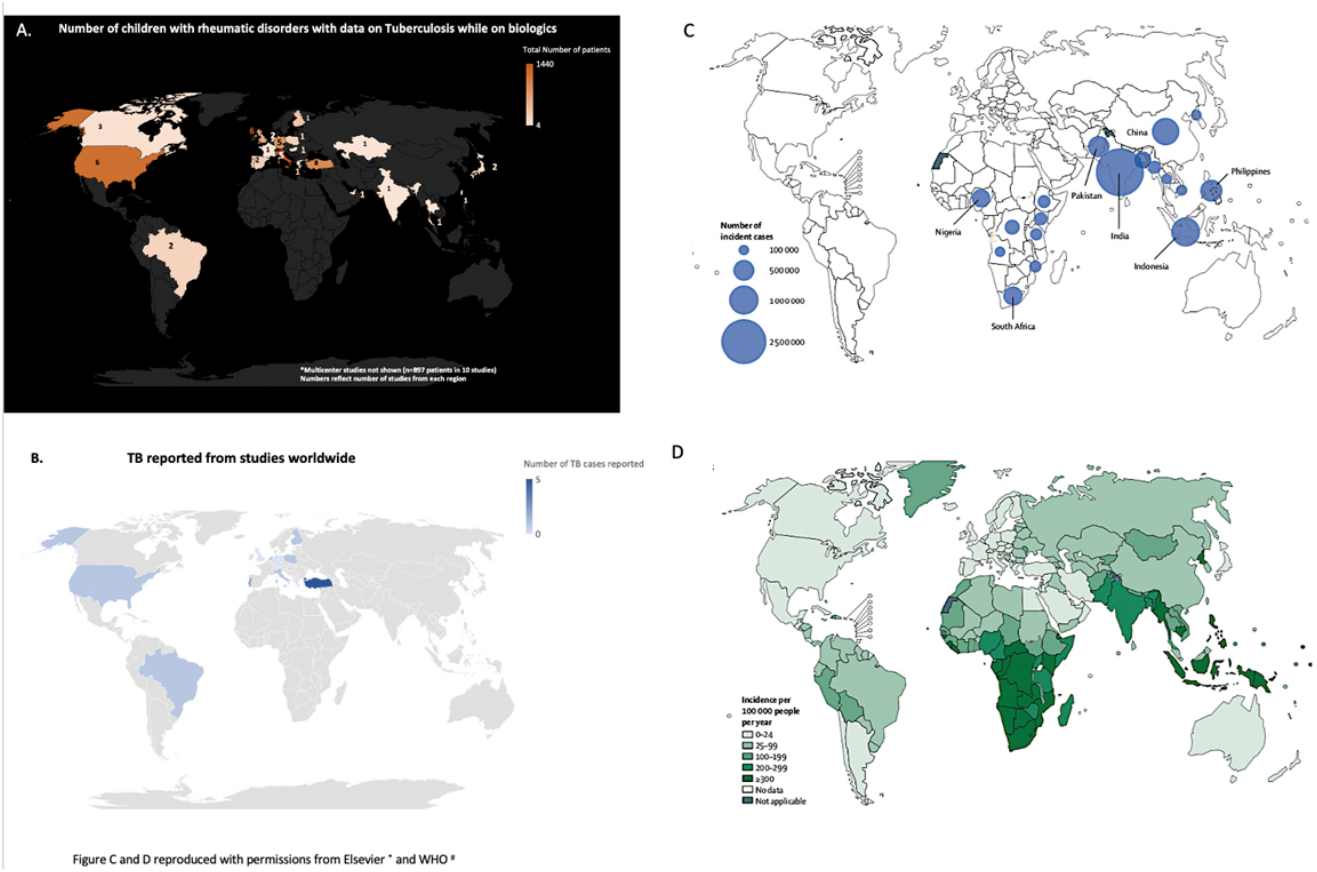

Figure 2. Global distribution of cases.
A. Data available on children with paediatric rheumatic disorders on biologics. **B.** Number of tuberculosis cases reported from studies summarised in **Figure 2A**. **C.** Number of incident tuberculosis cases worldwide*. **D.** Global incidence of tuberculosis per 10000 people#.

Choice of biologics and risk of TB in children

Children with rheumatic disorders might be predisposed to Tuberculosis due to the intrinsic mechanism of action of biologics, anti-TNFs in particular, as they target TNF-α, the key cytokine for the Th1 axis. Experience from the biologic usage in adult rheumatic diseases has shown higher chances of TB reactivation with anti TNF agents. We identified 37 episodes of TB in 34 patients out of the 14,218 patients treated with anti TNF agents. In the non-TNF biologic group, a single case of TB has been reported with tocilizumab (OR-6.92 95% CI 0.95,50.56) (**Table 4**). Anti-TNF therapy may not be a cause for TB reactivation among children with autoimmune diseases on biological agents. The role of TNF in controlling TB infection is reflected by the mice models deficient in TNF. These rodents are unable to control M. tuberculosis infection and form granulomas in their lungs.[24] TNF-α is required in the protective immune response against M.tuberculosis (MTB) in mice.[25] TNF is an important signal for macrophage activation, in conjunction with IFN-γ. This cytokine has a key role in the immune responses to MTB, because it is involved in multiple processes, such as macrophage activation and cell recruitment to the sites of infection (natural killer cells, granulocytes, fibroblasts, and T cells), which either leads to granuloma formation or kills the pathogen. Furthermore, it activates CD8+ T cell that could directly kill the bacteria, TNF-α additionally activates CD8+ cytotoxic T cells (CTLs) that may be important because these cells release granulysin and directly kill intracellular bacteria. TNF-α also promotes the maturation of monocytes to dendritic cells (DCs) and/or macrophages, inducing the antigen presentation of intracellular mycobacteria. TNF-α produced in a local infection site allows macrophages, natural killer (NK) cells and γδ T cells gather at the infection site and bring their activation.[26] The activated CTL cells have the ability to produce perforin protein and TNF-α by itself, which guide TB-infected monocytes to apoptosis, which involves intracellular living TB bacilli, and to induce the autophagy of infected cells via activated.[24]

