Absence of Association Between Drug Exposure and Infection in Patients With Polyarticular-Course Juvenile Idiopathic Arthritis and Inadequate Response to Biologic or Non-Biologic DMARDs Treated With SC and IV Abatacept

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N Ruperto,[1] *H Brunner*,[2] *N Tzaribachev*,[1] *I Louw*,[1] *I Calvo*,[1] *G Horneff*,[1] *M Henrickson*,[2] *ME Rama*,[1] *M Fischbach*,[1] *T Miraval*,[1] *MM Ally*,[1] *X Li*,[3] *R Wong*,[3] *M Nys*,[4] *B Murthy*,[3] *K Lin*,[5] *JA Passarell*,[5] *A Martini*,[1] *DJ Lovell*[2]

[1]*PRINTO, Istituto Gaslini, Genoa, Italy;* [2]*PRCSG, CHMC Cincinnati, Cincinnati, OH, USA;* [3]*Bristol-Myers Squibb, Princeton, NJ, USA;* [4]*Bristol-Myers Squibb, Braine-L'Alleud, Belgium;* [5]*Cognigen Corporation, a SimulationsPlus Company, Buffalo, NY, USA*

Introduction

- Compared with adults, children are more susceptible to infections.
- In paediatric patients with juvenile idiopathic arthritis (JIA), infections are the most commonly reported AEs linked to biologic (b)DMARDs.[1]
- bDMARDs are an effective treatment option for JIA.[1]
- Compared with adult patients with RA, paediatric patients with polyarticular-course JIA (pJIA) receiving abatacept had a numerically higher rate of infections.[2]
- Blood concentrations achieved with bDMARDs may vary greatly between individual patients.
- It is not known whether the infection risk is linked to abatacept exposure in patients with pJIA following the approved IV or SC dosing regimen.

Objective

- To assess the relationship between the incidence of infection and abatacept exposure in patients with pJIA following SC (50, 87.5 or 125 mg weekly) and IV (10 mg/kg monthly) abatacept.

Methods

Data sources and assessments

- Data from the open-label SC (4-month short-term and 24-month cumulative periods) and IV (4 month short-term period) abatacept studies in paediatric patients with pJIA were used:
  - the Phase III SC abatacept trial (ClinicalTrials.gov, NCT01844518) included two cohorts of patients (cohort 1, patients aged 6–17 years and cohort 2, patients aged 2–5 years) who received SC abatacept based on body-weight tier (10–<25 kg [50 mg], 25–<50 kg [87.5 mg], ≥50 kg [125 mg]) weekly for 4 months; JIA-ACR30 responders at Month 4 could receive SC abatacept for another 20 months[2,3]
  - the Phase III IV abatacept trial (ClinicalTrials.gov, NCT00095173) included patients aged 6–17 years who received IV abatacept 10 mg/kg monthly.[4]
- The following serum abatacept exposure measures, estimated by population pharmacokinetic analysis, were employed:
  - steady-state trough serum concentration (C_{minss})
  - steady-state maximum serum concentration (C_{maxss})
  - steady-state time-averaged serum concentration (C_{avgss}).
- The association between serum abatacept exposure measures and time to first infection (regardless of seriousness) was assessed.

