

Efficacy and Safety of Etanercept Biosimilars Compared With the Originator for Treatment of Juvenile Arthritis: A Prospective Observational Study

Franz Thiele,¹ Ariane Klein,² Anton Hospach,³ Daniel Windschall,⁴ Sonja Mrusek,⁵ J. Michael Ruehlmann,⁶ and Gerd Horneff²

Objective. Analysis of etanercept biosimilars in pediatric patients with juvenile idiopathic arthritis (JIA) in comparison with the etanercept originator in terms of efficacy and safety.

Methods. Patients diagnosed with JIA who started treatment with either the etanercept originator or a biosimilar after January 1, 2017, were selected from the German BIKER registry (Biologics in Paediatric Rheumatology Registry). Furthermore, patients who started therapy with the originator and switched to a biosimilar during the course of therapy were identified. For both patient groups, disease activity and safety were examined and compared separately.

Results. After January 1, 2017, 348 patients started treatment with the etanercept originator (n = 293) or a biosimilar (n = 55). Another 57 patients switched to a biosimilar during the course of therapy. A significant decrease or a stable remission of disease activity was observed in both patient groups. The safety profiles were comparable, and frequencies and types of adverse events (AEs) and serious AEs were similar in patients starting therapy with the originator or a biosimilar. Only injection site reactions occurred slightly more frequently under biosimilar therapy, without having an impact on therapy adherence. In patients who switched therapy, the AE rate per 100 patient-years was comparable before (26.4) and after (32.1) the switch.

Conclusion. In patients with JIA who require treatment with etanercept, the originator is still used much more frequently. However, our study highlights the equivalence of etanercept biosimilars for therapy for JIA. Increased use of these biosimilars in pediatric patients can therefore be recommended without hesitation.

INTRODUCTION

Disease and problem of interest. Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in childhood and can lead to severe physical damage (1). The use of biologics has greatly improved the treatment options for JIA. Especially for the treatment of nonsystemic JIA, the class of tumor necrosis factor α (TNF α) inhibitors has proven to be highly effective (2). Etanercept, which was the first biologic that received U.S. Food and Drug Administration approval for

treatment of JIA in 1999 and European Medicines Agency (EMA) approval in 2000 (3), belongs to this class. It is a recombinant human TNF α receptor–p75Fc fusion protein that binds soluble TNF α with high affinity to biologically inactivate it. For the last 20 years, etanercept has been successfully used in clinical practice. However, the high costs of biologics prevent their use as a first-line therapy despite their favorable efficacy and tolerability. In order to at least partially reduce the high costs of biologics such as etanercept, several biosimilars have been developed in recent years. The EMA defines a biosimilar as “a biological

The German BIKER registry is supported by an unrestricted grant from Pfizer, Germany; AbbVie, Germany; Merck Sharp & Dohme, Germany; Roche, Germany.

¹Franz Thiele: Asklepios Clinic Sankt Augustin, Sankt Augustin, Germany; ²Ariane Klein, MD, Gerd Horneff, MD: Asklepios Clinic Sankt Augustin, Sankt Augustin, Germany, and University of Cologne, Cologne, Germany; ³Anton Hospach, MD: Klinikum Stuttgart, Olgahospital Stuttgart, Stuttgart, Germany; ⁴Daniel Windschall, MD: Northwest German Rheumatology Center, St. Josef Stift, Sendenhorst, Germany; ⁵Sonja Mrusek, MD: Practice for Paediatric Rheumatology, Baden-Baden, Germany; ⁶J. Michael Ruehlmann, MD: Practice for Paediatric Rheumatology, Goettingen, Germany.

Dr. Hospach has received consulting fees, speaking fees, and/or honoraria from Sobi and Novartis (less than \$10 000 each). Dr. Windschall

has received consulting fees, speaking fees, and/or honoraria from AbbVie, Novartis, and Pfizer (less than \$10 000 each). Dr. Mrusek has received speaking fees from Novartis (less than \$10 000). Dr. Ruehlmann has received consulting fees from AbbVie, Biogen, BMS, Hexal, Novartis, and Pfizer; speaking fees and honoraria from AbbVie, Biogen, BMS, Hexal, Novartis, and Pfizer; and invitations to meetings from AbbVie, Biogen, BMS, Hexal, Novartis, and Pfizer (less than \$10 000 each). No other disclosures relevant to this article were reported.

Address correspondence to Franz Thiele, Department of General Paediatrics, Asklepios Clinic Sankt Augustin, Arnold-Janssen-Strasse 29, Sankt Augustin, Germany 53757. Email: franz.thiele@hotmail.com.

Submitted for publication April 27, 2021; accepted in revised form July 13, 2021.

SIGNIFICANCE & INNOVATIONS

- This is the first prospective study providing data on the use of etanercept biosimilars in children.
- For the treatment of juvenile idiopathic arthritis, etanercept biosimilars are equivalent to the originator in terms of efficacy and safety.
- Increased use of biosimilars will enable more patients to benefit from therapy with biologics.

product that is highly similar but not identical to the licensed originator biological medicine and shows no clinically meaningful difference in terms of quality, safety and efficacy" (4). It should be noted that biosimilars can only be manufactured after the original product's patent protection expires (5). Consequently, the first etanercept biosimilar, Benepali[®], was approved in 2016, and Erelzi[®] followed in 2017. The approval process for biosimilars is structured similarly to that of other biologic drugs. However, the process is accelerated by conducting a clinical trial only in the one condition the original drug was licensed for (6). Regarding Benepali, the corresponding phase III trial was conducted in adult patients with rheumatoid arthritis (RA) (7). The efficacy and tolerability of Erelzi were investigated in a phase III study in adult patients with plaque-type psoriasis (8). Both studies showed equivalent efficacy and safety of the biosimilars compared with the originator. In addition, extensive observational studies involving several thousand adult participants have been conducted for both switching from the originator to an etanercept biosimilar during the therapy course and starting therapy with an etanercept biosimilar (9,10).

