Long-term safety and effectiveness of etanercept in JIA: an 18-year experience from the BIKER registry

Giulia Armaroli (g.armaroli@asklepios.com)
Asklepios Kinderklinik Sankt Augustin https://orcid.org/0000-0001-6429-6718
Ariane Klein
Asklepios Kinderklinik Sankt Augustin
Gerd Ganser
Rheumatologisches Kompetenzzentrum Norwestdeutschland
Michael J. Ruehlmann
Praxis fuer Kinderrheumatologie Dr. M. Ruehlmann Goettingen
Frank Dressler
Medizinische Hochschule Hannover Zentrum fur Kinder- und Jugendmedizin
Anton Hospach
Klinikum Stuttgart Olgahospital Kinder- und Jugendmedizin
Kirsten Minden
Charite Universitatsmedizin Berlin
Ralf Trauzeddel
HELIOS Klinikum Berlin-Buch
Ivan Foeldvari
Hamburger Zentrum fuer Kinder- und Jugendrheumatologie
Jasmin Kuemmerle-Deschner
Universitatsklinikum Tubingen Klinik fur Kinder- und Jugendmedizin
Frank Weller-Heinemann
Prof. Hess Kinderklinik Klinikum Bremen mitte
Andreas Urban
Klinikum St. Marien Amberg
Gerd Horneff
Asklepios Kinderklinik Sankt Augustin

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Abstract

Background: At present, etanercept represents the most frequently prescribed biologic agent in patients with juvenile idiopathic arthritis (JIA). The following study evaluates the long-term safety and effectiveness of etanercept in JIA patients compared to a biologic-naïve JIA cohort using long-term data from the German biologics registry (BiKeR).

Methods: JIA patients newly exposed to etanercept were documented in the BiKeR registry from January 2001 till March 2019, and baseline characteristics, effectiveness, as well as safety parameters were analysed. Response to treatment was assessed according to 10-joint Juvenile Arthritis Disease Activity Score (JADAS10), JADAS-defined minimal disease activity and remission, JIA-American College of Rheumatology (ACR) improvement criteria, as well as ACR-inactive disease definition. Safety assessments were based on adverse events (AE) reports.

Results: Over 18 years, a total of 2725 new etanercept users with a diagnosis of JIA were registered. Of these, etanercept was received as a first-line biologic by 95.8% and as monotherapy without concomitant methotrexate by 31.5%. The mean disease duration at baseline was 4.1±3.7 years. Already after three months of treatment, the mean JADAS10 decreased from 15.3±7.5 at baseline to 5.6±5.7 ($p<0.0001$) and JADAS-minimal disease activity was reached by 844 (45.9%) patients. Following one year of therapy, JIA-ACR30/50/70/90 improvement was reached by 81/75/61/42% of patients. After nine years on continuous treatment, 31(43.1%) patients were in JADAS-defined remission on drug. During the 5988 patient-years (PY) of etanercept exposure, 2053 AEs (34.3/100PY) were observed, including 226 serious AEs (3.8/100PY). Observed exposure-adjusted rates were 0.9/100PY for serious infections, 0.4/100PY for zoster reactivation, 0.3/100PY for inflammatory bowel disease and 1.9/100PY for uveitis. There were three malignancies and three deaths.

Conclusions: The current analysis adds to the established good safety profile of etanercept and reveals a durable long-term tolerability in JIA patients. Etanercept treatment provided rapid clinical improvement which was maintained up to nine years of drug use.

Background

Treatment of juvenile idiopathic arthritis (JIA) represents a major challenge in paediatric rheumatology. Diverse treatment options are currently available. Methotrexate is the most commonly prescribed conventional disease-modifying anti-rheumatic drug (DMARD). Within biologics, etanercept, a tumor necrosis factor inhibitor (TNFi), was the first drug to be approved for JIA in 2001 and represents at present the favoured first-line biologic agent for JIA patients [1]. Etanercept is approved for use in polyarticular JIA in children older than 2 years of age, and for use in psoriatic arthritis (PsA) and enthesitis-related arthritis (ERA) in patients older than 12 years of age. For systemic JIA or persistent oligoarthritis, etanercept is not approved, so that its use in these conditions is mostly reserved for children who experience refractory disease [2]. From 2001 to present, the increasing use of etanercept in patients with JIA has raised awareness of rare serious adverse events, such as malignancies and autoimmune conditions, including, but not limited to uveitis, inflammatory bowel disease and demyelinating disorders [3–5]. Also, children and adolescents with JIA are often treated with etanercept over long periods of time, sometimes even into adulthood. Yet, knowledge about its safety and effectiveness in the long-term is limited.

The German registry for biologics in paediatric rheumatology (BiKeR) is one of the largest national registries on the use of biologics in JIA. Over a period of 18 years, it has accumulated a large quantity of data on etanercept treated JIA patients. We performed a systematic review of the BiKeR registry to evaluate the long-time safety and effectiveness of etanercept in JIA using a biologic-naïve cohort as a comparator.

Methods

The German BiKeR registry has been documenting treatment of JIA with biologics since 2001 and has been extensively described in previous reports [6–7]. It was approved by the ethics committee of the physician board Aerztekammer Nordrhein, Duesseldorf. The BiKeR registry is registered in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP [8]). Written consent was obtained from patients and parents, and repeated when the patient became an adult. Pseudonymized data were collected for each JIA patient starting a biologic therapy and belonging to the seven ILAR-defined JIA categories [9] as determined by the reporting physician. Patient assessment regarding effectiveness and occurrence of adverse events (AEs) was performed at baseline and at follow-up after three and six months and every six months thereafter. After discontinuation of treatment, patients were followed up every six months with a request to report any AE, and patients transitioning to adult care are followed up by the JuMBO registry [10]. Patients of the registry newly starting treatment with etanercept from January 2001 to March 2019 were included in the study if they had assessments at baseline and at least at the three-month visit, irrespective of diagnosis. All follow-up forms received prior to April 2019 were evaluated. JIA patients who newly started methotrexate treatment and never received biologics were recruited between 2005 and 2011 till inclusion of 1500 patients and served as the control group.