Statistical analysis

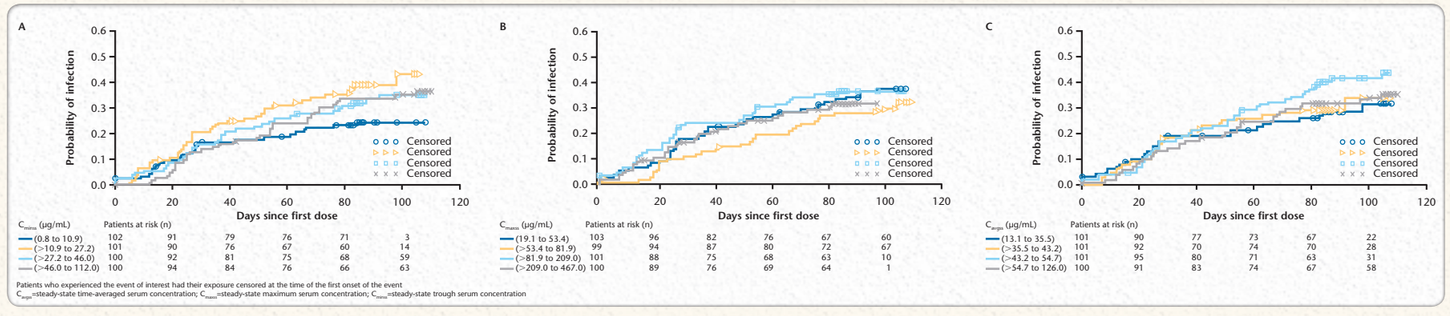
- Kaplan–Meier (KM) plots of infection probability versus time to first infection by abatacept exposure quartiles were created from pooled SC and IV data and also separately by route of administration over time to Month 4 and by age cohort over the 24 month-cumulative period (SC abatacept only).
- A log-rank test was performed to evaluate the differences in distribution of time to first infection across abatacept exposure quartiles.
- An exploratory graphical analysis (box plot) of the relationship between abatacept exposure measures (C_{minss}, C_{maxss} and C_{avgss}), and the occurrence or absence of infection over time to Month 4, was conducted.

Results

Patient disposition and baseline characteristics

- A total of 403 patients were analysed:
  - 219 patients in the SC abatacept trial (cohort 1 [patients aged 6–17 years], n=173; cohort 2 [patients aged 2–5 years], n=46)
  - 184 patients in the IV abatacept trial.
- Baseline demographic and clinical characteristics were comparable between the SC and IV trials.[3,4]

Figure 1. Kaplan–Meier Plots of Probability of First Infection, Regardless of Seriousness, Versus Days From First Dose to Infection, by Abatacept Exposure Quartiles Over 4 Months (Pooled SC and IV Analysis; 2–17-Year-Old Patient Population): A) C_{minss}, B) C_{maxss} and C) C_{avgss}



Patients who experienced the event of interest had their exposure censored at the time of the first onset of the event
C_{avgss}=steady-state time-averaged serum concentration; C_{maxss}=steady-state maximum serum concentration; C_{minss}=steady-state trough serum concentration

Pooled SC and IV analysis in the 4-month short-term period

- Overall, 135/403 patients (33.5%) had ≥1 infection over 4 months:
  - 77/219 (35.2%) in the SC abatacept trial
  - 58/184 (31.5%) in the IV abatacept trial.
- KM plots for pooled SC and IV abatacept data showed no statistically significant difference (log-rank test) in infection probability across four quartiles of abatacept exposure measures in the 4-month short-term period in the 2–17-year-old patient population (Figure 1A–C): C_{minss} (p=0.2317), C_{maxss} (p=0.5501) and C_{avgss} (p=0.3808).
- A graphical analysis (box plot) did not show an association between abatacept exposure and infection risks in the 4-month short-term period (data not shown).
  - The median exposure measures (C_{minss}, C_{maxss} and C_{avgss}) were similar by infection status (occurrence or absence) in patients with pJIA treated with abatacept.

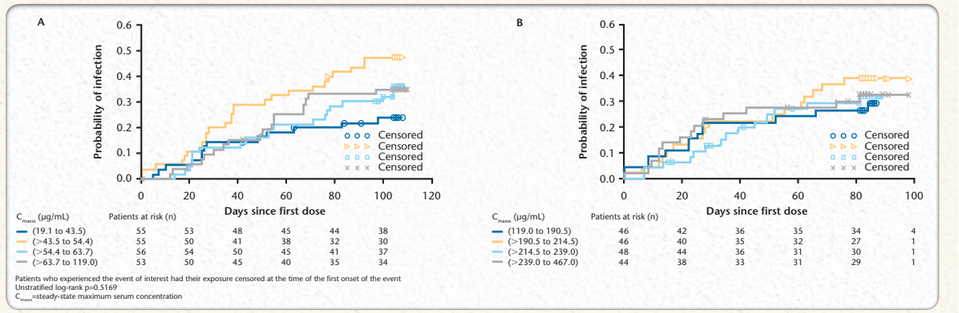
Separate analysis by route of administration in the 4-month short-term period