Gap of knowledge. On the basis of these studies and extrapolation, approval was also granted for use in children. Consequently, there are no reference studies in pediatric patients (3). Because children show significant differences in pharmacokinetics and dynamics compared with adults, clinical data on the use of biosimilars in children appear to be particularly valuable (11). In addition, JIA, as a separate clinical entity with its own subgroups, specific complications, and separate therapeutic concepts, must be clearly distinguished from adult RA. The subgroup of seropositive polyarticular JIA, which closely resembles adult RA, occurs only in a significant minority of childhood JIA cases (12).

Objectives. In this prospective observational study, we aimed to add important information regarding the efficacy and safety of the two approved etanercept biosimilars, Benepali and Erelzi, in the treatment of JIA. Therefore, we compared clinical courses of patients with JIA who started treatment either with the originator or a biosimilar. Furthermore, clinical courses of patients who started treatment with the originator and switched to a biosimilar during the therapy course were analyzed.

METHODS

Study characteristics. The data used for this study were collected within the framework of the German BIKER registry. This prospective, observational registry has existed since 2001 and has already been described in various publications (13–15). "BIKER" is an acronym in the German language and stands for "Biologics in Paediatric Rheumatology Registry." The registry is covering the whole of Germany, with more than 80 participating pediatric rheumatology units and may, therefore, be representative not only for Germany but for a number of comparable countries. Approval was granted by the local ethics committee of the Aerztekammer Nordrhein, Duesseldorf, Germany (reference number 2/2015/7441). Written informed consent was obtained (and repeated if the patient became an adult), and pseudonymized data were collected for each patient. Patient assessment was performed at baseline, after 3 and 6 months, and every 6 months thereafter. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

We included patients who were treated with the etanercept originator Enbrel[®] or with the etanercept biosimilars Benepali or Erelzi. Patients were only eligible if they were younger than 18 years at baseline and had at least one follow-up.

For the comparison of etanercept-naïve patients who started treatment with Enbrel or a biosimilar, only patients who started therapy after January 1, 2017, were included, as the possibility to use a biosimilar was not given before this date. However, this inclusion criteria did not apply to patients who initially received Enbrel and then switched to a biosimilar. These patients were included regardless of the date they started treatment with Enbrel to evaluate whether their clinical course changed after switching to a biosimilar. The patient selection progress is shown in Figure 1. On the basis of the aforementioned inclusion and exclusion criteria, data documented from April 1, 2008, to December 1, 2020, were included.

Definitions. This study aimed to investigate whether the efficacy and safety of etanercept biosimilars differ significantly in comparison with the originator. To compare the efficacy, we collected various parameters that quantify the disease activity of JIA. For this purpose, two indices, Juvenile Arthritis Disease Activity Score (JADAS-10) (16) and the Childhood Health Assessment Questionnaire Disability Index (CHAQ-DI) (17), were used. In addition, the current disease activity of JIA was assessed at baseline and at each follow-up by the treating physician and the patient on a visual analog scale (VAS) by indicating a rating between 0 and 100.

Analysis regarding safety was based on AE reports. According to International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use E6 section 1.2 (18), an AE is any untoward medical occurrence in a subject temporarily associated with a pharmaceutical product, even without causality or relationship. AEs were queried and documented at

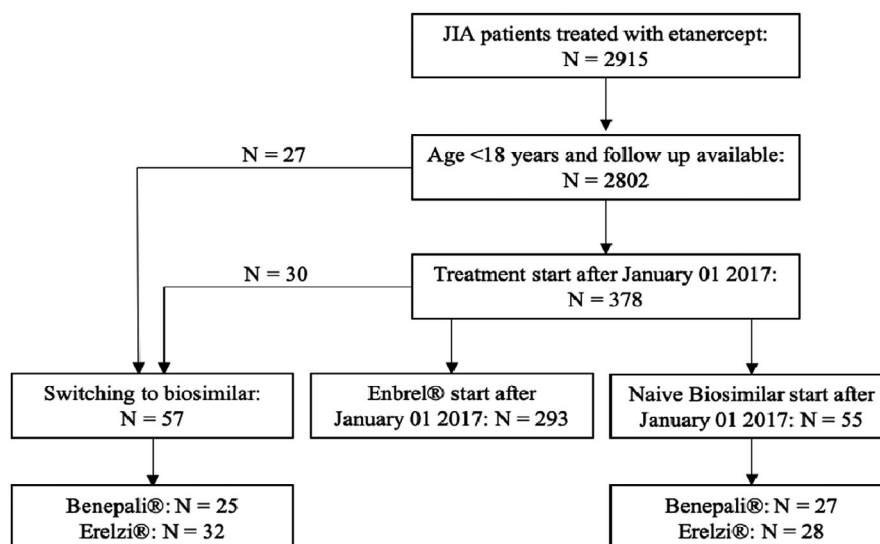


Figure 1. Patient selection progress from the BIKER registry (Biologics in Paediatric Rheumatology Registry) according to inclusion and exclusion criteria. JIA, juvenile idiopathic arthritis.

every visit. Furthermore, patients and treating physicians had the possibility to report AEs directly at any time. The Medical Dictionary for Regulatory Activities system (19) was used to categorize the AE reports. In the framework of this study, particular attention was paid to local injection site reactions occurring during or after the subcutaneous injection of a biosimilar or the originator. We defined local reactions as pain, stinging, erythema, swelling, pruritus, or induration of the skin at the injection site.

In addition to safety analysis, we examined the discontinuation rates of the originator and the biosimilars. If the corresponding drug was not taken for at least 3 months, we classified this as a discontinuation of therapy.

Statistical analysis. Statistical analyses show frequencies, percentages, median values with the 25% and 75% quartiles, and incidence rates per 100 patient-years with the 95% confidence interval. All continuous variables we assessed were not normally distributed, so we refrained from giving a mean value and indicated the median instead.

