Absence of association between abatacept exposure levels and initial infection in patients with RA: a post hoc analysis of the randomized, placebo-controlled AVERT-2 study

Paul Emery,[1,2] Roy Fleischmann,[3] Robert Wong,[4]* Karissa Lozenski,[4] Yoshiya Tanaka,[5] Vivian Bykerk,[6] Clifton O Bingham,[7] Thomas WJ Huizinga,[8] Gustavo Citera,[9] Yedid Elbez,[10] Vidya Perera,[4] Bindu Murthy,[4] Kelly Maxwell,[11] Julie Passarell,[11] William Hedrich,[4] Daphne Williams[4]

[1]University of Leeds, Leeds, UK; [2]Leeds Teaching Hospitals NHS Trust, Leeds, UK; [3]University of Texas, Dallas, TX, USA; [4]Bristol Myers Squibb, Princeton, NJ, USA; [5]University of Occupational and Environmental Health, Kitakyushu, Japan; [6]Hospital for Special Surgery, New York, NY, USA; [7]Johns Hopkins University, Baltimore, MD, USA; [8]Leiden University Medical Center, Leiden, Netherlands; [9]Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina; [10]Signifience, Paris, France; [11]Cognigen Corporation, a Simulations Plus company, Buffalo, NY, USA
*At the time of analysis

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Introduction

- Infections are the most commonly reported AEs in patients with RA treated with immunosuppressive therapies, and they can be clinically significant
- A recent review reported differences in the risk of infection for some biologics such as tocilizumab and TNF inhibitors[1]
- Abatacept selectively modulates T-cell co-stimulation and is approved for the treatment of RA
- In patients with polyarticular-course juvenile idiopathic arthritis, no association was found between higher serum abatacept exposure and the incidence of infection[2]
  - This has not been evaluated for adult patients with RA

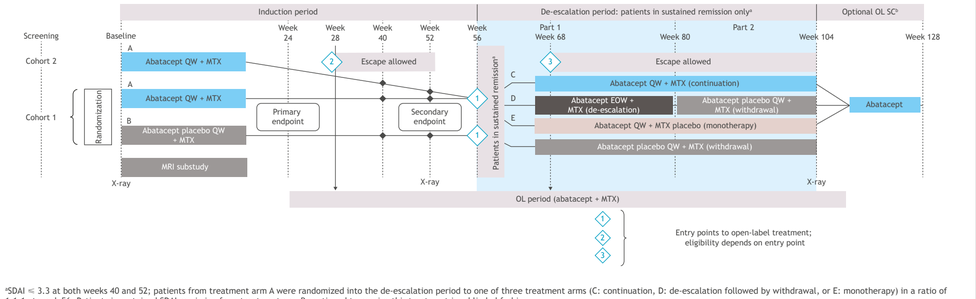
Objective

- To determine if higher serum abatacept exposure during treatment with SC abatacept was associated with an increased risk of infection in adult patients with RA

Methods

- AVERT-2 (Assessing Very Early Rheumatoid arthritis Treatment-2; NCT02504268) was a randomized, placebo-controlled study of SC abatacept + MTX versus abatacept placebo + MTX in MTX-naive, anti-citrullinated protein antibody-positive patients with early, active RA[3] (**Figure 1**)
- A population pharmacokinetic (PK) model was developed for abatacept using data from 13 studies of adult patients with RA
  - Based on the model, a post hoc population PK analysis was performed using PK-evaluable patient data from the induction period (year 1) of AVERT-2
- Association between steady-state abatacept exposure (minimum plasma concentration [C_{min}], maximum plasma concentration [C_{max}], and average plasma concentration [C_{avg}]) and time to first infection (response) was evaluated using Kaplan–Meier (KM) plots of the probability of infection versus time on treatment, by abatacept exposure quartiles
  - Cox proportional hazards models were used to test the significance of abatacept exposure (C_{avg}, C_{min}, C_{max}) as predictors of time to first infection (significance level of 0.05)

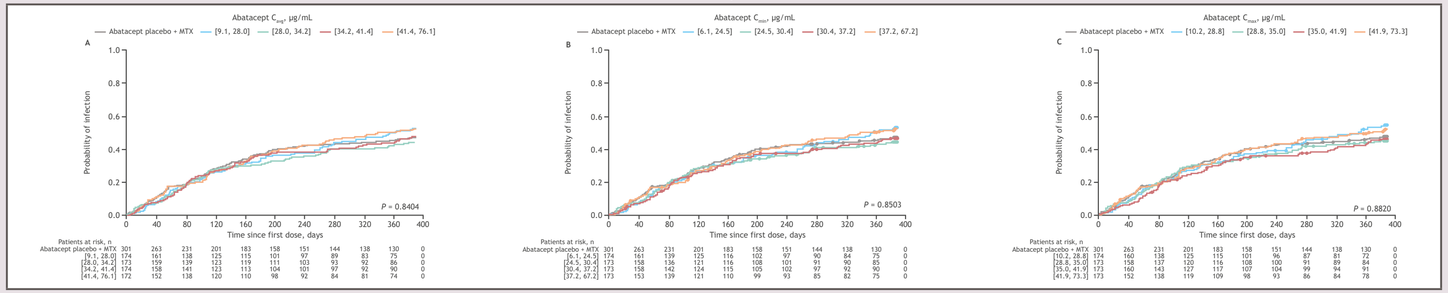
Figure 1. Study design



[a]SDAI ⩽ 3.3 at both weeks 40 and 52; patients from treatment arm A were randomized into the de-escalation period to one of three treatment arms (C: continuation, D: de-escalation followed by withdrawal, or E: monotherapy) in a ratio of 1:1:1 at week 56. Patients in sustained SDAI remission from treatment arm B continued to receive this treatment in a blinded fashion.
[b]De-escalation period completers.
EOW, every other week; QW, once weekly.

