SMT19969 for Clostridium difficile infection (CDI): in vivo efficacy compared with fidaxomicin and vancomycin in the hamster model of CDI

Abdul Sattar1, Pia Thommes1, Lloyd Payne1, Peter Warn1 and Richard J. Vickers2*

1Evotec (UK), Williams House, Manchester Science Park, Lloyd Street North, Manchester M15 6SE, UK; 2Summit plc, Abingdon, Oxfordshire, UK

*Corresponding author. Tel: +44-(0)1235-443945; Fax: +44-(0)1235-443999; E-mail: richard.vickers@summitplc.com

Received 23 October 2014; returned 26 November 2014; revised 15 December 2014; accepted 31 December 2014

Objectives: SMT19969 is a novel narrow-spectrum antimicrobial under development for the treatment of Clostridium difficile infection (CDI). The objectives were to assess the relative efficacies of SMT19969, vancomycin and fidaxomicin in the hamster model of CDI.

Methods: Hamsters were infected with either C. difficile BI1 (ribotype 027) or C. difficile 630 (ribotype 012) prior to treatment with vehicle, SMT19969, fidaxomicin or vancomycin for 5 days. Animals were further monitored through to day 28 and survival recorded. Plasma and gastrointestinal concentrations of SMT19969 following single and repeat administration in infected hamsters were determined.

Results: Following infection with C. difficile BI1, treatment with SMT19969, vancomycin and fidaxomicin resulted in 100% survival during the 5 day dosing period, with 90%–100% of animals receiving SMT19969 and fidaxomicin surviving during the post-dosing follow-up period. Whilst protective during treatment, onset of mortality was observed on day 11 in animals treated with vancomycin, with a 10% survival recorded by day 28. Similar results were observed for SMT19969 and vancomycin following infection with C. difficile 630, with day 28 survival rates of 80%–100% and 0%, respectively. Fidaxomicin protected animals infected with C. difficile 630 from mortality during dosing, although day 28 survival rates varied from 0% to 40% depending on dose. Plasma levels of SMT19969 were typically below the limit of quantification, but levels in the gastrointestinal tract remained far in excess of the MIC.

Conclusions: These data show that SMT19969 is highly effective at treating both acute infection and preventing recurrent disease and support continued investigation of SMT19969 as a potential therapy for CDI.

Keywords: C. difficile, treatment, antimicrobial

Introduction

Over the past two decades, the emergence of hypervirulent epidemic strains of Clostridium difficile has been associated with increasing prevalence and severity of disease with a recognition of disease occurring in the community and primary care facilities.1,2

Although the molecular epidemiology of C. difficile infection (CDI) differs across geographical locations, the hypervirulent ribotype 027 (BI/NAP1) remains the predominant strain in the USA,3 accounting for approximately one-third of cases and continues to be the most commonly isolated ribotype in many Central and Eastern European countries.4

Conventional agents (metronidazole and vancomycin) are associated with high rates of recurrent disease.5 Fidaxomicin, which received approval in 2011, has been shown to be non-inferior to vancomycin on clinical response at end of therapy but superior to vancomycin in sustaining clinical response to 25 days post end of therapy.6,7 Currently, there is little supporting clinical evidence for the use of fidaxomicin in subjects suffering multiple recurrences of CDI.8 In addition, metronidazole is inferior to vancomycin in treating severe CDI.9

SMT19969 is a novel non-absorbable antibiotic in Phase 2 clinical development for the treatment of CDI. With a narrow spectrum of activity and high selectivity for C. difficile over Gram-positive and Gram-negative anaerobic and facultative faecal flora,10,11 SMT19969 has therapeutic potential for the treatment of CDI.

Here, we report the results from studies in an established hamster model12 comparing the efficacy of SMT19969, fidaxomicin...
and vancomycin following infection with either C. difficile ribotype 027 or 012. In addition, plasma and gastrointestinal (GI) concentrations of SMT19969 following single and repeat administration in infected hamsters were determined.