We used the χ^2 test to compare categorical variables between different cohorts. For continuous variables, the Mann-Whitney U test was used. To compare the incidence rates of AEs, we performed the Wald test.

In order to search for possible differences between biosimilars and the originator, we essentially conducted two different comparisons; on the one hand, we compared etanercept-naïve patients who either started treatment with the originator or a biosimilar after January 1, 2017. On the other hand, we observed the clinical courses of patients who began treatment with the originator and then switched to a biosimilar.

The significance level was set at 5%, and analyses were performed with SPSS version 25 (IBM).

RESULTS

Patient characteristics. We identified 348 patients starting treatment with etanercept after January 1, 2017. Among them, 293 patients received the originator Enbrel, and 55 patients received a biosimilar (Benepali, $n = 27$; Erelzi, $n = 28$). In addition, a total of 57 patients started therapy with Enbrel and then switched to a biosimilar during the course of therapy (Figure 1).

Of the 35 pediatric rheumatology units that initiated treatment with etanercept after January 1, 2017, 12 units used biosimilars in at least one patient. The remaining 23 units exclusively used Enbrel. Thus, the use of the originator far exceeded the use of biosimilars.

Table 1 presents the patient characteristics of the included patients. It is noticeable that patients who primarily received a biosimilar were older at baseline and had already received another biologic as a premedication slightly more frequently than patients who received the originator. In patients who switched to a biosimilar during the course of therapy, the drug exposure time to the biosimilar (21.8 years) was significantly shorter than the exposure time to the originator (238.7 years). For the majority of these patients, the switch from Enbrel to a biosimilar took place in 2019 or 2020, so the exposure time after the switch was correspondingly short. In contrast, the originator was often administered for several years before switching.

The type of health insurance did not differ between patients receiving the originator or a biosimilar. In both cohorts, approximately 80% of patients had statutory health insurance and 20% of patients had private insurance.

Efficacy. Regarding the treatment efficacy, there were no significant differences between patients treated with either the originator or a biosimilar. Figure 2 shows a comparison of patients who started treatment with Enbrel or a biosimilar after January 1,

Table 1. Characteristics of patients at baseline, grouped by originator/biosimilar

	Enbrel Start After January 1, 2017	Biosimilar Start After January 1, 2017	Enbrel Start With Later Switch to Biosimilar
Patients, n	293	55	57
Total exposure time, y	424.2	35.4	260.5
Age at baseline, y, median (25% quartile-75% quartile)	12.6 (8.3-15.5)	15 (13-16.6)	10.6 (8.3-14.2)
Female sex, n (%)	197 (67.2)	33 (60)	34 (59.6)
Diagnosis, n (%)			
Systemic JIA	0 (0)	1 (1.8)	0 (0)
Polyarticular arthritis, RF-	106 (36.2)	21 (38.2)	13 (22.8)
Polyarticular arthritis, RF+	22 (7.5)	6 (10.9)	4 (7)
Persistent oligoarthritis	6 (2)	1 (1.8)	1 (1.8)
Extended oligoarthritis	68 (23.2)	8 (14.5)	22 (38.6)
Psoriatic arthritis	12 (4.1)	4 (7.3)	6 (10.5)
Enthesitis-related arthritis	75 (25.6)	13 (23.6)	9 (15.8)
Undifferentiated arthritis	4 (1.4)	1 (1.8)	2 (3.5)
ANA positive, n (%)	169 (57.7)	31 (56.4)	30 (52.6)
Patients with complete data regarding disease activity, n	237	43	45
Active joint count at baseline, median (25% quartile-75% quartile)	3 (1-6)	2 (1-6)	3 (2-6)
CHAQ-DI at baseline, median (25% quartile-75% quartile)	0.25 (0-0.75)	0.12 (0-0.75)	0.25 (0-0.5)
JADAS-10 at baseline, median (25% quartile-75% quartile)	11.1 (8-15.2)	10.8 (5.3-16.1)	10.4 (8.8-15.6)
Physician VAS at baseline, median (25% quartile-75% quartile)	38 (27-55)	36 (21.5-56.5)	35 (26.5-56)
Patient VAS at baseline, median (25% quartile-75% quartile)	40.5 (20-74.8)	39.5 (9.5-79)	39.5 (20.3-76.8)
Number of previous biologics, n (%)			
N = 0 (first-line biologic therapy)	276 (94.2)	48 (87.3)	55 (96.5)
N = 1 (second-line biologic therapy)	15 (5.1)	6 (10.9)	2 (3.5)
N > 1 (third- or higher-line biologic therapy)	2 (0.7)	1 (1.8)	0 (0)
MTX pretreatment, n (%)	230 (78.5)	41 (74.5)	44 (77.2)
NSAID pretreatment, n (%)	245 (83.6)	45 (81.1)	52 (91.2)
Corticosteroid pretreatment, n (%)	123 (42)	22 (40)	23 (40.4)

Abbreviation: ANA, antinuclear antibody; CHAQ-DI, Childhood Health Assessment Questionnaire Disability Index; JADAS-10, Juvenile Arthritis Disease Activity Score; JIA, juvenile idiopathic arthritis; MTX, methotrexate; NSAID, nonsteroidal anti-inflammatory drug; RF, rheumatoid factor; VAS, visual analog scale on disease activity.

2017. Disease activity at baseline as well as at the last follow-up was similar in both cohorts. All etanercept preparations used led to a significant reduction in disease activity.

We also examined the efficacy of treatment in patients who initially received Enbrel and then switched to Benepali or Erelzi in the further course of therapy. The parameters that quantify disease activity of JIA were at a fairly comparable level before and after switching to a biosimilar. Figure 3 illustrates the development of JIA disease activity throughout the course of therapy.

Safety. Various AEs occurred during treatment with both the originator and the biosimilars. The most frequent AEs were viral infections of the upper respiratory tract, gastrointestinal disorders, and local reactions at the injection site after subcutaneous administration.

