

SHORT REPORT

Open Access



Maintenance of antibody response to diphtheria/tetanus vaccine in patients aged 2–5 years with polyarticular-course juvenile idiopathic arthritis receiving subcutaneous abatacept

Hermine I. Brunner^{1*} , Nikolay Tzaribachev², Gabriel Vega Cornejo³, Rik Joos⁴, Elisabeth Gervais⁵, Rolando Cimaz^{6,7}, Inmaculada Calvo Penadés⁸, Rubén Cuttica⁹, Thomas Lutz¹⁰, Pierre Quartier¹¹, Yash Gandhi¹², Marleen Nys¹³, Robert Wong¹², Alberto Martini¹⁴, Daniel J. Lovell¹, Nicolino Ruperto¹⁴ and for the Pediatric Rheumatology Collaborative Study Group and the Paediatric Rheumatology International Trials Organisation

Abstract

Background: Patients with polyarticular-course juvenile idiopathic arthritis (pJIA), receiving disease-modifying anti-rheumatic drugs with immunosuppressive effects, may be at increased risk of vaccine-preventable infections. This substudy assessed protective antibody responses to diphtheria and tetanus vaccination given prior to study enrolment in patients with pJIA.

Findings: This was a substudy of a 24-month, single-arm, open-label, multicenter, Phase III trial (NCT01844518) of subcutaneous abatacept in children with active pJIA ($N = 219$). Patients aged 2–5 years, with ≥ 2 continuous months of weekly weight-tiered (10–< 25 kg [50 mg], 25–< 50 kg [87.5 mg]) subcutaneous abatacept treatment (with/without methotrexate and/or low-dose corticosteroids), who received diphtheria/tetanus vaccine prior to enrolment, were eligible. Protective antibody levels to diphtheria/tetanus (> 0.1 IU/mL), and safety, were assessed. Overall, 29 patients were analyzed: 19 (65.5%), 1 (3.4%) and 9 (31.0%) patients had > 12 , 6–12 and 2–< 6 months of abatacept exposure, respectively. All patients had protective antibody levels to tetanus and 26 (89.7%) patients had protective antibody levels to diphtheria. Of the 3 patients without protective antibody levels to diphtheria, each had an antibody level of 0.1 IU/mL, bordering the lower threshold of protection. Concomitant use of methotrexate and/or low-dose corticosteroids had no evident effect on antibody levels. No unexpected adverse events, including cases of diphtheria or tetanus, were reported during the 24-month period.

Conclusions: Patients aged 2–5 years with pJIA who received 2–24 months of weekly subcutaneous abatacept, with or without concomitant methotrexate and/or low-dose corticosteroids, maintained effective diphtheria and tetanus vaccination protection without new safety signals.

Trial registration: [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT01844518); registered May 1, 2013; <https://clinicaltrials.gov/ct2/show/NCT01844518?term=NCT01844518&rank=1>

Keywords: Juvenile idiopathic arthritis, Abatacept, Biologic DMARDs, Vaccination

* Correspondence: hermine.brunner@cchmc.org

¹Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Full list of author information is available at the end of the article



Findings

Introduction

Patients with polyarticular-course juvenile idiopathic arthritis (pJIA) receiving disease-modifying antirheumatic drugs (DMARDs) with immunosuppressive effects may be at increased risk of vaccine-preventable infections such as diphtheria and tetanus. The European League Against Rheumatism recommendations for the vaccination of children with rheumatic diseases endorse adherence to national guidelines for very young, healthy children [1]. However, due to ongoing maturation of the immune system in young children [2, 3], immune responses to vaccination in this population may be compromised by immunosuppressive medications more so than in older children [4].

Abatacept, a selective T-cell co-stimulation modulator [5], was effective and well-tolerated in children with pJIA aged 2–17 years (subcutaneous [SC] formulation) [6], and in children aged 6–17 years (intravenous [IV] formulation) [7]. In healthy adults, a single 750-mg dose of IV abatacept did not prevent induction of protective antibodies to tetanus toxoid or standard 23-valent pneumococcal vaccine [8]. Adults with rheumatoid arthritis (RA) who received ≥ 3 months' SC abatacept treatment (125 mg/week with concomitant methotrexate [MTX] and/or low-dose corticosteroids) could mount an appropriate immune response to the 23-valent pneumococcal vaccine and 2011–2012 trivalent seasonal influenza vaccine [9]. However, studies investigating the effects of abatacept on vaccination in very young children with JIA are lacking. This substudy assessed protective antibody response to diphtheria and tetanus vaccination given prior to study enrolment in patients aged 2–5 years with pJIA.