Assessment of effectiveness

Effectiveness parameters were defined as follows. The JIA-American College of Rheumatology (ACR) improvement criteria and the Juvenile Arthritis Disease Activity Score (JADAS) were calculated as previously described [11–12]. JIA-ACR core set parameters consist of (i) physician global assessment of disease activity (PhysVAS) on a 10 cm visual analogue scale (VAS); (ii) parent/patient global assessment of overall well-being (PatVAS) on a 10 cm VAS; (iii) the Childhood Health Assessment Questionnaire (CHAQ); (iv) the number of joints with active arthritis, defined by the presence of swelling or, if no swelling is present, limitation of motion accompanied by pain, tenderness or both; (v) the number of joints with limited range of motion; and (vi) the erythrocyte sedimentation rate (ESR). The ACR-inactive disease definition was used according to Wallace et al. [13], requiring no active uveitis or arthritis, no fever, rash, splenomegaly, serositis, generalized lymphadenopathy or elevation of ESR/C-reactive protein (CRP), best possible PhysVAS, and duration of morning stiffness of ≤ 15 minutes. JADAS10 was chosen, which considers a maximum of 10 active joints besides PatVAS, PhysVAS, and ESR or CRP, all equally weighted. Rates of JADAS-minimal disease activity and JADAS-remission, respectively defined as JADAS10 ≤ 3.8 and JADAS10 ≤ 1, were calculated according to the definition of Consolaro et al. [14]. Reports with missing data were excluded.

Safety analysis

Safety was analysed based on AE reporting for all patients during the whole period of etanercept treatment. According to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for

Human Use (ICH) E6 Sect. 1.2 [15], an AE is defined as any untoward medical occurrence in a subject temporarily associated with an administered pharmaceutical product, even without causality or relationship to the drug. Serious AEs (SAEs) include death, life-threatening events, events leading to or prolonging hospitalization, persistent or significant disability/incapacity, or important medical events requiring medical or surgical intervention to prevent a serious outcome or congenital anomaly/birth defect. Exposure-adjusted AE rates were calculated per 100 patient-years (PY) with 95% confidence interval (CI). AEs and SAEs were attributed to the etanercept treatment if the patient had been treated with etanercept at the time of the occurrence of the AE or during the last 90 days prior to the AE occurrence, regardless of a possible cotreatment with methotrexate. Malignancies, pregnancies and deaths were additionally analysed in the ever-treated population. Reasons for discontinuation of etanercept treatment were also documented. Multiple reasons could be given.

Statistical analysis

For the comparison of baseline characteristics, the chi-squared, Fisher's exact or Mann-Whitney U-test was used, depending on data distribution. Mean changes from baseline in each effectiveness parameter were compared using the unpaired t-test. Differences in AE rates were analysed using risk ratios (RRs) and the Wald test. A p-value < 0.05 was considered statistically significant. Analyses were conducted with IBM SPSS Statistics version 23 (IBM Corp., Armonk, NY, USA) and SAS 9.3 (SAS Institute, Cary, NC, USA).

Results

Study population

Within the JIA patients who initiated etanercept treatment for the first time between 2001 and 2019, 2725 were eligible for the analysis. The cohort subtype distribution varied considerably over the years (Fig. 1). Rates of etanercept treated patients with rheumatoid factor (RF)-negative polyarthritis and with ERA increased over time (23.5 and 9.8% in 2001, 37.2 and 22.1% in 2018, respectively), while percentages of patients with systemic JIA or RF-positive polyarthritis decreased (20.4 and 19.4% in 2001, 0.9 and 8.0% in 2018, respectively). The comparison cohort of 1517 JIA biologic-naïve patients starting methotrexate significantly differed from the etanercept cohort for subtype distribution (Table 1). More patients in the etanercept group had a polyarticular course ($p < 0.0001$ for extended oligoarthritis, RF-negative- and positive polyarthritis). Also, more patients were diagnosed with ERA ($p = 0.001$), and significantly more patients were human leucocyte antigen (HLA)-B27 positive ($p < 0.0001$). Patients with persistent oligoarthritis or PsA were more frequent in the biologic-naïve cohort ($p < 0.0001$ and $p = 0.017$, respectively). The main demographic characteristics are summarised in Table 1. While age at disease onset was comparable, age at baseline was significantly higher in the etanercept group (12.1 ± 4.4 versus 9.8 ± 4.8 years; $p < 0.0001$). Disease duration at baseline, as calculated from symptom onset to start of cohort defining treatment, was also significantly higher in the etanercept cohort (4.1 ± 3.7 versus 2.1 ± 2.8 years; $p < 0.0001$). However, a significant decrease in the mean disease duration at etanercept start was observed over time (from 6.0 ± 3.9 in 2001 to 3.3 ± 3.1 years in 2018; $p = 0.0001$; Supplementary figure S1a). Pretreatment with systemic steroids was more frequent in the etanercept cohort than in the biologic-naïve group (52.6 versus 23.5%; $p < 0.0001$). At baseline, 86.5% of etanercept patients had been pretreated with methotrexate, while only 4.2% had been preexposed to other biologics. Concomitant treatment at baseline with nonsteroidal anti-inflammatory drugs (NSAIDs) was observed more frequently in the etanercept group (79.2

versus 23.7%; p = 0.0001), whereas biologic-naïve patients were significantly more often cotreated with systemic steroids (91.9 versus 35.7%; p = 0.0001). All disease activity parameters at baseline, except for mean ESR levels, were significantly higher in the etanercept cohort (Table 1). However, the mean JADAS10 at etanercept treatment initiation showed to decrease significantly over the years (from 20.6 ± 7.8 in 2001 to 10.7 ± 5.8 in 2018; p = 0.003; Supplementary figure S1b).