**Methods**

**Regulatory**

Animal experiments were performed under UK Home Office ASPA Licence 40/3644 and with ethics committee clearance (the University of Manchester Committee). All experiments were performed by technicians who have completed parts 1–3 of the Home Office Personal Licence course and hold current personal licences.

**Animal strain**

Golden Syrian hamsters used in these studies were supplied by Janvier Laboratories (France) and were specific pathogen free. Hamsters were housed in sterile individual ventilated cages exposing hamsters at all times to HEPA-filtered sterile air. Hamsters had free access to food and water and sterile aspen chip bedding.

**Bacterial isolates**

C. difficile strains BI1 (ribotype 027) and 630 (ribotype 012) used in these studies were supplied by B. Wren, London School of Hygiene and Tropical Medicine, UK.

**Pre-infection**

Hamsters were identified by subcutaneous implantation of temperature-recording identification chips (Plexx IPPT 300 programmable non-contact temperature transponders). Hamsters were rendered susceptible to infection by C. difficile by administration of 30 mg/kg oral clindamycin (Villerton, Berkshire, UK). As soon as death was confirmed, the abdomen of the animals was opened and the entire gut carefully opened lengthwise. A portion of the contents of the stomach, upper small intestine, caecum and colon was removed and immediately frozen at −80°C until shipment to CEMAS for SMT19969 quantification. Bioanalysis of the plasma and gut content samples for SMT19969 was performed by CEMAS using LC-MS/MS. The lower limit of quantification (LOQ) was 1 ng/mL for both plasma and GI samples.

**Infection**

All hamsters were infected with ~100–350 C. difficile spores by oral gavage 24 h post-clindamycin administration.

**Preparation of test articles and dosing**

SMT19969 (manufactured to Good Manufacturing Practice guidelines by CML, Weert, The Netherlands) was first suspended in 50 mg/mL DMSO (Sigma) and then further diluted in aqueous 0.5% methyl cellulose to provide a suspension for administration. Fidaxomicin (Dificlir, 200 mg film-coated tablets, Astellas Pharma Europe) was ground to a powder, suspended in 20 mg/mL DMSO and then further diluted in aqueous 0.5% methyl cellulose to provide a suspension for administration. Vancomycin (Vancocin®, Flynn Pharma, Stevenage, UK) was freshly prepared once daily from a 50 mg/mL stock solution made up in water for injection. The 50 mg/mL stock solution was diluted in physiological saline for dosing solutions. Vehicle-treated animals were administered aqueous 0.5% methyl cellulose. All solutions were prepared once daily and stored at 4°C between doses. Animals were treated at 10 mL/kg by oral gavage. Treatment was initiated 20 h post-infection and administered twice daily for 5 days using a sterile plastic disposable 1.5 mm diameter (4.5 FG) dosing catheter.

**In-life sample collection**

Faecal samples were collected from all surviving animals on days 1, 7, 12, 19 and 28 post-infection. Faecal samples were cultured for the presence of C. difficile spores after treatment with 70% ethanol for 5 min.

**Endpoints**

The efficacy of the test agents was assessed by monitoring and comparing daily survival rates. The hamsters were monitored at a frequency appropriate to their clinical condition. Hamsters that developed hypothermia (<33°C), diarrhoea, weight loss (>20%) or other signs of severe disease were euthanized by an overdose of pentobarbitone. As soon as death was confirmed, the abdomen of the hamsters was dissected and the presence or absence of megacolon and any other obvious features or pathology was recorded. Samples of the distal small intestine (ileum) contents, caecum contents and colon contents were collected for culture. Anaerobic cultures of the gut contents were established on selective media to assess the C. difficile vegetative bacteria and spore burdens (material cultured for spore burden was exposed for 5 min to 70% ethanol). All surviving animals were euthanized 28 days post-infection (5 days of dosing and 23 days of observation) and C. difficile vegetative bacteria and spore burdens were determined in small intestine (ileum) contents, caecum contents and colon contents.