The other possibility is an increased risk due to the presence of an autoimmune disease. The risk of infections seems to be increased in rheumatic diseases not only from the drugs used, but also the presence of T lympho-

cytes dysfunction and cytokine imbalance. Azfar et al. have shown that lupus patients have suppressed reactive oxygen species and tumour necrosis factor-alpha activity in human monocytes in response to mycobacterium TB.[27] Previously, the risk of TB has been shown to be increased in children with JIA independent of the use of anti-TNFs.[28,29] However, in this study, the risk of TB was equal to the general population for children who either received anti-TNFs, or non TNF biological agents. This in sharp contrast to numerous other reports of TB in adults, suggesting that anti-TNFs might be safer in children than reported adults. Though this could also be attributed to smaller numbers in subgroup analysis, and remains to be confirmed.

Presence of other infections can be risk factors for subsequent infections, though there is limited data from the current searches to substantiate that. One of the children who had CMV infection also had TB. In addition, primary immunodeficiencies such as X-linked agammaglobulinemia can mimic JIA and put the children at risk for infections.[30,31]

Causes for low TB in children in current data set

Low numbers due to studies in regions with low incidence of TB

The number of studies from the various countries along with the reported number of TB cases, are plotted on a world map (**Figure 2A,B**). This pictorial view of the geographic distribution of the data obtained shows the stark distinction where most of the studies are concentrated in the affluent European and North American countries. Understandably, the reports of TB (**Figure 2B**) available are also from these countries. It is evident that the countries with the highest burden of TB (**Figure 2C**) have hardly any data on the biological use in children with RDs. Our literature search has brought out the inequalities in data availability across the world, and this has resulted in the probable assumption of low risk of TB among children with RDs on bDMARDs. Although the data review here suggested limited cases of TB on biologics, closer examination of the worldwide prevalence of TB makes paucity of data to be a possibility. The data from the PharmaChild registry had 17 episodes of TB in 14 children receiving biologicals for JIA.[32] All the cases were reported from children on TNF inhibitors. TB was most reported from Asian patients - 52%, followed by 37% among the European patients, and 11% in the children treated at the centres in the USA. Since the registry covered 32 countries across the globe, the data seem to point at the fact that the low incidence of TB in other studies seen in **Figure 2**, is due to a concentration of studies from countries which are not endemic to TB.[33] Studies from areas with moderate TB burden like Turkey and Brazil did report tuberculosis (**Figure 2**).

Low number of TB cases as consequence of the methodologies used to collect data

Moreover, the low reporting of adverse events could be relevant to the kind of data collected. Many articles in paediatric rheumatology focus on response to therapy. Thus, data recording of infections takes a backseat. Two cases of tuberculosis were reported in a single study from Turkey, with the use of etanercept and adalimumab, which focused on collecting infection related data (**Table 4**). The total numbers of infections reported were also remarkably higher in this study, suggesting possible geographic influence as well as methods/intent of data collection. Both developed TB despite a negative latent TB infection (LTBI) screen. Recently, a survey was conducted amongst physicians treating children with rheumatic disorders in India, that suggested a high incidence of TB, more so while the children were on biologics than after they were stopped.[34] Thus, it seems here that what we see in Turkey is just the tip of the iceberg, and the problem might be much severe in areas of TB endemicity. In the current era of biosimilars, data from post marketing surveillance records in the developed world can be mined to gain insight into TB incidence rates.[35]

Varied screening strategies before administering biologics

On a different note, low number of TB cases could also be due to varied TB and LTBI screening strategies before using bDMARDs. However, the recent survey from Indian rheumatologists suggests screening is universally practiced, though there is no consensus on the optimum method of screening.[34] Thus, a closer look into the prevalent practices and cost-benefit ratios of the strategy used for screening might be insightful in the future. Recently, Hassanzadeh et al. established that blanket screening for TB using the TB Spot assay increased the risk of polypharmacy, adverse drug effects and increased cost manifold.[36] Glasgow, an area of low TB prevalence and high BCG vaccination. Chest radiograph and clinical interview were used to identify risk factors for LTBI. The annual risk of TB was calculated using tables from BTS recommendations and then compared to the risk of drug-induced hepatitis. All patients were given a T-SPOT according to current local policy. Indeterminate T-SPOTs were recorded and repeated. Results . For 130 patients, a total of 160 tests were required resulting in a cost of £ 24,000. 99 (76% A recent systematic review confirmed the lack of consensus in screening strategies for TB in the immunosuppressed in guidelines across countries.[37] Thus, region-specific data needs to be gathered before implementing screening strategies in rheumatology as the risk and cost efficacy ratios might differ significantly according to TB incidence rates.[37]

Shorter follow-up duration in children

Moreover, studies can be marred by short follow-up

period, as post-marketing surveillance offers best insight into rare adverse effects.[35] Thus, registries are likely to provide a better overview. The PharmaChild registry which involved 32 countries across the globe reported 24 cases (17 on biological DMARDS) of tuberculosis in children with JIA.[38] Similar compilations are particularly needed from parts the world with high background prevalence of tuberculosis. The short window of childhood might limit study periods as children move on to adulthood, as compared with studies in adults, which are likely to have longer follow-up periods.

TB risk in children in comparison with adults

TB screening practices could vary in children, as can be the threshold to prescribe biologics. Varied Tuberculosis incidence in different regions call for region specific guidelines in screening keeping the risk benefit ratio in mind. Lack of clarity in current guidelines is likely to accentuate the problem.