Table 1
Baseline characteristics.

	Etanercept cohort (N = 2725)	Biologic-naïve cohort (N = 1517)	p†
Gender, female	1829 (67.1)	1023 (67.4)	0.8
Age at onset (years)	7.9 ± 4.7	7.7 ± 4.6	0.18
Age at baseline (years)	12.1 ± 4.4	9.8 ± 4.8	< 0.0001*
Disease duration (years)	4.1 ± 3.7	2.1 ± 2.8	< 0.0001*
JIA category			
systemic JIA	146 (5.3)	58 (3.8)	0.025*
RF-negative polyarthritis	904 (33.1)	415 (27.3)	< 0.0001*
RF-positive polyarthritis	223 (8.1)	52 (3.4)	< 0.0001*
Persistent oligoarthritis	120 (4.4)	390 (25.7)	< 0.0001*
Extended oligoarthritis	570 (20.9)	204 (13.4)	< 0.0001*
ERA	486 (17.8)	213 (14.0)	0.001*
PsA	191 (7.0)	138 (9.0)	0.017*
Unclassified JIA	85 (3.1)	47 (3.0)	1.0
ANA	1290 (47.3)	725 (47.8)	0.8
HLA-B27	643 (23.6)	265 (17.5)	< 0.0001*
Pretreatment at baseline			
NSAIDs	2478 (90.9)	1329 (87.6)	0.0007*
Systemic steroids	1434 (52.6)	357 (23.5)	< 0.0001*
MTX	2358 (86.5)	0 (0)	< 0.0001*
Biologics	114 (4.2)	0 (0)	< 0.0001*
Other DMARDs	1232 (45.2)	149 (9.8)	< 0.0001*
SFZ	415 (15.2)	67 (4.4)	< 0.0001*
HCQ	228 (8.4)	53 (3.5)	< 0.0001*
AZA	237 (8.7)	14 (0.9)	< 0.0001*
LEF	85 (3.1)	6 (0.4)	< 0.0001*
CSA	140 (5.1)	8 (0.5)	< 0.0001*
Chlorambucil	19 (0.7)	0 (0)	0.0004*

	Etanercept cohort (N = 2725)	Biologic-naïve cohort (N = 1517)	p†
Cyclophosphamide	10 (0.4)	0 (0)	0.0175*
Gold salts	36 (1.3)	0 (0)	< 0.0001*
Immunoglobulins	48 (1.8)	1 (0.1)	< 0.0001*
MMF	14 (0.5)	0 (0)	0.0034*
Concomitant treatment at baseline			
NSAIDs	2158 (79.2)	360 (23.7)	0.0001*
Systemic steroids	974 (35.7)	1394 (91.9)	0.0001*
MTX	1867 (68.5)	1517 (100.0)	< 0.0001*
Other DMARDs			
SFZ	145 (5.3)	36 (2.4)	0.0001*
HCQ	37 (1.4)	14 (0.9)	0.24
AZA	80 (2.9)	4 (0.3)	0.0001*
LEF	59 (2.2)	1 (0.1)	0.0001*
CSA	57 (2.1)	2 (0.1)	0.0001*
Disease activity parameters at baseline			
Active joints	6.7 ± 8.1	5.8 ± 7.6	0.0004*
Swollen joints	5.3 ± 7.4	4.8 ± 6.8	0.03*
Tender joints	6.5 ± 8.4	5.8 ± 7.8	0.007*
PhysVAS	52.2 ± 32.3	47.2 ± 25.9	0.0001*
PatVAS	43.7 ± 27.4	39.0 ± 26.0	0.0001*
Joints with LOM	7.4 ± 8.9	5.7 ± 7.6	0.0001*
CHAQ-DI	0.7 ± 0.6	0.6 ± 0.6	0.0001*
ESR (mm/h)	23.5 ± 23.4	24.2 ± 23.0	0.35
CRP (mg/L)	16.8 ± 32.7	13.9 ± 27.9	0.004*
JADAS10	15.3 ± 7.5	13.9 ± 7.1	0.0001*
Data are shown as n (%), mean ± SD, or n.			
†By t-test or Fisher's exact test, as appropriate. *p < 0.05.			

	Etanercept cohort (N = 2725)	Biologic-naïve cohort (N = 1517)	p†
JIA, juvenile idiopathic arthritis; RF, rheumatoid factor; ERA, enthesitis-related arthritis; PsA, psoriatic arthritis; ANAs, antinuclear antibodies; HLA, human leucocyte antigen; NSAID, non-steroidal anti-inflammatory drug; MTX, methotrexate; DMARD, disease-modifying anti rheumatic drug; SFZ, sulfasalazine; HCQ, hydroxychloroquine; AZA, azathioprine; LEF, leflunomide; CSA, cyclosporine; PhysVAS, physician global assessment of overall well-being; PatVAS, parent/patient global assessment of overall well-being; LOM, limitation of motion; CHAQ-DI, Childhood Health Assessment Questionnaire disability index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; JADAS10, 10-joint Juvenile Arthritis Disease Activity Score.			
Additional files			
File name:			
Supplementary figure S1			
File format:			
.docx			
Title and description of data:			
Supplementary figure S1. Disease duration and activity per recruitment year in the etanercept cohort. (a) Disease duration at the start of etanercept treatment per recruitment year. (b) Mean 10-joint Juvenile Arthritis Disease Activity Score (JADAS10) at baseline and after 12 months of etanercept treatment per recruitment year. (c) Patients reaching JADAS-minimal disease activity (MDA) and JADAS-remission at month 12 upon etanercept per recruitment year. ***p < 0.001, **p < 0.01			

Table 1. *Baseline characteristics*.