Methods

Study design and patient population

This substudy of a 24-month, Phase III trial (NCT01844518) of SC abatacept in patients (cohort 1: 173 patients aged 6–17 years; cohort 2: 46 patients aged 2–5 years) with active pJIA and inadequate response/intolerance to ≥ 1 DMARD [6] was conducted across 48 centers worldwide by members of the Paediatric Rheumatology International Trials Organisation [10] and the Pediatric Rheumatology Collaborative Study Group [11]. Patients received weight-tiered weekly SC abatacept (10–< 25 kg [50 mg], 25–< 50 kg [87.5 mg]) for 4 months. JIA-American College of Rheumatology criteria 30% improvement responders at Month 4 could receive treatment for another 20 months. Stable doses of concomitant MTX (≤ 30 mg/m²/week) and low-dose oral corticosteroids (≤ 10 mg/day or ≤ 0.2 mg/kg/day [whichever was less] prednisone equivalent) were permitted if used at baseline. The concomitant use of a tumour necrosis factor inhibitor (TNFi) was prohibited; 10/46 (22%) patients had prior TNFi treatment (adalimumab, etanercept or tocilizumab) [6]. Patients from cohort 2,

with ≥ 2 continuous months of abatacept treatment, who received diphtheria/tetanus vaccine prior to enrolment and who were consented to participate by their legal guardians, were included in this substudy. A 60-day washout period was required for other biologics prior to the first dose of abatacept; therefore, levels of other biologics would be non-existent and should not influence the results of this analysis.

Outcomes and analysis

A single blood sample was obtained to assess antibody levels to tetanus and diphtheria. Assessment of blood antibody levels was performed by a central laboratory (ARUP Laboratories, Salt Lake City, UT, USA) using quantitative multiplex bead assays [12]. Protective antibody levels to diphtheria and tetanus were defined as > 0.1 IU/mL by the central laboratory, Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) criteria [12–15]. Immunogenicity of the pertussis component of this vaccine was not studied, as there is no established WHO-defined measure of protection against pertussis following immunization or natural infection [16] and the central laboratory used WHO-defined protective antibody levels for diphtheria and tetanus [13, 14]. Potential impact of concomitant immunosuppressive medications (MTX and/or low-dose corticosteroids [prednisone]) on diphtheria and tetanus antibody levels was evaluated descriptively by medication at the time of blood sample collection. Patient demographics, antibody level data and safety were analyzed descriptively.

Results

Patient disposition and baseline characteristics

Overall, 29/46 (63.0%) patients from cohort 2 participated in this substudy. Baseline characteristics of the patients who participated versus those who did not participate were similar (Table 1). Among participants, 19 (65.5%), 1 (3.4%) and 9 (31.0%) had > 12 , 6–12 and 2–< 6 months of abatacept exposure, respectively. All patients were vaccinated before abatacept initiation; one patient received a single vaccination during the study after 3 months of abatacept treatment.

Protective antibody assessment

Antibody assessment in individual patients is presented in Table 2. All patients had protective antibody levels to tetanus after ≥ 2 months of abatacept treatment and 26/29 (89.7%) patients had protective antibody levels to diphtheria. Of the remaining 3 patients (Table 2; patients 18, 20 and 24), each had a protective antibody level to diphtheria of 0.1 IU/mL, which bordered the lower threshold of protection [12, 14]. These 3 patients received 4 injections (3 initial injections and one booster shot) of combined diphtheria, hepatitis B, *Haemophilus*

Table 1 Baseline demographics and disease characteristics of patients who participated in the vaccination substudy and of those who did not

