International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 1547-1551 www.ijprajournal.com ISSN: 2249-7781

Gepotidacin: A Novel, Oral, 'First-In-Class' Triazaacenaphthylene Antibiotic for the Treatment of Uncomplicated Urinary Tract Infections

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Submitted: 10-04-2024 Accepted: 20-04-2024

ABSTRACT

The ongoing spread of antimicrobial resistance has made the treatment of uncomplicated urinary tract infections (UTIs) and urogenital gonorrhoea increasingly difficult. New oral treatment options are urgently needed. Gepotidacin (previously GSK2140944) is a novel, bactericidal, oral, 'first-in-class' triazaacenaphthylene antibiotic that inhibits bacterial DNA replication by blocking two essential topoisomerase enzymes. Mutations in both enzymes would likely be necessary for resistance to occur, thus raising hopes that the drug will be able to maintain long-term effectiveness. Data from Phase II clinical trials of gepotidacin in UTIs and urogenital gonorrhoea appear promising, and Phase III trials are underway. In this review we summarize the development of gepotidacin and discuss its potential role in clinical practice. If approved, gepotidacin will be the first new oral antibiotic for UTIs in more than 20 years.

KEY WORDS:-gepotidacine,urinary tract infection, antimicrobial resistance.

I. INTRODUCTION

Uncomplicated urinary tract infections (uUTIs) are among the most common community-acquired infections for women worldwide. UTIs are among the most frequently encountered conditions in clinical practice, with an estimated 50%–60% of adult women developing at least once during their lifetime.Given this high prevalence and the associated healthcare costs, optimizing antibiotic therapy for UTIs is paramount.

The ongoing spread of antimicrobial resistance has made the treatment of uncomplicated UTI difficult.The current IDSA guidelines recommend nitrofurantoin, fosfomycin and trimethoprim/sulfamethoxazole (as long as local resistance rates do not exceed 20% or if the infecting strain is known to be susceptible) as first-line agents for uncomplicated UTIs.Experts have been ardent about discouraging the use of quinolones due to their propensity to cause 'collateral damage', such as disruption of the gut microbiome, Clostridiodes difficile, tendonitis and abdominal aneurysm rupture, and to reduce the dissemination of quinolone-resistant strains. Whereas older studies demonstrated a high rate of quinolone prescribing for UTIs,more recent data suggest quinolone use has been curtailed.

The urgency for additional oral agents to treat MDR UTIs has been a driving factor in the development of the novel antibiotic gepotidacin.

GEPOTIDACINE

Gepotidacin is a novel, bactericidal, first-in-class triazaacenaphthylene antibiotic that inhibits bacterial deoxyribonucleic acid (DNA) replication by a distinct mechanism of action, which confers activity against most strains of target pathogens, such as Escherichia coli and Staphylococcus saprophyticus, including those resistant to current antibiotics.This agent, designated GSK2140944, has since progressed through Phase I, II and III clinical trials, along with a multitude of PK/PD and in vitro activity studies. Gepotidacin formulations used in the PK evaluations included mesylate salt for an IV solution, tablets, capsules and the free base for capsules and tablets. As clinical development progressed, the mesylate salt oral tablet formulation was selected for potential commercialization. Oral formulations are potentially useful for treating MDR UTIs and gonorrhoea because most current therapies are parenteral.Oral antibiotics have several advantages compared with many parenteral formulations, for patients and healthcare organizations alike, including lower overall costs, reduced hospital length of stay, fewer complications and more convenience.

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MECHANISM OF ACTION OF GEPOTIDACINE

Topoisomerases are important enzymes that regulate DNA topology by causing temporary single or double stand DNA breakage. Most of the bacteria has both DNA gyrase and topoisomerase 4.gepotidacine being the novel bacterial topoisomerase inhibitor, it inhibitstopoisomerase 4 and B subunit of DNA gyrase. This mechanism results in low rate of spontaneous single step resistance. Structural data also shows the Novel binding mode of gepotidacine that distinguishes it from fluoroquinolones.

