The Journal of Rheumatology 2021;48:1073–81
doi:10.3899/jrheum.200154
First Release May 1 2021

The Journal of Rheumatology

Absence of Association Between Abatacept Exposure and Initial Infection in Patients With Juvenile Idiopathic Arthritis

Nicolino Ruperto[1], Hermine I. Brunner[2], Nikolay Tzaribachev[3], Gabriel Vega-Cornejo[4], Ingrid Louw[5], Rolando Cimaz[6], Jason Dare[7], Graciela Espada[8], Enrique Faugier[9], Manuel Ferrandiz[10], Valeria Gerloni[11], Pierre Quartier[12], Clovis Artur Silva[13], Linda Wagner-Weiner[14], Yash Gandhi[15], Julie Passarell[16], Marleen Nys[17], Robert Wong[15], Alberto Martini[18], and Daniel J. Lovell[2], for the Pediatric Rheumatology Collaborative Study Group (PRCSG) and the Paediatric Rheumatology International Trials Organisation (PRINTO)

ABSTRACT. ***Objective.*** To assess the relationship between infection risk and abatacept (ABA) exposure levels in patients with polyarticular-course juvenile idiopathic arthritis (pJIA) following treatment with subcutaneous (SC) and intravenous (IV) ABA.

Methods. Data from 2 published studies (ClinicalTrials.gov: NCT01844518, NCT00095173) of ABA treatment in pediatric patients were analyzed. One study treated patients aged 2–17 years with SC ABA and the other treated patients aged 6–17 years with IV ABA. Association between serum ABA exposure measures and infection was evaluated using Kaplan-Meier plots of probability of first infection vs time on treatment by ABA exposure quartiles and log-rank tests. Number of infections by ABA exposure quartiles was investigated.

Results. Overall, 343 patients were included in this analysis: 219 patients received SC ABA and 124 patients received IV ABA. Overall, 237/343 (69.1%) patients had ≥ 1 infection over 24 months. No significant difference in time to first infection across 4 quartiles of ABA exposure levels was observed in the pooled ($P = 0.45$), SC (2–5 yrs: $P = 0.93$; 6–17 yrs: $P = 0.48$), or IV ($P = 0.50$) analyses. Concomitant use of methotrexate and glucocorticoids (at baseline and throughout) with ABA did not increase infection risk across the ABA exposure quartiles. There was no evidence of association between number of infections and ABA exposure quartiles. No opportunistic infections related to ABA were reported.

Conclusion. In patients aged 2–17 years with pJIA, no evidence of association between higher levels of exposure to IV ABA or SC ABA and incidence of infection was observed.

Key Indexing Terms: biological therapy, disease-modifying antirheumatic drugs, infection, juvenile idiopathic arthritis

This study was funded by Bristol Myers Squibb. Professional medical writing and editorial assistance was provided by Lola Parfitt, MRes, at Caudex and was funded by Bristol Myers Squibb. The study was designed jointly by academic authors and Bristol Myers Squibb, with data collected by PRINTO/PRCSG investigators. Consistency in reporting the study data to healthcare authorities and institutional review boards was ensured by Bristol Myers Squibb. All authors attest to the completeness and veracity of data and data analyses. All authors had full access to study data, reviewed and revised the manuscript, and approved the final version to be published.

[1]N. Ruperto, MD, MPH, IRCCS Istituto G Gaslini, Clinica Pediatrica e Reumatologia-UOSID Centro Trial, Genoa, Italy; [2]H.I. Brunner, MD, MSc, MBA, D.J. Lovell, MD, MPH, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA; [3]N. Tzaribachev, MD, Pediatric Rheumatology Research Institute, Bad Bramstedt, Germany; [4]G. Vega-Cornejo, MD, CREA Hospital México Americano, Guadalajara, Jalisco, Mexico; [5]I. Louw, MMED, MBChB, Panorama Medical Centre, Cape Town, South Africa; [6]R. Cimaz, MD, University Hospital Meyer, Florence, Italy and Department of Clinical Sciences and Community Health, University of Milano, Milan, Italy; [7]J. Dare, MD, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA; [8]G. Espada, MD, Hospital de Niños Dr Ricardo Gutiérrez, Buenos Aires, Argentina; [9]E. Faugier, MD, Hospital Infantil de México Federico Gómez, Mexico City, Mexico; [10]M. Ferrandiz, MD, Instituto Nacional de Salúd del Niño, Breña, Peru; [11]V. Gerloni, MD, Istituto Ortopedico Gaetano Pini, Milan, Italy; [12]P. Quartier, MD, Université de Paris, IMAGINE Institute, RAISE reference centre for rare diseases, Necker-Enfants Malades hospital, AP-HP, Paris, France; [13]C.A. Silva, MD, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, Brazil; [14]L. Wagner-Weiner, MD, MS, University of Chicago, Chicago, Illinois, USA; [15]Y. Gandhi, PhD, R. Wong, MD, Bristol Myers Squibb, Princeton, New Jersey, USA; [16]J. Passarell, MA, Cognigen Corporation, Buffalo, New York, USA; [17]M. Nys, MSc, Bristol Myers Squibb, Braine-L'Alleud, Belgium; [18]A. Martini, MD, IRCCS Istituto G Gaslini, Clinica Pediatrica e Reumatologia, Genoa, Italy and Università di Genova, Genoa, Italy.

N. Ruperto and H.I. Brunner contributed equally to the manuscript.

NR has received honoraria for consultancy or speakers' bureaus from AbbVie, Ablynx, AstraZeneca, Biogen Idec, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, EMD Serono, F. Hoffman-La Roche, GlaxoSmithKline, Janssen, Novartis, Pfizer, R-Pharm, Sanofi, Sinergie, Sobi, and Takeda. The Gaslini Hospital has received contributions from the following companies: Bristol Myers Squibb, F. Hoffman-La Roche, Janssen, Novartis, Pfizer, and Sobi. This money has been reinvested for the research activities of the hospital in a fully independent manner besides any commitment with third parties. HIB has served on speakers bureaus for Genentech, GlaxoSmithKline, and

Juvenile idiopathic arthritis (JIA) is a term encompassing 7 clinically heterogeneous groups of arthritides of unknown cause in children.[1] For patients with polyarticular-course (p)JIA (JIA of any category with ≥ 5 affected joints),[1] methotrexate (MTX) is the recommended first-line disease-modifying antirheumatic drug (DMARD) therapy.[2,3] Addition of a biologic (b)DMARD (tumor necrosis factor inhibitor [TNFi], anti–interleukin-6 inhibitors, or abatacept [ABA]) is suggested if moderate or high disease activity persists after 3 months of treatment with MTX.[2,3] Concomitant corticosteroid use is permitted with both MTX and bDMARDs, if required. Due to the chronic nature of pJIA, treatment agents are usually administered for a prolonged time, and blood concentrations achieved with bDMARDs may vary greatly between individual patients[4]; thus, the safety of the treatment option is of utmost importance.