	Participated <i>n</i> = 29	Did not participate <i>n</i> = 17	Total cohort 2 ^a <i>n</i> = 46
Age at enrolment, years	4.2 (0.9)	3.8 (1.2)	4.1 (1.0)
Female, <i>n</i> (%)	16 (55.2)	12 (70.6)	28 (60.9)
Weight, kg	18.4 (3.6)	18.0 (3.5)	18.2 (3.5)
Weight categories, kg, <i>n</i> (%)			
< 25	27 (93.1)	16 (94.1)	43 (93.5)
25–50	2 (6.9)	1 (5.9)	3 (6.5)
≥ 50	0	0	0
Race, <i>n</i> (%)			
White	29 (100.0)	15 (88.2)	44 (95.7)
Black/African American	0	1 (5.9)	1 (2.2)
Other	0	1 (5.9)	1 (2.2)
Geographic region, <i>n</i> (%)			
South America	4 (13.8)	4 (23.5)	8 (17.4)
Europe	25 (86.2)	11 (64.7)	36 (78.3)
Rest of world	0	2 (11.8)	2 (4.3)
Duration of JIA, years	0.8 (1.0)	0.8 (1.0)	0.8 (1.0)
JIA disease onset categories, <i>n</i> (%)			
Polyarthritis RF–	18 (62.1)	12 (70.6)	29 (63.0)
Polyarthritis RF+	0	2 (11.8)	3 (6.5)
Extended oligoarthritis	8 (27.6)	2 (11.8)	10 (21.7)
Psoriatic arthritis	3 (10.3)	1 (5.9)	4 (8.7)
No. of active joints	10.0 (6.4)	8.1 (5.2)	9.3 (6.0)
No. of joints with limitation of motion	9.6 (5.9)	7.1 (4.8)	8.7 (5.6)
CHAQ-DI score	1.0 (0.7)	1.2 (0.6)	1.1 (0.7)
Parent global assessment score	37.0 (22.9)	41.4 (26.0)	38.6 (23.9)
Physicians global assessment score	50.2 (16.1)	41.9 (20.4)	47.1 (18.0)
CRP, mg/dL	0.8 (1.4)	2.3 (3.4)	1.3 (2.4)
MTX dose ay Day 1, mg/m ² /week	<i>n</i> = 22 13.5 (4.5)	<i>n</i> = 14 12.0 (2.3)	<i>n</i> = 37 12.9 (3.8)
Prednisone dose at Day 1, mg/kg/day	<i>n</i> = 3 0.2 (0.0)	<i>n</i> = 5 0.3 (0.2)	<i>n</i> = 8 0.2 (0.1)

Data are mean (SD) unless otherwise specified. Baseline is Day 1 of the study or the last measurement prior to short-term dose. Cohort 2 included all patients aged 2–5 years. Minor differences between the data for total cohort 2 and those for the participated patients and patients who did not participate in the substudy are due to the different dates of database lock (participated patients and patients who did not participate: July 2, 2018; total cohort 2: February 16, 2017)

^aIncludes all patients who did or did not participate in the vaccination substudy

CHAQ-DI Childhood Health Assessment Questionnaire-Disability Index, CRP C-reactive protein, JIA juvenile idiopathic arthritis, MTX methotrexate, RF rheumatoid factor

influenzae type b, pertussis, poliomyelitis and tetanus vaccine or combined diphtheria, tetanus and pertussis vaccine with 21–49 months between last injection and abatacept initiation and 24–79 months between last injection and antibody assessment. No differences were noted in types of vaccines received by, or in the vaccine schedules of, patients who maintained protective antibody levels to diphtheria or the 3 patients with borderline levels. Concomitant use of MTX and/or low-dose

corticosteroids had no evident effect on antibody levels: 19/20 (95.0%) patients receiving MTX and/or low-dose corticosteroids maintained protective levels to diphtheria and tetanus compared with 7/9 (77.8%) patients receiving no MTX or corticosteroids.

Safety

A safety summary of cohort 2 is presented in Table 3. Abatacept safety profile was consistent between age cohorts [6].