Effectiveness

A significant improvement in the mean JADAS10 was observed as early as three months after etanercept treatment initiation, with a decrease from 15.3 ± 7.5 at baseline to 5.6 ± 5.7 ($p < 0.0001$). After 12 months of continuous treatment, a further significant improvement of the mean JADAS10 to 4.1 ± 5.3 was observed ($p < 0.0001$; Fig. 2). Patients recruited in the most recent years achieved a lower JADAS10 after 12 months on etanercept compared to those enrolled in the earlier years, although the difference did not reach significance (2.3 ± 2.0 in 2018 compared to 6.9 ± 7.2 in 2001; $p = 0.0637$; Supplementary figure S1b).

JADAS-defined minimal disease activity (MDA; JADAS ≤ 3.8) was reached at month 3, 12, 24 in 844 (45.9%), 990 (58.6%) and 734 (61.8%) etanercept patients. After 5, 7, 9 years of ongoing treatment, 252 (63.0%), 120 (63.8%) and 49 (68.1%) patients showed minimal disease activity. JADAS-remission (JADAS ≤ 1) was reached at month 3, 12, 24 in 315 (17.2%), 591 (35.0%) and 449 (37.8%) patients. After 5, 7, 9 years of etanercept treatment, 175 (43.8%), 76 (40.4%) and 31 (43.1%) patients were in JADAS-defined remission on drug (Fig. 3). Over the course of the years, the percentage of patients who reached JADAS-MDA and JADAS-remission following 12 months of etanercept treatment increased, respectively, from 43.1 and 20.9% in 2001 to 72.8 and 45.6% in 2018 (Supplementary figure S1c).

ACR-inactive disease according to Wallace [13] was reached at month 3, 12, 24 by 166 (25.0%), 248 (42.8%) and 180 (46.3%) etanercept patients. After 5, 7, 9 years of continuous treatment, 84 (46.9%), 43 (48.9%) and 15

(36.6%) patients presented ACR-inactive disease (Fig. 3). Improvement according to JIA-ACR30/50/70/90 criteria was reached in 74/64/45/24% of patients at month 3, in 81/75/61/42% of patients at month 12 and in 82/76/64/46% of patients at month 24 (Fig. 4). JIA-ACR30/50/70/90 response rates were 84/80/68/53% after 5 years, 82/79/69/57% after 7 years and 82/79/71/54% after 9 years on etanercept, remaining therefore stable under prolonged therapy.

Discontinuations

Over 18 years of observation, etanercept was discontinued by 1655 (60.7%) patients. Rates and reasons for discontinuation are listed in Table 2. Multiple reasons could be given by the patient/caregiver. The most common reason for discontinuation was remission (n = 652 [23.9%]), followed by inefficacy (n = 594 [21.8%]) and intolerance (n = 192 [7.1%]).

Table 2
Rates and reasons for discontinuation.

	Etanercept cohort (N = 2725)
Discontinuations	1655 (60.7)
Remission	652 (23.9)
Inefficacy	594 (21.8)
Intolerance	192 (7.1)
Patient´s demand	504 (18.5)
Others	287 (10.5)
Data are shown as n (%). Multiple reasons could be given.	

Safety

During 5988 patient years of etanercept exposure, a total of 2053 AEs was reported to the registry (Table 3). No significant difference in exposure-adjusted AE rates was observed between etanercept (34.3/100PY) and biologic-naïve patients (35.6/100PY; p = 0.3). The AEs qualifying as serious (SAEs) were significantly more frequent in the etanercept cohort (3.8 versus 1.4/100PY; p = 0.0001). The incidence of serious infections was significantly higher in the etanercept group (0.9 versus 0.2/100PY; p = 0.0001), while neutropenia rates were comparable in the two cohorts (0.07 versus 0.05/100PY; p = 0.8). All reported opportunistic infections, but for one case of latent tuberculosis, were herpes zoster reactivation, and were more often observed under etanercept (0.4 versus 0.1/100PY; p = 0.01). The case of latent tuberculosis consisted in a positive Quantiferon Gold test without any clinical symptom or change in chest radiograph and was documented in a patient on methotrexate and with previous etanercept treatment. Inflammatory bowel disease (IBD) occurred with significantly greater frequency in etanercept patients (0.3 versus 0.03/100PY; p = 0.015). Rates of psoriasis (0.07 versus 0.003/100PY; p = 0.4) and aggravation/new onset of uveitis (1.9 versus 1.4/100PY; p = 0.09) did not differ significantly between the two cohorts. One patient in the etanercept cohort developed demyelination and none in the biologic-naïve control cohort. The lesion, a minor alteration of the periventricular white matter, was

discovered incidentally in an asymptomatic patient, and has been described earlier [7]. Other reported immune-mediated events were Henoch-Schoenlein Purpura, leukocytoclastic cutaneous vasculitis and lupus-like syndrome in one patient each. All three patients were on etanercept treatment. Fifteen reports of suicidal intention or ideation, suicide attempt or depression were documented in the etanercept cohort. Six were observed in RF-negative- and one in RF-positive polyarthritis patients, two cases in extended- and one in persistent oligoarthritis patients, two in ERA and three in PsA patients. In all, the occurrence of suicide intention/depression was significantly higher than in the biologic-naïve group (0.25 versus 0.05/100PY; p = 0.04).

Three pregnancies occurred in patients under etanercept treatment at the time of conception. A 17-year-old patient who was treated with etanercept and methotrexate delivered at term a healthy 3360-g male infant after a pregnancy without complications. Treatment was interrupted as her pregnancy was diagnosed at six weeks of gestation. The child was developing normally at two months of age. An 18-year-old patient gave birth to a healthy male infant, weight and gestational age of which have not been reported by the documenting physician. At the age of six months, the child showed normal growth and development. The third patient decided on an induced abortion at 12 weeks of gestation. Additionally, a miscarriage after 12 weeks of gestation was reported to the registry in an 18-year-old patient, two years after discontinuation of etanercept. She had been treated with etanercept 50 mg weekly over nine months. The patient received hydroxychloroquine 300 mg daily from 20 months before conception through eight weeks of pregnancy. No pregnancy was recorded in the biologic-naïve cohort.