Infections have been shown to be the most frequent adverse event (AE) associated with some non-bDMARD and bDMARD treatments in both adult and pediatric patient populations.[5,6,7,8,9] While information regarding the association between bDMARD treatment and infections in pediatric patients with JIA is limited, varied data exist for adult patients with rheumatoid arthritis (RA). A database study of 703 patients with RA indicated that high biologic drug levels (arbitrarily defined using concentration-effect curves for each drug), compared with low/normal levels, were associated with a higher risk of infection.[10] In a multicenter retrospective cohort study of patients with RA in Japan, the risk of overall hospitalized infections did not correlate with the specific bDMARD, but the use of adalimumab (ADA) was significantly associated with a greater risk of pulmonary hospitalized infections vs other agents.[11] However, a recent study of data from administrative health databases suggested that among patients with RA treated with bDMARDs, ABA was associated with the lowest risk of hospitalized infections across all studied biologic agents.[12]

ABA is an immunomodulator that disrupts the continuous cycle of T cell activation that characterizes rheumatic diseases, thereby inhibiting the production of B cell–derived autoantibodies and proinflammatory cytokines.[13,14,15] In an integrated data analysis of 9 RA clinical trials, no increased risk of infections, including opportunistic infections, with ABA vs placebo was identified.[16] Risk of infections is a particularly important consideration in pediatric patients due to their susceptibility to infections.[17] Patients with JIA have also been reported to have an increased risk of hospitalized bacterial infections, compared with children without JIA, independent of treatment with MTX, corticosteroids, or TNFi.[18]

Intravenous (IV) ABA has been proven to be effective and well tolerated in patients with pJIA in clinical trials and real-world settings.[19,20,21,22] Further, in patients with pJIA, weight-tiered subcutaneous (SC) ABA has achieved the target therapeutic exposure threshold and has been effective and well tolerated.[23] Results of clinical trials have shown that, compared with adult patients with RA treated with SC ABA, patients aged 2–5 years with pJIA who received SC ABA had a numerically higher rate of minor infections; no increase in infection rate was noted in patients aged 6–17 years.[23,24]

It is not known whether infection risk is linked to the level of ABA exposure in patients with pJIA following the approved SC or IV dosing regimen. As such, the aims of this analysis were to assess the relationship between the incidence of infection, regardless of seriousness, and levels of ABA exposure in patients with pJIA following SC ABA and IV ABA treatment, and to compare the risk of infection between the IV and SC routes of administration.

METHODS

Data sources. The data from 2 previously published studies of ABA in pediatric patients were analyzed.[19,23] One study included in this analysis was a phase III, single-arm, open-label, international, multicenter, 2-part study comprised of 2 age cohorts of patients with pJIA (patients aged 6–17 yrs and patients aged 2–5 yrs; ClinicalTrials.gov: NCT01844518).[23] Patients received SC ABA based on body-weight tier (10 to < 25 kg [50 mg], 25 to < 50 kg [87.5 mg], and ≥ 50 kg [125 mg]) weekly for 4 months.[23] Responders with at least 30% improvement according to the American College of Rheumatology Criteria for JIA (JIA-ACR30) at Month 4 could receive SC ABA for another 20 months; JIA-ACR30 nonresponders at Month 4 were given the option to continue SC ABA for an additional 3 months

Novartis. The Cincinnati Children's Hospital Medical Center has received consulting fees from AbbVie, AstraZeneca, Bristol Myers Squibb, Centocor, Eli Lilly, F. Hoffman La-Roche, Genentech, Novartis, Pfizer, Regeneron, UBC, and Xoma for the work of HIB. NT has nothing to declare. GVC has received consulting fees from AbbVie, Bayer, Bristol Myers Squibb, Janssen, Sanofi, and UCB. IL has received consulting fees from Amgen, Janssen, Novartis, Pfizer, and Roche. RC has received consulting fees from or participated on speakers bureaus for AbbVie, Novartis, Sanofi, and Sobi. JD has received support for clinical trials/registries from AbbVie, AstraZeneca, Bristol Myers Squibb, Horizon Pharma, Medac, Pfizer, Roche, and UCB. GE has nothing to declare. EF has nothing to declare. MF has nothing to declare. VG has nothing to declare. PQ has received consulting fees from AbbVie, Bristol Myers Squibb, Eli Lilly, Novartis, Novimmune, Pfizer, Roche, and Sobi; has served on speakers bureaus for AbbVie, Bristol Myers Squibb, MedImmune, Novartis, Pfizer, Roche, and Sobi; has served on a safety monitoring board for Sanofi; has acted as a trial investigator for AbbVie, Bristol Myers Squibb, Eli Lilly, Novartis, Novimmune, Pfizer, Roche, and Sanofi; and has received congress financial support from AbbVie, Bristol Myers Squibb, Novartis, Pfizer, and Sobi. CAS has nothing to declare. LWW has nothing to declare. YG, MN, and RW are employees and shareholders of Bristol Myers Squibb. JP is an employee of Cognigen Corporation. AM has received consulting fees from Janssen, Novartis, and Pfizer; Istituto G Gaslini, Clinica Pediatrica e Reumatologia has received consulting fees from AbbVie, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, EMD Serono, Janssen, Novartis, Pfizer, and R-Pharm for the work of AM. DJL has served on speakers bureaus for Bristol Myers Squibb and Genentech; and has served on Data and Safety Monitoring Boards for Forest Research and the National Institutes of Health's National Institute of Arthritis and Musculoskeletal and Skin Diseases. Cincinnati Children's Hospital Medical Center has received consulting fees from AbbVie, AstraZeneca, Bristol Myers Squibb, Centocor, F. Hoffman La-Roche, Genentech, Novartis, Pfizer, Regeneron, UBC, and Xoma for the work of DJL.

Address correspondence to Dr. N. Ruperto, Istituto G. Gaslini Clinica Pediatria e Reumatologia-UOSID Centro Trial, PRINTO, EULAR Centre of Excellence in Rheumatology 2008-2023, Via Gaslini, 5, 16147 Genova, Italy. Email: nicolaruperto@gaslini.org.