Patients who started treatment with Enbrel or a biosimilar after January 1, 2017, were affected by a total of 201 AEs in 133 patients. Another 70 AEs in 31 patients were reported for

patients who initially received Enbrel and switched to a biosimilar during the course of therapy. Table 2 lists the frequencies of AEs in the specific cohorts and highlights significant differences. When comparing the AE frequencies per patient starting treatment with Enbrel or a biosimilar, no significant difference is evident. However, when examining the AE rates per 100 patient-years, there is a significant clustering of AEs in patients who started treatment with a biosimilar. This significant difference is mainly due to injection site reactions, which occurred more frequently in the biosimilar cohort: 20% of all patients who started treatment with Benepali or Erelzi were affected by a local reaction. Among patients who started therapy with Enbrel after January 1, 2017, the respective proportion was 6.8%. The rate of local reactions per 100 patient-years was even more than six times higher in the biosimilar cohort compared with the Enbrel cohort. However, this increased rate of local reactions had no impact on treatment adherence (see DISCONTINUATION RATES).

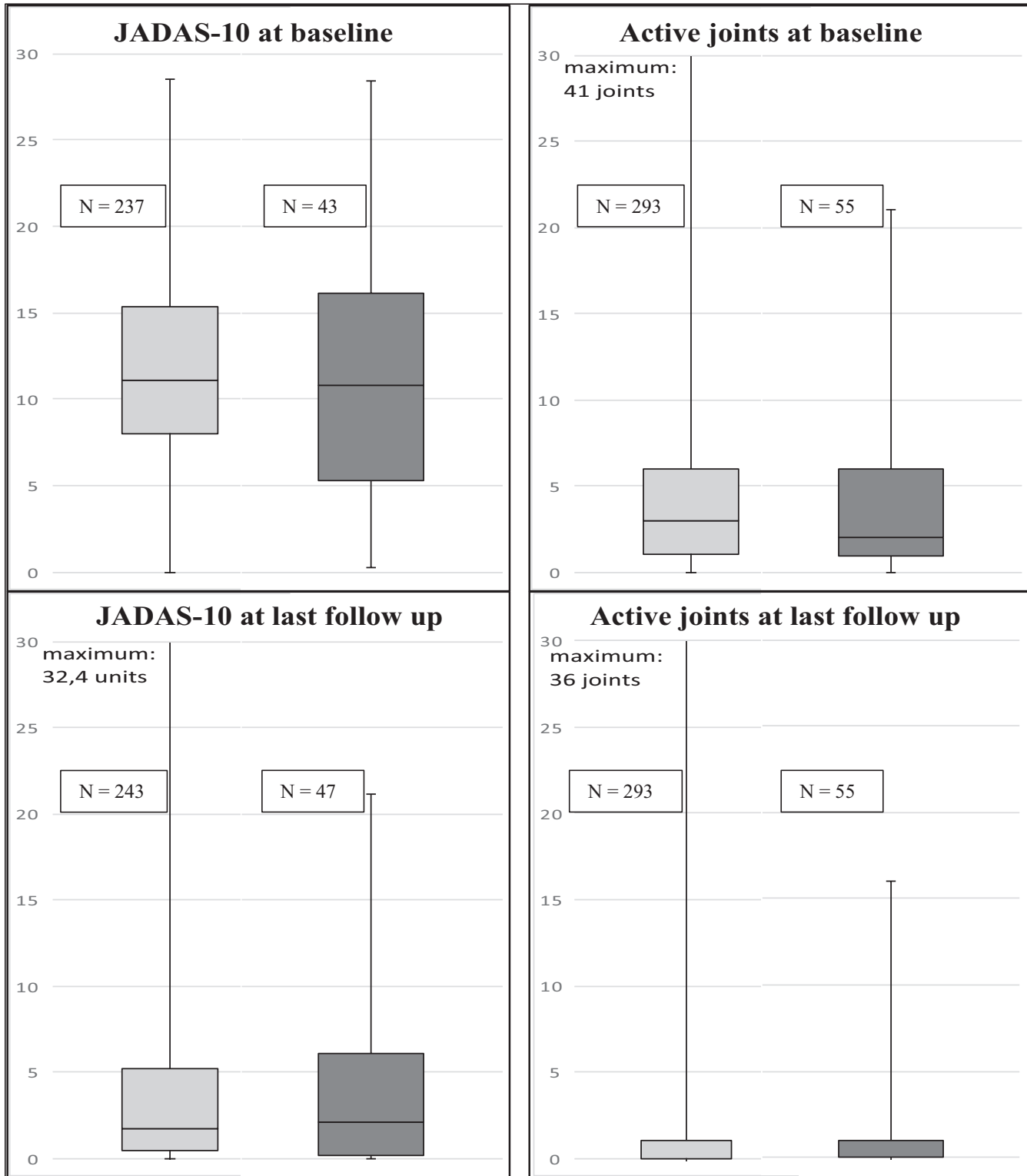


Figure 2. Comparison of JADAS-10 and number of active joints between patients receiving Enbrel (light grey) and patients receiving a biosimilar (dark grey). Medians and quartiles as well as minimum and maximum are shown as boxplot. The upper side shows disease activity at baseline; the lower side presents disease activity at the time of last follow-up. The number of patients with complete data sets who were included for each comparison is given next to each boxplot. JADAS-10, Juvenile Arthritis Disease Activity Score.

No significant differences were found when comparing the biosimilars with each other. From a total of 34 AEs in patients who started treatment with a biosimilar, 20 AEs occurred in patients

receiving Erelzi and 14 AEs occurred in patients receiving Bene-pali. The rate of local reactions did also not differ significantly between the two biosimilars.