Table 2 Line listing of baseline characteristics, treatment and antibody assessment of patients

Patient number	Age, sex (years; female or male)	Abatacept dose (mg); duration of exposure ^a (months)	Number of vaccine injections	Duration between last vaccination and abatacept initiation (months)	Duration between last vaccination and antibody sample collection (months)	Blood antibody level to diphtheria ^b (IU/mL)	Blood antibody level to tetanus ^c (IU/mL)	Concomitant MTX dose ^e (mg/m ² /week; oral or SC)	Concomitant prednisone dose ^f (mg/kg/day)
1	5, F	50; 27	N/A	N/A	N/A	0.6	5.4	-	-
2	3, F	50; 19	4	30	49	0.8	0.4	7.9, O	-
3	3, M	50; 4	4	27	30	0.2	0.8	16.6, O	-
4	5, F	50; 24	4	-3	21 ^d	0.8	2.2	15.5, O	-
5	5, F	50; 22	5	N/A	N/A	0.5	4.9	3.4, O	-
6	5, F	50; 22	4	52	73	0.9	1.0	9.9, O	-
7	4, M	87.5 ^e ; 19	4	47	66	0.5	5.9	-	-
8	4, M	50; 19	5	43	62	0.7	8.2	13.1, SC	-
9	4, F	50; 16	3	52	67	0.5	0.6	16.2, SC ^f	-
10	5, M	50; 19	5	54	72	0.7	8.3	16.0, SC	-
11	3, F	50; 19	4	36	54	0.5	0.4	-	-
12	4, M	87.5; 4	4	35	39	0.4	2.3	14.0, O	-
13	3, F	50; 4	4	30	34	0.6	2.0	11.7, SC	-
14	4, F	50; 2	4	46	48	0.5	1.8	10.4, SC	-
15	2, F	50; 2	3	24	26	0.6	3.1	14.3, SC	-
16	5, M	50; 3	4	57	60	0.4	0.6	-	-
17	5, M	87.5; 3	4	57	60	0.3	1.1	-	-
18	2, F	50; 3	4	21	24	0.1	0.2	-	-
19	4, F	50; 3	4	46	49	0.5	1.4	11.5, SC	-
20	5, M	50; 30	4	49	79	0.1	0.3	-	-
21	5, M	50; 24	5	54	78	1.1	5.7	10.0, SC	-
22	4, F	87.5 ^e ; 24	4	45	69	1.5	23.2	-	-
23	5, M	50; 16	4	31	47	0.2	3.2	-	-
24	4, M	87.5 ^e ; 16	4	35	51	0.1	1.8	11.7, O	-
25	5, F	50; 19	N/A	N/A	N/A	0.5	0.8	22.9, O	0.1
26	5, F	87.5 ^e ; 19	N/A	N/A	N/A	3.8	3.8	11.5, O	-
27	5, M	50; 19	N/A	N/A	N/A	0.6	3.3	20.1, O	0.1
28	4, M	87.5 ^e ; 21	N/A	N/A	N/A	0.5	0.5	14.8, O	-
29	5, F	87.5 ^e ; 10	N/A	N/A	N/A	8.0	12.5	12.2, O	-

^aAt time of blood sample collection

^bProtective antibody threshold > 0.1 IU/mL

^cConcurrent medication use assessed at the time of blood sample collection, or at the closest date before with available status

^dA single vaccination was administered during the study period after 3 months of abatacept treatment. Antibody sample collection was carried out 21 months after the final vaccination dose was administered

^ePatient initiated abatacept 50 mg before dose escalation

^fPatient switched from 16.2 mg/m²/week SC MTX to 12.9 mg/m²/week oral MTX on the day of blood sample collection

^gPatient initiated abatacept 50 mg, received 5 doses of abatacept at 125 mg before returning to 50 mg, and later escalated to 87.5 mg

F female, M male, MTX methotrexate, N/A not available, O oral, SC subcutaneous

Table 3 Safety summary for patients who participated in the vaccination substudy and for those who did not

Event	Participated <i>n</i> = 29	Did not participate <i>n</i> = 17	Total cohort 2 ^a <i>n</i> = 46
Deaths	0	0	0
SAEs	4 (13.8) ^b	1 (5.9)	5 (10.9)
Related SAEs ^c	2 (6.9)	0	2 (4.3)
Discontinued due to SAEs	0	0	0
AEs	29 (100.0)	15 (88.2)	44 (95.7)
Related AEs	23 (79.3)	7 (41.2)	30 (65.2)
Discontinued due to AEs	0	1 (5.9)	1 (2.2)

Data are number (%) of patients. Cohort 2 included all patients aged 2–5 years

^aIncludes all patients who did or did not participate in the vaccination substudy

^bSAEs included febrile convulsions, tendon disorder, limb abscess, cellulitis and an overdose of mild intensity (administration of a higher abatacept dose due to misclassification by weight tier)

^cTreatment-related SAEs included a limb abscess that was severe in intensity and an overdose of mild intensity (administration of a higher abatacept dose due to misclassification by weight tier)

AE adverse event, SAE serious adverse event

Related serious adverse events (SAEs), SAEs and related AEs were reported in a higher proportion of patients who participated versus those who did not participate in this substudy. Due to the relatively small sample size, these data should be interpreted with caution. No cases of diphtheria or tetanus, or symptoms suggestive of an untoward reaction to the vaccine, were reported during the 24-month period.