Accepted for publication December 18, 2020.

and discontinued treatment if a JIA-ACR30 response was not achieved by Month 7.[23] The other study included in this analysis was a phase III, double-blind, randomized, placebo-controlled withdrawal trial, in which patients with pJIA aged 6–17 years received IV ABA 10 mg/kg monthly (ClinicalTrials.gov: NCT00095173).[19] JIA-ACR30 responders at Month 4 were randomized to receive either ABA or placebo for 6 months, or until a flare occurred.[19] Patients in this study also had the option of continuing ABA in an open-label, long-term extension. In both studies, patients who were taking oral glucocorticoids (GCs) at baseline were allowed to remain on a stable dose (0.2 mg/kg/d or 10 mg/d prednisone equivalent, whichever was lower) throughout the study. Adjustments to GC doses were permitted in the IV study during the long-term extension phase, provided the total prednisone equivalent dose was ≤ 10 mg/day. Short courses (< 2 weeks) of oral GCs (≥ 0.5 mg/kg/d) were permitted in the SC study if clinically indicated.

Eligibility criteria have been described previously.[19,23] Briefly, in both trials, patients had a history of ≥ 5 joints with active articular disease at baseline (defined as ≥ 2 active joints and ≥ 2 joints with limitation of motion), and were naïve to ABA treatment, but may have had an inadequate response or prior intolerance to ≥ 1 nonbiologic DMARD or bDMARD, including TNFi. Patients diagnosed with systemic JIA must have had an absence of systemic features for ≥ 6 months prior to enrollment. Patients were enrolled from 48 centers in 12 countries for the SC trial and from 43 centers in 11 countries for the IV trial, including the Paediatric Rheumatology International Trials Organisation (PRINTO)[25] and the Pediatric Rheumatology Collaborative Study Group (PRCSG) sites.[26]

Both studies were 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.[19,23] For a full list of the institutional review boards involved in these studies, please see the Supplementary Material for this article (available with the online version of this article; note, the review boards did not provide ethics approval numbers).

Assessments and statistical analyses. The data from the 2 studies were analyzed both pooled and separately by route of ABA administration. Data for SC ABA were evaluated by age (6–17 yrs and 2–5 yrs) due to the previously noted numerically higher infection rate among 2- to 5-year-old patients with JIA treated with SC ABA compared with patients in this study aged 6–17 years.[23] The association between serum ABA exposure measures and time to first infection (regardless of seriousness) was assessed. The relationship between levels of ABA exposure measures and the occurrence or absence of infection was also investigated. The following serum ABA exposure measures, estimated by population pharmacokinetic analysis, were used: steady-state maximum serum concentration (C_{maxss}), steady-state trough serum concentration (C_{minss}), and steady-state average serum concentration (C_{avss}).

All patients who received at least 1 dose of study drug in the 2 studies were evaluated for safety, including infections. In the SC trial, infections were recorded as events of special interest, whereas in the IV trial, infections were recorded as part of routine AE reporting and then reclassified as events of special interest thereafter. In the SC trial, opportunistic infections were defined according to recent consensus statements in adults and children.[27,28] In the IV study, similar organisms to those reported in the SC study, including active cytomegalovirus, active *Pneumocystis carinii*, aspergillosis, or atypical mycobacterium infection, were considered to be opportunistic infections. The potential effects of a concomitant stable dose of MTX and GC treatment (at baseline and throughout) on the association between ABA exposure measures and time to first infection (regardless of seriousness) were evaluated.

Kaplan-Meier (KM) plots of probability of first infection vs time on treatment by ABA exposure quartiles were created over time to Month 24 (pooled and separately by SC ABA and IV ABA administration). Quartiles of ABA exposure were generated based on drug concentrations at steady-state. Patients who experienced an infection had their exposure censored at the time of the first onset of the event. Log-rank tests were performed to evaluate the differences in probability of first infection at any time point across ABA exposure quartiles. Exposure-response analysis in the safety analysis dataset confirmed a high degree of correlation among exposure parameters (Supplementary Figure 1, available with the online version of this article); when combining the SC and IV data, the analysis between level of ABA exposure measures suggested that C_{minss} was correlated ($r > 0.66$ or $r < -0.66$) with C_{avss} and C_{maxss}. However, C_{maxss} and C_{avss} were not highly correlated, which was expected due to differences in SC and IV routes of administration. C_{maxss} was chosen as the main exposure measure in this analysis. The incidence of multiple infections was also investigated by quartiles of ABA exposure and age categories (2–17 yrs, 2–5 yrs, and 6–17 yrs). Exploratory graphical analyses (box plots) of the relationship between level of ABA exposure measures and the occurrence or absence of infection to Month 24 were performed. Quartiles of ABA exposure in which infectious serious AEs occurred were also examined. The proportions of patients with infections deemed related to ABA exposure were reported.

RESULTS

Patient disposition and baseline characteristics. Overall, there were 219 patients in the SC ABA trial (age 6–17 yrs, n = 173; age 2–5 yrs, n = 46) and 190 patients in the IV ABA trial. A total of 219 patients treated with SC ABA and 124 of those treated with IV ABA were included in the current analysis. From the IV ABA study, 62 patients who did not receive continuous ABA treatment (patients randomized to receive placebo at Month 4) and 4 patients who did not have ABA exposure measures were excluded from this analysis. Overall baseline demographics and disease characteristics have been reported previously.[19,23] Briefly, in the SC ABA and IV ABA studies, median (min–max) age was 11.0 (2.0–17.0) years and 13.0 (5.0–17.0) years, disease duration was 1.0 (0.0–15.0) and 3.0 (0.0–14.0) years, Childhood Health Assessment Questionnaire–Disability Index was 1.0 (0.0–2.9) and 1.2 (0.0–2.9), and C-reactive protein was 0.2 (0.1–21.1) and 1.3 (0.0–26.0) mg/dL (≤ 0.6 mg/dL defined as normal by the central laboratory), respectively.