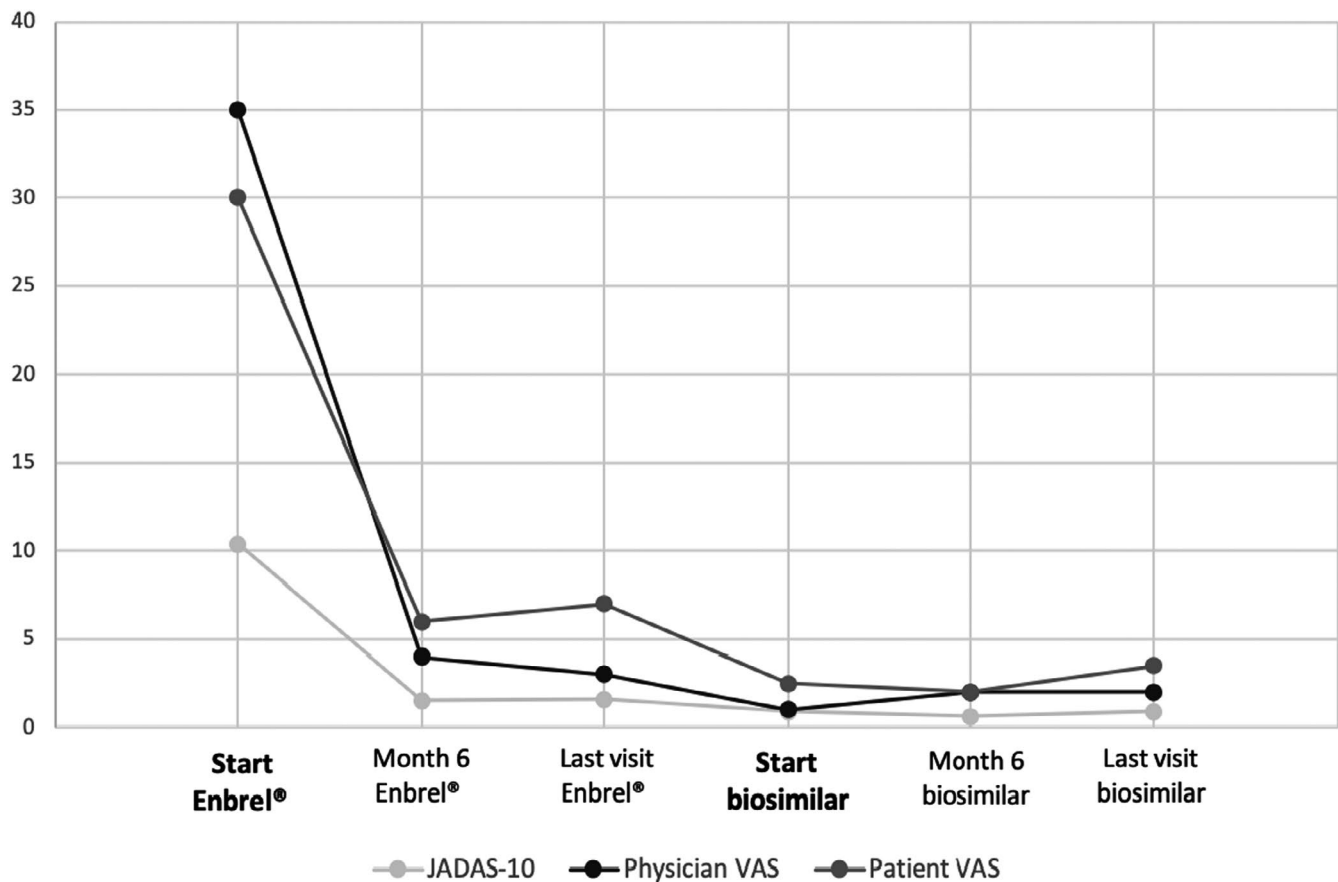


Figure 3. Clinical course of patients starting with Enbrel and switching to biosimilars. Forty-five patients with complete data sets were included for this figure. JADAS-10, Juvenile Arthritis Disease Activity Score (range 0-40); VAS, visual analog scale (range 1-100).

For patients who started treatment with the originator and switched to a biosimilar during the course of therapy, no significantly increased frequency of AEs was observed after the switch. Rather, AE rates per 100 patient-years were at comparable levels before and after the switch.

Severe AEs leading to hospitalization occurred in 19 patients. There were no significant differences in the occurrence of severe AEs in patients treated with Enbrel or those treated with a biosimilar.

Discontinuation rates. Of the 55 patients who started therapy with a biosimilar after January 1, 2017, 16 patients (29.1%) discontinued therapy. In the comparator cohort of patients who started with Enbrel, the corresponding proportion was 37.2%, with 109 discontinuations in 293 patients. When examining the reasons for discontinuation, achievement of stable remission, lack of efficacy, and AEs emerged as the three most common reasons (Table 2).

Among the 57 patients who initially received Enbrel and switched to a biosimilar during the therapy course, eight patients discontinued treatment with the biosimilar. Fifty percent of these discontinuations were due to stable remission. The remaining four discontinuations were caused by AEs or lack of efficacy.

DISCUSSION

Especially for pediatric patients, data on the use of biosimilars are limited. This analysis adds an evaluation of the efficacy and safety of biosimilars, which are based on the active agent etanercept and are used in the treatment of JIA. Our analysis is based on data from clinical practice collected in the BIKER registry. Because of the broad coverage and the large number of participating centers in Germany, the collected data correspond to clinical reality in Germany and comparable industrial nations.

Our study gains particular significance through the exclusively minor study participants. Previous studies on the efficacy and safety of etanercept biosimilars have been conducted in adults only. However, JIA as a disease entity with its own subgroups, therapies, and complications must be clearly distinguished from adult RA (20). Therefore, data on the use of biosimilars in patients with JIA are indispensable.

The originator Enbrel and the biosimilars Benepali and Erelzi did not significantly differ when comparing efficacy in the treatment of JIA. In both cohorts, a significant reduction in disease activity was achieved through therapy. The approval phase III studies for Benepali (7) and Erelzi (8) also showed similar efficacy for both biosimilars compared with the originator in adult patients.