PK/PD CHARACTERISTICS OF GEPOTIDACINE

The PK characteristics of gepotidacine was well explained in phase 1,2 clinical trails and the PK/PD index associated with efficacy was found to be similar to fluoroquinolones.The MIC for gepotidacine for E.coli isolates in Mueller Hinton broth was found to be in a range of 1-4mg/L.A free drug AUC/MIC ratio of 275 and greater was enough to suppress the antimicrobial resistance.Peak plasma concentration for gepotidacine was found at 3.00h with a single dose administration and two peak plasma concentration observed at 1.5 h and 2.25 h after two dose administration of gepotidacine at an interval of 12 or 6 hours.For a single dose of 1500 mg mesylate salt capsule of gepotidacin while fasting, the mean AUC0–∞ value was 15.8, and the mean Cmax was 4.37 µg h/mL, with a mean terminal elimination t½ of 11.8 h.

In a Phase IIa PK trial in female participants with an uncomplicated UTI, a free-base 750 mg tablet formulation showed an adequate plasma concentration and an acceptable risk-safety profile.One study demonstrated gepotidacin urine concentrations of >4 mg/L after administration of 1500 mg gepotidacin that was maintained for 24 h.Another found that approximately 50% of the oral dose is absorbed and eliminated mainly as unchanged drug in the urine (~20% of dose).Earlier clinical trials provided evidence for the dose selection and interval for Phase III clinical trials of gepotidacin to be 1500 mg twice daily for 5 days to treat uncomplicated UTI, and two doses of gepotidacin 3000 mg 10–12 h apart to treat urogenital gonorrhoea. The increased time interval is felt to be helpful in gastrointestinal tolerance and minimizing C_{max}-related adverse effects such as QT prolongation, while reducing the risk of N. gonorrhoeae becoming resistant to gepotidacin.

A dose related gastrointestinal side effects such as nausea, emesis, diarrhea, abdominal pain and flatulence was recognised side effects related to acetylcholinesterase inhibition including cardiovascular side effects was recognised but they are found to be very rare in the study.

CLINICAL TRIALS

In a Phase I study with healthy volunteers, doses of 1000 and 1800 mg of IV gepotidacin caused a mild increase (7–10 beats/min) in resting heart rate and slight QT prolongation. The IV formulation was chosen in order to achieve supra-therapeutic plasma levels. A second Phase I non-randomized, open-label, multicentre clinical trial evaluated 1500 mg of oral gepotidacin in three different hepatic settings (normal, moderate impairment and severe impairment). Gepotidacin was determined to be safe and generally well tolerated in all subjects. Based on these results, dosing adjustments will not likely be necessary for patients with mild to moderate hepatic impairment. However, severe hepatic impairment may require an increase in dosing interval or a dose reduction.

A Phase II clinical trial evaluated the efficacy and safety of gepotidacin in adult patients with suspected or confirmed Gram-positive acute bacterial skin and skin structure infections (ABSSSIs). The mean exposures to IV and oral gepotidacin were 3.4 days and 7.5 days, respectively. There were 122 patients included in the modified ITT and safety populations using three gepotidacin doses. Most had a wound infection (44%), followed by a cutaneous abscess (32%) or cellulitis (24%). The study met the protocol-defined primary objective, which was a composite of efficacy (cure rate) and safety (withdrawal rate). The most common adverse events were gastrointestinal, mainly nausea (20%) and diarrhoea (13%). Four patients (3%) experienced an adverse event that led to study withdrawal (one patient) or permanent discontinuation of study treatment (three patients). This study further determined microbiological efficacy as a secondary endpoint; 76% of isolates were S. aureus (69% MRSA, 31% MSSA), the remaining isolates were other Gram-positive aerobes (11%), Gram-negative aerobes (12%) and anaerobes (1%). Post-therapy microbiological success (by culture-confirmed eradication of pre-treatment pathogen or presumed eradication based on clinical success) for S. aureus was 90% in the 750 mg q12h dosing, 89% in the 1000 mg q12h dosing, and 73% in the 1000

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mg q8h dosing groups. A similar pattern was observed for other Gram-positive pathogens.