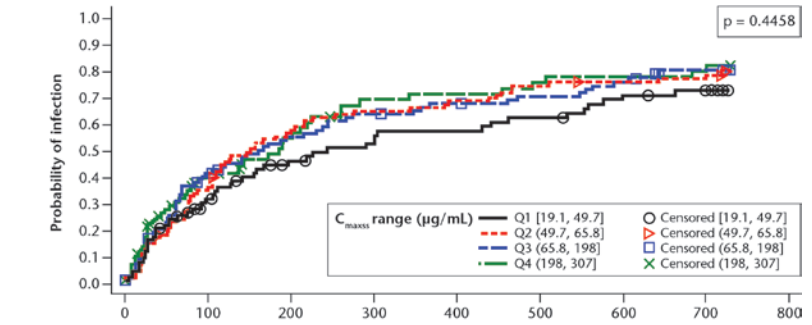
In the SC ABA and IV ABA studies, a total of 172/219 (78.5%) and 91/124 (73.4%) patients, respectively, received concomitant MTX treatment at baseline, at mean (SD) doses of 12.3 (4.1) and 13.6 (4.6) mg/m^2/week, respectively. Over the 24-month period, 177/219 (80.8%) patients in the SC study received MTX treatment at a mean (SD) dose of 12.1 (4.0) mg/m^2/week; the median (Q1–Q3) duration of MTX treatment among these patients was 717 (414–722) days. In the IV study, 92/124 (74.2%) received MTX in the 24-month period at a mean (SD) dose of 13.4 (5.1) mg/m^2/week for a median (Q1–Q3) of 729 (211–729) days. Overall, 60/219 (27.4%) patients in the SC ABA study and 60/124 (48.4%) patients in the IV ABA study received oral GCs at baseline. The mean (SD) doses of oral GCs (prednisone equivalents) at baseline were 0.15 (0.08) and 0.15 (0.07) mg/kg/day in the SC ABA and IV ABA groups, respectively. Over the 24-month period, 82/219 (37.4%) patients in the SC ABA group and 65/124 (52.4%) patients in the IV ABA group received oral GCs for a median (Q1–Q3) of 359 (78–722) and 393 (85–729) days, respectively; mean (SD) doses were 0.19 (0.16) and 0.17 (0.14) mg/kg/day, respectively.

A total of 58/219 (26.5%) patients in the SC ABA study and 49/124 (39.5%) in the IV ABA study received both concomitant MTX and GCs at baseline. Over 24 months, 71/219 (32.4%) patients in the SC ABA group and 52/124 (41.9%) patients in the IV ABA group received both concomitant MTX and GCs for a median (Q1–Q3) of 361 (108–722) and 449 (119–729) days, respectively (data not shown).

ABA exposure and infections: pooled SC and IV analysis. Overall, 237/343 (69.1%) patients treated with either SC ABA or IV ABA had at least 1 infection over 24 months. No statistically significant ($P = 0.45$) difference in probability of first infection at any timepoint across the 4 quartiles of ABA exposure (C_{maxss}) in the 2- to 17-year-old patient population was observed (Figure 1, Table 1). Similar findings in infection probability across the 4 quartiles were also observed for C_{minss} and C_{avss} (Supplementary Figure 2, available with the online version of this article). The median (95% CI) time to first infection in the lowest to highest quartiles of ABA exposure (C_{maxss}) was 244 (129–462), 152 (106–216), 162 (91–246), and 186 (82–224) days. There was no apparent relationship between the numbers of infections per patient seen with increasing exposure to ABA (Supplementary Table 1). Median level of exposure measures by infection status (occurrence or absence) did not show an association between ABA exposure and occurrence of infection (Figure 2). Median values and distributions of level of ABA exposure measures were similar in patients who experienced infections vs those who did not. A total of 3 serious infection AEs were reported: varicella in a 6-year-old patient treated with IV ABA (C_{maxss} = 213 μg/mL; Q2), cellulitis in a 2-year-old patient treated with SC ABA (C_{maxss} = 49.7 μg/mL; quartile 1), and appendicitis in a 17-year-old patient treated with SC ABA (C_{maxss} = 70.5 μg/mL; Q4). All 3 serious infections were resolved and deemed unrelated to ABA treatment. No opportunistic infections related to ABA were reported,[29,30] including no cases of herpes zoster (HZ) in either study during the 24-month period (data not shown).

ABA exposure and infections: analysis by route of administration. A total of 156/219 (71.2%) and 81/124 (65.3%) patients receiving SC ABA and IV ABA, respectively, had at least 1 infection over 24 months. No statistically significant difference in probability of first infection at any timepoint was observed among the exposure quartiles for C_{maxss} following SC ABA (Figure 3, Table 1) or IV ABA (Figure 4, Table 1). Likewise, KM curves were similar across the quartiles for C_{minss} and C_{avss} (Supplementary Figures 3 and 4, available with the online version of this article). Median level of exposure measures and distribution by occurrence or absence of infection did not show an association between ABA exposure and occurrence of infection in either the SC or IV populations (data not shown). Infections considered related to ABA exposure were reported in 60/219 (27.4%) and 18/124 (14.5%) patients receiving SC ABA and IV ABA, respectively.

ABA exposure and infections: analysis of SC ABA by age. Among patients aged 6–17 years, a total of 116/173 (67.1%) patients receiving SC ABA experienced an infection within the 24-month cumulative period; no statistically significant ($P = 0.48$) difference in probability of first infection at any timepoint across ABA exposure quartiles (C_{maxss}) was evident (Figure 3; Table 1). In these patients, the median (95% CI) time to first infection in the lowest to highest quartiles of ABA exposure (C_{maxss}) was 430 (156–577), 108 (63–291), 204 (113–466), and 266 (152–448) days, respectively. A higher proportion of patients aged 2–5 years, compared with patients aged 6–17 years, experienced an infection within the 24-month cumulative period (40/46; 87.0%); however, no statistically significant ($P = 0.93$) difference in probability of first infection at any timepoint across ABA exposure quartiles was observed (Figure 3, Table 1). Among the patients aged 2–5 years receiving SC ABA, the median (95% CI) time to first infection in the lowest to highest quartiles of ABA exposure (C_{maxss}) was 77 (10–511), 77 (27–439), 87 (36–200), and 67 (25–245) days, respectively. The number of infections per patient did not show an association with ABA



Patients at risk (n)

Q1 [19.1, 49.7]	86	67	54	42	36	31	30	27	27	25	24	22	18	17	15
Q2 (49.7, 65.8]	86	71	55	43	36	32	30	29	27	25	22	20	20	19	18
Q3 (65.8, 198]	89	67	50	42	37	32	30	28	26	25	23	22	19	13	13
Q4 (198, 307]	82	54	35	28	24	19	15	14	14	14	12	11	11	11	10

Figure 1. Pooled SC and IV analysis: Kaplan-Meier plots of probability of first infection (regardless of seriousness), from first dose, by ABA exposure quartiles over 24 months in a 2- to 17-year-old patient population (C_{maxss}). For PK ranges, a square bracket indicates the respective endpoint is included in the interval. A round bracket indicates the respective endpoint is not included in the interval. Q1 and Q4 represent the lowest and the highest quartile, respectively. ABA: abatacept; C_{maxss}: steady-state maximum serum concentration; IV: intravenous; PK: pharmacokinetic; Q: quartile; SC: subcutaneous.