Discussion

In this substudy of patients aged 2–5 years with pJIA and prolonged exposure to SC abatacept, all patients maintained protective antibody levels to tetanus, and all but 3 to diphtheria following vaccination prior to study enrolment. Addition of MTX and/or low-dose corticosteroid to SC abatacept treatment did not appear to prevent the maintenance of protective antibody levels in this population. Immune system maturation takes place over the early years of life [2, 3]; therefore, ensuring that very young patients who are receiving immunosuppressive medication can maintain protective antibody levels in response to vaccination is important.

According to the CDC, a complete vaccine series leads to development of protective antibody levels in nearly 100% of healthy children for tetanus and 95% for diphtheria [15], which corresponds to the findings of this study. In the substudies of two trials that included adults with RA who received ≥ 3 months of treatment with abatacept, 74% of patients achieved an immunological response to influenza vaccination and 61% to standard 23-valent pneumococcal polysaccharide vaccine [9], similar to the responses seen in the general population [17, 18]. Importantly, in the present trial, patients were vaccinated before abatacept treatment, whereas in the aforementioned trials, vaccination was administered to patients after treatment with abatacept.

Published research of vaccination in patients with JIA receiving treatment with biologics is limited. Among 15 patients with JIA aged 6–17 years, neither low-dose MTX

nor etanercept caused statistically relevant differences in protective antibody levels following measles, mumps and rubella vaccination compared with untreated healthy controls [19]. Similarly, among 27 patients with mean (standard deviation [SD]) age of 10.4 (5.6) years with systemic-onset JIA who received tocilizumab for a mean (SD) of 1.9 (1.4) years and 17 healthy controls, efficacy of influenza vaccination did not differ significantly between the groups [20]. In addition, in a double-blind, randomized controlled trial, anakinra treatment did not prevent the generation or maintenance of protective antibody levels to standard 23-valent pneumococcal vaccine after 12 months in patients with systemic-onset JIA and a mean (SD) age of 9.5 (5.2) years [21]. In a study of the effects of TNFi treatment on the immunogenicity of 7-valent conjugate pneumococcal vaccine in patients with JIA aged 4–18 years, 87–100% of patients generated protective antibody levels, depending on vaccine serotype [22].

As shown in other studies evaluating vaccination in patients with JIA (reviewed in Groot N, et al. [4]), including a large retrospective cross-sectional analysis [23], concomitant treatment with MTX and/or low-dose corticosteroids does not prevent the generation of protective antibody titres in patients with JIA. Patients receiving treatment with corticosteroids may show lower seroconversion rates, but they usually still reach protective antibody titres [24].

The limitations of this study should be considered. All patients included in this study were of a similar background (100% white; 86% from Europe), which may limit the generalizability of the findings. In addition, the sample size was relatively small and as the analysis was not a classically designed vaccination study, where vaccination is administered during the trial, it was not possible to determine if the patients with borderline protective antibody titres ever had protective levels following vaccination, or the rate at which these titres decreased; therefore, the data should be interpreted with caution.

Overall, paediatric patients with pJIA as young as 2 years old who received 2–24 months of SC abatacept treatment, with the possible addition of MTX and low-dose corticosteroids, were able to maintain effective diphtheria and tetanus vaccination protection without unexpected AEs. These results show that SC abatacept does not prevent the maintenance of protective antibody levels against tetanus and diphtheria, even if the booster dose was not administered recently.