**Pharmacokinetics**

At the appropriate timepoints, hamsters were administered an overdose of pentobarbitone. When animals were deeply unconscious, blood was collected into a heparinized syringe by cardiac puncture. The blood samples were placed on ice immediately after collection and centrifuged as soon as possible at 3000 rpm for 5 min. The plasma was removed and stored at −80°C until shipment to CEMAS (Wokingham, Berkshire, UK). As soon as death was confirmed, the abdomen of the animals was opened and the entire gut carefully opened lengthwise. A portion of the contents of the stomach, upper small intestine, caecum and colon was removed and immediately frozen at −80°C until shipment to CEMAS for SMT19969 quantification. Bioanalysis of the plasma and gut content samples for SMT19969 was performed by CEMAS using LC-MS/MS. The lower limit of quantification (LOQ) was 1 ng/mL for both plasma and GI samples.

**Results**

The comparative efficacies of orally administered SMT19969, vancomycin, fidaxomicin and vehicle were assessed in hamsters following infection with either C. difficile strain BI1 (ribotype 027) or 630 (ribotype 012). All animals that were euthanized during the course of the study were considered to have succumbed to CDI following macroscopic examination of the GI tract on necropsy and positive culture of C. difficile from the GI contents. Animals treated with vehicle and study drug that succumbed to CDI all showed significant inflammation of the GI tract, which was particularly apparent in the ileum. Animals that survived to the end of the study showed no inflammation of the GI tract on necropsy.

SMT19969 was assessed at two different doses (12.5 and 25 mg/kg) with twice-daily dosing. SMT19969 dose level and regimen selection was based on published data and preliminary dose-ranging studies carried out as part of the studies described here (data not shown). Based on published data on the efficacy and dosing of fidaxomicin in the hamster model of CDI, treatment regimens of 1 and 2.5 mg/kg twice daily were assessed following infection by C. difficile strains BI1 and 630 with additional regimens of 12.5 and 25 mg/kg twice daily used following infection with C. difficile 630.

**Hamster survival, ribotype 027**

A severe model of CDI was established following infection with C. difficile BI1 with survival data shown in Figure 1. All vehicle-
treated animals succumbed to infection (100% mortality) with the deaths occurring by 72 h post-infection. On day 11 post-infection (6 days following cessation of treatment), 7 of 10 hamsters administered 10 mg/kg vancomycin twice daily developed CDI and were euthanized with a further 2 vancomycin-treated hamsters euthanized due to severe diarrhoea and hypothermia on day 12 post-infection. A single animal treated with 10 mg/kg vancomycin twice daily survived until the end of the study.

On day 16 post-infection (11 days following cessation of treatment), one hamster treated with 2.5 mg/kg fidaxomicin twice daily and another treated with 12.5 mg/kg SMT19969 twice daily were euthanized due to significant cumulative weight loss and the development of CDI. All other animals in these treatment groups and all animals treated with either 1 mg/kg fidaxomicin twice daily or 25 mg/kg SMT19969 twice daily survived until the end of the study.

**Hamster survival, ribotype 012**

The comparative efficacy of the test agents was also assessed in hamsters infected with *C. difficile* 630 (Figure 2). As discussed below, an unexpectedly high level of mortality due to CDI was observed in animals treated with 1 or 2.5 mg/kg fidaxomicin during the post-treatment observation period. To address the potential for a suboptimal dosing regimen of fidaxomicin for this strain, an additional study was conducted that included higher doses (12.5 and 25 mg/kg twice daily) of fidaxomicin and the results discussed are a pooled analysis of these studies based on the statistically indistinguishable outcomes of treatment in groups that were included in both models.

As observed for infection with *C. difficile* BI1, infection with *C. difficile* 630 resulted in a severe model of CDI with 100% mortality observed in vehicle-treated animals by day 3 post-infection. Vancomycin-treated animals all survived the course of dosing with rapid onset of disease observed during the post-treatment follow-up period with 100% mortality observed on day 13.