Table 1. Median time to first infection for C_{maxss} quartiles.

Exposure Quartile	C_{maxss} Range, μg/mL[a]	Time to First Infection, Days, Median (95% CI)	Log-rank *P*
Pooled SC and IV, 2–17 yrs			
Q1	[19.1–49.7]	244 (129–462)	0.45
Q2	(49.7–65.8]	152 (106–216)	
Q3	(65.8–198.0]	162 (91–246)	
Q4	(198.0–307.0]	186 (82–224)	
SC, 2–5 yrs			
Q1	[37.7–54.4]	77 (10–511)	0.93
Q2	(54.4–61.1]	77 (27–439)	
Q3	(61.1–69.2]	87 (36–200)	
Q4	(69.2–119.0]	67 (25–245)	
SC, 6–17 yrs			
Q1	[19.1–42.4]	430 (156–577)	0.48
Q2	(42.4–52.8]	108 (63–291)	
Q3	(52.8–62.5]	204 (113–466)	
Q4	(62.5–101.0]	266 (152–448)	
IV, 6–17 yrs			
Q1	[119.0–192.5]	188 (91–473)	0.50
Q2	(192.5–214.5]	76 (51–211)	
Q3	(214.5–238.5]	186 (49–684)	
Q4	(238.5–307.0]	192 (81–224)	

Q1 and Q4 represent the lowest and the highest quartile, respectively. [a] For PK ranges, a square bracket indicates respective endpoint is included in the interval. A round bracket indicates respective endpoint is not included in the interval. $C_{maxss:}$ steady-state maximum serum concentration; IV: intravenous; PK: pharmacokinetic; Q: quartile; SC; subcutaneous.

exposure quartiles (Supplementary Table 1, available with the online version of this article).

ABA exposure and infections: analysis of pooled SC ABA and IV ABA by concomitant MTX and GC use at baseline and throughout. Overall, an infection was reported within the 24-month period in 73/107 (68.2%) patients receiving triple immunosuppression with ABA, concomitant MTX, and GCs in this analysis. No difference in probability of first infection at any time point across the 4 quartiles of ABA exposure measures was observed (Figure 5; Supplementary Figure 5, available with the online version of this article). Similarly, no difference in probability of first infection at any time point across the 4 quartiles of ABA exposure measures was seen in patients receiving SC ABA or IV ABA monotherapy (Supplementary Figures 6 and 7). Some differences in the shapes of KM curves for ABA monotherapy analyses (Supplementary Figure 7), compared with all other analyses, could be attributed to very small sample sizes.

DISCUSSION

Among patients aged 2–17 years with pJIA who received the approved SC ABA or IV ABA dose, with the possibility of MTX and/or GCs, no association of level of ABA exposure with risk of infections over a 24-month period was seen. While patients aged 2–5 years had a numerically greater rate of infections than patients aged 6–17 years,[23] as one might expect to observe in these 2 age groups among the general population, the level of ABA exposure was not associated with time to first infection

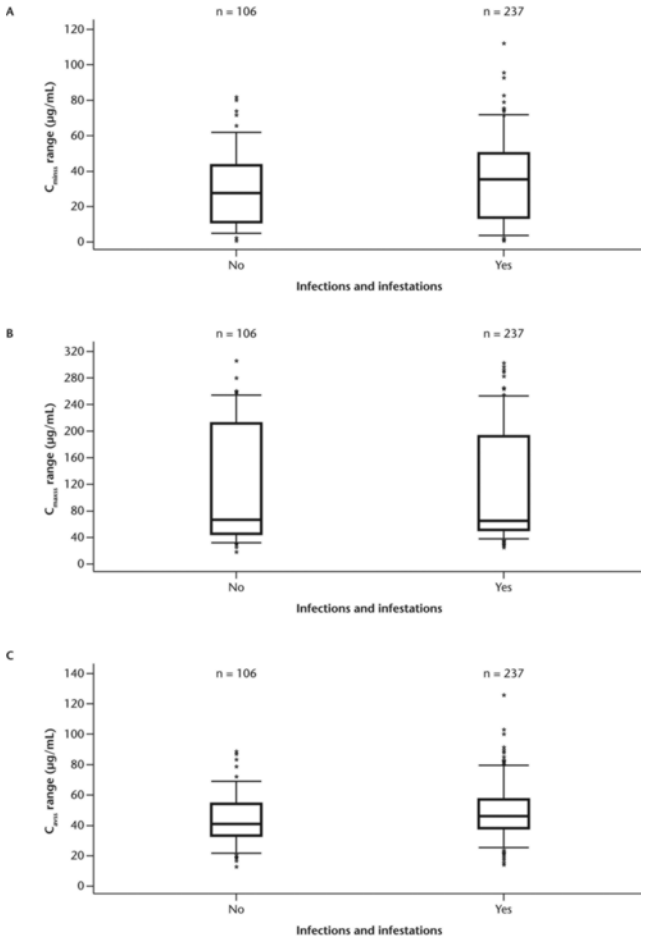


Figure 2. Pooled SC and IV analysis: boxplots of ABA exposure measurements vs the occurrence of infections over 24 months (2- to 17-year-old patient population). (A) C_{minss}; (B) C_{maxss}; and (C) C_{avss}. ABA: abatacept; C_{avss}: steady-state average serum concentration; C_{maxss}: steady-state maximum serum concentration; C_{minss}: steady-state trough serum concentration; IV: intravenous; SC: subcutaneous.

or occurrence of multiple infections in either population. The median values and distributions of ABA exposure measures were similar between patients with pJIA in whom infection occurred and those in whom infections were not reported. There was no consistent association with infectious serious AEs with ABA level of exposure.