Abbreviations

AE: Adverse event; CDC: Centers for Disease Control and Prevention; DMARD: Disease-modifying antirheumatic drug; IV: Intravenous; JIA: Juvenile idiopathic arthritis; MTX: Methotrexate; pJIA: Polyarticular-course juvenile idiopathic arthritis; RA: Rheumatoid arthritis; SAE: Serious adverse event; SC: Subcutaneous; SD: Standard deviation; TNFi: Tumour necrosis factor inhibitor; WHO: World Health Organization

Acknowledgments

The authors would like to thank the following Paediatric Rheumatology International Trials Organisation investigators for their participation in the study: Jordi Anton, Graciela Espada, Bernard Lauwerys, Ingrid Louw, Kirsten Minden, Mahmood Moosa Ally, Riana Van Zyl, Diego Oscar Viola, Richard Mouy, Brigitte Bader-Meunier and Michaela Semeraro. The authors would like to thank Subhashis Banerjee, Bristol-Myers Squibb, for his contribution to the conception of this study, Mary Swingle, Bristol-Myers Squibb, for her contributions as protocol manager and Marco Garrone, Paediatric Rheumatology International Trials Organisation, for editorial assistance. Professional medical writing and editorial assistance was provided by Lola Parfitt, MRes, at Caudex and was funded by Bristol-Myers Squibb.

Authors' contributions

The study was designed jointly by academic authors (HIB, NR, AM, DJL) and Bristol-Myers Squibb, with data collected by Paediatric Rheumatology International Trials Organisation/Pediatric Rheumatology Collaborative Study Group and the investigators. All authors attest to the completeness and veracity of data and data analyses. Consistency in reporting the study data to healthcare authorities and institutional review boards was ensured by Bristol-Myers Squibb. All authors had full access to study data, reviewed and revised the manuscript and approved the final version to be published. All authors were involved in the decision to submit the manuscript for publication, and had the right to accept or reject comments or suggestions. HIB, YG, MN, RW, AM, DJL and NR were involved in study conception and design; HIB, NT, GVC, RJ, EG, RCi, ICP, RCu, TL, PQ, AM, DJL and NR were involved in the acquisition of data; and HIB, YG, MN, RW, AM, DJL and NR analyzed and interpreted data. 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.

Funding

This study was funded by Bristol-Myers Squibb.

Availability of data and materials

Bristol-Myers Squibb policy on data sharing may be found at <https://www.bms.com/researchers-and-partners/clinical-trials-and-research/disclosure-commitment.html>

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Guidelines for Good Clinical Practice, and local regulations. At every study site, the protocol and amendments were reviewed and approved by the relevant independent review boards or ethics committees.

Consent for publication

Not applicable.

Competing interests

HIB: speakers' bureaus: Genentech, GlaxoSmithKline and Novartis; Cincinnati Children's Hospital Medical Center has received consulting fees from AbbVie, AstraZeneca, Bristol-Myers Squibb, Centocor, Eli Lilly, Genentech, Hoffmann-La Roche, Novartis, Pfizer, Regeneron, UBC and Xoma and for the work of HIB. NT: No conflicts to declare. GVC: consulting fees: AbbVie, Bayer, Bristol-Myers Squibb, Janssen, Sanofi and UCB. RJ: No conflicts to declare. EG: speaking fees: AbbVie, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Pfizer and Roche. RCi: consulting fees or speakers' bureau: AbbVie, Novartis, Sanofi, Sobi. ICP: speaking fees: AbbVie, Novartis, Roche and Sobi; research support: Novartis. RCu: Principal Investigator, medical advisor, speaker: AbbVie, Bristol-Myers Squibb, GlaxoSmithKline, Lilly, Novartis, Pfizer, Roche and Sanofi Aventis. TL: No conflicts to declare. PQ: consulting fees: AbbVie, Bristol-Myers Squibb, Lilly, Novartis, Novimmune, Pfizer, Roche and Sobi; speakers' bureau: AbbVie, Bristol-Myers Squibb, MedImmune, Novartis, Pfizer, Roche and Sobi; safety monitoring board: Sanofi; trial investigator: AbbVie, Bristol-Myers Squibb, Lilly, Novartis, Pfizer, Roche and Sanofi; congress financial support: AbbVie, Bristol-Myers Squibb, Novartis, Pfizer and Sobi. YG, MN and RW: employees and shareholders: Bristol-Myers Squibb. AM: During the last 3 years AM did not have any conflict of interest to declare because starting March 1, 2016, he'd been the Scientific Director of the Giannina Gaslini Hospital, and this role did not allow him to render private consultancies resulting in personal income. Prior to this, AM was a consultant for AbbVie, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, EMD Serono, Janssen, Novartis, Pfizer and R-Pharm. The money received for these activities was directly transferred to the Gaslini Institute's bank account. Since January 2019, AM is no longer the Scientific Director of Istituto Gaslini; therefore, he can perform private consultancy services. Currently he has active consultancy agreements with Janssen, Novartis and Pfizer. DJL: speakers' bureau: Bristol-Myers Squibb and Genentech; Data and Safety Monitoring Board: Forest Research and the National Institutes of Health-NIAMS; Cincinnati Children's Hospital Medical Center has received consulting fees from AbbVie, AstraZeneca, Bristol-Myers Squibb, Centocor, Genentech, Hoffmann-La Roche, Novartis, Pfizer, Regeneron, UBC and Xoma for the work of DJL. NR: honoraria for consultancy or speakers' bureaus: AbbVie, Ablynx, AstraZeneca, Biogen Idec, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, EMD Serono, GlaxoSmithKline, Hoffmann-La Roche, Janssen, Novartis, Pfizer, R-Pharm, Sanofi, Sinergie, Sobi and Takeda. The Gaslini Hospital has received contributions from the following companies: Bristol-Myers Squibb, Hoffman-La Roche, Janssen, Novartis, Pfizer, Sobi. This money has been reinvested for the research activities of the hospital in a fully independent manner besides any commitment with third parties.

