RHEUMATOLOGY

Rheumatology 2022;00:1–12
https://doi.org/10.1093/rheumatology/keac463

Original article

Successful stopping of biologic therapy for remission in children and young people with juvenile idiopathic arthritis

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Abstract

Objectives. Clinicians concerned about long-term safety of biologics in JIA may consider tapering or stopping treatment once remission is achieved despite uncertainty in maintaining drug-free remission. This analysis aims to (i) calculate how many patients with JIA stop biologics for remission, (ii) calculate how many later re-start therapy and after how long, and (iii) identify factors associated with re-starting biologics.

Methods. Patients starting biologics between 1 January 2010 and 7 September 2021 in the UK JIA Biologics Register were included. Patients stopping biologics for physician-reported remission, those re-starting biologics and factors associated with re-starting, were identified. Multiple imputation accounted for missing data.

Results. Of 1451 patients with median follow-up of 2.7 years (IQR 1.4, 4.0), 269 (19%) stopped biologics for remission after a median of 2.2 years (IQR 1.7, 3.0). Of those with follow-up data ($N = 220$), 118 (54%) later re-started therapy after a median of 4.7 months, with 84% re-starting the same biologic. Patients on any-line tocilizumab (prior to stopping) were less likely to re-start biologics (*vs* etanercept; odds ratio [OR] 0.3; 95% CI: 0.2, 0.7), while those with a longer disease duration prior to biologics (OR 1.1 per year increase; 95% CI: 1.0, 1.2) or prior uveitis were more likely to re-start biologics (OR 2.5; 95% CI: 1.3, 4.9).

Conclusions. This analysis identified factors associated with successful cessation of biologics for remission in JIA as absence of uveitis, prior treatment with tocilizumab and starting biologics earlier in the disease course. Further research is needed to guide clinical recommendations.

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Submitted 13 May 2022; accepted 7 August 2022

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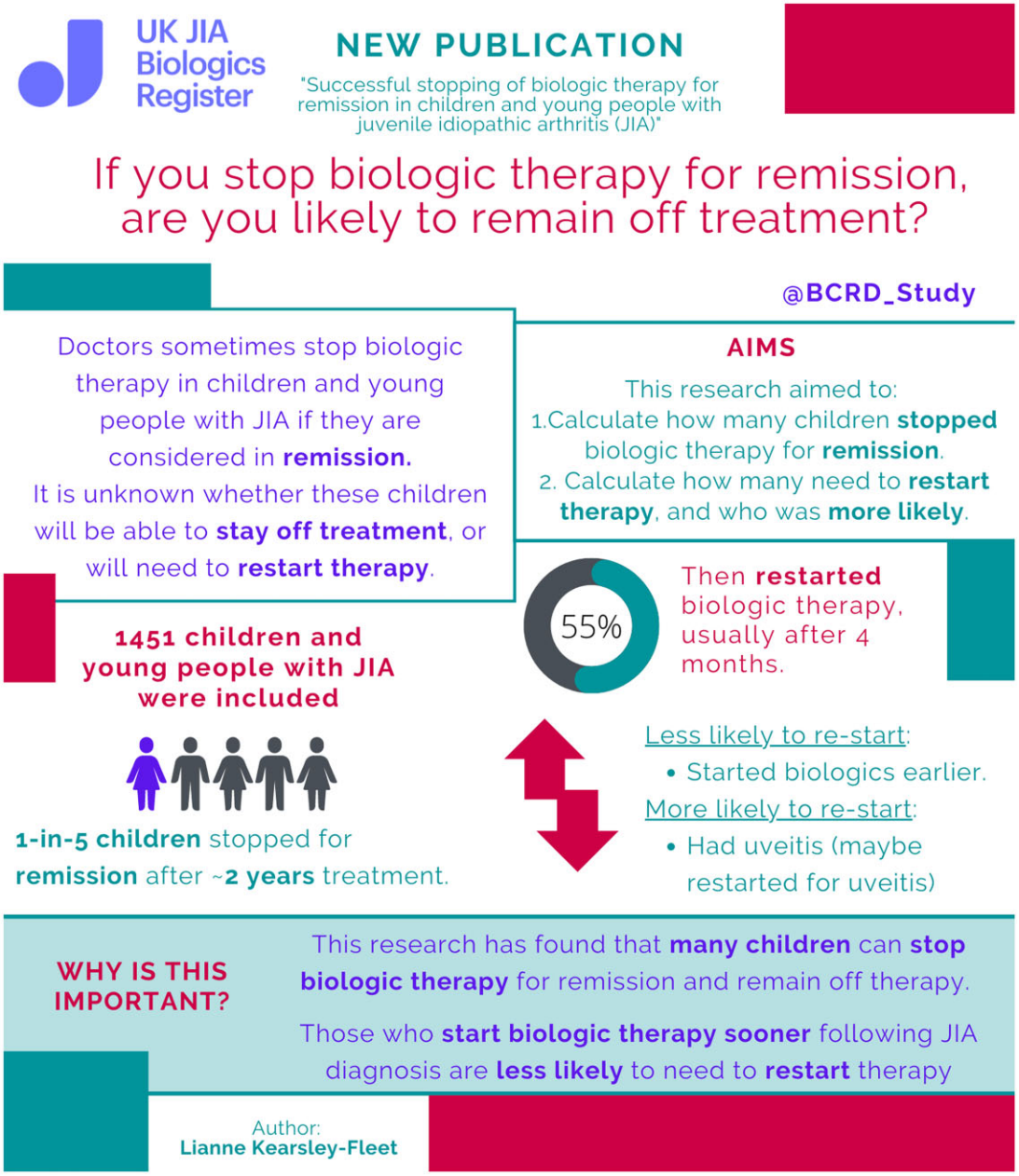
This manuscript was presented at the 2021 Paediatric Rheumatology European Society (PReS) e-congress and PReS (virtual) young investigators meeting, 18–20 September 2021.