Three malignancies were documented in patients on etanercept at the time of diagnosis (0.05/100PY). An 18-year-old male patient developed a non-familial thyroid carcinoma. One case each of Hodgkin´s and Non-Hodgkin´s lymphoma were reported in two male patients. Malignancies were reported to the registry in five other patients who had been exposed to etanercept in the past. Two cases of lymphoproliferative disorder and one case each of anaplastic ependymoma, Yolk sac carcinoma and cervix dysplasia. All patients recovered. In the biologic-naïve cohort with methotrexate, two cases of acute lymphatic leukaemia (ALL) were documented (0.05/100PY). One patient recovered, the second died. All malignancy cases have been previously described [16].

In all patients ever treated with etanercept, five deaths were reported, three of these during drug exposure. Two deaths occurred during adolescence and three in adulthood. One patient with systemic JIA died due to septic shock while on treatment with etanercept, after having been pretreated with cyclophosphamide and chlorambucil years before. A second patient with systemic JIA succumbed to heart failure by macrophage activation syndrome (MAS), one year after discontinuation of etanercept due to inefficacy. Both deaths occurred at the age of 16 years, and have been formerly reported [17]. Of the three deaths during adulthood, one occurred in a 22-year old due to perimyocarditis with arrhythmia, eight weeks after voluntary discontinuation of etanercept. A second patient died at the age of 22 years by suicide, seven years after etanercept discontinuation, and a third one died at the age of 23 years due to pseudomembranous enterocolitis by a septic urinary tract infection with renal failure and pancytopenia after 13 years of etanercept exposure. The events were considered as not related to etanercept treatment. In the biologic-naïve group, one death was reported. A 13-year-old female patient on methotrexate succumbed to ALL.

Table 3
Safety assessment: adverse event (AE) reports.

	Etanercept 5988 PY	Biologic-naïve 3782 PY		
	E/E/100PY (95% CI)	E/E/100PY (95% CI)	RR (95% CI)	p†
AE	2053/34.3(32.8–35.8)	1345/35.6(33.7–37.5)	1.0 (0.9–1.03)	0.3
SAE	226/3.8(3.3–4.3)	52/1.4(1.1–1.8)	2.8 (2.0-3.7)	0.0001*
Serious infection	54/0.9(0.7–1.2)	8/0.2(0.1–0.4)	4.3 (2.0–9.0)	0.0001*
Herpes zoster	24/0.4(0.3–0.6)	4/0.1(0.04–0.3)	3.8 (1.3–10.9)	0.01*
Neutropenia	4/0.07(0.03–0.18)	2/0.05(0.01–0.2)	1.3 (0.2–6.9)	0.8
MAS	2/0.03(0.008-0.3)	1/0.03(0.004–0.19)	1.3 (0.1–13.9)	0.9
High transaminases	97/1.6(1.3-2.0)	175/4.6(4.0-5.4)	0.4 (0.3–0.5)	0.0001*
IBD	19/0.3(0.2–0.5)	1/0.03(0.004–0.19)	12.0 (1.6–89.7)	0.015*
Uveitis	113/1.9(1.6–2.3)	54/1.4(1.1–1.9)	1.3 (0.96–1.8)	0.09
Psoriasis	4/0.07(0.03–0.18)	1/0.03(0.004–0.19)	2.5 (0.3–22.6)	0.4
Demyelination	1/0.02(0.002-0.1)	0/n. a.	n. a.	n. a.
Depression	15/0.25(0.2–0.4)	2/0.05(0.01–0.2)	4.7 (1.1–20.7)	0.04*
Malignancy	3/0.05(0.02–0.2)	2/0.05(0.01–0.2)	1.0 (0.2–5.7)	0.95
Death	3/0.05(0.02–0.2)	1/ 0.03(0.004–0.19)	1.9 (0.2–18.2)	0.6

†By Wald test. *p < 0.05.

PY, patient-years; E, event; E/100PY, rate; CI, confidence interval; RR, risk ratio; SAE, serious adverse event; MAS, macrophage activation syndrome; IBD, inflammatory bowel disease; n. a., not applicable.

Discussion

The current registry study represents the largest cohort of etanercept treated JIA patients studied. To our knowledge, it is the first report on safety and effectiveness of etanercept including all JIA categories and following patients up to nine years of continuous treatment. By interpreting the results, it should be considered that the etanercept- and the biologic-naïve group differ in baseline characteristics. This can likely be explained by the start of the cohort defining treatment at a different point of the disease course in the two groups. Patients initiating etanercept treatment according to JIA therapy recommendations were mostly those who failed to respond or responded inadequately to treatment with ≥ 1 conventional DMARD, hence, those with a refractory JIA. They were older, presented longer disease duration and higher disease activity at therapy start,