BCG vaccination

Difference in TB occurrence in children as compared with adults on anti-TNFs could also be a function of prevalent vaccination practices. Infant BCG vaccination has shown high efficacy of 70%-80% against childhood TB, especially meningeal and disseminated forms.[39] Sara Suliman et al have shown that BCG re-vaccination in adults with LTBI induces long-lived BCG-reactive NK cell responses.[40] This was in contrast to the limited cytokine change by Isoniazid preventive therapy, which was administered in 33 patients (39 in control group). Recently Katelaris et al. found that LTBI prevalence was lower amongst contacts of TB patients even 20 years after the initial vaccination, though vaccine efficacy declined as a function of time since vaccination.[41] In light of waning vaccine efficacy in adulthood, BCG re-vaccination could possibly reduce TB incident rates while on bDMARDs.

CONCLUSION

To conclude, there is dearth of data on incident TB rates in children with rheumatic disorders with exposure to bDMARDs from TB endemic countries. There is a felt need for regional registries to understand the prevalence, patterns, and prevalent screening practices to chalk out cost effective approaches with the intent to prevent long term debility.

AUTHOR CONTRIBUTION

All authors were involved in ideation and manuscript preparation.

ACKNOWLEDGEMENTS

The authors thank Dr Durga P Misra for conducting Scopus searches for the review.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPLEMENTARY TABLES

Details of Selection of articles

Screening by title

The Scopus searches were imported into Zotero, and articles were first screened by title by one author, and those without relevance, systematic reviews, meta-analysis, narratives, and in languages other than English were removed (**Figure 1**).

Screening by abstract

The list of articles remaining after the initial screen was passed on to another author, to screen the individual abstracts for relevance, type of study and study population (children or adults). During the article screening, the initial rounds of elimination by screening titles and abstracts was done by one author each and subsequent rounds by two different authors.

Screening by reading full-text

The full text of articles obtained after two rounds of exclusions was then accessed. Those deemed irrelevant at this stage or where full-text was not available on the internet were then excluded. Similar screening strategy as delineated above was followed. The approach was mostly inclusive. Randomised placebo-controlled studies or any other controlled trials, retrospective case series, published data from registries, correspondence with data from more than 3 patients were included for data synthesis. Case reports, systematic reviews and metanalysis were excluded. Predesigned data extraction form (DEF), **Table 1** was used to record data from the articles obtained after the above three stages of screening. The DEF was devised by two rheumatologists individually who then discussed and merged the variables suggested by each.

Differences were resolved by consensus between two rheumatologists. DOI numbers, year and author names were recorded to avoid duplication of studies. TB was defined as in the individual studies.

Further, the number of studies from the various countries was tabulated and the number of participants, as well as TB cases, reported recorded for each. These were plotted on a world map (**Figures 1A,B**) to get a pictorial view of the geographic distribution of the data obtained. Multicentre studies were excluded from the above figure as attributions to individual countries were not possible. **Tables 1, 2 and 3** summarise data on tuberculosis in different paediatric rheumatic diseases, while **Table 4** summarises data obtained from various registries. Furthermore, the quality of evidence of each study was recorded and summarised as a **Table 2**, disease wise, to understand the weightage that can be accorded to each of these.

Table 1. Data of tuberculosis in retrospective studies of patients with Juvenile arthritis on biologics.

Retrospective					
Country	Italy	Taiwan	Italy	Turkey	Canada
Year	2012	2015	2017	2010	2015
Author	Bracaglia[42]	Hsin[29]	Favalli[43]	Ayaz[44]	Hugle[45]with a median follow-up period of 7.2 years. Prospective data was collected according to a standardized protocol. Outcomes examined were TEC, TAJC, markers of inflammation (ESR, CRP
Tuberculosis-No of patients	0	1	0	0	0
Type of article/ paper	Retrospective analysis of a cohort	Nested case control analysis of Taiwan National Health Insurance Research Database	Data extracted from local registry looking at the causes for anti TNF withdrawal	Retrospective chart review	Retrospective chart review
Type of JIA	N=25	N=111	N=360	N=36	N=16
PA-RF+	3(12)	NA	31	6 (16.7)	0
PA-RF -	1(4)	NA	75	0	0
OA	3 (12)	NA	101	0	0
OA Extended	9(36)	NA	70	3 (8.3)	0
ERA	0	NA	26	12 (33.3)	16
SJIA	8(32)	NA	48	14 (38.9)	0
PsA	1(4)	NA	9	1 (2.8)	0
Undiff	0	NA	0	0	0
Duration of follow-up (Median)	10 months (2-41)	3.49 ± 1.79 years (Mean)	10 years	36 months (range 4-216 months)	7.2 years (4.5 – 12.1) 117.1 patient-years
N total whose complete data is available	25	111	354	36	16
Drug	ETN 25	Anti TNF (Mainly ETN)-111	IFX-89 ETN- 205 ADA-66	ETN-36	IFX, ADA and ETN combinations-16 IFX alone 8 ETN alone 5 ETN followed by ADA 1 IFX followed by ADA 1 IFX followed by ETN, then by ADA 1
Biologic Doses received	ETN0.8–1 mg/kg once weekly	Anti TNF (No data on individual drugs)	NA	NA	NA
Duration of biologic treatment	23 months (mean)	Max 8 years	NA	11.5 months (3-48 months)	NA
Concomitant drugs	MTX 24 (96%) CYS 3 (1.6%)	MTX (number NA)	NA	NA	NA
Steroids	10 952.6%)	NA	NA	NA	NA

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Table 1. Data of tuberculosis in retrospective studies of patients with Juvenile arthritis on biologics. *(continued)*

