27th ECCMID Vienna, Austria 22 – 25 April 2017
The congress of ESCMID

Session: OS042 Late-breaker: Recent clinical trials

Category: Other

22 April 2017, 17:48 - 17:59
OS0250G

Adjunctive Rifampicin to Reduce Early mortality from Staphylococcus aureus bacteraemia: final results from the multi-centre, randomised blinded placebo-controlled ARREST trial

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Background: Mortality following *Staphylococcus aureus* bacteraemia remains high. Current treatment guidelines do not generally recommend combination antimicrobial treatment. The ARREST trial (ISRCTN37666216) tests the hypothesis that adjunctive rifampicin would enhance early killing of *S. aureus*, sterilise infected foci/blood faster, and thereby reduce the risk of dissemination, metastatic infection and death.

Material/methods: Adults (≥18 years) with *S. aureus* bacteraemia with ≤96 hours of active antibiotic therapy, without contraindications to rifampicin, were randomized 1:1 to receive 2 weeks' rifampicin versus placebo plus standard antibiotic therapy. The primary endpoint was bacteriological failure/recurrence or death (all-cause) through 12 weeks from randomization. All potential failures/recurrences were adjudicated by a blinded independent review committee. Preliminary results are presented below (some events not yet adjudicated): final results comparing randomized groups and outcomes will be presented at ECCMID.

Results: 770 patients were randomized between December 2012 and October 2016 from 29 UK hospital groups. 12 had major eligibility criteria violations and were excluded from the analysis. Of the included 758, 495(65.3%) were men, with median(IQR) age 65(50-76) years, Charlson co-morbidity score 2(0-3), and CRP 156(86-224) mg/L. 485(64.0%) bacteraemias were community-acquired, with only 132(17.4%) nosocomial; 51(6.7%) were caused by methicillin-resistant *S. aureus* (MRSA). The initial focus was non-device-related in 436(57.5%) (including skin/soft-tissue infection in 255(33.6%)), intra-vascular in 164(21.6%), non-vascular prosthetic device/implants in 14(1.8%), another identified focus in 24(3.2%) and not established in 139(18.3%). At randomization, patients had received median(IQR) 62.1(41.1-75.3) hours' active antibiotics and 70 (9.2%) patients were in intensive care. 744(98.2%) patients initiated blinded study-drug (96(12.7%) intravenous), a median(IQR) 68(47-85) hours after starting active antibiotics. Study drug was continued for median(IQR) 12.8(7.9-13.4) days. Backbone active antibiotics included flucloxacillin in 485(65.5%) and a glycopeptide in 312(41.2%); for median(IQR) 17(9-36) days. 23(3.0%) patients withdrew consent; 11 weeks post-randomization only 17(2.2%) had unknown vital status and 45(5.9%) were not assessed for signs/symptoms of *S. aureus*. Overall, 133(17.5%) patients experienced bacteriological failure/recurrence or died by 12 weeks; 9(1.2%) failures, 19(2.5%) recurrences and 105(13.9%) deaths without bacteriological failure/recurrence. 112(14.8%) died by 12 weeks, 42(5.5%) before 2 weeks. 30(26.8%)/26(23.2%)/12(10.7%) deaths were definitely/probably/possibly *S. aureus*-related, 41(36.6%) were not attributed to *S. aureus*, and 3 (2.7%) were unattributable. 160(21.1%) patients experienced clinically-defined failure/recurrence or died by 12 weeks; 44(5.8%) failures, 27(3.6%) recurrences and 89(11.7%) deaths without clinically-defined failure/recurrence. Failure of infection focus management was implicated in 57 failures/recurrences, 16 where the focus was not recognized. 2(0.3%) patients developed rifampicin-resistant *S. aureus* bacteraemia. 197(26.0%) patients experienced serious adverse events (AEs), 263(34.7%) grade 3/4 AEs, 80(10.6%) antibiotic-modifying AEs.

Conclusions: In the last 50 years, fewer than 1500 patients have entered into 16 randomised controlled trials of *S. aureus* bacteraemia antimicrobial therapy. ARREST will provide definitive evidence on the benefits and risks of adjunctive rifampicin in this serious infection.