CLINICAL SCIENCE

Graphical Abstract



Key words: JIA, biologic therapy, outcomes, remission

Rheumatology key messages

- In this analysis, one in five children with JIA stopped biologic therapy for remission after 2.2 years.
- Approximately one-half later re-started therapy after a median of 4.7 months, usually the same biologic.
- Children without uveitis, with shorter disease duration, were more likely to remain off biologics following remission.

Introduction

JIA is the most common chronic inflammatory rheumatic condition in children and young people (patients). Biologic treatments are most commonly used in JIA patients when conventional synthetic DMARDs (csDMARDs) or steroid and non-steroidal anti-inflammatory drugs have not been effective or cause side effects, with choice often based on their JIA phenotype [1]. However, there are concerns about the long-term safety of these therapies in patients, which has prompted many clinicians to consider tapering or stopping biologic treatments in individuals who have achieved remission [2–5]. It is currently unclear whether this is an effective strategy, and once therapy is stopped, what proportion of patients with JIA flare and require further biologic therapy. It is also unclear which factors, such as the duration of disease remission prior to stopping or tapering, disease phenotype, patient preferences, poor prognostic factors, type of biologic therapy and concomitant csDMARDs, are associated with successful tapering. In addition, the way clinicians define 'remission' in clinical practice may vary.

The aims of this analysis are to: (i) calculate the proportion of, and describe, patients with JIA receiving biologic therapy who stop their biologic treatment for remission, (ii) describe what happens following biologic treatment cessation, including how many patients later re-start biologic therapy and after how long, and (iii) identify factors associated with patients having to re-start biologic therapy.

Methods

Study design and participants

The UK JIA Biologics Registers represent two parallel ongoing national biologic cohort studies of patients with JIA in the UK: the British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study (BSPAR-ETN; established 2004), and the Biologics for Children with Rheumatic Diseases (BCRD; established 2010) study [6]. Patients (aged $<$16 years) are eligible for inclusion if they have JIA (physician-diagnosed) as per the International League of Associations for Rheumatology (ILAR) criteria [7] and are starting any biologic (or targeted synthetic DMARD) therapy. All participants or their legal guardians provided written informed consent in accordance with the Declaration of Helsinki. BSPAR-ETN was approved by the West Midlands Research Ethics Committee and BCRD was approved by the North West 7 REC Greater Manchester Central Ethics Committee.

At the point of registration (start of biologic therapy), data are collected regarding patient demographics (age, gender), ILAR category, disease activity (active and limited joint counts [71 joints], physician's global assessment of overall disease activity, patient [or parent] global assessment of overall wellbeing), ESR, CRP concentration, pain visual analogue scale (VAS), functional ability using the Childhood HAQ (CHAQ), previous and current methotrexate or biologic DMARD therapy, and history of uveitis. Follow-up data are obtained from routine clinical practice (via patient medical records) by the prescribing team and transferred to the study database via an online web system at 6 months, 1 year and annually thereafter. Data include changes to disease activity, changes to anti-rheumatic therapies (including start/stop dates, and reasons for stopping of therapy) and adverse events.

Patient inclusion

All patients were included if they enrolled in the UK JIA Biologic Registers at point of starting a biologic therapy from 1 January 2010 (the start date of the BCRD study) until 7 September 2021 (cut-off date). Patients were excluded if ILAR category or biologic medication history was unknown. It was not a national requirement to enter the register at the start of the patients' first biologic therapy, so some patients may have entered the register at a later date when starting a second or subsequent biologic therapy, although details of prior biologics would be captured in all cases.

Exposure period

Patients entered the analysis at start of registered biologic therapy. Patients who stopped biologic therapy for the clinician-reported reason of 'remission' (tick-box; no definition required) were identified. Time on drug prior to stopping for remission was calculated from the original start date of the biologic therapy, until the date the therapy was stopped for remission, regardless of whether they had stopped therapy intermittently for non-remission reasons (i.e. adverse event, non-adherence) prior to this date. In patients who restarted biologic therapy following a gap for remission (no guidance or definition required for restart), time on biologic therapy was calculated from biologic re-start date until first recorded stop date (regardless of stop reason). Follow-up stopped on the date of the patient's final follow-up form, death, or 7 September 2021 (cut-off date), whichever came first. If patients started a different biologic, the exposure period started again from start date of that new biologic therapy.

Statistical analysis

Patient characteristics at start of registered therapy were described. The proportion of patients who stopped therapy for clinician-reported remission, and time on drug prior to stopping for remission, were calculated. Patients could be included in the model for each line of therapy they started under follow-up.