Table 2. Comparison of frequencies and rates per 100 patient-years of all AEs, local reactions, and discontinuation rates between patients treated with Enbrel or a biosimilar

Drug Class	No switch during therapy course		Before and after Switch to Biosimilar	
	Enbrel	Benepali/Erelzi	Enbrel	Benepali/Erelzi
Patients, n	293	55	57	57
Total exposure time, y	424.2	35.4	238.7	21.8
Patients with at least one AE, n (%)	114 (38.9)	19 (34.5)	29 (50.9)*	6 (10.5)*
Incidence rate (95% CI)	39.4 (33.8-45.8)*	96.1 (68.6-134.4)*	26.4 (20.6-33.8)	32.1 (15.3-67.4)
Local reactions, n (%)	20 (6.8)*	11 (20)*	3 (5.3)	2 (3.5)
Incidence rate (95% CI)	4.7 (3-7.3)*	31.1 (17.2-56.1)*	1.3 (0.4-3.9)*	9.2 (2.3-36.7)*
Patients with at least one SAE, n (%)	14 (4.8)	1 (1.8)	3 (5.3)	1 (1.8)
Incidence rate (95% CI)	3.3 (2-5.6)	2.8 (0.4-20.1)	1.3 (0.4-3.9)	4.6 (0.7-32.6)
Patients who discontinued treatment, n (%)	109 (37.2)	16 (29.1)	8 (14)	4 (7)
Because of remission	45 (15.4)*	2 (3.7)*		
Because of lack of efficacy	37 (12.6)	7 (12.7)	2 (3.5)	
Because of AE	21 (7.2)	5 (9.1)	2 (3.5)	
Because of other reasons	6 (2)	2 (3.6)	0 (0)	

Abbreviation: AE, adverse event; CI, confidence interval; SAE, serious adverse event.

Incidence rates and 95% CIs are per 100 person-years.

* $P < 0.05$ versus comparison group.

As already described, the corresponding phase III study for Erelzi was conducted in patients with plaque psoriasis. However, the efficacy of Erelzi was also proven in patients with RA in a prospective study by Matucci-Cerinic et al (21).

Furthermore, data from clinical practice are available for adult patients. Lindström et al observed 1015 patients who primarily had spondyloarthritis. No increase in disease activity was observed in these patients 6 months after switching from Enbrel to Benepali (10). The same conclusion was reached by Holroyd et al, who followed-up 92 adult patients with various rheumatic diseases for at least 6 months after switching from Enbrel to Benepali (22). Our analysis is in line with these results, as patients who initially received Enbrel and then switched to a biosimilar were not found to have an increase in disease activity after the change of therapy. According to a publication by Gerdes et al (23) using data from the EGALITY-study (a randomized, double-blind, multicenter study to demonstrate equivalent efficacy and to compare safety and immunogenicity of a biosimilar etanercept [GP2015] and Enbrel in patients with moderate to severe chronic plaque-type psoriasis), even multiple switches between the etanercept originator and biosimilars do not impact the efficacy of therapy.

For pediatric patients with JIA, there are no data available on this issue so far. Prospective data are available on the treatment of pediatric patients with inflammatory bowel disease using biosimilars of infliximab. These data also showed comparable efficacy between the biosimilars and the originator (24). Our results are therefore consistent with the existing literature regarding the efficacy of biosimilars.

According to our study, the safety profiles of biosimilars and the originator were comparable. Only local reactions at the injection site occurred more frequently in patients treated with biosimilars.

During the 1-year observation periods of the phase III studies on Benepali and Erelzi, 55% (7) and 60% (8) of patients treated

with either the respective biosimilar or the originator were affected by at least one AE. When comparing these data with the results we obtained, it must be taken into account that the follow-up controls in a pivotal trial are much closer than in a clinical registry. This could contribute to the comparatively higher proportion of patients with AEs in the pivotal studies.

Interestingly, in both phase III studies, local reactions at the injection site were less frequent in the biosimilar cohort than in the Enbrel cohort. It is possible that the differences between the two phase III trials and our data can be explained, at least in part, by the placebo effect. Because of the double-blind design, this effect could not occur in the pivotal studies. In clinical reality, the placebo effect is certainly of importance, as described in various publications (25–27). Particularly when regarding the use of biosimilars, the placebo effect seems to be relevant. In a prospective observational study on patients with rheumatic diseases receiving infliximab, either the originator or a biosimilar, more patients in the biosimilar cohort discontinued therapy for nonspecific reasons. The authors of the study attributed this in part to negative patient expectations of the biosimilar (28). The impact of the placebo effect on the outcome of treatment with biosimilars is also highlighted in a review from 2017 (29). In order to keep this impact as low as possible, the authors recommend providing detailed information to patients about data on the safety and efficacy of biosimilars. The positive impact of an enhanced communication strategy is also pointed out in a publication by Tweehuysen et al (30). This comparative analysis included patients with rheumatic diseases who had been switched from the infliximab originator to an infliximab biosimilar and from Enbrel to Benepali. Patients treated with etanercept received more comprehensive information about the switch and the current data on biosimilars than patients who received infliximab. The number of patients who discontinued therapy after the switch differed significantly in both cohorts (6% in the etanercept cohort and 24% in the infliximab cohort).

The discontinuation rates of patients on biosimilar or Enbrel therapy were rather high compared with the literature. According to two other studies, the discontinuation rates of etanercept biosimilars in real-world patients were 14% (31) and 9% (32). However, the observation periods of the two studies were 8 and 5 months, which is distinctly shorter than the observation period of our study. Furthermore, in 38% of all discontinuations documented in our study, stable remission was the reason for discontinuation. The proportion of discontinuations due to remission was higher in the Enbrel cohort than in the biosimilar cohort, which can be explained by the higher average drug exposure time in the Enbrel cohort. Excluding all discontinuations due to stable remission, the general discontinuation frequency in our study is 22% and thus converges with the results of the two studies mentioned above. Similar results were obtained by Lindström et al (10), who found a discontinuation rate of 27% after 1 year of Benepali use in adult patients.

