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Xacduro: A Comprehensive Overview of the New Drug for Bacterial Pneumonia Treatment"

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ABSTRACT

In this article we discussed about the approval of Xacduro, a novel treatment for hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) caused by susceptible strains of Acinetobacter baumannii-calcoaceticus complex bacteria by the U.S. Food and Drug Administration marks a pivotal moment in pneumonia treatment. As antimicrobial resistance escalates globally, Xacduro emerges as a vital tool in combating these drug-resistant infections. Phase 3 ATTACK trial results and in vitro studies demonstrate its efficacy, with non-inferiority to colistin and superior clinical cure rates.

Understanding the complex pathophysiology of Acinetobacter baumannii, including resistance mechanisms, biofilm formation, and virulence factors, highlights the urgency for innovative treatments. Xacduro's arrival holds promise in addressing the growing mortality rates associated with multidrug-resistant Acinetobacter strains.

The article also highlights Xacduro's potential to mitigate the risks of VAP and HAP offers hope for improved patient outcomes and reduced healthcare system burdens. In essence, Xacduro represents a beacon of progress in the battle against drug-resistant Acinetobacter infections. As we navigate the ever-evolving landscape of antimicrobial resistance, Xacduro represents a significant stride forward in the realm of bacterial pneumonia treatment, providing healthcare professionals with a potent weapon to confront one of modern medicine's most formidable adversaries.

Keywords: Xacduro, hospital-acquired bacterial pneumonia (HABP) , ventilator-associated bacterial pneumonia (VABP), antimicrobial resistance

I. INTRODUCTION

The U.S. Food and Drug Administration approved Xacduro (sulbactam for injection; durlobactam for injection), a new treatment that targeted hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP). It was specifically designed for patients aged 18 years and above, and it addressed infections caused by susceptible strains of Acinetobacter baumannii-calcoaceticus complex bacteria.

According to the World Health Organization, Acinetobacter species topped the list of critical bacterial pathogens that posed the greatest threat to human health, highlighting the high level of need for additional treatment options amid the growing global resistance to antimicrobial medicines.[1]

Xacduro, a combined product comprising sulbactam and durlobactam, both beta-lactamase inhibitors, was evaluated against colistin in the phase 3 ATTACK trial (ClinicalTrials.gov identifier: NCT03894046). The study focused on patients with documented A. baumannii infections, predominantly pneumonia. Xacduro demonstrated non-inferiority to colistin, with a 19.0% mortality rate in the Xacduro group versus 32.3% in the colistin group for the primary endpoint of 28-day

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all-cause mortality. Additionally, Xacduro showed significantly higher clinical cure rates (61.9% vs. 40.3%). [2] A study evaluated the in vitro activity of sulbactam-durlobactam against 5,032 Acinetobacter baumannii-calcoaceticus complex isolates from 2016 to 2021 across various regions. The mortality rates attributed to multidrug-resistant A. baumannii range from 40% to 75% in critically ill patients. The CDC reported increased carbapenem-resistant Acinetobacter spp. cases, with hospital-associated carbapenem-resistant A. baumannii infections rising by 78% from 2019 to 2020. Hospital-acquired pneumonia (HAP) is a prevalent issue, affecting approximately 1 in 100 patients and 1 in 10 ventilated patients. Non-ventilator-associated HAP carries over 8 times the risk of inpatient mortality compared to those without.

[3] The international ATTACK trial took place across 59 clinical sites in 16 countries. It enrolled adults aged 18 and above with confirmed hospital-acquired bacterial pneumonia, ventilator-associated bacterial pneumonia, or bloodstream infections caused by carbapenem-resistant A. baumannii. Patients received sulbactam-durlobactam or colistin along with background therapy. Sulbactam-durlobactam's safety was evaluated in various trials, with the phase 3 trial showing comparable efficacy to colistin in treating A. baumannii infections. Adverse reactions included liver test abnormalities, diarrhea, anemia, and hypokalemia. [4]

Acinetobacter Baumannii Multi Resistant And Carbapenem-Resistant (Crab) Stains

Acinetobacter baumannii, a Gram-negative bacterium, is typically present in soil and water. It acts as an opportunistic pathogen causing a variety of infections like pneumonia, septicemia, meningitis, urinary tract infections, and wound infections.[5]

Acinetobacter baumannii is renowned for its ability to develop resistance to various antimicrobial agents, posing a significant concern in global healthcare settings. The emergence of strains resistant to multiple drugs has escalated into a notable public health menace due to the limited treatment avenues. [6]

This bacterium exhibits resistance to drugs through several mechanisms, including:

1.Genetic mutations that modify bacterial DNA, altering antibiotic efficacy or reducing their capacity to eliminate the bacteria.

2.Efflux pumps, proteins located on the bacterial cell membrane, expel antibiotics from the cell, lowering the antibiotic concentration and efficacy.