Of those patients who stopped biologic therapy for remission, the proportion who re-started therapy (either the same or different biologic) and time to re-start were calculated, and patient characteristics described for those who re-started therapy and those who did not.

Multivariable Cox proportional hazard models were used to identify factors associated with patients re-starting biologic therapy after remission, adjusted for clusters of each rheumatology centre. Variables were chosen *a priori* and number limited based on the rule of 10 [8]: type of biologic therapy (etanercept, infliximab, adalimumab, anakinra, tocilizumab), order of biologic therapy (first, second, third or ≥4th), time on biologic therapy prior to stopping, gender, ILAR category (due to limited patient numbers polyarticular RF^+, psoriatic, enthesitis-related, and undifferentiated JIA were grouped together), age and disease duration (at biologic start), history of uveitis (at biologic start), 71-joint juvenile arthritis disease activity score (JADAS-71) [9] at biologic start, and clinically inactive disease status [10] after initial 6 months on biologic therapy as a measure of initial response to treatment (range 3–9 months).

Multiple imputation, using chained equations, was used to account for missing data (87 dataset based on proportion of incomplete cases [11]). Complete variables included: rheumatology centre, gender, age (at biologic start), biologic therapy (generic drug), line of biologic therapy (first, second, third or ≥4th), concomitant steroids or methotrexate (at biologic start) and ILAR category. Imputed variables included: disease duration (at biologic start), history of uveitis (at biologic start), and disease activity at biologic start and 6 months (active joint count, limited joint count, physician global assessment of disease activity, patient/parent global assessment of wellbeing, CHAQ, pain VAS, ESR, CRP). JADAS-71 (at biologic start and 6 months) and 6 months' clinically inactive disease were calculated from imputed values.

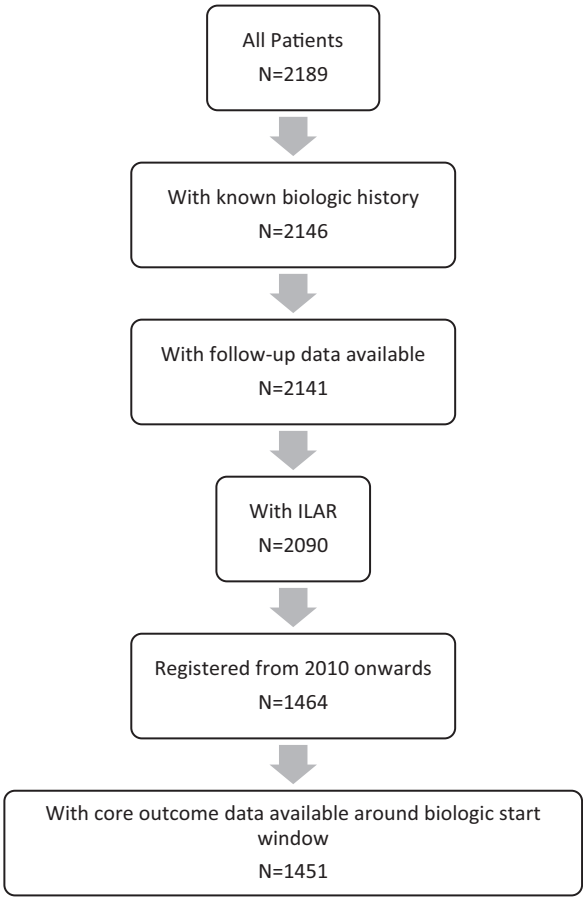
Sensitivity analysis

Due to the heterogeneity of patients and data available, two sensitivity analyses were performed. (i) Excluding systemic JIA patients: the main analysis was repeated excluding all patients with systemic JIA; to avoid over fitting the Cox-proportional hazards model, inactive disease after 6 months of biologic therapy was excluded from the model. (ii) Starting first-line biologic therapy without a history of uveitis: the main analysis was repeated including only those patients starting their first biologic therapy without a history of uveitis; patients were categorized into two distinct cohorts (not to be compared): (i) those patients without systemic JIA (i.e. all other JIA patients) starting a TNF inhibitor, and (ii) those with systemic JIA starting an IL-1 or IL-6 inhibitor; and patient characteristics were described at registration (start of therapy).

The proportion who stopped therapy for clinician reported remission and time to remission were calculated. Of those patients who stopped biologic therapy for remission, the proportion who re-started therapy and time to re-start were calculated. Multivariable Cox proportional hazard models were used to identify factors associated with patients re-starting biologic therapy after remission (separate model for each cohort), adjusted for clusters of each rheumatology centre. Variables were chosen *a priori* and number limited based on the rule of 10 [8]: time on biologic therapy prior to stopping, gender, age and disease duration (at biologic start), concomitant methotrexate at remission (biologic stop), and JADAS-71 at biologic start.

All analyses were completed using Stata version 14 (StataCorp, College Station, TX, USA).

Fig. 1 Flow diagram of patient inclusion into the analysis



ILAR: International League of Associations for Rheumatology.

Results

Included in this analysis were a total of 1451 patients with JIA registered starting a biologic therapy from 2010 onwards (Fig. 1), contributing 2040 therapy exposures. Of these 1451 patients, 79% registered at the point of starting their first biologic therapy, with the majority of all patients starting either etanercept (41%) or adalimumab (35%), and 61% received concomitant methotrexate (Table 1).