Infections and infestations are the most frequently reported AEs associated with ABA treatment in pediatric patients, with nasopharyngitis and upper respiratory tract infections being the most common.[19,23] No new cases of opportunistic infections, including HZ and tuberculosis, were reported in either SC or IV studies, despite the presence of some study sites in tuberculosis-endemic, or high tuberculosis incidence, locations.[19,23] In addition, an integrated data analysis of 9 clinical trials identified no increased risk of HZ infection in ABA-treated patients with RA, compared with patients receiving placebo.[16] A large analysis combining data from clinical trials and registries revealed that in pediatric patients, ABA had a similar infection profile to both ADA and etanercept; all 3 of these agents had favorable infection

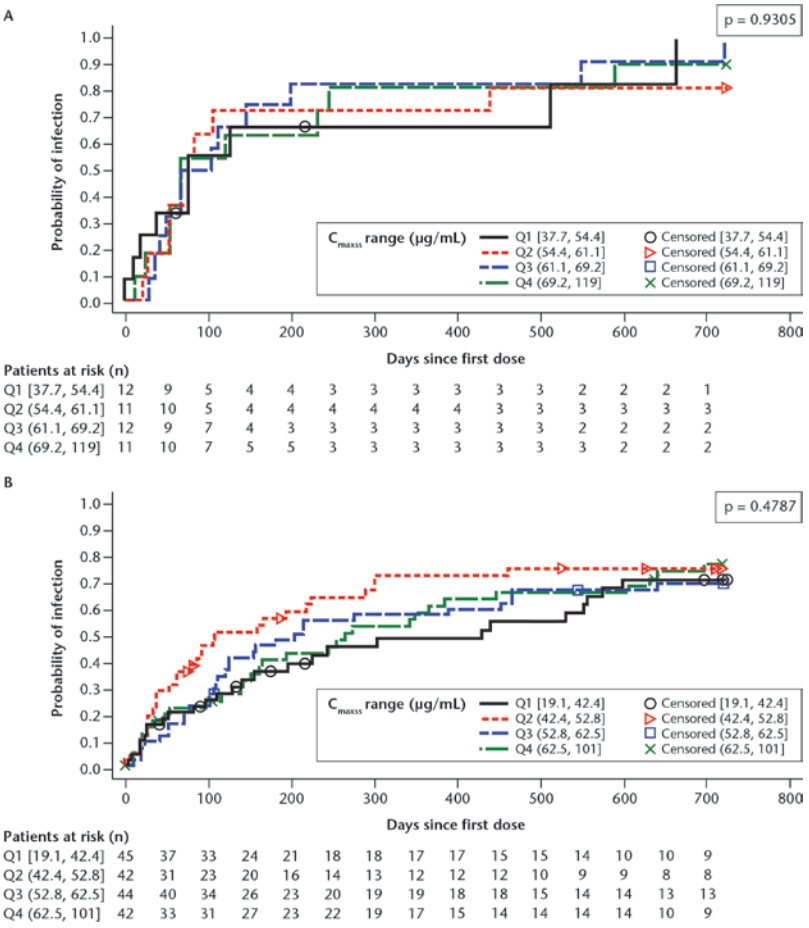


Figure 3. SC ABA analysis: Kaplan-Meier plots of probability of first infection (regardless of seriousness), from first dose, by ABA exposure quartiles over 24 months (C_{maxss}): A) 2- to 5-year-old patient population, B) 6- to 17-year-old patient population. For PK ranges, a square bracket indicates respective endpoint is included in the interval. A round bracket indicates respective endpoint is not included in the interval. Q1 and Q4 represent the lowest and the highest quartile, respectively. ABA: abatacept; C_{maxss}: steady-state maximum serum concentration; PK: pharmacokinetic; Q: quartile; SC: subcutaneous.

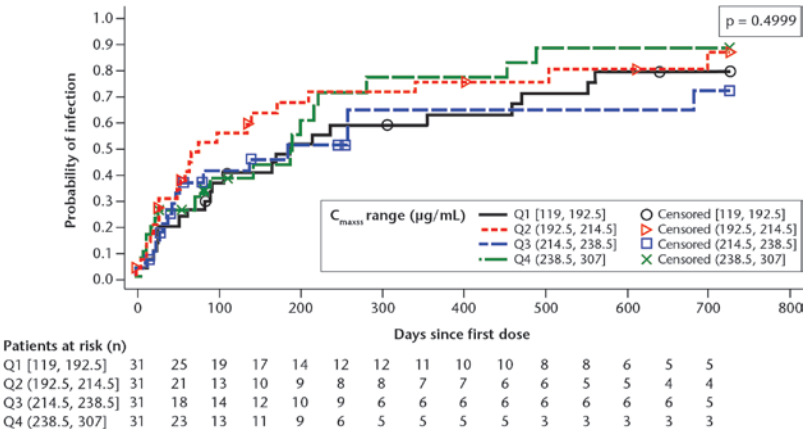


Figure 4. IV ABA analysis: Kaplan-Meier plots of probability of first infection (Regardless of seriousness), from first dose, by ABA exposure quartiles over 24 months in a 6- to 17-year-old patient population (C_{maxss}). For PK ranges, a square bracket indicates respective endpoint is included in the interval. A round bracket indicates respective endpoint is not included in the interval. Q1 and Q4 represent the lowest and the highest quartile, respectively. ABA: abatacept; C_{maxss}: steady-state maximum serum concentration; IV: intravenous; PK: pharmacokinetic; Q: quartile.

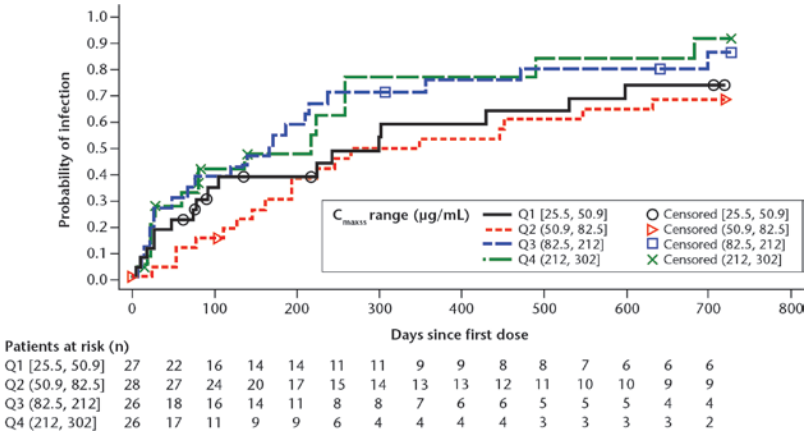


Figure 5. Pooled SC and IV analysis: Kaplan-Meier plots of probability of first infection (regardless of seriousness), from first dose, by ABA exposure quartiles over 24 months, 2- to 17-year-old patient population with concomitant MTX and GCs at baseline and throughout (C_{maxss}). For PK ranges, a square bracket indicates respective endpoint is included in the interval. A round bracket indicates respective endpoint is not included in the interval. Q1 and Q4 represent the lowest and the highest quartile, respectively. ABA: abatacept; C_{maxss}: steady-state maximum serum concentration; GC: glucocorticoid; IV: intravenous; MTX: methotrexate; PK: pharmacokinetic; Q: quartile; SC: subcutaneous.