Brazil	Turkey	Poland	Italy	India	Turkey
2017	2011	2011	2016	2016	2016
Brunelli[46]	Kilic[47]	Żuber[48]	Verazza[49]	Saini[50]	B A Atikan[51]
0	0	1	1	0	0
Retrospective cohort that included JIA patients eligible to anti-TNF therapy	Retrospective chart review	Polish registry data collected between January 2003 and March 2010	Retrospective Multicentre Italian Paediatric Rheumatology Study Group led chart-based review	Research letter	Retrospective chart review of patients who were given biologicals and had received BCG vaccines
N =69	N=132	N=188	N=1038	N=10	N=71
9 (13)	73, (50.7)	13 (7)	50 (4.8)	3	18
22 (32)		79 (42)	329 (31.7)		
0	22, (15.3)	27 (14)	139 (13.4)	0	5
12 (17)		30 (16)	325 (31.3)	0	
6 (9)	14, (9.7)	1 (0.5)	48 (4.6)	0	20
19 (28)	19, (13.2)	28 (15)	106 (10.2)	7	23
1 (1)	4, (2.8)	2(1)	34 (3.3)	0	5
0	0	8 (4)	7 (0.7)	0	0
2.9 years(0.3–24.6)	5.86 ± 3.77 years	Mean ±SD 52 (41.7) months Range- 2–183 months	2.1 (0.6–5.5)years	11 (range 4-41) months	3 years
69	132	39	NA	10	NA
ADA-12 ETN-35 ETN switched to→ ADA 17 ADA → ETN 2 ETN → IFX 1 IFX → ETN → ADA 1 ETN → ADA → IFX 1	ETN 115 IFX 17 ETN + IFX 6 IFX + ADA 4 ETN + ADA 2,	ETN-188	ETN-1038	ETN-5 TCZ-5 ABA-1 (switched from TCZ)	ETN-41 ADA-21 CANA-5 TCZ-4
NA	NA	NA	NA	NA	NA
ADA-21.4 (2.3–73.5) ETN-25.6 (0.5–95) IFX-1.9 (0.03–8.5)	NA	393 patient-years	2.1 (0.6–5.5)	11 (range 4-41) months	3 years
MTX-60 (87) Dose 25 (5–50) LEF- 23 (33) CYS-13(19)	NA	37(95)	Mtx749 (72.2)	NA	NA
31 (45)	NA	35(92)	267 (25.7)	NA	NA

ADA: Adalimumab; ETN: Etanercept; IFX: Infliximab; ABA: Abatacept; CER: Certolizumab; GOL: Golimumab; JIA: Juvenile idiopathic arthritis; AZA: Azathioprine; MTX: Methotrexate; CYS: Cyclosporine; LEF: Leflunomide; SSZ: Sulfasalazine; CAN: Canakinumab; RTX: Rituximab; ANK: Anakinra; TCZ: Tocilizumab; JIA: Juvenile idiopathic arthritis; PA: Polyarticular; SJIA: Systemic onset juvenile idiopathic arthritis; ERA: Enthesitis related arthritis; OA: oligoarticular; Undiff: Undifferentiated.

Table 2. Data of tuberculosis in prospective studies of patients with juvenile arthritis on biologics.

Prospective								
Country	Turkey	Portugal	Germany	USA and Canada	The Netherlands	Multicentre- Europe, Latin America and USA	Multicenter- 19 countries	Japan
Year	2018	2016	2015	2009	2009	2010	2015	2011
Author	Aygun[52]	Mourão[53]	Horneff[54]	Giannini[55]	Prince[56]	Ruperto[57]	Constantin[58]	Imagawa[59]
Tuberculosis- No of patients	2 (1-ETN) (1-ADA)	2 1- ADA 1-ETN (Skin test conversion)	0	0	0 (But 1 had TB after switching to IFX- Reported as a case report)	0	0	0
Type of article/ paper	Single centre cohort	From Reuma.pt. database	Phase III Randomise Double-Blind Study	Phase IV, open-label, multicenter registry	Multi-centre (Dutch national registry)	Long-term, open-label extension phase of a double-blind, random-ised, controlled withdrawal trial	Phase IIIb, open label, multicentre study	Open-labelled multicentre study
Type of JIA	N =307	N=227	N=41	N=397	N=146	N=186	N=127	N=19
PA-RF+	18 (5.9)	36 (17.5)	0	351	11 (8)	38 (20%)	0	9
PA-RF -	85 (27.7)	48 (23.3)	0	0	55 (38)	84 (44)	0	8
OA	100 (32.6)	20 (9.7)	0	0	0	0	0	0
OA Extended		33 (16)	0	Included as PA	28 (19)	27 (14%)	60(47.2)	2
ERA/SpA	42 (13.6)	31 (15.1)	20	0	5 (3)	0	38(29.9)	0
SJIA	52 (16.9)	28 (13.6)	0	45	39 (27)	37 (20%)	0	0
PsA	10 (3.3)	10 (4.8)	0	0	8 (5)	0	29(174)	0
Undiff	0	21 (9.8)	0	1	0	0	0	0
Duration of JIA before biologics (Median, IQR)	NA	13.7 (10.1) years	2.4 ± (2.1) years	58.1±44.5 ETN 40.7±41.7 ETN+MTX	4.1 years	1,069 days (range 168–1,457 days)	NA	4.7 yrs (1-17)
Duration of follow-up (Median)	12 months	At least 12 months	48 weeks	36 months (41% completed 36 months)	2.5 years per patient, (range 0.3 to 7.3 years)	589 days	96-weeks	48 weeks* all except 2

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Table 2. Data of tuberculosis in prospective studies of patients with juvenile arthritis on biologics. *(continued)*