No association between abatacept exposure levels and initial infection was observed in patients with RA

Figure 2. KM plots of time to first infection for patients with RA treated with abatacept + MTX and abatacept placebo + MTX (C_{avg}, C_{min}, C_{max})



P values are from Cox proportional hazards models (alpha = 0.05).

Results

Population PK analysis

- PK of SC abatacept was defined as a linear two-compartment model with first-order absorption and first-order elimination
- The findings of the updated PK analysis were consistent with those reported in prior population analyses of abatacept PK in adults with RA
- The PK model included effects of baseline body weight, estimated glomerular filtration rate, sex, age, albumin, MTX use, NSAID use, SJC, and race on abatacept clearance
- The only covariate with a clinically relevant effect was higher body weight, which caused an increase in clearance and volume
- In the PK analysis population, the baseline mean (SD) study exposure was 373.5 (66.2) days for patients taking abatacept. The baseline mean (SD) prednisone equivalent dose was 6.7 (3.7) mg/day and the mean (SD) MTX dose was 9.6 (3.0) mg/week (**Table 1**)
- A summary of the overall safety results is provided in **Table 2**

Table 1. Baseline demographics and disease characteristics of PK population (N = 693)

Characteristic	Mean (SD)[a]
Age, years	49.3 (12.8)
Sex, n (%)	
Male	155 (22.4)
Female	538 (77.6)
Race, n (%)	
White	488 (70.4)
Asian	88 (12.7)
Black/African American	27 (3.9)
American Indian/Alaska Native	1 (0.1)
Other	89 (12.8)
Weight, kg	72.2 (16.6)
Median (Q1, Q3)	70 (61, 80)
Disease duration, months	1.3 (1.5)
SDAI score	38.8 (13.8)
DAS28 (CRP) score	5.6 (1.0)
HAQ-DI score	1.6 (0.7)
CRP score	2.0 (2.9)
RF+, n (%)	654 (94.4)
TJC28	13.5 (6.7)
SJC28	10.2 (5.6)
Physician Global Assessment, mm	65.6 (17.7)
Prior bDMARD use, n (%)	0 (0)
MTX dose, mg/week	9.6 (3.0)
Prednisone equivalent dose (oral), mg/day	6.7 (3.7)
Patients receiving prednisone, n (%)	316 (45.6)

[a]Unless otherwise stated.
bDMARD, biologic DMARD.

Table 2. Overall safety summary (N = 693)

	Patients, n (%)
Overall AEs	544 (78.5)
Related AEs (investigator opinion)	244 (35.2)
Discontinuations due to AEs	36 (5.2)
AEs of special interest	
Malignancy	5 (0.7)
Autoimmune disorders	10 (1.4)
Local injection-site reaction	11 (1.6)
Systemic injection reactions[a] (within 24 hours of injection)	42 (6.1)
Serious AEs	55 (7.9)
Deaths	1 (0.1)
Related serious AEs (investigator opinion)	12 (1.7)
Discontinuations due to serious AEs	10 (1.4)

[a]Systemic injection reactions are defined as systemic AEs (such as hypersensitivity reactions) occurring during the first 24 hours after SC injection.

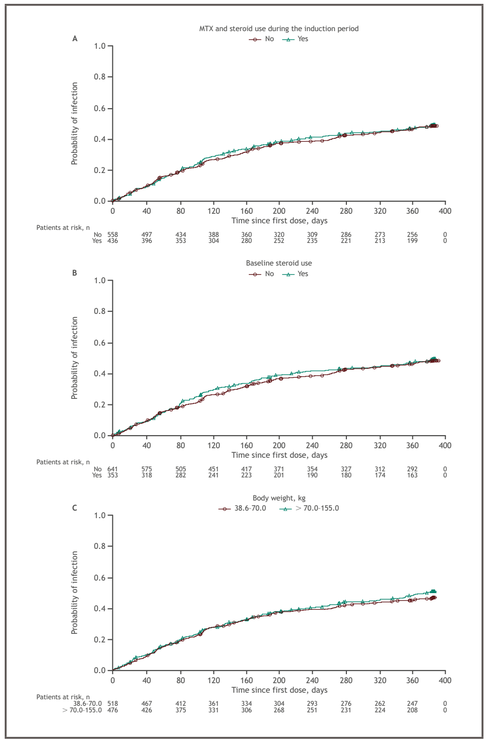
Exposure-response relationship

- Infections occurred in a total of 330/693 (47.6%; serious, 1.6%) patients treated with abatacept and 134/301 (44.5%; serious, 1.3%) with placebo during the first year of AVERT-2
- No exposure-response relationship was observed between the probability of first infection and steady-state abatacept exposure quartiles (C_{avg}, C_{min}, and C_{max}) compared with placebo (**Figure 2A-C**) based on the Cox proportional-hazards analysis (all nonsignificant, $P > 0.05$)
- KM assessment also showed no increase in the risk of infection with concomitant use of MTX and glucocorticoids during the induction period, baseline steroid use, or higher than median body weight at baseline (⩾ 70 kg; **Figure 3A-C**)

Conclusions

- No association was found between initial infection and steady-state abatacept exposure (C_{avg}, C_{min}, C_{max}) or MTX and glucocorticoid use in patients with RA treated with SC abatacept

Figure 3. KM plots of probability of first infection by covariates: (A) MTX and steroid use, (B) baseline steroid use, and (C) baseline body weight



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