and had received more previous treatments than the biologic-naïve patients. In contrast, the latter were patients just initiating methotrexate treatment, which was the first DMARD prescribed in 90.2% of the cases. The majority of etanercept treated patients in Germany showed to be diagnosed with (RF-negative) polyarthritis, extended oligoarthritis or, though in lower numbers, ERA. From 2001 to present, a dramatic decrease in the use of etanercept in patients with systemic JIA could be observed. This is consistent with the fact that etanercept has not been approved for systemic JIA treatment, while interleukin (IL)1- and IL6 inhibitors are approved and currently represent the recommended biologic therapies [2]. Though etanercept monotherapy without methotrexate is approved for polyarticular JIA, ERA and PsA, more than two thirds of patients received methotrexate at baseline. Other conventional DMARDs were rarely used as cotreatment. In the earlier years, patients were pretreated with a large number of different antirheumatic drugs, including toxic drugs such as cyclophosphamide or chlorambucil. More recently, disease duration at etanercept initiation markedly decreased, and so did disease activity at baseline, indicating that etanercept was initiated earlier and in patients with less severe disease. Notably, in 95.8% of patients etanercept was used as a first line biologic. Moreover, in the most recent years, patients reached a lower disease activity following one year of etanercept treatment and more patients reached minimal disease activity and remission compared to previous years. This is consistent with increasing evidence in the literature indicating a positive prognostic effect of an early aggressive treatment due to a suggested window of opportunity [18]. A rapid improvement in disease activity upon etanercept treatment could be shown with 75% of patients reaching JIA-ACR30 after three months of therapy. The response rates thereafter further increased. We observed 71% and 57% of patients reaching JIA-ACR70 and JIA-ACR90, respectively, and 48.9% of patients reaching ACR-defined inactive disease under therapy with etanercept. These results are comparable to observations from other groups [19–21]. Our analysis included also data from 72 patients who had completed their ninth year of continuous etanercept treatment. The improvement in disease activity reached in the first year showed to be maintained during up to nine years of continuous drug use, in accordance to observations in previous studies [21–23].

Exposure-adjusted rates of adverse events on etanercept were low, and only few patients discontinued treatment because of intolerance. However, serious adverse events were more common under etanercept than under non-biological treatment, though no new major safety signal was observed. On etanercept, the exposure-adjusted rate of serious infections, the most frequent SAE, was low (0.9/100PY), although significantly higher than in biologic-naïve patients. Similar rates were reported in other long-term registry studies of etanercept in JIA (0.25/100PY in the Polish registry [20], 1.28/100PY in the Dutch registry [21] and 1.8/100PY in an American registry study [23]). In contrast, serious infection rates described in long-term trials were higher [19, 22]. Consistently with our findings, other groups have found increased risk ratios for serious infections on etanercept compared to non-biological treatments [3, 23], whereas others have described comparable rates for treatment with etanercept and methotrexate [24–25]. In an analysis of 2713 new TNFi users from the national US Medicaid data, Beukelman et al. found no significant differences in hospitalized infection rates for TNFi (monotherapy or in combination with methotrexate) compared to non-biological treatment with methotrexate, with a rate of 1.43/100PY on etanercept and 1.46/100PY on methotrexate [24]. Also, previous work of the same group described an increased risk of hospitalized bacterial infections in JIA patients not treated with either TNFi or methotrexate, suggesting that the underlying disease process itself, independently from treatment, could increase the rate of serious infections [25]. In our study, herpes zoster reactivation was the only opportunistic infection reported, and it was more often observed in etanercept than in biologic-naïve patients with methotrexate, similarly to what described by others [22–23]. Regarding the incidence of autoimmune disorders,

the rates for psoriasis and new onset or recurrence of uveitis did not significantly differ between etanercept- and biologic-naïve treated patients. New-onset IBD was described in 19 etanercept patients, which is consistent with previous findings [26]. Since etanercept was shown to be ineffective in Crohn´s disease, gastrointestinal manifestations in patients with IBD-associated arthritis may occur more likely under treatment with etanercept [27]. Only one case of suspected demyelination has been reported to our registry in conjunction with etanercept exposure. In the data from the large multinational Pharmachild/PRINTO pharmacovigilance study, demyelination was also a rare event [28]. The higher occurrence of depression under etanercept compared to biologic-naïve controls could be explained by the older age and more severe disease in the former. Depressive symptoms are not as common in younger patients, and sustained pain and disease-induced disability in refractory disease constitute well-known risk factors for depression [29]. Comparable to observations from the Pharmachild registry [28], as well as from American and Scandinavian registry studies [4–5], treatment with etanercept did not associate with an increased risk for malignancies.

The interpretation of the results provided here is potentially influenced by the classic limitations accompanying registry studies. The control group of biologic-naïve patients presented significant differences at baseline to the etanercept group, due to the fact that while the latter had a refractory and more active disease, the former had just begun treatment with methotrexate as first line DMARD. The two study groups differed also in JIA subtype distribution. Furthermore, lack of blinding and randomization must be considered when interpreting the results. Yet, registry studies remain of great importance because they reflect routine care and allow investigation of safety and effectiveness in a complete spectrum of patients and in a real-world setting. Differently, decisions in randomized clinical trials (RCTs) may be influenced by protocol and inclusion/exclusion criteria generate a mostly homogeneous study population of selected patients, e. g. by excluding determinate subtypes, comorbidities or concomitant drugs. Moreover, in the present analysis the high number of patients and the long study period allow detection of rare adverse events and adverse events occurring with long-term exposure.

Conclusions

The present analysis demonstrates that etanercept provides a rapid initial response and a sustained clinical benefit up to nine years of continuous drug use by a positive long-term safety profile in children with JIA. No new safety signal specific to the paediatric population was identified in this large cohort of JIA patients.

List Of Abbreviations

ACR: American colleague of rheumatology; AE: Adverse event; ALL: Acute lymphatic leukaemia; BiKeR: Biologics in paediatric rheumatology registry; CHAQ: Childhood health assessment questionnaire; CI: Confidence interval; CRP: C-reactive protein; DMARD: Disease-modifying anti-rheumatic drug; ENCePP: European network of centres for pharmacoepidemiology and pharmacovigilance; ERA: Enthesitis-related arthritis; ESR: Erythrocyte sedimentation rate; HLA: Human leucocyte antigen; IBD: Inflammatory bowel disease; ICH: International council for harmonisation of technical requirements for pharmaceuticals for human use; IL: Interleukin; ILAR: International league of associations for rheumatology; JADAS: Juvenile disease activity score; JADAS10: 10-joint juvenile disease activity score; JIA: Juvenile idiopathic arthritis; JIA-ACR: American college of rheumatology improvement criteria for JIA; JRA: Juvenile rheumatoid arthritis; JuMBO: Juvenile arthritis-methotrexate-biologics long-term observation; MAS: Macrophage activation syndrome; MDA: Minimal disease

activity; NSAIDs: Nonsteroidal anti-inflammatory drugs; PatVAS: Parent/patient global assessment of overall well-being on a 10 cm VAS; PhysVAS: Physician global assessment of disease activity on a 10 cm VAS; PRINTO, Paediatric Rheumatology International Trials Organisation; PsA: Psoriasis arthritis; PY: Patient-years; RCTs: Randomized clinical trials; RF: Rheumatoid factor; RR: Risk ratio; SAE: Serious adverse event; SD: Standard deviation; TNF: Tumour necrosis factor; TNFi: Tumour necrosis factor inhibitor; VAS: Visual analogue scale.