SMT19969 conferred significant protection from CDI during both the initial dosing and follow-up periods. At a dose of 12.5 mg/kg twice daily, 100% survival was observed during dosing and through to the end of study (day 28). Administration of SMT19969 at a dose of 25 mg/kg twice daily resulted in 100% survival during dosing with mortality onset at day 18 resulting in 80% survival, which was maintained to the end of the study.

All doses of fidaxomicin conferred protection from CDI during the course of dosing, although onset of mortality was observed between days 6 and 8 for animals administered 1 or 2.5 mg/kg twice daily with a gradual loss of animals observed through to day 22 resulting in 30% and 40% survival, respectively, which was maintained to day 28. Higher doses of fidaxomicin (12.5 and 25 mg/kg twice daily), whilst protecting from CDI during the course of dosing, resulted in high mortality during the follow-up period with mortality starting on day 10 resulting in 0% survival on days 12 and 13, respectively.

**Spore counts**

Faecal samples were collected from treated animals on days 1, 7, 12, 19 and 28 post-infection for semi-quantitative culture of *C. difficile* spores (Figures 3 and 4).

Following infection with *C. difficile* ribotype 027 (BI1), spores were isolated on day 1 for 13 of 20 animals administered SMT19969 and 5 of 20 animals administered fidaxomicin. For animals administered the lower doses of either SMT19969 (12.5 mg/kg) or fidaxomicin (1 mg/kg), spores were isolated from two animals administered SMT19969 from samples collected on days 12 and 19 and in seven animals administered fidaxomicin from samples collected on day 7. At the higher doses of SMT19969 (25 mg/kg) and fidaxomicin (2.5 mg/kg), no spores were recovered from any faecal sample from day 7 onwards.

For animals infected with *C. difficile* ribotype 012 (630), faecal samples from animals administered SMT19969 were negative for spores on days 7 and 12 post-dosing, although a significant proportion of samples were spore positive on days 19 and 28 post-infection. For animals administered fidaxomicin, the majority of faecal samples on days 12, 19 and 28 post-infection were positive for spores. Day 1 and 7 faecal samples (with the exception of a single animal) following administration of 2.5 mg/kg fidaxomicin were spore negative, although at the lower dose of fidaxomicin (1 mg/kg), 2 of 10 and 5 of 8 surviving animals were positive for spores on days 1 and 7 post-infection, respectively.

Faecal samples from animals treated with either 12.5 or 25 mg/kg fidaxomicin twice daily were not assessed for the presence of spores, although the colon and caecum contents of all animals that succumbed to CDI were positive for the presence of *C. difficile* vegetative cells and spores at the time of euthanasia (data not shown).

**Pharmacokinetics**

Following oral administration of either 12.5 or 25 mg/kg SMT19969, plasma concentrations of SMT19969 at all timepoints were
typically below the LOQ (1 ng/mL), indicating very low absorption
from the GI tract of infected hamsters. SMT19969 was quantified
in isolated plasma samples (two animals at 8 h post 12.5 mg/kg
dose, one animal at 1 h post 25 mg/kg dose and one animal at
8 h post 25 mg/kg dose), although concentrations were very low,
range from 1.3 to 7.1 ng/mL.

Data for the concentrations of SMT19969 in sections of the GI
tract following either a single or two (12 h apart) oral doses of

Figure 3. Semi-quantitative spore counts for faecal samples recovered from individual animals post-infection with C. difficile BI1. Spore counts: 1, ≤10 colonies; 2, 11–100 colonies; and 3, >100 colonies.

Figure 4. Semi-quantitative spore counts for faecal samples recovered from individual animals post-infection with C. difficile 630. Spore counts: 1, ≤10 colonies; 2, 11–100 colonies; and 3, >100 colonies.