Author details

¹Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA. ²Pediatric Rheumatology Research Institute, Bad Bramstedt, Germany. ³CREA de Guadalajara, Guadalajara, Jalisco, Mexico. ⁴Universitair Ziekenhuis Ghent, Ghent, Belgium. ⁵CHU de Poitiers, Rheumatology, Poitiers, France. ⁶Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy. ⁷Azienda Ospedaliera Universitaria Anna Meyer, Florence, Italy. ⁸Hospital Universitario y Politécnico de La Fe, Valencia, Spain. ⁹Hospital General de Niños Pedro de Elizalde, Buenos Aires, Argentina. ¹⁰Center for Pediatric and Adolescent Medicine/Pediatric Rheumatology, University Hospital Heidelberg, Heidelberg, Germany. ¹¹Paris University, IMAGINE Institute, RAISE reference centre, Necker-Enfants Malades Hospital, Assistance Publique-Hopitaux de Paris, Paris, France. ¹²Bristol-Myers Squibb, Princeton, NJ, USA. ¹³Bristol-Myers Squibb, Braine-L'Alleud, Belgium. ¹⁴Istituto Giannina Gaslini, Genoa, Italy.

Received: 12 September 2019 Accepted: 3 February 2020

Published online: 22 February 2020

References

- Heijstek MW, Ott de Bruin LM, Bijl M, Borrow R, van der Klis F, Koné-Paut I, et al. EULAR recommendations for vaccination in paediatric patients with rheumatic diseases. *Ann Rheum Dis*. 2011;70(10):1704–12.
- Comans-Bitter WM, de Groot R, van den Beemd R, Neijens HJ, Hop WCJ, Groeneveld K, et al. Immunophenotyping of blood lymphocytes in childhood. Reference values for lymphocyte subpopulations. *J Pediatr*. 1997; 130(3):388–93.
- Ygberg S, Nilsson A. The developing immune system - from foetus to toddler. *Acta Paediatr*. 2012;101(2):120–7.