The median follow-up time for all 1451 patients from first registration was 2.7 years (IQR 1.4, 4.0). During this time, 269 (19%) patients reported stopping biologic therapy for remission after a median time on biologic therapy of 2.2 years (IQR 1.7, 3.0), of which 188 (70%) had been

TABLE 1 Characteristics of patients enrolled on biologic (or targeted-synthetic) therapy in the UK JIA Biologic Registers from ≥2010

Characteristic	Initial registration (n = 1451)
At start of therapy (initial course)	
Registered biologic (or targeted-synthetic) therapy, *n* (%)	
Etanercept	593 (41)
Infliximab	135 (9)
Anakinra	35 (2)
Adalimumab	503 (35)
Rituximab	9 (1)
Tocilizumab	145 (10)
Abatacept	27 (2)
Golimumab	1 (<1)
Baricitinib	1 (<1)
Secukinumab	2 (<1)
Line of therapy, *n* (%)	
First	1150 (79)
Second	231 (16)
Third	57 (4)
≥4th	13 (1)
Concomitant methotrexate, *n* (%)	888 (61)
Concomitant corticosteroids (any route), *n* (%)	336 (23)
Gender, *n* (%)	
Female	991 (68)
Male	460 (32)
Age, median (IQR) (range), years	11 (7, 14) (1–20)
Disease duration, median (IQR) (range), years	2 (1, 5) (0–18) (n = 1426)
ILAR category, *n* (%)	
Oligoarticular (persistent)	162 (11)
Oligoarticular (extended)	285 (20)
Systemic	128 (9)
Polyarticular RF-negative	493 (34)
Polyarticular RF-positive	121 (8)
Psoriatic	81 (6)
Enthesitis-related	160 (11)
Undifferentiated	21 (1)
History of uveitis, *n* (%)	277 (22) (n = 1269)
Disease activity, median (IQR)	
Active joint count (71 joints)	3 (1, 6) (n = 1200)
Limited joint count (71 joints)	2 (0, 5) (n = 1187)
Physician global assessment of disease activity (0–10 cm VAS)	3 (1, 5) (n = 863)
Patient (parent) global assessment of wellbeing (0–10 cm VAS)	3 (1, 6) (n = 876)
Childhood Health Assessment Questionnaire (range 0–3)	0.75 (0.13, 1.44) (n = 908)
Pain VAS (0–10 cm VAS)	4 (1, 6) (n = 856)
ESR, median (IQR), mm/h	10 (5, 22) (n = 1089)
CRP concentration, mg/l	5 (2, 8) (n = 1089)
JADAS-71	10 (6, 16) (n = 614)
For systemic JIA only, systemic features, *n* (%)	52 (60) (n = 87/128)
Remission	
Follow-up, median (IQR), years	2.7 (1.4, 4.0)
Remission (% of whole cohort)	269 (19)
Time from biologic start to remission, median (IQR), years	2.2 (1.7, 3.0)
After remission	
Patients with at least 6 months of follow-up after stopping for remission available	220/269
Time to end of follow-up, median (IQR), years	2.0 (1.2, 2.9)
Re-started biologic therapy, *n* (%)	118 (54)
Time to re-start, median (IQR), years	0.39 (0.25, 0.73)
Re-started same biologic, *n* (%)	99/118 (84)

ILAR: International League of Associations for Rheumatology; IQR: interquartile range; JADAS-71: 71-joint juvenile arthritis disease activity score; VAS: visual analogue scale.

TABLE 2 Factors associated with patients re-starting biologic following remission off-drug ($n = 220$); a multivariable analysis clustered by rheumatology centre ($n = 48$)

Factor	Re-started biologic therapy ($n = 118$)	Did not re-start biologic therapy ($n = 102$)	Hazard ratio (95% CI) ($n = 220$)
Biologic therapy, %			
Etanercept	53	43	[Reference]
Infliximab	11	9	0.7 (0.3, 1.4)
Anakinra	2	4	0.4 (0.1, 2.1)
Adalimumab	25	20	0.7 (0.4, 1.3)
Tocilizumab	9	25	0.3 (0.2, 0.6)
Line of therapy, %			
First	80	79	[Reference]
Second	14	13	1.1 (0.5, 2.4)
Third	4	5	0.7 (0.3, 1.8)
≥4th	3	3	1.0 (0.2, 4.5)
Time on biologic therapy, median (IQR), years	2.3 (2.0, 3.1)	2.2 (1.9, 3.0)	1.0 (0.8, 1.2)
Female (*vs* male), %	74	70	0.9 (0.5, 1.5)
Age at biologic start, median (IQR), years	9.0 (5.9, 11.3)	9.8 (6.3, 12.3)	1.0 (0.9, 1.1)
Disease duration at biologic start, median (IQR), years	3 (1, 6)	2 (1, 4)	1.1 (1.0, 1.2)*
ILAR category, %			
Oligoarticular (persistent)	14	3	1.7 (0.9, 3.2)
Oligoarticular (extended)	30	22	0.9 (0.5, 1.4)
Systemic	10	25	1.0 (0.5, 2.0)
Polyarticular RF-negative	38	33	[Reference]
Other[a]	8	18	0.6 (0.3, 1.3)
Concomitant methotrexate at remission (biologic stop), %	25	31	1.0 (1.0, 1.0)
History of uveitis at biologic start, %	28	7	2.4 (1.2, 4.8)*
JADAS-71 at biologic start, median (IQR)	8.0 (3.5, 13.6)	9.8 (4.3, 15.4)	1.0 (1.0, 1.1)
Inactive disease after 6 months of therapy, %	38	37	1.1 (0.7, 1.8)