Figure 5. Mean concentrations (+SD) of SMT19969 in sections of the GI tract following (a) single or (b) two doses at 25 mg/kg.
25 mg/kg SMT19969 are shown in Figure 5 (data for stomach contents not shown in Figure 5 for clarity). Following a single dose, mean levels of SMT19969 in the stomach and small intestine peaked at 2.8 and 55.1 μg/mL, respectively, and were largely cleared by 1 or 4 h post-dose, respectively. Mean levels of SMT19969 in caecum contents peaked at 25.2 μg/mL 4 h post-dose and persisted slightly longer than in the stomach and small intestine, falling to 8.3 μg/mL 12 h post-dose. Mean levels of SMT19969 were significantly higher in colon contents than other sections of the GI tract, peaking at 195.7 μg/mL 4 h post-dose, with significant levels of drug (mean = 20.9 μg/mL) persisting to 24 h post-dose.

Following a second dose of SMT19969 12 h later, a similar profile in stomach and small intestine contents was observed with mean levels of drug falling to <10 μg/mL by 4 h post-dose. However, consistent with significant levels of SMT19969 persisting to 24 h following a single dose, enhanced exposure was observed in caecum and colon contents following a second dose. Mean peak SMT19969 levels were ~2-fold higher in caecum than levels recorded following a single dose and significant levels of SMT19969 (53.0 μg/mL) persisted to 12 h post-dose. Mean peak SMT19969 levels of 312.4 μg/mL were observed in the colon 4 h post-dose and were ~1.5-fold higher than following a single dose. In addition, significant drug levels (189.1 μg/mL) were observed in the colon 1 h post-dosing and remained higher than following a single dose to 12 h post-dosing.

Discussion

The hamster model of clindamycin-induced CDI is the current standard in vivo model used to assess the potential efficacy of agents including antibiotics, toxin antibodies and vaccines. This model has also been used to assess virulence and disease pathogenesis of CDI. Replicating many of the features of CDI in humans, the model has been used to confirm that toxins A and B and binary toxin (C. difficile toxins) all play important roles in virulence and disease severity.

SMT19969 is a novel antibiotic, in clinical development for the treatment of CDI, with potent growth inhibition of C. difficile and a narrow spectrum of activity that may minimize further collateral damage to the gut microbiota during CDI therapy. Susceptibility testing in previous studies has shown excellent inhibitory activity against C. difficile with an MIC90 value of 0.25 mg/L, which was 2–4-fold more potent than those of either metronidazole or vancomycin and 2-fold more active than fidaxomicin. Following infection with C. difficile BI1, both SMT19969 and fidaxomicin conferred significant protection from CDI with 100% survival recorded during the course of dosing and a 90%–100% survival rate observed during the post-treatment follow-up period (Figure 1). As expected, vancomycin-treated animals survived the course of dosing with onset of mortality observed on day 11 with only a 10% survival rate recorded by day 28. SMT19969 administered at 12.5 and 25 mg/kg twice daily was associated with improved survival rates when compared with vehicle-, vancomycin- or fidaxomicin-treated hamsters following infection with C. difficile 630 (Figure 2). Although all doses of fidaxomicin resulted in 100% survival during the course of dosing, recurrent disease following withdrawal of treatment was observed with a 0%–40% survival recorded by day 28. Higher doses of fidaxomicin (12.5 and 25 mg/kg twice daily) did not result in increased protection from disease. This observation was unexpected based on the previously reported efficacy of fidaxomicin in the hamster model of CDI, although the high variability of dose regimens and experimental methods used in the hamster model can make comparison between studies problematic. However, a significant number of faecal samples collected during the course of the study (days 1, 7, 12, 19 and 28 post-infection) were positive for C. difficile spores (Figure 4) following administration of fidaxomicin whereas samples were spore negative on days 7 and 12 following administration of SMT19969. Further studies are warranted to investigate and confirm the unexpectedly high levels of recurrent disease seen with fidaxomicin against C. difficile 630.