3.Certain Acinetobacter baumannii strains produce enzymes capable of degrading or modifying antibiotics, diminishing their effectiveness.

4.Modification of antibiotics themselves, rendering them inactive. For instance, bacteria can alter the structure of commonly used aminoglycoside antibiotics in treating Acinetobacter baumannii infections.

5.Formation of biofilms, bacterial communities encased in a protective matrix, hindering antibiotic penetration and access to the bacteria, thus promoting antibiotic resistance.

6.Acquisition of antibiotic resistance genes from other bacteria through horizontal gene transfer, a process where bacteria exchange genetic material, leading to the emergence of resistant strains. [7]

CRAB - Acinetobacter baumannii strains that have developed resistance to carbapenem antibiotics are referred to as carbapenem-resistant Acinetobacter baumannii (CRAB) strains. Carbapenems, a class of antibiotics, are often employed as a final resort to treat illnesses caused by bacteria that are resistant to multiple drugs. [8]

Acinetobacter baumannii CRAB strains have developed resistance to carbapenems through various mechanisms. These include the creation of enzymes capable of degrading the antibiotic or modifications in the bacterial cell wall that hinder the drug from binding to its intended target location.[9]

Carbapenem-resistant bacteria, known as Acinetobacter baumannii (CRAB), are extremely challenging to eliminate from the environment and show resistance to nearly all antibiotics. Consequently, CRAB can lead to severe outbreaks and fatal infections among patients in hospitals and nursing homes. While all CRAB strains are harmful to individuals, certain CRAB possess genes enabling them to produce carbapenemase enzymes that break down carbapenem antibiotics. [10] Xacduro presents a valuable addition to the limited array of options available for treating CRAB infections, which are prevalent in healthcare settings globally each year. CRAB infections exhibit mortality rates approaching 50%, with pneumonia accounting for the majority of cases. [11]

Sulbactam, due to its effectiveness against Acinetobacter baumannii, is often utilised in conjunction with other antibiotics to treat CRAB.

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However, the broad spectrum of beta-lactamase enzymes produced by Acinetobacter species as a defence mechanism can render sulbactam ineffective. Durlobactam shields sulbactam from these enzymes. Intravenous infusion is employed to administer this combination. [12]

HAP, short for Hospital Acquired Pneumonia, and VAP, which stands for Ventilator-Associated Pneumonia, are two types of pneumonia that originate in healthcare settings. HAP refers to pneumonia that develops 48 hours or more after a patient's admission to a hospital, excluding cases already incubating upon admission. In intensive care units (ICUs), VAP occurs when pneumonia sets in more than 48 to 72 hours following tracheal intubation. This variant of pneumonia affects approximately 10% to 20% of patients who undergo mechanical ventilation for over 48 hours, representing a significant subset of HAP [13]. Commonly implicated microorganisms responsible for both HAP and VAP encompass aerobic gram-negative bacteria like Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Enterobacter spp, and Acinetobacter spp, as well as gram-positive cocci including Staphylococcus aureus, which encompasses methicillin-resistant S. aureus, and Streptococcus spp. Distinct host factors and the specific microbial environment of a medical institution contribute to the variations in the types of pathogens involved in these conditions.

A notable subtype of HAP is ventilator-associated pneumonia (VAP), which emerges at least 48 hours after mechanical ventilation commences. Over recent years, the incidence of both HAP and VAP has notably risen. This increase can be attributed, in part, to the ongoing COVID-19 pandemic, leading to a surge in ICU admissions and the heightened use of invasive mechanical ventilation (IMV), thereby escalating the risk of VAP. Studies have indicated a mortality rate of 60% from VAP among COVID-19 patients, with VAP occurring in ventilated COVID-19 cases at rates ranging from 40% to 86%. Key factors that predispose individuals to VAP include the use of proton-pump inhibitors and histamine-2-receptor blocker medications, the patient's respiratory history, age, and immune condition. Additionally, other significant risk factors within a hospital environment contributing to VAP include extended periods of mechanical ventilation, prolonged hospital stays, altered consciousness, burn injuries, invasive medical procedures, underlying health conditions, and genetic variations.

Symptoms associated with these conditions encompass malaise, fever, chills, cough, chest pain, rigour, and dyspnea. The diagnosis is typically confirmed through a blood culture or bronchoscopy sampling of the lower respiratory tract, guided by the clinical presentation and chest imaging. Treatment primarily involves the administration of antibiotics.

Pathophysiology of A. Baumannii

Pathogenesis of A. baumannii When a microorganism enters the body, it needs to adhere to cells to establish an infection. However, A. baumannii has a lower ability to attach to cells or mucosal cells compared to other microorganisms like Pseudomonas aeruginosa, Neisseria meningitidis, Campylobacter, Yersinia enterocolitica, and Helicobacter pylori. This reduced attachment contributes to its lower virulence. Nonetheless, A. baumannii possesses hydrophobic properties that allow it to attach to foreign materials such as plastics found in intravascular devices. Studies have shown that strains isolated from patients express higher surface hydrophobicity compared to normal skin flora.