- Consistent with the results observed for pooled data, no statistically significant difference in infection probability was observed for individual SC (2–17-year-old patients) or IV (6–17-year-old patients) abatacept exposure measures in the 4-month short-term period (Figure 2A, B; C_{maxss}).
- The median and distribution of abatacept exposure measures (C_{minss}, C_{maxss} and C_{avgss}) were similar by infection status (occurrence or absence) in separate SC and IV analyses in the 4-month short-term period (data not shown).

SC analysis by age cohort in the 24-month cumulative period

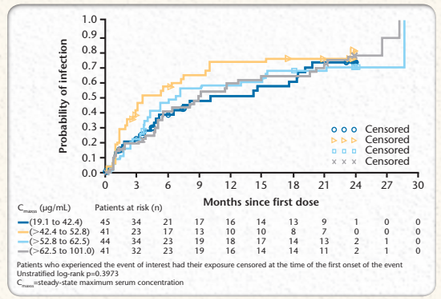
- The 4-month short-term period results for SC abatacept were further supported by the findings in the 24-month cumulative period:
  - In the 6–17-year-old cohort: C_{minss} (log-rank p=0.4346; not shown), C_{maxss} (p=0.3973; Figure 3) and C_{avgss} (p=0.1776; not shown)
  - In the 2–5-year-old cohort: C_{minss} (log-rank p=0.9236; not shown), C_{maxss} (p=0.9450; Figure 4) and C_{avgss} (p=0.9982; not shown).
- No cases of tuberculosis were reported in the 4-month short-term and the 24-month cumulative periods.

Figure 2. Kaplan–Meier Plots of Probability of First Infection, Regardless of Seriousness, Versus Days From First Dose to Infection, by Abatacept C_{maxss} Quartiles and Route of Administration Over 4 Months: A) SC Abatacept (2–17-Year-Old Patients) and B) IV Abatacept (6–17-Year-Old Patients)



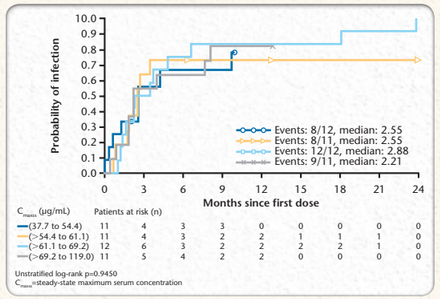
Patients who experienced the event of interest had their exposure censored at the time of the first onset of the event
Unstratified log-rank p=0.5169
C_{maxss}=steady-state maximum serum concentration

Figure 3. Kaplan–Meier Plots of Probability of First Infection, Regardless of Seriousness, Versus Days From First Dose of SC Abatacept to Infection, by Abatacept C_{maxss} Quartiles Over the 24-Month Cumulative Period in the 6–17-Year-Old Cohort



Patients who experienced the event of interest had their exposure censored at the time of the first onset of the event
Unstratified log-rank p=0.3973
C_{maxss}=steady-state maximum serum concentration

Figure 4. Kaplan–Meier Plots of Probability of First Infection, Regardless of Seriousness, Versus Days From First SC Abatacept Dose to Infection, by Abatacept C_{maxss} Quartiles Over the 24-Month Cumulative Period in the 2–5-Year-Old Cohort



Unstratified log-rank p=0.9450
C_{maxss}=steady-state maximum serum concentration

Conclusions

- In paediatric patients with pJIA who received the approved SC or IV abatacept dose, the infection risk over the 4-month short-term (SC, IV) or 24-month (SC) cumulative periods was not associated with abatacept exposure.
- The median abatacept exposure measures were similar between patients with pJIA in whom infection occurred and those in whom infections were not reported in the 4-month short-term period.
- No cases of tuberculosis were reported in the 4-month short-term or 24-month cumulative periods.

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