profiles compared with golimumab, infliximab, and tocilizumab (TCZ).[31] Consistent with the results seen with ABA, IV and SC TCZ treatment in patients with RA resulted in similarly low rates of serious infections.[32]

Due to a potential immunosuppressive effect, MTX and GCs may lead to a possible increase in infection risk, particularly in a susceptible population[33,34]; as such, it is important to investigate their use concomitantly with bDMARDs. A systematic literature review and metaanalysis of randomized controlled trials demonstrated that combination therapy with bDMARDs and MTX did not increase the risk of serious infections vs bDMARD monotherapy,[35] in line with the results observed in this analysis (Supplementary Figures 5 and 6, available with the online version of this article). In addition, a systematic literature review of 88 studies showed that long-term (≥ 2 yrs) use of MTX monotherapy was not a risk factor for serious infections, including HZ.[36] This is potentially due to the fact that the mechanism of action of MTX in RA may be mediated by its antiinflammatory rather than immunosuppressive properties.[37] Conversely, the use of GCs has been associated with increased risk of infections in patients with RA[31,38,39,40] and JIA.[18] In a longitudinal study of complete patient medical records, a dose-dependent association of use of GCs with risk for serious infections was observed in patients with RA[41]; in addition to this, an association between HZ infection and GC use was also seen.[42] In this study, concomitant use of MTX, GCs, and ABA did not markedly increase risk of infection across the level of ABA exposure quartiles, which may indicate that even a relatively high degree of immunosuppression is well tolerated in this population (Supplementary Figure 5).

The limitations of this study should be considered. First, these were posthoc analyses and neither study was designed or powered specifically to investigate time to first infection. Due to the relatively small sample size in each quartile of the patients aged 2–5 years, these data must be interpreted with caution. In addition, due to the sample size, analysis of specific infections was not conducted. It should also be considered that due to limited patient exposure to triple immunosuppression with concomitant MTX and GCs in this analysis, detection of immunosuppressive effects might have also been limited. In addition, patients were restricted to relatively low doses of GCs (IV pulse steroids were not permitted); as a result, the effects of high-dose GCs could not be studied. However, in children, long-term treatment with high doses of GCs is not desirable due to their negative effect on growth and development in addition to well-known AEs.

In conclusion, no association of ABA (SC or IV) exposure with risk of infections, including opportunistic infections, was found in pediatric patients aged 2–17 years with pJIA over a 24-month period, including with concomitant MTX and GC treatment at baseline and throughout. These findings provide further support for the use of ABA in patients as young as 2 years with pJIA.

ACKNOWLEDGMENT

The authors would like to thank Mary Swingle for her contributions as protocol manager and Kuan-Ju (Lisa) Lin for her contributions to the data analyses. The authors would like to thank the following investigators for their contributions to this study: Brigitte Bader-Meunier and Richard Mouy, RAISE Centre, Necker, Paris, France; Michaela Semeraro, Solimda Sotou-Bere, and Mame Diagne, Clinical Research Centre, Necker, Paris, France. Professional medical writing and editorial assistance was provided by Lola Parfitt, MRes, at Caudex and was funded by Bristol Myers Squibb.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