Data presented here confirm that SMT19969 is minimally systemically absorbed, even in the presence of GI inflammation due to CDI, with plasma concentrations typically below the LOQ (1 ng/mL). Following a single dose of 25 mg/kg, mean concentrations of SMT19969 in small intestine, caecum and colon samples of 9.70, 8.26 and 40.46 μg/mL, respectively, were recorded at 12 h post-dosing, which were significantly in excess of the typical C. difficile MIC value of 0.125–0.25 mg/L. A second dose administered after 12 h resulted in increased drug concentrations in the caecum and colon (53.0 and 155.3 μg/mL at 12 h post-dosing, respectively) and these data indicate that twice-daily dosing increased both the peak drug concentration and the time the drug concentration was significantly (~100-fold) in excess of MIC. This was most apparent in the colon, the site of infection in humans. These observations following twice-daily dosing may contribute to the reduced rates of mortality observed in these studies during the post-dosing observation period (following infection with ribotype 027) compared with both the previously reported studies and the preliminary dose-ranging studies carried out as part of this study (data not shown) where once-daily dosing was used.

All currently available therapies are generally effective at treating the initial period of CDI, although they are associated with high rates of recurrent disease. Phase 3 studies have demonstrated that fidaxomicin is associated with reduced rates of recurrence compared with vancomycin, although rates of recurrence were comparable for subjects infected with hypervirulent ribotype 027 strains. Fidaxomicin has been shown to inhibit C. difficile sporulation and is superior to vancomycin in inhibiting the outgrowth of vegetative cells from germinated spores. Spores are the most common vector by which C. difficile is transmitted and are able to persist in the environment for extended periods; inhibition of sporulation may therefore impact on rates of recurrent disease. In this study, animals administered SMT19969 remained culture negative for spores for longer and had a lower rate of relapse than those administered fidaxomicin, although further studies are needed to examine the effect of SMT19969 on sporulation. In addition, narrow-spectrum antibiotics, such as SMT19969 and fidaxomicin, may also be associated with an improvement in microbiota recovery time and subsequent return of colonization resistance.

The results of these studies, in conjunction with previously reported data, show that SMT19969 is highly effective against different strains of C. difficile in the hamster model of CDI with significant protection from mortality observed during both the acute infection and post-dosing observation periods. Although
SMT19969 was detected at low levels in isolated plasma samples, the data confirmed that SMT19969 is largely restricted to the GI tract in infected animals and twice-daily dosing resulted in more favourable intraluminal GI drug concentrations. Furthermore, SMT19969 has demonstrated potent and selective inhibition of C. difficile and was shown to be safe and well tolerated in a Phase 1 clinical trial. Continued investigation of SMT19969 as a therapy for CDI is warranted.

Acknowledgements
These data were presented in part at the Twenty-fourth European Congress of Clinical Microbiology and Infectious Diseases, Barcelona, Spain, 2014 (Abstract P0798).

Funding
This study was initiated and financially supported by Summit plc through a Seeding Drug Discovery Award (grant number 091055) and a Translation Award from the Wellcome Trust (grant number 099444).

Editorial support provided by Innovative Strategic Communications, LLC, was funded by Summit plc.

Transparency declarations
This study was performed as contract research by Evotec. A. S., P. T., L. P. and P. W. are employees of Evotec and R. J. V. is an employee of Summit plc and holds share options.

The editorial support of Innovative Strategic Communications, LLC, in the preparation of this manuscript is acknowledged.