Using imputed data. [a]Other JIA includes: polyarticular RF+, psoriatic, enthesitis-related and undifferentiated JIA. *$P < 0.05$. ILAR: International League of Associations for Rheumatology; JADAS-71: 71-joint juvenile arthritis disease activity score.

on combination therapy with methotrexate: 106 (56%) stopped methotrexate prior to stopping biologic therapy, and 82 (44%) remained on methotrexate therapy after stopping biologic therapy. Of those patients who stopped biologic therapy for remission (with at least 6 months of follow-up after stopping for remission available), 118/220 (54%) later re-started biologic therapy after a median of 4.7 months, with the majority (84%) re-starting the same biologic. Of those who re-started biologic therapy, 30 (25%) were on concomitant methotrexate. In the multivariable Cox regression analysis, those who were on tocilizumab (any line of therapy) were less likely to re-start biologic therapy (odds ratio [OR] 0.3; 95% CI 0.2, 0.6) compared with patients on etanercept (Table 2). In addition, those with longer disease duration prior to biologic start (OR 1.1 per year increase; 95% CI 1.0, 1.2), and those with prior uveitis were more likely to re-start biologic therapy (OR 2.4; 95% CI 1.2, 4.8).

Sensitivity analysis

Excluding systemic JIA patients

There were 1323 patients with non-systemic JIA in this analysis with median follow-up time from first registration 2.7 years (IQR 1.4, 4.0) (Supplementary Table S1, available at *Rheumatology* online). During this time, 223 (17%) patients reported stopping biologic therapy for remission after a median time on biologic therapy of 2.3 years (IQR 1.8, 3.1). Of those patients who stopped biologic therapy for remission (with at least 6 months of follow-up after stopping for remission available; $n = 183$), 106 (58%) later re-started biologic therapy after a median of 4.7 months, with the majority (83%) re-starting the same biologic. In the multivariable Cox regression analysis, those who were on tocilizumab originally (any line) were less likely to re-start biologic therapy (OR 0.3; 95% CI: 0.1, 0.9) compared with patients on etanercept. In addition, those with longer disease duration prior to biologic start (OR 1.1 per year increase; 95% CI: 1.0, 1.2), and those with prior uveitis were more likely to re-start biologic therapy (OR 2.4; 95% CI: 1.2, 4.7) (Supplementary Table S2, available at *Rheumatology* online).

Starting first-line biologic therapy without a history of uveitis

Non-systemic JIA starting TNF inhibitors. There were 770 patients without uveitis starting a first-line TNF

Table 3 Characteristics of patients enrolled on their first biologic from ≥2010 without a history of uveitis

	Non-systemic JIA starting TNF inhibitors (n = 770)	Systemic JIA starting IL-1/6 inhibitors (n = 85)
At start of therapy		
Registered biologic therapy, *n* (%)		
Etanercept	525 (68)	—
Infliximab	27 (4)	—
Anakinra	—	28 (33)
Adalimumab	218 (28)	—
Tocilizumab	—	57 (67)
Concomitant methotrexate, *n* (%)	438 (57)	58 (68)
Concomitant steroids (any route), *n* (%)	145 (19)	48 (56)
Gender, *n* (%)		
Female	514 (67)	49 (58)
Male	256 (33)	36 (42)
Age, median (IQR) (range), years	12 (9, 15) (1–20)	7 (4, 12) (1–17)
Disease duration, median (IQR) (range), years	1 (1, 4) (0–18) (n = 760)	1 (0, 1) (0–9) (n = 85)
ILAR category, *n* (%)		
Oligoarticular (persistent)	68 (9)	—
Oligoarticular (extended)	149 (19)	—
Systemic	—	85 (100)
Polyarticular RF-negative	292 (38)	—
Polyarticular RF-positive	78 (10)	—
Psoriatic	52 (7)	—
Enthesitis-related	119 (15)	—
Undifferentiated	12 (2)	—
Disease activity		
Active joint count (71 joints), median (IQR)	3 (1, 6) (n = 725)	2 (0, 5) (n = 76)
Limited joint count (71 joints), median (IQR)	2 (1, 5) (n = 715)	1 (0, 4) (n = 76)
Physician global assessment of disease activity (0–10 cm VAS), median (IQR)	3 (2, 5) (n = 514)	2 (1, 5) (n = 51)
Patient (parent) global assessment of well-being (0–10 cm VAS), median (IQR)	3 (1, 6) (n = 536)	4 (1, 6) (n = 51)
Childhood HAQ (range 0–3), median (IQR)	0.75 (0.25, 0.38) (n = 566)	0.62 (0.13, 1.63) (n = 49)
Pain VAS (0–10cm VAS), median (IQR)	4 (1, 6) (n = 531)	2 (1, 5) (n = 49)
ESR, median (IQR), mm/h	8 (5, 20) (n = 658)	29 (9, 60) (n = 75)
CRP concentration, median (IQR), mg/l	5 (2, 8) (n = 644)	32 (5, 71) (n = 81)
JADAS-71, median (IQR)	11 (6, 17) (n = 374)	10 (5, 19) (n = 33)
History of MAS, systemic only, *n* (%)	—	20 (26) (n = 78)
For systemic JIA only, systemic features, *n* (%)	—	37 (60) (n = 62)
Remission		
Follow-up time, median (IQR), years	2.3 (1.2, 3.8)	2.5 (1.6, 4.1)
Remission (% of whole cohort)	139 (18)	26 (31)
Time to Remission, median (IQR), years	2.3 (2.0, 3.0)	2.3 (1.5, 3.2)
After Remission		
Patients with at least 6 months of follow-up after stopping for remission available	113/139	20/26
Time to end of follow-up, median (IQR), years	2.0 (1.1, 2.8)	2.3 (1.7, 2.8)
Re-started biologic therapy, *n* (%)	59 (52)	5 (25)
Time to re-start, median (IQR), years	0.40 (0.23, 0.73)	0.37 (0.10, 0.37)
Re-started same biologic, *n* (%)	51/59 (86)	4/5 (80)