Brazil	Finland	USA and EU	Japan	Multicentre	Multicentre	Germany	Multicentre – North America, South America and Europe
2017	2015	2014	2012	2008	2008	2015	
Brunelli[60]	Maarit Tarkiainen[61]	Kingsbury[62]	Imagawa[63]	Lovell[64]	Lovell[65]	Gerd Horneff[54]	Ruperto N[66]
1- With TCZ	0 1 case of MAC with ADA	0	0	0	0	0	1 Lung infiltrate with negative sputum AFB
Longitudinal data of patients with JIA receiving at least 8 weeks of biological agent documented between August 2004 to March 2016	Observational multicentre study	multicentre, open-label, phase 3b	single-arm, open-label, multicentre study	Multicentre open label extension trial* **Not classified as per modified ILAR**	Randomised, double-blind, stratified, placebo-controlled, multicentre, medication-withdrawal study with a 16-week open-label lead-in phase, a 32-week double-blind withdrawal phase, and an open-label extension phase.	Phase III Randomised, Double-Blind Study	Randomised, Placebo-Controlled, Double blind Trial
N=107	N=348	N =32	N =25	N=58	n=171	N=20	N=117
52(48.6)	16 (4.6%)	1(3.1)	17(68)	5	40(23.4)	0	117
	175 (50.3%)	20(62.5)	8(32)	0	131(76.6)	0	0
19(17.8)	30 (8.6%)	0	0	34	0	0	0
	65 (18.7%)	8(25)	0	0	0	0	0
7 (6.5)	22 (6.3%)	0	0	0	0	20	0
28 (26.2)	19 (5.5%)	2(6.3)	0	19	0	0	0
1(0.9)	0	0	0	0	0	0	0
0	1(0.3%)	1(3.1)	0	0	0	0	0
Median 4.8 years (0.1–21)	NA	12.3 (9.3) mean months	4.7 (3.72) mean years	8 years	4.0±3.7 3.6±4.0 Years in ADA+MTX and ADA arms	2.4 ± (2.1) years	NA
median 3.0 years (0.15–11.5)	50.5 months (range 1.0154.7)	Max-120 weeks	60 weeks	58	48 weeks	48 weeks	52 weeks

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Table 2. Data of tuberculosis in prospective studies of patients with juvenile arthritis on biologics. *(continued)*

Prospective								
Exposure in patient years	NA	706.92 patient-years	35.6 patient year	NA	436.1 patient years	NA	NA	NA
N total whose complete data is available	307	227	38	397	146	153	109	17
Drug	ETN 189 ADA 60 ANK 22 CAN 12 IFX 11 TCZ 13	ETN 157 ADA 29 ABA 8 TCZ 2 ANK 11 IFX 19 RTX 1	ETN 41	ETN-397 ETX only 103 ETN+ MTX -294	ETN-146	ABA-186	ETN-127	TCZ-19
Biologic Doses received	NA	NA	ETN treatment (0.8 mg/kg BW, maximum dose 50 mg/week)	ETN 0.8 mg/kg/ week, maximum dose 50 mg	0.8 mg/kg once weekly	10mg/kg ABA q4W	ETN 0.8 mg/ kg once weekly (QW; max dose, 50 mg) for up to 96 weeks	8 mg/kg TCZ every 4 weeks.
Duration of biologic treatment	42.11 ± 35.78 months (range 2–380 months)	4.5 (3.1) Years	48 weeks	NA	1.7 years (range 0.1 to 6.8 years)	NA	96 weeks	48 weeks
Concomitant drugs	NA	MTX- 170 patients SSZ 16	SSZ was allowed	MTX 294 Dose-12.6 ±5.3 (ETN) 16.9± 5.9(MTX+ETN)	MTX-113 (77)	MTX in 74% 57 (30%) Prior biologics	NA	MTX 100%
Steroids (%)	NA	NA	No	NA	90 (62)		NA	
Other	NA	NA				NA	NA	NA

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Table 2. Data of tuberculosis in prospective studies of patients with juvenile arthritis on biologics. *(continued)*

398.3 patient-years (py): 179.1py for ETA, 92.5py for ADA, 21.7py for IFX, 77.8py for ABA and 27.2py for TCZ	710 py-ETN, 591PY-IFX, 188 PY-ADA, 8 PY-RTX, 5.3 PY-ANK, 6.4 PY-ABA, 6.4 PY- TCZ and 1.0 PY- GLM	45.1 PY	NA	NA	NA	29.9 patient year	NA
107	348	26	25	9	128	19	117
ETN ADA ABA TCZ IFX	ETN 213 IFX214 ADA94 RTX9 ANK-8 ABA-6 TCZ 4 GLM3	ADA31	ADA25	ETN58	ADA171	ETN 20	IFX-117
NA	NA	24 mg/m2 (maximum = 20 mg/dose) every other week up to 120 weeks	20 mg for patients weighing <30 kg, and 40 mg for patients weighing ≥30 kg) eow	ETN 0.8 mg/kg/week	fixed dose based on body weight (20 mg for patients weighing <30 kg, and 40 mg for patients weighing ≥30 kg) eow	NA	6mg/kg and 3mg/kg standard protocol
Median 3.0 years (0.15–11.5	NA	515 (245) days	24 weeks	318 PY	48 weeks	48 weeks	52 weeks and 38 weeks
NA	NA	MTX 27 (84.4)	MTX-20(80)	(100)	MTX-85(49.7)	NA	Mtxupto 15mg/m2
NA	NA	20(62.5)	NA	22 (38%)	NA	NA	NA
	NA	NA	NA	NA	NA	NA	NA

Table 3. Data from studies on cohorts/registries of children with Juvenile arthritis on biologics.

Country	Germany	UK	Multicenter member centres 32 countries	Germany
Year	2019	2011	2018	2014
Author	A Klein[67]	Southwood[68]	J Swart[32]	Schmeling[69]
Registry Name	BIKER	Biologics and New Drugs Registry (BNDR)	PharmaChild	German Biologics JIA Registry
Tuberculosis- No of patients	0	0	24 over all 14 on biologics Total 17 Tb in 14 patients on biologicals	0
Type of article/ paper	long-term data from the German BIKER registry	Prospectively collected Data	Combined data form PharmaChild registry along with German and Swedish registries	The registry is a longitudinal multicentre observational study that has been maintained since 2000
Biological agent	ADA 584	ETN-483	ETN-3600 ADA- 1778 IFX- 705 CER- 33 GOL- 161 TCZ-633 ABA- 420 RTX 103 ANK- 339 CAN- 145	ADA-289
Rheumatological condition	JIA N=584	JIA N=483	JIA N= 8274	JIA N=289
PA-RF+	34 (5.8)	48 (9)	322 (3.9)	17 (6.2)
PA-RF -	203 (34.7)	157 (33)	2183 (26.4)	101 (34.9)
OA	42	11 (2)	2011 (24.3)	28 (9.6)
OA Extended	0	79 (16)	1060 (12.8)	68 (23.5)
ERA	98	38 (8)	924 (11.2)	39 (13.5)
SJIA	0	77 (16)	911 (11)	8 (2.7)
PsA	49	30 (6)	285 (3.4)	14 (4.8)
Undiff	11	36 (7)	578 (7.0)	14 (4.8)
Unclassified	0	7 (1)	0	0
Duration of follow-up (Median)	NA	NA	NA	NA
Follow-up in patient years	1082 patient-years (PY)	941 patient-years of follow-up		435.7 patient-years
N total whose complete data is available	584	483	5173	289