References
1 Petrella LA, Sambol SP, Cheknis A et al. Decreased cure and increased recurrence rates for Clostridium difficile infection caused by the epidemic C. difficile BI strain. Clin Infect Dis 2012; 55: 351 – 7.
2 He M, Miyajima F, Roberts P et al. Emergence and global spread of epidemic healthcare-associated Clostridium difficile. Nat Genet 2013; 45: 109 – 13.
3 Tickler JA, Goering RV, Whitmore JD et al. Strain types and antimicrobial resistance patterns of Clostridium difficile isolates from the United States, 2011 to 2013. Antimicrob Agents Chemother 2014; 58: 4214 – 8.
4 Davies KA, Longshaw CM, Davis GL et al. Underdiagnosis of Clostridium difficile across Europe: the European, multicentre, prospective, biannual, point-prevalence study of Clostridium difficile infection in hospitalised patients with diarrhea (EUCLID). Lancet Infect Dis 2014; 14: 1208 – 19.
5 Kelly CP. Can we identify patients at high risk of recurrent Clostridium difficile infection? Clin Microbiol Infect 2012; 18 Suppl 6: 21 – 7.
6 Cornely OA, Crook DW, Esposito R et al. Fidaxomycin versus vancomycin for infection with Clostridium difficile in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial. Lancet Infect Dis 2012; 12: 281 – 9.
7 Louie TJ, Miller MA, Mullane KM et al. Fidaxomycin versus vancomycin for Clostridium difficile infection. N Engl J Med 2011; 364: 422 – 31.
8 Khanna S, Pardi DS. Clostridium difficile infection: management strategies for a difficult disease. Therap Adv Gastroenterol 2014; 7: 72 – 86.
9 Johnson S, Louie TJ, Gerdin DN et al. Vancomycin, metronidazole, or tolevaran for Clostridium difficile infection: results from two multinational, randomized, controlled trials. Clin Infect Dis 2014; 59: 345 – 54.
10 Goldstein EJ, Citron DM, Tyrrell KL. Comparative in vitro activities of SMT19969, a new antimicrobial agent, against 162 strains from 35 less frequently recovered intestinal Clostridium species: implications for Clostridium difficile recurrence. Antimicrob Agents Chemother 2014; 58: 1187 – 91.
11 Goldstein EJ, Citron DM, Tyrrell KL et al. Comparative in vitro activities of SMT19969, a new antimicrobial agent, against Clostridium difficile and 350 Gram-positive and Gram-negative aerobic and anaerobic intestinal flora isolates. Antimicrob Agents Chemother 2013; 57: 4872 – 6.
12 Douce G, Goulding D. Refinement of the hamster model of Clostridium difficile disease. Methods Mol Biol 2010; 664: 215 – 27.
13 Weiss W, Pulse M, Vickers R. In vivo assessment of SMT19969 in a hamster model of Clostridium difficile infection. Antimicrob Agents Chemother 2014; 58: 5714 – 8.
14 Mckenney D, Williams A, LaMarche M et al. Efficacy comparison between LFF571 and fidaxomicin in the hamster model of Clostridium difficile infection. In: Abstracts of the Fifty-second Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, 2012. Abstract B-664. American Society of Microbiology, Washington, DC, USA.
15 Swanson RN, Hardy DJ, Shipkowitz NL et al. In vitro and in vivo evaluation of tiacumicins B and C against Clostridium difficile. Antimicrob Agents Chemother 1991; 35: 1108 – 11.
16 Best EL, Freeman J, Wilcox MH. Models for the study of Clostridium difficile infection. Gut Microbes 2012; 3: 145 – 67.
17 Borriello SP, Ketley JM, Mitchell TJ et al. Clostridium difficile—a spectrum of virulence and analysis of putative virulence determinants in the hamster model of antibiotic-associated colitis. J Med Microbiol 1987; 24: 53 – 64.
18 Peterfreund GL, Vandivier LE, Sinha R et al. Succession in the gut microbiome following antibiotic and antibody therapies for Clostridium difficile. PLoS One 2012; 7: e46966.
19 Kuehne SA, Collery MM, Kelly ML et al. Importance of toxin A, toxin B, and CDT in virulence of an epidemic Clostridium difficile strain. J Infect Dis 2014; 209: 83 – 6.
20 Babakhanl L, Bouillaut L, Gomez A et al. Fidaxomycin inhibits spore production in Clostridium difficile. Clin Infect Dis 2012; 55 Suppl 2: S162 – 9.
21 Deakin LJ, Clare S, Fagan RP et al. The Clostridium difficile spo0A gene is a persistence and transmission factor. Infect Immun 2012; 80: 2704 – 11.
22 Lawley TD, Clare S, Walker AW et al. Antibiotic treatment of Clostridium difficile carrier mice triggers a supershedder state, spore-mediated transmission, and severe disease in immunocompromised hosts. Infect Immun 2009; 77: 3661 – 9.