ILAR: International League of Associations for Rheumatology; IQR: interquartile range; JADAS-71: 71-joint juvenile arthritis disease activity score; MAS: macrophage activation syndrome; VAS: visual analogue scale.

inhibitor for non-systemic JIA from 2010 onwards (Table 3). Of these, most were starting either etanercept (68%) or adalimumab (28%), and the median follow-up time was 2.3 years (IQR 1.2, 3.8). During this time, 139 (18%) patients reported stopping biologic therapy for remission after a median time from start of biologic therapy of 2.3 years (IQR 2.0, 3.0). Of those patients who stopped biologic therapy for remission with at least 6 months of follow-up available, 59 (52%) later re-started biologic therapy after a median of 4.8 months, with the majority (86%) re-starting the same biologic. In the multivariable Cox regression analysis, patients with shorter

TABLE 4 Factors associated with patients re-starting biologic following remission off-drug ($n = 113$); a multivariable analysis clustered by rheumatology centre ($n = 36$)

Factor	Re-started biologic therapy ($n = 59$)	Did not re-start biologic therapy ($n = 54$)	Non-systemic JIA starting TNF inhibitors ($n = 113$)
Time on biologic therapy, median (IQR), years	2.3 (2.0, 3.0)	2.1 (1.9, 2.8)	0.9 (0.7, 1.3)
Female (*vs* male), %	75	69	1.1 (0.5, 2.3)
Age at biologic start, median (IQR), years	9.5 (6.5, 11.8)	11.0 (7.2, 12.6)	1.0 (0.9, 1.1)
Disease duration at biologic start, median (IQR), years	2 (1, 4)	2 (1, 2)	1.1 (1.0, 1.2)*
Concomitant methotrexate at remission (biologic stop), %	15	22	1.0 (0.9, 1.0)
JADAS-71 at biologic start, median (IQR)	8.9 (4.9, 14.2)	10.2 (4.5, 15.3)	1.0 (1.0, 1.1)

Using imputed data. *$P < 0.05$. ILAR: International League of Associations for Rheumatology; IQR: interquartile range; JADAS-71: 71-joint juvenile arthritis disease activity score.

disease duration at the point of starting biologic therapy were less likely to need to restart biologic therapy following time off drug for remission (Table 4).

Systemic JIA starting IL-1/6 inhibitors. There were 85 patients with systemic JIA (without uveitis) starting a first-line IL-1 or IL-6 inhibitor from 2010 onwards (Table 3). Of these, most were starting tocilizumab (67%), and the median follow-up was 2.5 years. During this time, 26 (31%) patients reported stopping biologic therapy for remission after a median time on biologic therapy of 2.3 years. Of those patients who stopped biologic therapy for remission with at least 6 months of follow-up available, five (25%) later re-started biologic therapy after a median of 4.4 months, with the majority (80%) re-starting the same biologic. Factors associated with patients re-starting biologic therapy was not assessed in systemic JIA patients due to limited patient numbers.

Discussion

In this large analysis of over 1400 patients with JIA starting biologic therapy, 19% of patients stopped biologic therapy for remission (physician-reported) after a median time on biologic of 2.2 years. Of the patients who reported stopping biologic therapy for remission, with at least 6 months of follow-up after stopping available, 54% later re-started biologic therapy, usually restarting the same biologic. While patients on tocilizumab (prior to stopping) were less likely to re-start biologic therapy (*vs* etanercept), those with a longer disease duration prior to starting their biologic therapy and those with prior uveitis were more likely to need to re-start biologic therapy. These associations remained even when patients with systemic JIA were excluded from the analysis.

