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Case Report

SIGNIFICANCE OF CSE-1034 (ELORES™) IN TREATMENT OF URINARY TRACT INFECTIONS DUE TO MULTI-DRUG RESISTANT EXTENDED SPECTRUM BETA-LACTAMASES POSITIVE *ESCHERICHIA COLI*

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ABSTRACT

Urinary tract infection (UTI) is one of the most common infections of geriatric patients in community acquired and hospital acquired settings. *Escherichia coli* is usually the most common pathogen responsible for UTI. Antibiotic resistance is the main reason for the failure of therapy, especially in *E. coli*. Biofilm formation, extended spectrum beta-lactamases and metallo beta-lactamase production, and efflux pump overexpression are the main reasons for antibiotic resistance in *E. coli*. That's why management of UTI with multi-drug resistant (MDR) *E. coli* has always been challenge for the clinicians. We are reporting empiric use of new antibiotic adjuvant entity Elores™ (ceftriaxone/sulbactam/disodium edetate) in the management of UTIs caused by MDR *E. coli*.

Keywords: Elores™, Disodium edetate, Ethylenediaminetetraacetic acid, Urinary tract infections, *Escherichia coli*, Antibiotic resistance, CSE-1034.

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INTRODUCTION

Urinary tract infection (UTI) is one of the most common infections of geriatric patients in community acquired and hospital acquired settings. The prevalence of UTI increases in geriatric population [1,2]. Infections of genitourinary tract are defined as UTI and may involve lower or upper urinary tract [2,3]. UTI can be termed symptomatic only when patient presents with symptoms of UTI and has the presence of pathogen $\geq 10^5$ colony forming units of bacteria per milliliter (CFU/ml) in urine sample [2,4].

UTI is one of the most common community acquired and hospital acquired infections. *Escherichia coli* historically has been the most common pathogen responsible for UTI. Wada *et al*., in 2016, showed in 30-year study in Okayama University Hospital, Japan, *Pseudomonas aeruginosa* was the most common pathogen in 1984-1994, methicillin-resistant *Staphylococcus aureus* during 1995-2004, and *E. coli* during 2005-2014 [5]. In a study published by Stefanuk *et al.,* in 2016, 80.6% cases of UTI were due to *E. coli* in Poland [6]. In a retrospective study conducted in India, on 1061 isolates of *E. coli*, it showed a higher prevalence of extended spectrum beta-lactamases (ESBL) positive *E. coli* (64.2%) [7]. An Indian study on 464 clinical isolates of *E. coli* showed ESBL positive in 40.08%, metallo beta-lactamase (MBL) positive in 16.16%, and ESBL + MBL positive in 17.24% isolates [8].

As ESBL and MBL mediated resistance in Gram-negative bacteria, especially *E. coli* is increasing worldwide. *E. coli* has developed resistance by various mechanisms including biofilm formation, production of ESBL and MBL, overexpression of efflux pump, and target site modification [8-10]. It has been reported that in *E. coli*, biofilm formation incidence can be to the extent of 90% of UTI cases [10]. In the era of increasing antibiotic resistance, a novel and effective antibiotic will strengthen armamentarium against MDR uropathogens. Evidence from various studies supports Elores™ (ceftriaxone/sulbactam/disodium edetate) usage for treatment of UTI caused by multi-drug resistant (MDR) *E. coli* [7,11].

In the present case report, we are presenting a case of UTI caused by MDR ESBL positive *E. coli,* treated with CSE-1034 (Elores™).

CASE REPORT

An 87-year-old female patient was admitted to our hospital with chief complaints of dysuria for past 5 days, fever for last 3 days, and generalized weakness. On general examination, the patient was conscious and oriented. The patient presented with fever (101°F), dysuria, hypotension (100/60 mmHg), and pulse: 68/minute. The patient had renal insufficiency due to acute on chronic kidney disease (CKD). On systemic examination, cardiovascular system (S1, S2: Normal), respiratory system (bilateral equal air entry), and central nervous system (conscious and oriented) were stable and no abnormality detected. On day of admission, hematological and biochemical parameters were hemoglobin: 9.7 g/dl, total leukocyte count (TLC): 14200/cumm, neutrophil: 71%, lymphocytes: 26%, monocytes: 2%, eosinophil: 1%, platelets: 195000/cumm, MCV: 87.1 fl, Mean corpuscular volume (MCV); 27.8 pg, mean corpuscular hemoglobin concentration (MCHC): 34.1 g/dl, red blood cell (RBC) count: $4.0*10^6$, PCV: 29.1%, sodium: 134 mEq/L, potassium: 14.1 mEq/L, chloride: 98.1 mEq/L, creatinine: 2.0 mg/dl, and urea: 48 mg/dl. Urine analysis showed presences of 60-70 pus cells/HPF. The patient was presumptively diagnosed with symptomatic UTI. The patient was given budesonide nebulization BD and paracetamol SOS orally for conservative management of diseased condition. Injection Elores™ 1.5 g q12 h was started empirically. Urine cultures were sent for culture and sensitivity testing which revealed ESBL and MDR *E. coli*, susceptible towards meropenem, colistin, and Elores™. Based on presence of *E. coli*, the presence of acute on CKD and other investigations patient was diagnosed with symptomatic UTI. As the patient had started improving on Elores™, and relief was observed with respect to fever and dysuria, so Elores™ was continued for 10 days. On 10^{th} day of Elores™, hematological parameters were Hemoglobin: 8.50 g/dl, TLC: 11000/cumm, neutrophil: 78%, lymphocytes: 20%, monocytes: 1%, eosinophil: 1%, PCV: 27%, RBC count: $3.66 *10^6$, platelets: 195000/cumm, MCV: 75.2 fl, MCH; 26.4 pg, and MCHC: 32.1 g/dl. Urine sent for culture showed to be sterile on 10^{th} day. Gradual clinical improvement (counts settled, no dysuria, and fever) was observed in patient. Fig. 1 shows schematic presentation of clinical course during UTI. Complete bacterial eradication was achieved with Elores™, and the patient was clinically cured and was discharged.