4. Groot N, Heijstek MW, Wulffraat NM. Vaccinations in paediatric rheumatology: an update on current developments. *Curr Rheumatol Rep*. 2015;17(7):46.
5. Kremer JM, Westhovens R, Leon M, Di Giorgio E, Alten R, Steinfield S, et al. Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4lg. *N Engl J Med*. 2003;349(20):1907–15.
6. Brunner HI, Tzaribachev N, Vega-Cornejo G, Louw I, Berman A, Penadés IC, et al. Subcutaneous abatacept in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase III open-label study. *Arthritis Rheumatol*. 2018;70(7):1144–54.
7. Ruperto N, Lovell DJ, Quartier P, Paz E, Rubio-Perez N, Silva CA, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. *Lancet*. 2008;372(9636):383–91.
8. Tay L, Leon F, Vratsanos G, Raymond R, Corbo M. Vaccination response to tetanus toxoid and 23-valent pneumococcal vaccines following administration of a single dose of abatacept: a randomized, open-label, parallel group study in healthy subjects. *Arthritis Res Ther*. 2007;9(2):R38.
9. Alten R, Bingham CO III, Cohen SB, Curtis JR, Kelly S, Wong D, et al. Antibody response to pneumococcal and influenza vaccination in patients with rheumatoid arthritis receiving abatacept. *BMC Musculoskelet Disord*. 2016;17(1):231.
10. Ruperto N, Martini A. Networking in paediatrics: the example of the Paediatric Rheumatology International Trials Organisation (PRINTO). *Arch Dis Child*. 2011;96(6):596–601.
11. Brunner HI, Rider LG, Kingsbury DJ, Co D, Schneider R, Goldmuntz E, et al. Pediatric Rheumatology Collaborative Study Group - over four decades of pivotal clinical drug research in pediatric rheumatology. *Pediatr Rheumatol Online J*. 2018;16(1):45.
12. ARUP Laboratories. Diphtheria & Tetanus Antibodies, IgG. Accessed January 30, 2019. Available at: <http://td.aruplab.com/Tests/Pub/0050595>.
13. World Health Organization. Tetanus vaccines: WHO position paper - February 2017. 2017. Accessed January 30, 2019. Available at: https://www.who.int/immunization/policy/position_papers/tetanus/en/.
14. World Health Organization. Diphtheria vaccine: WHO position paper - August 2017. 2017. Accessed January 30, 2019. Available at: https://www.who.int/immunization/policy/position_papers/diphtheria/en/.
15. Centers for Disease Control and Prevention. Chapter 21: Tetanus. *Epidemiology and Prevention of Vaccine-Preventable Diseases*. 2015.
16. World Health Organization. Pertussis vaccines: WHO position paper - August 2015. 2015. Accessed January 30, 2019. Available at: <https://www.who.int/wer/2015/wer9035.pdf?ua=1>.
17. European Centre for Disease Prevention and Control. Influenza vaccine effectiveness. Accessed January 30, 2019. Available at: <https://ecdc.europa.eu/en/seasonal-influenza/prevention-and-control/vaccine-effectiveness>.
18. Wang Y, Li J, Wang Y, Gu W, Zhu F. Effectiveness and practical uses of 23-valent pneumococcal polysaccharide vaccine in healthy and special populations. *Hum Vaccin Immunother*. 2017;14(4):1003–12.
19. Borte M, Borte S, Sack U, Liebert UG. Efficacy of measles, mumps and rubella revaccination in children with juvenile idiopathic arthritis treated with methotrexate and etanercept. *Rheumatology*. 2009;48(2):144–8.
20. Shinoki T, Hara R, Kaneko U, Miyamae T, Imagawa T, Mori M, et al. Safety and response to influenza vaccine in patients with systemic-onset juvenile idiopathic arthritis receiving tocilizumab. *Mod Rheumatol*. 2012;22(6):871–6.
21. Quartier P, Allantaz F, Cimaz R, Pillet P, Messiaen C, Bardin C, et al. A multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial). *Ann Rheum Dis*. 2011;70(5):747–54.
22. Farmaki E, Kanakoudi-Tsakalidou F, Spoulou V, Trachana M, Pratsidou-Gertsis P, Tritsoni M, et al. The effect of anti-TNF treatment on the immunogenicity and safety of the 7-valent conjugate pneumococcal vaccine in children with juvenile idiopathic arthritis. *Vaccine*. 2010;28(31):5109–13.
23. Heijstek MW, van Gageldonk PG, Berbers GA, Wulffraat NM. Differences in persistence of measles, mumps, rubella, diphtheria and tetanus antibodies between children with rheumatic disease and healthy controls: a retrospective cross-sectional study. *Ann Rheum Dis*. 2012;71(6):948–54.
24. Aikawa NE, Campos LM, Silva CA, Carvalho JF, Saad CG, Trudes G, et al. Glucocorticoid: major factor for reduced immunogenicity of 2009 influenza A (H1N1) vaccine in patients with juvenile autoimmune rheumatic disease. *J Rheumatol*. 2012;39(1):167–73.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