Previous research has identified that younger patients [12–16] and those with a shorter disease duration [12, 16] are more likely to have a favourable treatment response to first-line etanercept therapy, while patients with systemic JIA are less likely to respond well [13, 15, 17]. Recent work by Klotsche *et al.* identified that after 12 months of first-line etanercept treatment in 1724 patients, 19% had achieved inactive disease and stopped treatment, matching the proportion found in the current analysis [18]. Of those who could be followed (only the 209 patients who were on etanercept monotherapy), for an average of 3.9 years, 77% either restarted biologic therapy or active disease reoccurred, although no predictive factors were identified with those patients who successfully maintained inactive disease. This proportion of patients restarting therapy was higher compared with our current analysis (77% *vs* 54%) although the average follow-up time was longer (3.9 *vs* 2.0 years). In an older analysis in which 39 patients with JIA stopped etanercept therapy for remission, 38% later flared and restarted etanercept treatment, with those on etanercept originally for longer being less likely to flare (45 months *vs* 29 months) [15]. A recent systematic review estimated the proportion of patients who flare after JIA biologic treatment withdrawal was 37% at 8 months [19] and 60–83% at 12 months [5]. Of the 37% patient who flared by 8 months following discontinuation of TNF inhibitor (106 out of 137 patients) with the polyarticular form of JIA (including RF-positive, RF-negative and extended oligoarticular JIA), older age at diagnosis and concomitant methotrexate were identified to reduce the risk of flare. In a study of 1497 newly diagnosed patients with JIA, 1146 achieved inactive disease (on treatment) at some point during follow-up. Of these, 627 (55%) flared at least once after attaining inactive disease, with systemic JIA patients being less likely to flare, and those with higher physician global assessments prior to inactive disease being more likely to flare [20]. Our current analysis did not support any of these findings, instead identifying that patients were less likely to flare if they

had been treated with tocilizumab, had a shorter disease duration (prior to starting biologic therapy) or had no history of uveitis.

Clinicians have ranked the most important factors in deciding to stop treatment for non-systemic JIA patients as the duration of both active disease and clinical remission, treatment tolerance, joint damage, parent and family preferences, and JIA category [21]. Although there was considerable variation in preferred strategies when it came to tapering dose or stopping medications, most clinicians reported that they would rarely use imaging. The outcome in this analysis was stopping biologic therapy with a physician-reported stop reason of remission; this was a tick-box stop reason based on the physician's opinion. It is possible that some of these patients had not achieved remission according to a validated definition, such as clinically inactive disease [10], patient or patient acceptable symptom state [22], minimal disease activity [23], or a specific disease activity score cut-off [24], which is the typical outcome used in clinical trials or effectiveness analyses. However, it is unlikely that a physician would stop biologic therapy in patients without first considering that disease activity was sufficiently 'controlled' for a certain period of time. It would be useful to investigate in the future the optimal time point for treatment tapering in patients with minimal disease activity or in remission based on validated criteria to offer the best chance for therapeutic success. This would require long-term follow-up of data collection to identify when patients achieve, and for how long they maintain, the treatment target (i.e. minimal disease activity or remission), as well as when they subsequently stop treatment, their disease control off treatment, and the time point and reasons for re-starting biologic therapy (i.e. due to disease activity or other reasons).

In this analysis, 54% of patients restarted biologic therapy after stopping for remission. While the reason for restarting treatment is not reported, this suggests that physician opinion alone (whether based on validated criteria or not) may not be enough to predict successful stopping. Well-designed trials that include serological or imaging biomarkers for absence of inflammation [25–27] are key to identify those patients with truly inactive disease *vs* those with subclinical inflammation not detectable by routine examination and tests, but likely to become apparent following a decrease or cessation of biologic therapy. The PREVENT-JIA trial, using pro-inflammatory protein biomarkers (S100A12 and high-sensitivity CRP) as a decision tool for stopping biologic therapy in patients in clinical remission, found fewer flares in those where biomarker levels were considered prior to stopping and longer time from stopping medication until first flare [28]. While CRP was available at start of biologic therapy in the current analysis, it was unavailable at the time of biologic stop and thus excluded from the Cox model. If we could identify when, how and in whom it is best to reduce biologic therapy after achieving good disease control, this will provide the much-needed reassurance for patients and their families that decision to taper/stop biologic treatment is the best decision for them individually.

Recent clinical/cost-effectiveness analysis suggests that most biologic therapies are superior to placebo (or methotrexate) and are similar with regard to reducing disease flares and sustained treatment response in those patients remaining on therapy [29]. While biologic therapies remain more expensive than methotrexate, the incremental cost-effectiveness ratios—which are used as a decision tool to identify cost of the drugs *vs* benefit—for the key three biologics in JIA (adalimumab, etanercept and tocilizumab) are similar, ranging from £32 256 to £38 656 per quality-adjusted life-year gained. This makes biologic therapies some of the most expensive treatments available [30], although with the introduction of biosimilar therapies to the market, this cost may reduce [31]. Unfortunately, these cost-effectiveness models do not include data on long-term disease progression/damage and there are no head-to-head trials of biologic therapies in JIA, which limits the clinical evidence for biologic treatment equivalence.