An increase in discontinuation frequency after switching from the originator to a biosimilar was not observed in our study or in other publications on this subject (9,22,31).

When comparing the two cohorts with treatment initiation of Enbrel or a biosimilar after January 1, 2017, the significantly higher number of patients receiving the originator is striking. This accumulation is attributable to the circumstance that 66% of all participating centers that started treatment with etanercept after January 1, 2017, exclusively used the originator. This high proportion is even more remarkable when taking into consideration that a medical indication for the exclusive use of the originator cannot be derived from this study or the current literature.

In Germany, the national directive on medicinal products was adjusted in November 2020, and physicians were urged to act more economically by prescribing biosimilars instead of biologics.

According to the German Joint Government Committee of physicians and health insurance companies, the use of biosimilars could lead to savings of up to 37% compared with the use of original preparations (33). However, there are exceptions if certain discount agreements exist between health insurance funds and pharmaceutical companies, as well as in medically justified exceptional cases. Reasons for the varying use of biosimilars in the different centers could therefore be the individual patient assessment of the treating physicians as well as existing discount agreements for the originator drug. However, because of the updated directive, it can be expected that biosimilars will be increasingly used in all parts of Germany.

Given the very high costs associated with biologic therapy, an increasing proportion of biosimilars in use is advisable and will be inevitable in the future (34). Access to biologics in different countries correlates strongly with the financial strength of the respective country, as stated by Putrik et al (35). The wider use of biosimilars has the potential to substantially reduce the costs of therapy with biologics without compromising on efficacy and safety (36). This cost reduction could be key to enabling even more people, especially in poorer countries, to access biologics regardless of their financial status.

Our analysis has limitations. The number of patients who started treatment with a biosimilar is limited, which slightly reduces the statistical reliability of our results. For adult patients, a few observational studies are investigating the use of biosimilars in larger numbers of patients (9,10). However, such studies do not exist for pediatric patients. The results of our analysis are therefore of particular interest.

Another limitation arises from the nonrandomized approach in a registry setting. The patients in the two comparison cohorts were not randomly selected and therefore differ partly in their characteristics. However, significant differences are limited to age at therapy start and the number of previously received biologics. Therefore, good comparability of the cohorts can be assumed.

With regard to the large number of different centers that participate in the BIKER registry, it could be suggested that the reporting behavior of AEs could differ between the treating physicians. This is especially relevant for nonserious AEs such as viral infections of the upper airways or mild local reactions. Although the majority of patient files were monitored, under-reporting may occur in some cases.

In summary, the data confirm the equivalence of the etanercept biosimilars Benepali and Erelzi compared with the originator Enbrel in terms of efficacy and safety. The occurrence of local reactions at the injection site was observed slightly more frequently in patients treated with biosimilars. However, this increased occurrence had no significant impact on therapy adherence. In accordance with the current literature, there are thus no medical concerns for increased use of the biosimilars Benepali and Erelzi. Such increased use is particularly recommended considering the very high costs and growing inequality in access to treatment with biologics.

ACKNOWLEDGMENTS

The authors thank the German and Austrian pediatric rheumatologists, the patients, and their parents for their collaboration.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Thiele, Horneff.

Acquisition of data. Thiele, Klein, Hospach, Windschall, Mrusek, Ruhlmann, Horneff.

Analysis and interpretation of data. Thiele, Horneff.

ROLE OF THE STUDY SPONSOR

Pfizer, AbbVie, MSD, and Roche had no role in the study design, or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent on approval by the study sponsors.