REFERENCES

1. Ravelli A, Martini A. Juvenile idiopathic arthritis. Lancet 2007;369:767-78.

2. Webb K, Wedderburn LR. Advances in the treatment of polyarticular juvenile idiopathic arthritis. Curr Opin Rheumatol 2015;27:505-10.
3. Beukelman T, Patkar NM, Saag KG, Tolleson-Rinehart S, Cron RQ, DeWitt EM, et al. 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. Arthritis Care Res 2011;63:465-82.
4. Reijers JAA, Moerland M, Burggraaf J. Remarkable pharmacokinetics of monoclonal antibodies: a quest for an explanation. Clin Pharmacokinet 2017;56:1081-9.
5. Woodrick RS, Ruderman EM. Safety of biologic therapy in rheumatoid arthritis. Nat Rev Rheumatol 2011;7:639-52.
6. Tarkiainen M, Tynjälä P, Vähäsalo P, Lahdenne P. Occurrence of adverse events in patients with JIA receiving biologic agents: long-term follow-up in a real-life setting. Rheumatology 2015;54:1170-6.
7. Kalden JR, Schattenkirchner M, Sörensen H, Emery P, Deighton C, Rozman B, et al. The efficacy and safety of leflunomide in patients with active rheumatoid arthritis: a five-year followup study. Arthritis Rheum 2003;48:1513-20.
8. Silverman E, Spiegel L, Hawkins D, Petty R, Goldsmith D, Schanberg L, et al. Long-term open-label preliminary study of the safety and efficacy of leflunomide in patients with polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum 2005;52:554-62.
9. Swart J, Giancane G, Horneff G, Magnusson B, Hofer M, Alexeeva E, et al. Pharmacovigilance in juvenile idiopathic arthritis patients treated with biologic or synthetic drugs: combined data of more than 15,000 patients from Pharmachild and national registries. Arthritis Res Ther 2018;20:285.
10. Singh JA, Guyatt G, Ogdie A, Gladman DD, Deal C, Deodhar A, et al. Special article: 2018 American College of Rheumatology/ National Psoriasis Foundation guideline for the treatment of psoriatic arthritis. Arthritis Care Res 2019;71:2-29.
11. Mori S, Yoshitama T, Hidaka T, Sakai F, Hasegawa M, Hashiba Y, et al. Comparative risk of hospitalized infection between biological agents in rheumatoid arthritis patients: a multicenter retrospective cohort study in Japan. PLoS One 2017;12:e0179179.
12. Carrara G, Bortoluzzi A, Sakellariou G, Silvagni E, Zanetti A, Govoni M, et al. Risk of hospitalisation for serious bacterial infections in patients with rheumatoid arthritis treated with biologics. Analysis from the RECord linkage On Rheumatic Disease study of the Italian Society for Rheumatology. Clin Exp Rheumatol 2019;37:60-6.
13. Ma CS, Deenick EK, Batten M, Tangye SG. The origins, function, and regulation of T follicular helper cells. J Exp Med 2012;209:1241-53.
14. Malmström V, Catrina AI, Klareskog L. The immunopathogenesis of seropositive rheumatoid arthritis: from triggering to targeting. Nat Rev Immunol 2017;17:60-75.
15. Laria A, Lurati AM, Marrazza M, Mazzocchi D, Re K, Scarpellini M. The macrophages in rheumatic diseases. J Inflamm Res 2016; 9:1-11.
16. Simon TA, Soule BP, Hochberg M, Fleming D, Torbeyns A, Banerjee S, et al. Safety of abatacept versus placebo in rheumatoid arthritis: integrated data analysis of nine clinical trials. ACR Open Rheumatol 2019;1:251-7.
17. World Health Organization. Children's environmental health. [Internet. Accessed March 3, 2021]. Available from: http://www.who.int/ceh/risks/en/
18. Beukelman T, Xie F, Chen L, Baddley JW, Delzell E, Grijalva CG, et al. Rates of hospitalized bacterial infection associated with juvenile idiopathic arthritis and its treatment. Arthritis Rheum 2012;64:2773-80.
19. Ruperto N, Lovell DJ, Quartier P, Paz E, Rubio-Pérez N, Silva CA, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet 2008;372:383-91.
20. Ruperto N, Lovell DJ, Quartier P, Paz E, Rubio-Pérez N, Silva CA, et al. Long-term safety and efficacy of abatacept in children with juvenile idiopathic arthritis. Arthritis Rheum 2010;62:1792-802.
21. Lovell DJ, Ruperto N, Mouy R, Paz E, Rubio-Pérez N, Silva CA, et al. Long-term safety, efficacy, and quality of life in patients with juvenile idiopathic arthritis treated with intravenous abatacept for up to seven years. Arthritis Rheumatol 2015;67:2759-70.
22. Lovell DJ, Ruperto N, Tzaribachev N, Zeft A, Cimaz R, Stanevica V, et al. Long-term effectiveness and safety of abatacept in juvenile idiopathic arthritis: interim results from the abatacept in JIA registry [abstract]. Arthritis Rheumatol 2017;69 Suppl 10:2272.
23. 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;70:1144-54.
24. Genovese MC, Schiff M, Luggen M, Becker JC, Aranda R, Teng J, et al. Efficacy and safety of the selective co-stimulation modulator abatacept following 2 years of treatment in patients with rheumatoid arthritis and an inadequate response to anti-tumour necrosis factor therapy. Ann Rheum Dis 2008;67:547-54.
25. Ruperto N, Martini A. Networking in paediatrics: the example of the Paediatric Rheumatology International Trials Organisation (PRINTO). Arch Dis Child 2011;96:596-601.
26. 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;16:45.
27. Winthrop KL, Novosad SA, Baddley JW, Calabrese L, Chiller T, Polgreen P, et al. Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance. Ann Rheum Dis 2015;74:2107-16.
28. Giancane G, Swart JF, Castagnola E, Groll AH, Horneff G, Huppertz HI, et al; Paediatric Rheumatology International Trials Organisation. Opportunistic infections in immunosuppressed patients with juvenile idiopathic arthritis: analysis by the Pharmachild Safety Adjudication Committee. Arthritis Res Ther 2020;22:71.
29. Brunner HI, Ruperto N, Tzaribachev N, Horneff G, Chasnyk VG, Panaviene V, et al; Paediatric Rheumatology International Trials Organisation, Pediatric Rheumatology Collaborative Study Group. Subcutaneous golimumab for children with active polyarticular-course juvenile idiopathic arthritis: results of a multicentre, double-blind, randomised-withdrawal trial. Ann Rheum Dis 2018;77:21-9.
30. Lovell D, Ruperto N, Quartier P, Paz E, Rubio-Perez N, Silva CA, et al. Clinically meaningful improvements in health-related quality of life, pain and sleep quality in children with polyarticular juvenile idiopathic arthritis treated with abatacept over the long term. Paper presented at: American College of Rheumatology Annual Meeting; November 6-11, 2010; Atlanta, GA. Oral presentation number 1407.
31. Horneff G. Biologic-associated infections in pediatric rheumatology. Curr Rheumatol Rep 2015;17:66.
32. Nakashima Y, Kondo M, Miyahara H, Iwamoto Y. Drug delivery options to increase patient adherence and satisfaction in the management of rheumatoid arthritis — focus on subcutaneous tocilizumab. Drug Des Devel Ther 2014;8:913-9.

33. Youssef J, Novosad SA, Winthrop KL. infection risk and safety of corticosteroid use. Rheum Dis Clin North Am 2016;42:157-76.
34. Zimecki M, Artym J. Effect of methotrexate on the immune response in selected experimental models. Postepy Hig Med Dosw 2004;58:226-35.
35. Baradat C, Degboé Y, Constantin A, Cantagrel A, Ruyssen-Witrand A. No impact of concomitant methotrexate use on serious adverse event and serious infection risk in patients with rheumatoid arthritis treated with bDMARDs: a systematic literature review and meta-analysis. RMD Open 2017;3:e000352.
36. Salliot C, van der Heijde D. Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: a systematic literature research. Ann Rheum Dis 2009;68:1100-4.
37. Segal R, Yaron M, Tartakovsky B. Methotrexate: mechanism of action in rheumatoid arthritis. Semin Arthritis Rheum 1990; 20:190-200.
38. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Predictors of infection in rheumatoid arthritis. Arth Rheum 2002;46:2294-300.
39. Smitten AL, Choi HK, Hochberg MC, Suissa S, Simon TA, Testa MA, et al. The risk of hospitalized infection in patients with rheumatoid arthritis. J Rheumatol 2008;35:387-93.
40. Lacaille D, Guh DP, Abrahamowicz M, Anis AH, Esdaile JM. Use of nonbiologic disease-modifying antirheumatic drugs and risk of infection in patients with rheumatoid arthritis. Arth Rheum 2008;59:1074-81.
41. Crowson CS, Hoganson DD, Fitz-Gibbon PD, Matteson EL. Development and validation of a risk score for serious infection in patients with rheumatoid arthritis. Arth Rheum 2012;64:2847-55.
42. Yun H, Xie F, Delzell E, Chen L, Levitan EB, Lewis JD, et al. Risks of herpes zoster in patients with rheumatoid arthritis according to biologic disease-modifying therapy. Arthritis Care Res 2015; 67:731-6.