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Table 3. Data from studies on cohorts/registries of children with Juvenile arthritis on biologics. *(continued)*

Germany	Hungary	The Netherlands	UK
2017	2011	2011	2019
Horneff[70]	Sevcic[71]	Otten[72]	Fleet[73]
BIKER Germany	National Institute of Rheumatology and Physiotherapy Registry: Hungary	Dutch Arthritis and Biologicals in Children Register	Biologics for Children with Rheumatic Diseases (BCRD) study
0	0	0	0
Cohort of Systemic JIA	Cohort	Cohort of children receiving Tumour Necrosis Factor-blocking Agents for in JIA-ERA —collected between 1999-2010	Cohort
ETN-143 TCZ-71 IL-1 Inhib-60	ETN- 72	ETN 20 ADA-2(1 switched) IFX-2 (1 switched)	RTX- 41
JIA- N=245	JIA- N=72	JIA- N=22	JIA- N=41
0	6(8)	0	13 (33)
0	36(50)	0	14 (35)
0	0	0	2 (5)
0	20(28)	0	9 (23)
0	3(4)	22	0
245	6(8)	0	1 (3)
0	1(2)	0	1 (3)
0	0	0	0
0	0	0	0
NA	12 months	14-28 months	177 days (IQR 109–398)
ETN-n = 143; 355.8PY TCZ-n = 72; 111.6PY n = 60; 116.8PY	NA	38.7 patient years	51 person-years
245		22	38

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Table 3. Data from studies on cohorts/registries of children with Juvenile arthritis on biologics. *(continued)*

Treatment duration and drugs	15.1 ± 12.8 months ADA 15.2 ± 13.3 months ADA+ MTX	NA	ETN- 719 (300–1338) days ADA- 442 (174–927) days IFX- 425 (160–951) days TCZ-351 (126–742) days ABA- 342 (156–715) days ANK- 299 (94–837) days GOL- 270 (106–623) days CAN-351 (133–1032) days RTX-42 (24–87) days CER-166 (106–309) days	1.2 years (IQR 0.58–1.88) in Biologics naïve groups and 1.13 years (IQR 0.61–1.94) in previous biologic usage group
Concomitant drugs	MTX in 356 patients	NA	NA	MTX- 171 (59.2) LEF-13 (4.5) SSZ- 6 (2.1)
Steroids	NA	NA	NA	102 (35.3)

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Table 3. Data from studies on cohorts/registries of children with Juvenile arthritis on biologics. (continued)

ETN-n = 143; 355.8PY TCZ-n = 72; 111.6PY n = 60; 116.8PY	ETN 0.4 mg/kg body weight twice weekly or ADA 40 mg every 2 weeks 12 months	NA	51 person-years
MTX-185	NA	MTX-17(77) SSZ-2 (9)	NA
176	NA	3 (14)	NA

Table 4. Summary of available data that could be analysed for tuberculosis incidence in paediatric rheumatology with various biologics.

Drug/disease	JIA	Lupus	Myositis	Autoinflammatory syndromes	Vasculitis
Infliximab	783(A) 547(B)	0	0		10(C)9(B)
Adalimumab	2925 (A) 489(B)	0	0		1(B)11(C)
Etanercept	6974 (A) 2019(B)	0	0		1(C)
Certolizumab	70 (A)0(B)	0	0		0
Golimumab	385 (A) 3(B)	0	0		0
Rituximab	210 (A) 51(B)	75(B)	48(E) 185(C)		3(C)
Belimumab	0(A) 0(B)	39(B)	0		0
Anakinra	810 (A) 63(B)	0	0	29(A) 27(B)1(D)	0
Canakinumab	241 (A)	0	0	4(A)109(E)	0
Tocilizumab	998 (A)	0	0		2(B) 9(C)
Abatacept	521 (A)	0	0		0
Combination of anti TNFs	3(A)	0	0		0

A: Registry data; B: Cohort; C: Case series; D: Anecdotal reports; E. Trials.

Supplementary Table 1. Data of tuberculosis in paediatric lupus and myositis on biologics.

Retrospective					
Drug	**RTX**	**RTX**	**RTX+CYC**	**RTX**	**RTX**
Country	Greece	Greece	Saudi-Arabia	Australia, CaNAda	CaNAda
Year	2011	2011	2013	2014	2015
Author	Maria TrachaNA[71]	Maria TrachaNA[71]	Ashwaq[72]	Dale[73]	M Olfat[74]
Tuberculosis- No of patients	**0**	**0**	**0**	**0**	**0**
Type of article/ paper	Case series	Case series	Case series	Case series	Case series
N with complete data	4	4	16	18	24
Disease classification	SLE-LN	SLE-LN	SLE	NPSLE	Hematologic SLE
Duration of follow-up (Median, IQR, years)	1.33	1.33	3.2	2.5	3.6 (1.9–5.7)
Total no of infection events	0	0	2	NA	1
Major/ serious Infections- Number of events	0	0	2	NA	1
Opportunistic infections	0	0	NA	NA	NA
Minor Infections- Number of events	0	0	NA	NA	NA
Death			0	0	0
Biologic Doses received	375/m^2, 4 doses	375/m^2, 4 doses	375mg/m^2, 2 doses	NA	375/m^2, 4 doses
Duration of biologic treatment	One cycle	One cycle	One cycle for 12, 2 cycle for 2,4 cycles for 2. Each 6 months apart	NA	NA
Concomitant drugs	MMF (all)	MMF (all)	CYC, HCQ	NA	MMF (5), CYC (1)
Steroids	Yes (all)	Yes (all)	NA	Yes (all)	Yes, in 17