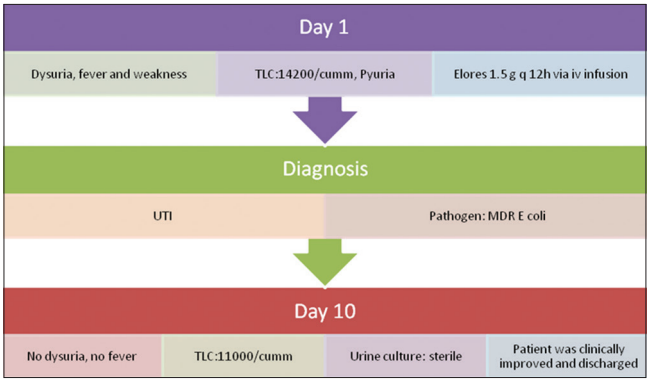

Fig. 1: Schematic presentation of clinical course of patient diagnosed with urinary tract infection

Table 1: Susceptibility study of *E. coli* [8]

Antibiotic	Susceptibility toward *E. coli* (%)	Resistance toward *E. coli* (%)
Elores™	92.6	2.5
Meropenem	74.4	20.3
Imipenem	71.2	23.3
Piperacillin plus tazobactam	52.1	39.3
Cefoperazone plus sulbactam	46.0	43.6
Amoxicillin plus clavulanic acid	23.6	72.8

E. coli: Escherichia coli

DISCUSSION

UTI is the third common infection found in India [12]. Different antibiotics are recommended for treatment of UTI. Resistance toward antibiotics has been increasing as reported in recent years [13]. Many pathogens including *E. coli* are becoming resistant toward third generation cephalosporins [11,13]. Broad spectrum penicillins (>50%) have been found to be resistant toward *E. coli* [12]. Antibiotic resistance is the main reason for failure of therapy, especially in *E. coli*. Biofilm formation, efflux pump overexpression, and ESBL and MBL production are the main reasons for antibiotic resistance in *E. coli* [8-11,14,15].

In the present case, the patient was diagnosed with UTI because of presentation of renal dysfunction due to acute on CKD and microbial pathogen *E. coli*. Due to coverage of most of the pathogens by broad spectrum antibiotic Elores™ and its indication in UTIs, Elores™ was started empirically [11,16,17] and before antibiotic initiation, urine samples were sent for culture and susceptibility testing.

Elores™ is an antibiotic adjuvant entity which works on different resistance mechanisms adopted by bacteria such as production of ESBL and MBLs, overexpression of efflux pump, membrane impermeability, and biofilm [11,14-16]. Ceftriaxone, sulbactam, and disodium edetate work synergistically to achieve therapeutic effect [16]. Ceftriaxone is a third generation broad spectrum cephalosporin, and sulbactam is irreversible beta-lactamase inhibitor. disodium edetate enhances the membrane permeability, chelates Calcium and zinc ions (required for MBL activity), inhibit efflux pump and make biofilms porous via chelation of divalent ions of lipopolysaccharides [11,14-16]. A prospective study on antimicrobial susceptibility published in 2012 on 464 isolates showed 92.6% *E. coli* isolates were susceptible to Elores™ (ceftriaxone/sulbactam/disodium edetate) as shown in Table 1 [8].

In culture and susceptibility test, *E. coli* was susceptible to meropenem, colistin, and Elores™. As the patient responded well to Elores™, so it was continued after culture and susceptibility test. Moreover, colistin was not used because of nephrotoxicity and neurotoxicity [18,19].

In a phase 3 trial, significantly better cure rates were achieved in Elores™ arm as compared to ceftriaxone arm [11]. Moreover, Elores™ (20.59% [21/102]) produces less adverse events as compared to ceftriaxone (36.27% [37/102]) [11]. As the patient was febrile, so paracetamol was given to normalize body temperature.

Microbiological eradication, normal TLC, and improvement in other symptoms, e.g. dysuria, fever confirms the clinical cure of patient of UTI with Elores™ in 10 days. Thus, the present case suggests that empirical use of CSE-1034 (Elores™) is safe and effective in the treatment of UTIs.

CONCLUSION

Based on evidence in the present case study, Elores™ may be considered as empirical therapy for the safe and efficacious treatment for the UTI including MDR and ESBL positive *E. coli*.

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