A protein called Outer membrane protein A (OmpA) is associated with enhancing adhesion to epithelial cells in the respiratory tract. OmpA localizes in the mitochondria and nuclei of cells, inducing the expression of a molecule called cytochrome c, which leads to cell death. A. baumannii uses OmpA to evade the immune response triggered by the alternative complement pathway by neutralizing a key regulator called factor H. This phenomenon is referred to as serum resistance. OmpA also plays a role in differentiating CD4+ cells, activating and maturing dendritic cells, and causing premature apoptosis.

The release of outer membrane vesicles containing various virulence-related proteins (proteases, phospholipases, superoxide dismutase, and catalase) at the site of infection accelerates the local innate immune response, ultimately causing tissue damage. These vesicles also contribute to the formation of biofilms on surfaces. A polysaccharide capsule found in Gram-negative bacteria acts as a virulence factor, protecting bacteria from phagocytosis by the host's immune system. Lipopolysaccharides (LPSs) in A. baumannii consist of an O-antigen, a carbohydrate core, and a lipid A moiety. LPS acts as a chemotactic agent, recruiting inflammatory cells and prompting them to release cytotoxic substances.

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Quorum sensing is a bacterial ability to communicate with neighboring bacteria to collectively respond to changes in the environment. Bacteria produce small molecules called autoinducers that can diffuse easily and serve to monitor population density and adapt to the changing surroundings. Like other Gram-negative bacteria, Acinetobacter produces acylhomoserine lactones as signaling molecules for communication between different species and within the same species. It also generates lesser-known signaling molecules such as diketopiperazines, 2-heptyl-3-hydroxy-4-quinolone, and retention factor 1.

Despite the abundance of iron in biological systems, biologically active ferric iron is relatively scarce due to its low solubility in aerobic environments and its binding to other compounds like hemoglobin and transferrin. A. baumannii cannot acquire iron from transferrin or lactoferrin but employs siderophores to acquire iron from heme.

A significant mechanism of A. baumannii's resistance is its ability to form biofilms on both living and non-living surfaces. In these biofilms, the bacterium becomes metabolically inactive in deeper layers, making it resistant to antibiotics that cannot penetrate effectively. A. baumannii involved in epidemics demonstrates high resistance to drying and can form biofilms on biological surfaces. The polysaccharide, poly-N-acetyl glucosamine, and csuA/B usher protein enable A. baumannii to form a pellicle, which further shields it from the effects of antibiotics. Other factors such as biofilm-associated protein (BAP), OmpA, BAP-like protein-1 (BLP-1), and BAP-like protein-2 (BLP-2) also contribute to biofilm formation.[16]

II. CONCLUSION

In conclusion, the emergence of Xacduro (sulbactam for injection; durlobactam for injection) marks a significant milestone in the field of bacterial pneumonia treatment. With its approval by the U.S. Food and Drug Administration, Xacduro presents a promising solution for addressing hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) caused by susceptible strains of Acinetobacter baumannii-calcoaceticus complex bacteria. In a world where antimicrobial resistance is a growing concern, the introduction of Xacduro provides healthcare professionals with a much-needed weapon against the escalating threat of drug-resistant Acinetobacter infections.

The comprehensive evaluation of Xacduro through the phase 3 ATTACK trial and in vitro studies underscores its efficacy and potential to revolutionize the treatment landscape. Its non-inferiority to colistin and superior clinical cure rates highlight its capacity to combat Acinetobacter infections effectively. With the critical need for new treatment options for these infections, Xacduro offers renewed hope, particularly in the face of rising mortality rates associated with multidrug-resistant Acinetobacter strains.

The pathophysiology of Acinetobacter baumannii, elucidated through its mechanisms of resistance, biofilm formation, and virulence factors, underscores the complexity of combating this formidable pathogen. The ability of A. baumannii to adapt, evolve, and develop resistance underscores the urgency of innovative treatment strategies, making Xacduro's arrival all the more significant.

In an era where hospital-acquired pneumonia poses a substantial threat, the impact of Xacduro extends beyond its direct efficacy. Its potential to mitigate the risks of ventilator-associated pneumonia (VAP) and hospital-acquired pneumonia (HAP) carries the promise of improving patient outcomes and reducing the burden on healthcare systems worldwide.

In essence, the approval and introduction of Xacduro bring renewed optimism to the realm of bacterial pneumonia treatment. As we navigate the complex landscape of antimicrobial resistance, Xacduro stands as a beacon of progress, providing healthcare professionals with a potent tool to combat drug-resistant Acinetobacter infections. The journey of medical advancements is ongoing, and with Xacduro, we take a significant step forward in the fight against one of the most challenging adversaries in modern medicine.

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