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Supplementary Table 1. Data of tuberculosis in paediatric lupus and myositis on biologics. (continued)

	Prospective				
RTX	**RTX**	**RTX**	**Belimumab**	**RTX**	**RTX**
Portugal	USA	UK	USA	USA	Multicenter
2016	2015	2015	2015	2014	2013
Reis[75]4 with JSLE and 1 with extended oligoarticular JIA, received 10 cycles of RTX (23 infusions	Tambrelli[76]	Watson[77]	Hui yen[78]	Lehman[79]	Oddis[80]
0	**0**	**0**	**0**	**0**	**0**
Case series	Case series	Cohort	Cohort (adult and paediatric)	Cohort	randomized, placebo-phase controlled trial
5	104	63	39	12	48
SLE, JIA	50 SLE + 54 other AIRD	SLE	SLE	SLE-LN	JDM
2	2.2	NA	0.5	5	44 weeks
2	22	2	NA	2	NA*
2	20	2	7	2	NA*
1 (Cryptococcosis)	0	1 CMV	NA	NA	NA*
NA	2	NA	NA	NA	NA*
0	1 ILD	0	0	0	
750 mg, 2 doses	750 mg/ m^2 (maximum 1 g), administered 2 weeks apart	NA	750 mg/m^2 administered twice 2 weeks apart	750mg/m^2, 2 doses at 0,6,18 months	575 mg/m2 if BSA<1.5 m2 and 750 mg/m2 if BSA>1.5m2
NA	Median 2 (1–11) courses	NA	104 courses	18 months	NA
MMF (4)	MMF, CYC, HCQ	MMF, CYC, AZA (24)	MMF (49%), HCQ (92%), AZA (23%)	CYC	NA
Yes (all)	Yes, in all	Yes, in 93%	Yes, in 82%	Yes, in all	Yes, in all

RTX: Rituximab; CYC: Cyclophosphamide; USA: United States of America; UK: United Kingdom; SLE: Systemic lupus erythematosus; NPSLE: neuropsychiatric systemic lupus erythematosus; JIA: Juvenile idiopathic arthritis; LN: Lupus nephritis; AIIRD: Autoimmune inflammatory rheumatic diseases; IQR: Interquartile range; NA: Not available; CMV; Cytomegalovirus; ILD: Interstitial lung diseases; MMF: Mycophenolate mofetil; HCQ: hydroxychloroquine; AZA: Azathioprine; JDM: Juvenile dermatomyositis; BSA: Body surface area. **cannot differentiate between data from adult and juvenile DM*

Supplementary Table 2. Data of tuberculosis in paediatric vasculitis on biologics.

Retrospective						**Prospective**
Drug	**IFX 5 ETN 1 RTX 3**	**IFX 3 ADA 2 TCZ 3**	**IFX 9 ADA 1 TCZ 2**	**TCZ 6**	**ADA-9**	**IFX 1**
Country	UK	UK	Canada	Turkey	Kazakhstan	Turkey
Year	2013	2015	2017	2018	2019	2017
Author	Despina Eleftheriou[81]	Despina Eleftheriou[82]	Florence A. Aeschlimann[83]	SezginSahin[84]	Dimitri Poddighe[85]	Nikos N. Markomichelakis[86]
Tuberculosis- No of patients	**0**	**0**	**0**	**0**	**0**	**0**
Type of article/ paper	Single centre	Single tertiary referral centre	Single-centre cohort	Review of hospital records	Case-based review	Case series (adults and juvenile)
N with complete data	9	6	10	NA	9	1 (rest were adults)
Disease	Polyarteritis nodosa	Takayasu arteritis	Takayasu arteritis	Takayasu arteritis	Bechet's Diseases	Behcet's Disease
Duration of follow-up (Median, years)	3 (2.1-5)	NA	2.1 (IQR1.2–5.5)	NA	0.25-2	1
Total no of infection events	NA	NA	0	NA	NA	NA
Major/ serious Infections- No of events	NA	NA	0	NA	NA	NA
Opportunistic infections	NA	NA	NA	NA	NA	NA
Minor Infections- No of events	NA	NA	NA	NA	NA	NA
Tuberculosis- No of patients	NA	NA	0	NA	0	0
Duration of biologic treatment (months)	NA	NA	Variable, 3-20	NA	3-24	3-24
Concomitant drugs	NA	NA	MTX (3), AZA (1)	NA	MMF (1), AZA (1)	AZA
Steroids	Yes, all	NA	Yes, in 3	NA	NA	Yes

IFX: Infliximab; ETN: Etanercept; RTX: Rituximab; ADA- Adalimumab; TCZ: Tocilizumab; UK: United Kingdom; USA: United States of America; IQR: Interquartile range; NA: Not available.

Supplementary Table 3. Data from paediatric biologic registries.