Declarations

Ethics approval and consent to participate

The German BiKeR Registry was approved by the responsible independent ethics committee of the Aerztekammer Nordrhein, Duesseldorf. Written informed consent was obtained from patients and parents/legal guardians and repeated if patient became adult. Only pseudonymized data were collected.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Competing interests

AK has received congress travel fees from Sobi and Sandoz as well as advisory board honoraria from Celgene. FD has received honoraria for lectures from Pfizer, Abbvie, and Novartis. AH has received advisory board honoraria from Novartis, Chugai-Roche, and Sobi. KM has received honoraria from Abbvie, GSK, Biermann, Medac and Sanofi. IF discloses advisory board participation for Novartis, Genzyme, Bayer, Lilly, Pfizer, Abbvie, and Sanofi. JKD has received consultants/speakers fees from Novartis and Sobi, as well as pharmaceuticals and grant support from Sobi and Novartis. FWH has received speaker honoraria from Pfizer, Abbvie, Novartis, Sobi, and Roche. GH has received research funds, advisory board membership and honorary fees from Abbvie, Pfizer, Novartis and Roche/Chugai. The other Authors have declared no competing interests.

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Authors' contributions

All authors made substantial contributions to acquisition of data. AG, GH and AK analysed and interpreted the data. All authors approved the final version of the manuscript for publication.

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Supplementary Figure Legend

Supplementary figure S1. Disease duration and activity per recruitment year in the etanercept cohort. (a) Disease duration at the start of etanercept treatment per recruitment year. (b) Mean 10-joint Juvenile Arthritis Disease Activity Score (JADAS10) at baseline and after 12 months of etanercept treatment per recruitment year. (c) Patients reaching JADAS-minimal disease activity (MDA) and JADAS-remission at month 12 upon etanercept per recruitment year. ***p < 0.001, **p < 0.01

Figures

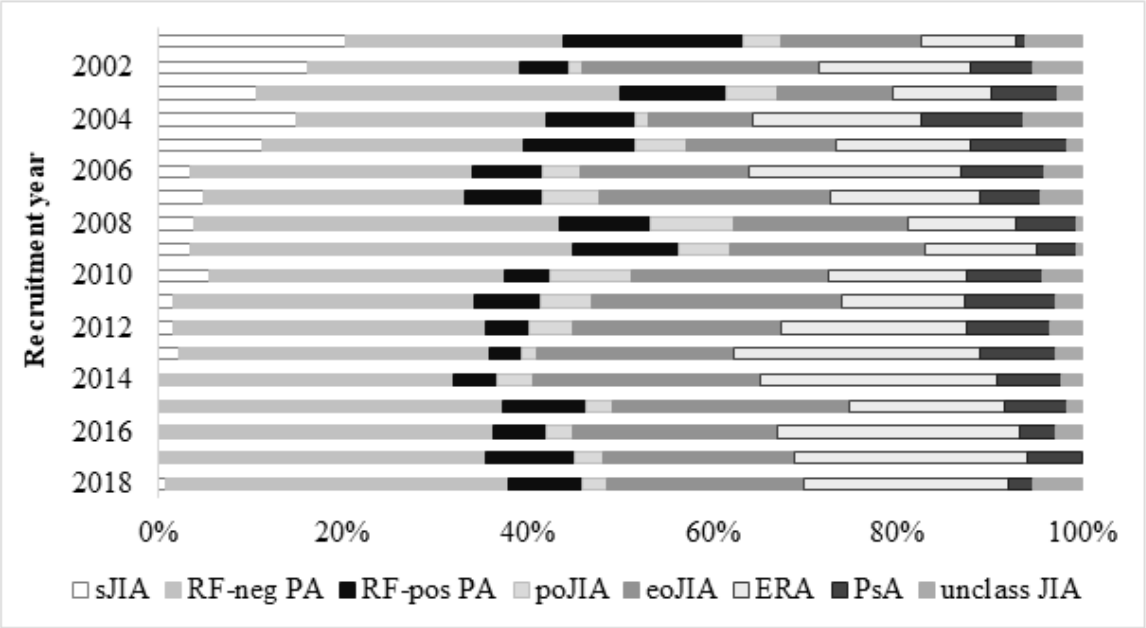

Figure 1

Subtype distribution per recruitment year in the etanercept cohort. sJIA, systemic juvenile idiopathic arthritis; RF-neg PA, rheumatoid factor negative polyarthritis; RF-pos PA, rheumatoid factor positive polyarthritis; poJIA, persistent oligoarthritis; eoJIA, extended oligoarthritis; ERA, enthesitis-related arthritis; PsA, psoriatic arthritis; unclass JIA, unclassified juvenile idiopathic arthritis.