REFERENCES

1. Hurd A, Beukelman T. Infectious complications in juvenile idiopathic arthritis. *Curr Rheumatol Rep* 2013;15:327.

2. Horneff G, Klein A, Klotsche J, Minden K, Huppertz H-I, Weller-Heinemann F, et al. Comparison of treatment response, remission rate and drug adherence in polyarticular juvenile idiopathic arthritis patients treated with etanercept, adalimumab or tocilizumab. *Arthritis Res Ther* 2016;18:272.
3. Cuevas OA, Hedrich CM. Biosimilars in pediatric rheumatology and their introduction into routine care. *Clin Immunol* 2020;216:108447.
4. European Medicines Agency. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. 2014. URL: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active_en-2.pdf.
5. Nick C. The US biosimilars act: challenges facing regulatory approval. *Pharmaceutical Medicine* 2012;26:14–152.
6. Tesser JR, Furst DE, Jacobs I. Biosimilars and the extrapolation of indications for inflammatory conditions. *Biologics* 2017;11:5–11.
7. Emery P, Vencovský J, Sylwestrzak A, Leszczyński P, Porawska W, Baranauskaitė A, et al. A phase III randomised, double-blind, parallel-group study comparing SB4 with etanercept reference product in patients with active rheumatoid arthritis despite methotrexate therapy. *Ann Rheum Dis* 2017;76:51–7.
8. Griffiths CEM, Taçi D, Gerdes S, Arenberger P, Pulka G, Kingo K, et al. The EGALITY study: a confirmatory, randomized, double-blind study comparing the efficacy, safety and immunogenicity of GP2015, a proposed etanercept biosimilar, vs. the originator product in patients with moderate-to-severe chronic plaque-type psoriasis. *Br J Dermatol* 2017;176:928–38.
9. Grintborg B, Loft AG, Omerovic E, Hendricks O, Linauskas A, Espesen J, et al. To switch or not to switch: results of a nationwide guideline of mandatory switching from originator to biosimilar etanercept. One-year treatment outcomes in 2061 patients with inflammatory arthritis from the DANBIO registry. *Ann Rheum Dis* 2019;78:192–200.
10. Lindström U, Grintborg B, Di Giuseppe D, Nordström D, Provan SA, Gudbjornsson B, et al. Treatment retention of infliximab and etanercept originators versus their corresponding biosimilars: Nordic collaborative observational study of 2334 biologics naïve patients with spondyloarthritis. *RMD Open* 2019;5:e001079.
11. Ferro A. Paediatric prescribing: why children are not small adults. *Br J Clin Pharmacol* 2015;79:351–353.
12. Ravelli A, Martini A. Juvenile idiopathic arthritis. *Lancet* 2007;369:767–78.
13. Horneff G, Schmeling H, Biedermann T, Foeldvari I, Ganser G, Girschick HJ, et al. The German etanercept registry for treatment of juvenile idiopathic arthritis. *Ann Rheum Dis* 2004;63:1638–44.
14. Horneff G, Schulz AC, Klotsche J, Hospach A, Minden K, Foeldvari I, et al. Experience with etanercept, tocilizumab and interleukin-1 inhibitors in systemic onset juvenile idiopathic arthritis patients from the BIKER registry. *Arthritis Res Ther* 2017;19:256.
15. Thiele F, Klein A, Windschall D, Hospach A, Foeldvari I, Minden K, et al. Comparative risk of infections among real-world users of biologics for juvenile idiopathic arthritis: data from the German BIKER registry. *Rheumatol Int* 2021;41:751–62.
16. Consolaro A, Ruperto N, Bazso A, Pistorio A, Magni-Manzoni S, Filocamo G, et al. Development and validation of a composite disease activity score for juvenile idiopathic arthritis. *Arthritis Rheum* 2009;61:658–66.
17. Sontichai W, Vilaiyuk S. The correlation between the Childhood Health Assessment Questionnaire and disease activity in juvenile idiopathic arthritis. *Musculoskeletal Care* 2018;16:339–44.
18. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH Harmonized Guideline. Integrated addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2). URL: <http://www.ich.org>.
19. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). *Drug Saf* 1999;20:109–17.
20. Prahalad S, Glass D. Is juvenile rheumatoid arthritis/juvenile idiopathic arthritis different from rheumatoid arthritis? *Arthritis Res Ther* 2002;4:303.
21. Matucci-Cerinic M, Allanore Y, Kavanaugh A, Buch MH, Schulze-Koops H, Kucharz EJ, et al. Efficacy, safety and immunogenicity of GP2015, an etanercept biosimilar, compared with the reference etanercept in patients with moderate-to-severe rheumatoid arthritis: 24-week results from the comparative phase III, randomised, double-blind EQUIRA study. *RMD Open* 2018;4:e000757.
22. Holroyd C, Wallis D, Bennett S, Clayton P, Edwards CJ. AB0377 Switching from bio-original etanercept to biosimilar etanercept sb4: patient acceptability and outcomes in the real world. *Ann Rheum Dis* 2017;76:1180.
23. Gerdes S, Taçi D, Griffiths CEM, Arenberger P, Poetzl J, Wuertth G, et al. Multiple switches between GP2015, an etanercept biosimilar, with originator product do not impact efficacy, safety and immunogenicity in patients with chronic plaque-type psoriasis: 30-week results from the phase 3, confirmatory EGALITY study. *J Eur Acad Dermatol Venereol* 2018;32:420–7.
24. Richmond L, Curtis L, Garrick V, Rogers P, Wilson M, Tayler R, et al. Biosimilar infliximab use in paediatric IBD. *Arch Dis Child* 2018;103:89–91.
25. Faasse K, Petrie KJ. The nocebo effect: patient expectations and medication side effects. *Postgrad Med J* 2013;89:540–6.
26. Barsky AJ, Saintfort R, Rogers MP, Borus JF. Nonspecific medication side effects and the nocebo phenomenon. *JAMA* 2002;287:622–7.
27. Atlas LY, Wager TD. How expectations shape pain. *Neurosci Lett* 2012;520:140–8.
28. Nikiphorou E, Kautiainen H, Hannonen P, Asikainen J, Kokko A, Rannio T, et al. Clinical effectiveness of CT-P13 (Infliximab biosimilar) used as a switch from Remicade (infliximab) in patients with established rheumatic disease. Report of clinical experience based on prospective observational data. *Expert Opin Biol Ther* 2015;15:1677–83.
29. Rezk MF, Pieper B. Treatment outcomes with biosimilars: be aware of the nocebo effect. *Rheumatol Ther* 2017;4:209–18.
30. Tweehuysen L, Huiskes VJB, van den Bemt BJB, van den Hoogen FHJ, den Broeder AA. FRI0200 Higher acceptance and persistence rates after biosimilar transitioning in patients with a rheumatic disease after employing an enhanced communication strategy. *Ann Rheum Dis* 2017;76:557.
31. Sigurdardottir V, Husmark T, Svärd A. Switching from reference product etanercept to the biosimilar sb4 in a real-life setting: follow-up of 147 patients. Poster Presentations: *Ann Rheum Dis* 2017;76:835.
32. Grintborg B, Sørensen IJ, Loft AG, Esbesen J, Lindegaard H, Jensen DV, et al. FRI0190 Clinical outcomes from a nationwide non-medical switch from originator to biosimilar etanercept in patients with inflammatory arthritis after 5 months follow-up. results from the danbio registry. *Ann Rheum Dis* 2017;76:553–4.
33. Gemeinsamer Bundesausschuss. Biologische Arzneimittel: G-BA beschließt Hinweise für eine wirtschaftliche Verordnungsweise von Biologika und Biosimilars. 2020. URL: <https://www.g-ba.de/presse/pressemitteilungen-meldungen/886/>.
34. Dörner T, Strand V, Cornes P, Gonçalves J, Gulácsi L, Kay J, et al. The changing landscape of biosimilars in rheumatology. *Ann Rheum Dis* 2016;75:974–82.
35. Putrik P, Ramiro S, Kvien TK, Sokka T, Pavlova M, Uhlig T, et al. Inequities in access to biologic and synthetic DMARDs across 46 European countries. *Ann Rheum Dis* 2014;73:198–206.
36. Gulácsi L, Brodszky V, Baji P, Kim H, Kim SY, Cho YY, et al. Biosimilars for the management of rheumatoid arthritis: economic considerations. *Expert Rev Clin Immunol* 2015;11:S43–52.