This analysis was conducted in a large national cohort study of patients with JIA starting biologic therapy, representing the majority of biologic prescribing in the UK. Data are collected from routine clinical care, with detailed information on start and stop dates of biologic therapy, as well as patient characteristics and disease activity data. However, there is no national guidance on when and how to stop biologic therapies (i.e. initial dose tapering through dose reduction or increased intervals between administration or sudden cessation of therapy) so practice is variable. The data recorded could not differentiate whether patients were initially tapered prior to stopping. Consequently, the analyses included a cluster variable for the treating rheumatology centre to take any local treatment guidelines into consideration, but could not account for individual clinician preferences. In addition, it was not possible to identify whether patients restarted biologic therapy due to a disease flare (i.e. increased disease activity) or for another reason such as uveitis or decision to reinitiate treatment during a time of stress (i.e. due to upcoming exams). The sensitivity analysis excluding patients with a history of uveitis aimed to minimize the impact of this factor on the model. As with all real-world studies, there were some missing data. Missing patient characteristics, and disease activity at start of therapy and after 6 months were accounted for using multiple imputation. Occasionally the physician-reported stop reason for biologic therapy was also missing. It is possible that some of the missing biologic stop reasons were for 'remission' and therefore the estimated proportion could be higher, although the authors assumed that stopping therapy for remission would be a well-documented reason and therefore should not have affected the results. The use of robust statistical methods enabled the investigation of factors associated with patients needing to re-start biologic therapy after stopping for remission. However, this study did not capture information regarding drug levels or anti-drug antibodies,

treatment adherence or CRP at the time of stopping biologic therapy, which may influence treatment response or a physician's decision to continue or stop biologic therapy.

In conclusion, in this large analysis of over 1400 patients with JIA starting biologic therapy, one-in-five patients stopped biologic therapy for remission after ~2.2 years on biologic therapy. Those patients who stopped biologic therapy and were less likely to need to re-start, included those without uveitis, those starting biologic therapy earlier in their disease course, or those who were treated with tocilizumab. Real-world studies and clinical trials with better patient stratification are needed to investigate a broad spectrum of clinical and laboratory information to identify which patients will successfully be able to taper or stop biologic therapy in the future.

Acknowledgements

We thank the patients, rheumatology and research nurses, and clinicians who have helped support this study, the original British Society for Paediatric and Adolescent Rheumatology (BSPAR) Consensus Group for Prescription of Biologics in Children (established in 2004), the BSPAR Clinical Affairs Committee and the NIHR CRN: Children/Arthritis Research UK Paediatric Rheumatology Clinical Studies Group for their generous support in the establishment of these registers. The recruiting centres were supported by the National Institute for Health Research (NIHR) Clinical Research Network in England. This report includes independent research supported by the NIHR Manchester Biomedical Research Centre. The views expressed in this Article are those of the authors and not necessarily those of the National Health Service, the National Institute for Health Research, or the UK Department of Health. The Biologics for Children with Rheumatic Diseases (BCRD) study is funded by Versus Arthritis (20747). The BSPAR Etanercept cohort study is funded by a research grant to the University of Manchester from the British Society for Rheumatology (BSR). The BSR has previously received restricted income from Pfizer to fund this project. This income finances a wholly separate contract between BSR and the University of Manchester who provide and oversee the data collection, management and analysis of the data. The principal investigator and her team have full academic freedom and are able to work independently of pharmaceutical industry influence. All decisions concerning analyses, interpretation and publication are made autonomously of any industrial contribution.

Ethics statement: The British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study (BSPAR-ETN) was approved by the West Midlands Research Ethics Committee, and the Biologics for Children with Rheumatic Diseases (BCRD) study was approved by the North West 7 REC Greater Manchester Central Ethics Committee. All participants or their legal guardians provided written informed consent in accordance with the Declaration of Helsinki. Patient consent for publication not required.

Patient and public involvement statement: The authors have reached out to young patients with JIA and their families to explore their opinion about stopping biologic therapy for remission and relevance of future research on this topic. Patients expressed concerns about continuing biologic medication indefinitely if they were in remission (93%), were keen to explore tapering their biologic treatment (93%), as well as be involved in research communications via email/social platforms/patient groups to enable them access to new knowledge that can inform future discussions with their clinicians about treatment management if in remission (100%). The authors plan to disseminate the results reported here through future PPI events.

Funding: The Biologics for Children with Rheumatic Diseases (BCRD) study is funded by Versus Arthritis (20747). The BSPAR Etanercept cohort study is funded by a research grant to the University of Manchester from the British Society for Rheumatology (BSR). K.L.H. is additionally supported by the NIHR Manchester Biomedical Research Centre and C.C. is additionally supported by the NIHR UCLH Biomedical Research Centre (BRC773/III/CC/101350) and Versus Arthritis (21593 and 20164).

Disclosure statement: L.K.F., E.B., M.W.B., S.D., H.E.F. and T.S.R. report no conflicts of interest. K.L.H. reports non-personal speaker's fees from Abbvie and grant income from BMS, UCB and Pfizer, all unrelated to this manuscript, and is supported by the NIHR Manchester Biomedical Research Centre. C.C. reports grant income from GSK and Pfizer unrelated to this manuscript and support from NIHR UCLH Biomedical Research Centre and Versus Arthritis.

Data availability statement

The data underlying this article cannot be shared publicly to maintain the privacy of the individuals who participated in the study. The data that support the findings of this study are available via application to the UK JIA Biologics Register Scientific Steering Committee (via the corresponding author). Restrictions apply to the availability of these data.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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