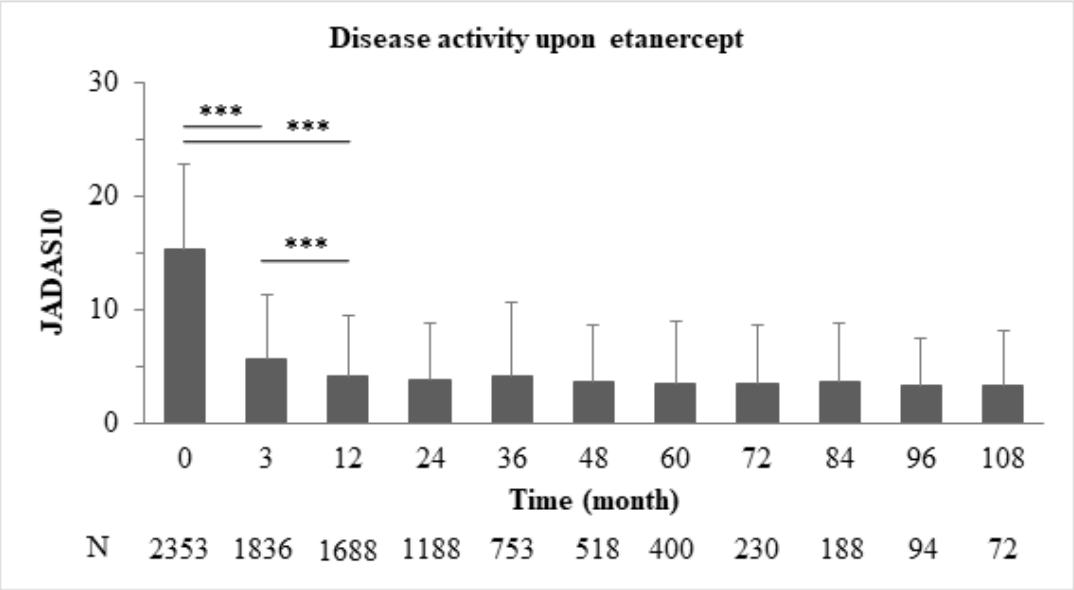

Figure 2

Mean JADAS10 as efficacy measure over time. Mean 10-joint Juvenile Arthritis Disease Activity Score (JADAS10) in JIA patients over the course of etanercept treatment. ***p < 0.001

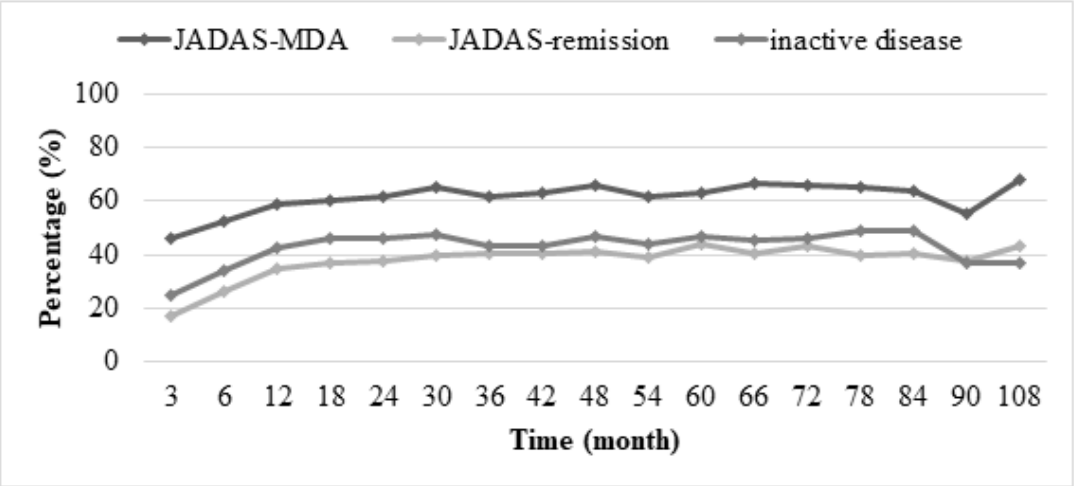

Figure 3

Measures of treatment efficacy over time. Rates of Juvenile Disease Activity Score (JADAS)10-minimal disease activity (JADAS10 ≤ 3.8), JADAS10-remission (JADAS10 ≤ 1) and rates of patients reaching inactive disease according to Wallace et al. [13] upon etanercept treatment.

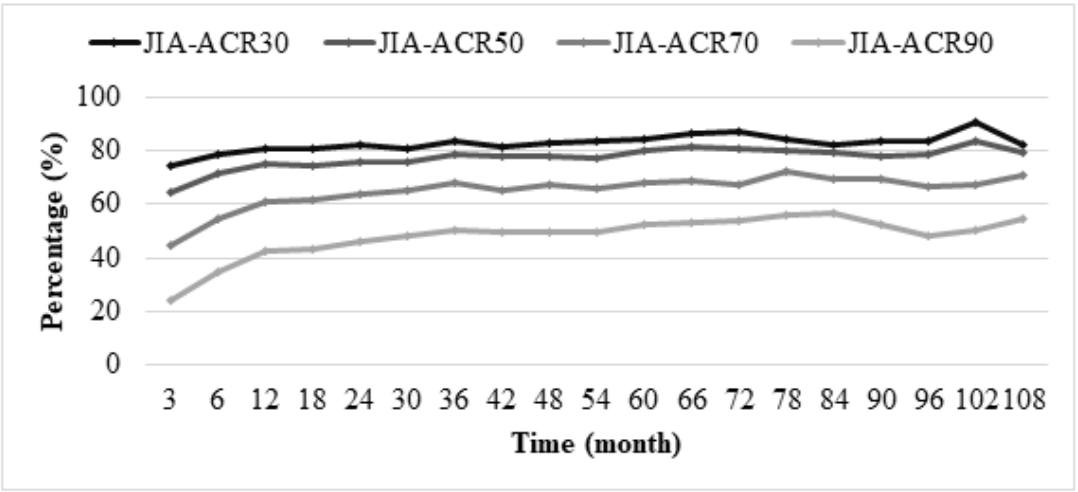

Figure 4

ACR improvement rates over time. Improvement rates of disease activity parameters over the course of etanercept treatment according to the JIA-American College of Rheumatology (ACR) criteria.

Supplementary Files

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- SupplementaryFigure1.jpg