A second Phase II clinical trial enrolled 69 adult patients with urogenital gonorrhoea and randomized them 1:1 to receive either a 1500 mg or 3000 mg single oral dose of gepotidacin. Microbiological eradication of N. gonorrhoeae was achieved by 97% and 95% of participants for the 1500 and 3000 mg dose groups, respectively. Of the three participants who were microbiological failures, all had N. gonorrhoeae isolates with a gepotidacin MIC of 1 µg/mL. Adverse events occurred in 27 of 52 (52%) participants in the 1500 mg group, and in 34 of 53 (64%) participants in the 3000 mg treatment group. The most frequently reported adverse events were diarrhoea (27%), flatulence (23%), abdominal pain (15%) and nausea (13%). Treatment-limiting adverse events did not occur for either dose. A third Phase II clinical trial enrolled 22 women with a UTI who were given 1500 mg of oral gepotidacin twice daily for 5 days and returned to the clinic for test-of-cure (TOC) (days 10 to 13) and follow-up (day 28±3) visits. At TOC, clinical success was observed for 19 of 22 participants (86%). Nearly all (21/22) had gastrointestinal adverse events, mainly diarrhoea (n=18, 82%), nausea (n=17, 77%) and vomiting (n=5, 23%). Clinically significant ECG findings or changes from baseline were not observed. Moreover, none of the participants had a QT interval corrected for heart rate according to Fridericiaof ≥480 ms or an increase of >30 ms.

In phase III, randomized, multicentre ,parallel-group, double-blind, double-dummy, comparator-controlled, non-inferiority studies, comparing the efficacy and safety of gepotidacin to nitrofurantoin in the treatment of uUTI. Eligible participants are women aged more than 12 years with more than 2 uUTI symptoms, randomized (1:1) to receive oral gepotidacin (1500 mg) plus placebo or nitrofurantoin (100 mg) plus placebo, twice daily for 5 days. The primary therapeutic endpoint is composite clinical and microbiological efficacy, with non-inferiority comparisons made in individuals with a qualifying ($\geq 10^5$ colony-forming units/mL urine) nitrofurantoin-susceptible uro-pathogen.

These trials were designed in accordance with US Food and Drug Administration (2019) and European Medicines Agency (2018) guidance, particularly the composite endpoint and microbiological evaluability requirements. Across the trials ~ 5000 participants are planned to be enrolled from > 200 centers globally.

In the EAGLE-2 and EAGLE-3 phase III trials, gepotidacin demonstrated non-inferiority to nitrofurantoin, an existing first-line treatment for uUTI, in patients with a confirmed uUTI and auropathogen susceptible to nitrofurantoin. Additionally, in the EAGLE-3 phase III trial, gepotidacin demonstrated statistically significant superiority versus nitrofurantoin. These results are based on a primary efficacy endpoint of therapeutic success, an endpoint comprised of combined clinical resolution and microbiological eradication of bacteria at the Test-of-Cure (ToC) visit 10-13 days after initiation of treatment.In the EAGLE-2 phase III trial, gepotidacin demonstrated therapeutic success in 50.6% of patients compared to 47% for nitrofurantoin. In the EAGLE-3 phase III trial, gepotidacin demonstrated therapeutic success in 58.5% of patients compared to 43.6% for nitrofurantoin. Across both trials, it was noted that 94% of patients treated with gepotidacin did not receive an additional antibiotic for uUTI during trial participation through the follow-up visit on day 28. The safety and tolerability profile of gepotidacin in the EAGLE-2 and EAGLE-3 phase III trials was consistent with previous trials of gepotidacin.

Gepotidacin also demonstrated consistent efficacy (therapeutic success) compared to nitrofurantoin in key subgroups, including patients with Escherichia coli pathogens resistant to other antibiotics, those with a history of recurrence and those over 50 years old. These subgroups are at higher risk of treatment failure.

MICROBIOLOGICAL SPECTRUM OF ACTIVITY OF GEPOTIDACINE

Gepotidacin demonstrates potent in vitro activity against a number of common bacterial pathogens. Using isolates from a global collection established between 2010 and 2012, Biedenbach et al. tested it against Streptococcus pneumoniae (n=549), Haemophilusinfluenzae (n=981), Moraxella catarrhalis (n=158), Streptococcus pyogenes (n=199), Staphylococcus aureus (n=1008), E. coli (n=1010), Shigella spp. (n=21) and Clostridium perfringens (n=101) (Table 1). For E. coli, the MIC90 was 2 mg/L (range: ≤0.03 to >32), whereas among levofloxacin-non-susceptible isolates the MIC90 increased to 4 mg/L (range: 0.06 to >32). MIC90 values increased from 2 to 4 mg/L against nitrofurantoin-non-susceptible, fosfomycin-non-susceptible and ESBL screen-positive isolates. Approximately 75% of the ESBL screen-positive E. coli isolates were resistant to

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levofloxacin, and the MIC90 was 4 mg/L against this subset.