Country	Turkey	Thailand	Alabama, USA	Spain
Year	2017	2009	2017	2015
Author	Acar[87]	SuwanNAlai[88]	Stoll M[89]	Hernández[90]
Tuberculosis- No of patients	1 (JIA) on ADA	0	1 (IBD) on ADA	0
Type of article/ paper	Retrospective analysis	Retrospective analysis of data from single centre	Retrospective analysis	Cohort observational study
Total number	N=73	N=5	N=1033	n=214
Type of AIIRD				
JIA	16 (21.9)	3	613	163 (73.6)
SLE	0	0	13	0
Vasculitis (Including BD)	3 (4.1)	0	5	0
SSc/MCTD	0	0	0	0
Sarcoidosis	3 (4.1)	0	17	0
IIM	0	1	3	0
PSS	0	0	7	0
Uveitis	39 (53.4)	0	31	8 (3.7)
IBD	8 (11)	0	265	46 (20.8)
Autoinflammatory	0	1	11	3 (1.5)
Others	4(5.5)	0	35	0
Duration of follow-up (Median)	18 (6-60) months	NA	1564 person-years	641 patients-year, Median- IQR 2.3 years (1.4–4.3).
N total whose complete data is available	73	5	1033	214
Total no of infection events	NA	NA	NA	NA
Major/ serious Infections- No of events	NA	NA	NA	NA
Opportunistic infections	NA	NA	NA	NA
Minor Infections- No of events	NA	NA	NA	NA
Drug	**ADA-39 ETN-22 IFX-12**	**ETN-3 IFX-2**	**IFX-527 ADA-469 ETN-324 CER-9 GOL-6**	**ETN-51.7% ADA (31.0 %) IFX-17.3%**
Biologic Doses received	NA	NA	NA	NA
Duration of biologic treatment	NA	NA	IFX- 840.6 ADA- 495.3 ETN-194.6 CER-2.0 GOL-1.5 Patient years	ETN 1.9 [1.8–3.7]; ADA 1.8 [1.2–2.6]; and IFX 2.1 [1.4–3.3] patient years
Concomitant drugs	MTX-37 (50.7) CYS-13 (17.8) AZA-9 (12.3)	NA	NA	NA
Steroids	45 (61.6)	NA	NA	NA
Other	NA	NA	NA	NA

Supplementary Table 4. Prevalence of tuberculosis in paediatric autoinflammatory diseases.

Retrospective				**Prospective**
Country	France	France	Italy	USA
Year	2012	2009	2010	2017
Author	Galeotti[91]	Neven[92]	Lepore[93]	Arostegui[94]
Tuberculosis- No of patients	**0**	**0**	0	0
Type of article/ paper	E-mail survey among the members of the French Paediatric Society for Paediatric Rheumatology (SOFREMIP) -Registry based	Data from medical records of NOMID/CINCA syndrome patients from 2 centres	Registry based	Open label Phase II
N with complete data	6	8	**17**	
Disease classification	MKD n=6	NOMID/CINCA n=8	CINCA/MWS-n=17	HIDS n-6
Duration of follow-up (Median, IQR, years)	11-21 months	26–42 months	37.5 months (range, 12 to 54 months)	Max-24 months
Total no of infection events	2	0	NA	NA
Major/ serious Infections- Number of events	1	0	NA	NA
Opportunistic infections	0	0	0	0
Minor Infections- Number of events	1	0	NA	NA
Death	0	0	0	0
Drug	**CAN-4 ANK- 4**	**ANK-8**	**ANK-17**	**CAN-6**
Biologic Doses received	ANK-1 to 5 mg/kg/day CAN-2 to 7 mg/kg every 8 weeks	ANK- 3-10 mg/kf/day	ANK-starting dosage of 1 mg/kg/d (maximum, 100 mg)	300 mg (or4 mg/kg for patients weighing<40 kg)
Duration of biologic treatment	15 (4–72) months	26-42 months	NA	NA
Concomitant drugs	NA	NA	NA	NA
Steroids	1	NA	NA	NA

MKD: Mevalonate kinase deficiency; NOMID: Neonatal-onset multisystem inflammatory disease; CINCA: Chronic infantile neurologic, cutaneous, articular syndrome; MWS: Muckle Wells Syndrome; crFMF: Colchicine resistant familial Mediterranean fever; TRAPS: Tumor necrosis factor associated periodic fever; FCAS: familial cold autoinflammatory syndrome; HIDS: Hyperimmunoglobulinemia D with Periodic Fever Syndrome; RTX: Rituximab; CYC: Cyclophosphamide; USA: United States of America; UK: United Kingdom; SLE: Systemic lupus erythematosus; NPSLE: neuropsychiatric systemic lupus erythematosus; JIA: Juvenile idiopathic arthritis;

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Supplementary Table 4. Prevalence of tuberculosis in paediatric autoinflammatory diseases. *(continued)*

UK	Multicenter Canada, USA, Germany, Ireland, Spain, Turkey, Switzerland, Russia, Japan	Multicenter	Germany	USA
2004	2018	2011	2011	2012
Hawkins[95]	Benedetti[96]	Kuemmerle-Deschner[97]	Kuemmerle-Deschner[98]	Sibley[99]
0	0	0	0	0
Prospective follow-up	Randomised controlled trial followed by an open label follow-up	open-label, phase III study conducted at 33 centres	Single centre observational study	Cohort-5 year follow-up
1	**53**	**46**	**5**	**20**
MWS-n=1	crFMF-n-14 MKD-n=28 TRAPS—n=14	FCAS-5 MWS-23 NOMID-18	MWS-5	NOMID-22
3 months	16 weeks	290 days (29–625 days)	11 months (range 5–14 months)	Max -5 years 148.1 patient-year
0	NA	NA	5	NA
0	8 cr-FMF-3/100 PY MKD-7/100 PY TRAPS-0/100 PY	NA	0	3
0	0	0	0	0
0	NA	NA	5	NA
0	0	0	0	0
ANK-1	CAN-56	**CAN-47**	**ANK-5**	**ANK-22**
ANK-100 mg once daily	CAN-150 mg, or 2 mg per kilogram of body weight for patients weighing ≤40 kg every week	150 mg or 2 mg/kg (≤40 kg) every 8 weeks for up to 2 years	1–2 mg/kg in patients weighing <40 kg and 100 mg for patients weighing >40 kg	started at 1 mg/kg by daily subcutaneous injection. Stepwise dose increases of 0.5–1 mg/kg per injection were made as frequently as every 2 weeks to achieve laboratory and organ inflammation remission
3 months	Exposure in PY crFMF- 45.6 MKD- 51.0 TRAPS-39.2	290 days (29–625 days)	At least 2 weeks	60 months
NA	Colchicine (100%)	NA	NA	NA
NA	NA	NA	NA	NA

LN: Lupus nephritis; AIIRD: Autoimmune inflammatory rheumatic diseases; IQR: Interquartile range; NA: Not available; CMV: Cytomegalovirus; ILD: Interstitial lung diseases; MMF: Mycophenolate mofetil; HCQ: hydroxychloroquine; AZA: Azathioprine.