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Assessment of the suitability and usefulness of a new antibiotic in Belgium in the absence of local clinical data using pharmacokinetics/ pharmacodynamics: an example with ceftaroline

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1. Introduction and background

Most drugs are developed today on a world-wide basis following the requirements of the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). While this has improved the quality of the clinical studies submitted for registration, it may make them poorly relevant to the situation prevailing in specific countries if epidemiology and/or comparators are different from those of these global studies.

Performing additional clinical studies in target markets is often financially difficult and raises both scientific (number of patients who can reasonably be enrolled) and ethical (delaying the introduction of a potentially useful drug) issues.

For anti-infective agents, this problem can be addressed by examining the susceptibility of the local target pathogens and using pharmacokinetic/pharmacodynamic (PK/PD) approaches to examine how the results of the global studies may apply to specific local situations.

Ceftaroline (CPT; as its prodrug ceftaroline fosamil) has been approved by EMA for
- community acquired pneumonia (CAP)
- complicated skin and skin structure infections (cSSSI)

As for all β-lactams, the PK/PD index governing the activity of CPT is the time during which the free drug concentration remains above the MIC of the target organism [*f*T> MIC]).

2. Objectives

To assess whether ceftaroline could be useful and efficacious in Belgium based on local epidemiology of the two main target organisms corresponding to its two indication (*S. pneumoniae* (SP) for CAP; methicillin-resistant *S. aureus* [MRSA] for cSSSI), using "normal and "worst" scenarios for its PK parameters.

3. Methods

Samples and MIC determinations:

- MRSA: isolates collected between 2011 and 2012 from patients suffering of wound infections in 3 hospitals (1 in South-East of Brussels; 1 in North of Brussels; 1 in Hainaut);
- SP: isolates collected between 2009 and 2012 obtained from patients with confirmed cases of CAP (clinical and radiological criteria) and seen at the Emergency Department of 4 hospitals (1 in East-Flanders, 1 in North Brussels, 1 in South-East Brussels, 1 in Hainaut);

Determination by broth microdilution (ISO standard) following the general recommendations of the US CLSI in comparison with 1st line comparators (amoxicillin [AMX; SP] and vancomycin [VAN; MRSA]).

Interpretative criteria (breakpoints) of the European Committee for Antibiotic Susceptibility Testing (EUCAST [4]).

Modeling and calculations of *f*T> MIC

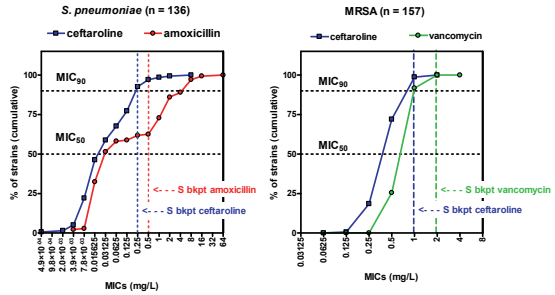
- public published data on ceftaroline pharmacokinetics and 20% protein binding [1,2];
- Batman's equation for description of the release of active CPT from its prodrug (k_a) and its elimination (k_e; one compartment only since the deep compartment is negligible);
- Monte-Carlo simulation for "worst" scenario based on covariance of published data [1].

References

[1] Biek *et al.* J Antimicrob Chemother. 2010; 65 Suppl 4:iv9-16
[2] Ceftaroline Summary of Product Characteristics (ZINFORO; http://www.ema.europa.eu)
[3] Laudano, 2011.J. Antimicrob. Chemother.2011; 66 Suppl 3:iii11-iii18 - PM:21482565
[4] EUCAST breakpoints and rational documents: http://www.eucast.org

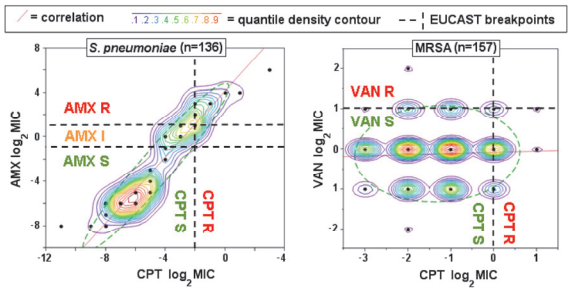
4. Results

Figure 1 shows the MIC cumulative percentages of CPT vs. amoxicillin (SP; left) and vancomycin (MRSA; right) in relation to EUCAST breakpoints [4].



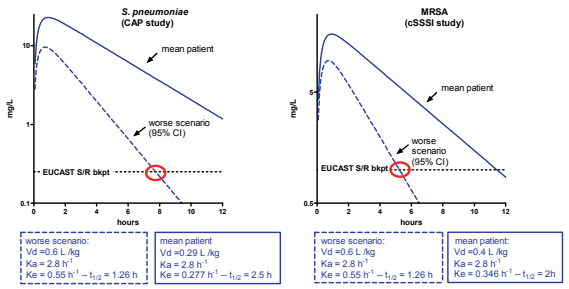
A significant proportion of SP isolates non-susceptible to AMX are susceptible to CPT. For MRSA, the two drugs behave essentially alike when taking EUCAST breakpoints into account

Figure 2 shows the correlations between MICs of individual strains for CPT vs AMX and VAN using quantile density contour analysis.



While CPT and AMX MICs are correlated, a subset of isolates intermediate or resistant to AMX are susceptible to CPT. Conversely, there is no correlation between CPT and VAN MICs and most isolates are susceptible to both antibiotics

Figure 3 shows simulations of "mean patient" and "worst scenarios" for "*free concentration > EUCAST breakpoints*" based on PK data from registration studies [2,3].



For mean patients, *f*T>EUCAST breakpoint exceeds 100 % for both pathogens. For "worst scenarios" (increase in V_d, reduced half-life), *f*T>EUCAST breakpoint still reaches 66% for *S. pneumoniae* and 41 % for MRSA. Both values exceed the minimum requirement for activity according to EUCAST [4].

5. Conclusions

- *S. pneumoniae* and CAP: CPT may provide better coverage when AMX non-susceptibility becomes worrisome (as in patients from whom this collection was assembled);
- MRSA and cSSSI: CPT is equivalent to VAN (but may be less toxic);
- In both situations, reporting susceptibilities using EUCAST interpretative criteria will ensure optimal efficacy.

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