Table 1.MIC data for gepotidacina

ORGANISM	MIC50 (mg/L)	MIC90 (mg/L)	RANGE
MRSA	0.25	0.5	<0.06 to 1
MSSA	0.5	0.5	0.12 to 2
S. pneumoniae	0.12	0.25	0.03 to 1
S. pyogenes	0.25	0.25	0.03 to 0.5
H. influenzae	0.5	1	<0.015 to 8
M. catarrhalis	<0.06	<0.06	<0.06 to 0.12
E. coli	2	2	<0.03 to >32
Shigella spp.	0.5	1	Not provided
C. perfringens	0.12	0.5	Not provided
N. gonorrhoeae	0.25	0.5	<0.015 to 1

Another study reported the activity of gepotidacin against 145 N. gonorrhoeae isolates as well as the effect of in vitro test conditions on susceptibility testing for gepotidacin and two other antibacterials (ciprofloxacin and ceftriaxone) against a separate set of nine N. gonorrhoeae isolates and a quality control strain (Table 1).Several factors were found that potentially influence gepotidacin MIC determinations including media type, inoculum concentration, media pH and incubation in 10% CO2. The ciprofloxacin and ceftriaxone MICs also tended to be slightly lower when agar plates were incubated in 10% CO2 compared with the reference MICs. Gepotidacin has also been tested against Gram-negative (n=333) and Gram-positive (n=225) anaerobes by agar dilution. It inhibited 90% of isolates at concentrations of 4 and 2 mg/L, respectively. A 5 day course of gepotidacin does not appear to have long-lasting effects on the human microbiome, with rebound to pre-dosing states evident within the first month post-treatment.

POTENTIAL ROLE IN CLINICAL PRACTICE FOR GEPOTIDACINE

UTIs

Given the frequency of UTI and the emergence of AMR the gepotidacine can fulfill the needs for the additional oral agent against E.coli and an optional treatment against MDR strains.The further data is required for considering gepotidacine as a treatment for complicated UTI and pyelonephritis although the drug was found to be effective in drug model of MDR E.coli pyelonephritis using recreated human drug exposure.investigation of gepotidacine against other common uropathogensbesides E.coli is warranted.

Urogenital gonorrhoea

The emergence of MDR N. gonorrhoeae worldwide has severely limited treatment options for urogenital gonorrhoea in recent years. A Phase II clinical trial of single-dose oral gepotidacin for urogenital gonorrhoea demonstrated >95% microbiological eradication.It is important to note that currently there is no evidence that gepotidacin is effective for gonorrhoea at other sites, e.g. rectal or pharyngeal.

Others

Because of its broad in vitro activity against Gram-positive, Gram-negative and anaerobic pathogens, a number of other clinical applications for gepotidacin are possible. As previously noted in Phase II trials, treatment of ABSSSIs appears clinically and microbiologically effective. Gepotidacin has shown efficacy against Yersinia pestis in a primate animal model.In vitro studies show promise against mycoplasma and ureaplasma infections, including drug-resistant Mycoplasma genitalium.In vitro and in vivo animal models have shown activity of gepotidacin against mycobacterial pathogens, including Mycobacterium tuberculosis and drug-resistant non-tuberculous mycobacteria. The antibacterial spectrum of gepotidacin also could give it a role in the treatment of pneumonia (especially against MDR nosocomial pathogens), but additional investigation, including clinical trials, is needed for this indication. A recent report demonstrated good activity against Stenotrophomonasmaltophilia, an

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Volume 9, Issue 2 Mar-Apr 2024, pp: 1547-1551 www.ijprajournal.com ISSN: 2249-7781

increasingly recognized nosocomial pathogen that is often resistant to multiple antibiotics

II. CONCLUSION

Gepotidacin represents an important potential treatment option being evaluated to address the need for novel oral antibiotics to treat uUTI.There is an urgent demand for new antibiotics to treat MDR infections, particularly agents with an oral formulation. Early trial data for gepotidacin appear promising in terms of safety and efficacy, although the high rate of gastrointestinal side effects is concerning. Hopefully the development of gepotidacin continues to progress as it would fulfil an important unmet need in the clinic. If approved, gepotidacin would be the first new antibiotic for UTIs in more than 20 years.

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