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General review

Vaccine strategies against bacterial pathogens in cystic fibrosis patients

Stratégies vaccinales contre les bactéries pathogènes chez les patients atteints de mucoviscidose

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Abstract

A large number of cystic fibrosis pathogens such as bacteria of the *Burkholderia cepacia* complex, *Pseudomonas aeruginosa*, or *Mycobacterium abscessus* are associated with complex therapeutic problems due to their inherent resistance to antibiotics. No vaccine is currently available against those pathogens. Vaccines are therefore crucial to combat these multidrug-resistant bacteria in specific clinical situations including cystic fibrosis. Various strategies may be considered to develop these vaccines. Similar virulence factors are expressed during the infection with various pathogens; they could thus be used as antigen to assess cross-protection. Many clinical trials are currently being conducted to try and develop a prophylactic treatment for patients presenting with cystic fibrosis.

Keywords: Cystic fibrosis; Vaccination; *Mycobacterium abscessus*; *Pseudomonas aeruginosa*; *Burkholderia* spp.

Résumé

De nombreux pathogènes associés à la mucoviscidose, tels que les bactéries du complexe *Burkholderia cepacia*, *Pseudomonas aeruginosa* ou *Mycobacterium abscessus* posent des problèmes thérapeutiques complexes en raison de leur multirésistance intrinsèque aux antibiotiques. De plus, aucun vaccin n'est actuellement disponible contre ces pathogènes. Les approches vaccinales représentent donc une arme clé pour combattre ces bactéries multirésistantes dans un certain nombre de cas cliniques, dont celui de la mucoviscidose. Différentes stratégies peuvent être envisagées pour développer ces vaccins. Certains facteurs de virulence similaires sont exprimés au cours de l'infection par différents pathogènes et pourraient ainsi être utilisés comme antigène pour évaluer une protection croisée. De nombreux essais sont en cours pour tenter de générer une prophylaxie dans le cadre de la mucoviscidose.

Mots clés : Mucoviscidose ; Vaccination ; *Mycobacterium abscessus* ; *Pseudomonas aeruginosa* ; *Burkholderia* spp.

Cystic fibrosis (CF) is a Mendelian genetic disease caused by a series of mutations occurring in the coding gene for the CFTR protein, which acts as a chloride channel [1]. The absence or lack of efficacy of that protein is responsible for the increased mucus viscosity, especially in the lungs. Bacteria can thus more easily accumulate and adhere to mucins. Chronic inflammation [2] and early bacterial infection are both responsible for the subsequent deterioration of the lungs. Lung infections in CF patients are the most frequent and severe presentations of the disease. They account for more than 90% of deaths [3]. Bacteria, fungi, and viruses can infect the patient's respiratory system. Bacterial colonization occurs very early in the disease progression [4]. Patients first present with *Haemophilus influenzae* and *Staphylococcus aureus* colonization. Months

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or years later patients are colonized with *Pseudomonas aeruginosa*. *Burkholderia cepacia* is the fourth bacterium mainly responsible for CF patients' lung infection. The administration of an antibiotic treatment is the only effective strategy to combat the infection. However, bacteria become resistant to antibiotics when repeatedly used. A single bacterium can have many different strains and can easily mutate. Developing effective treatment strategies is therefore difficult.

Resistance to antibiotics is a major problem for CF patients. Multidrug-resistant bacteria such as *B. cepacia*, *P. aeruginosa*, or *Mycobacterium abscessus* lead to therapeutic difficulties and are responsible for fatal infections [5].

Guidelines focusing on prophylaxis must therefore be drawn and therapeutic strategies for respiratory tract infections must be developed. Such therapeutic strategies should be integrated into the overall disease management.

The *Burkholderia cepacia* complex (Bcc) consists of 18 species responsible for opportunistic infections that can be life-threatening in CF patients. *Burkholderia cenocepacia* and *Burkholderia multivorans* are most frequently identified. These environmental and biofilm-forming intracellular bacteria are highly resistant to antibiotics. Bcc infections developing in CF patients are rarely eliminated once a patient is colonized. *Pseudomonas aeruginosa* is another environmental pathogen responsible for opportunistic infections. It is the most frequent bacterium isolated from CF patients. *P. aeruginosa* colonization and chronic infections affect up to 80% of CF adult patients [6]. This pathogen is responsible for chronic endobronchial infections and increases morbidity and mortality rates. *P. aeruginosa* is resistant to antibiotics. It is therefore a dangerous pathogen as once patients are colonized the pathogen is rarely, or even never, eliminated. *P. aeruginosa* colonization usually affects the lungs of CF patients. The bacterium forms a biofilm on the lungs and reduces the patient's immune response, thus contributing to the bacterium high level of resistance to antibiotics [7]. *Mycobacterium abscessus* is the most recently identified bacterium to be highly resistant to antibiotics. It is a rapidly-growing mycobacterium belonging to the *Mycobacterium abscessus* complex [8]. *Mycobacterium abscessus* is responsible for a wide variety of human diseases, especially in CF patients [9,10]. Person-to-person transmission has recently been reported in CF patients [11,12]. *M. abscessus* is associated with major therapeutic difficulties because of its natural resistance to most antibiotics [13,14]. Severe and even fatal infections have already been reported in CF patients due to the lack of therapeutic strategies [15]. Several countries consider that patients presenting with a *M. abscessus* infection cannot be eligible for lung transplant [16]. CF patients presenting with such infection are therefore left with no therapeutic option.

Acute or chronic bronchial infections and superinfections progressively deteriorate the patient's respiratory function. They are treated with antibiotics in light of the bacteriological examination results. Sputum culture (sputum cytobacteriological examination) or blood samples (blood cultures) allows for identifying the involved bacterium, evaluating the extent of the colonization, and determining the most effective antibiotics. The most frequently observed bacteria (*S. aureus*, *P. aeruginosa*, and *B. cepacia*) are rapidly resistant to antibiotics. The most effective doses are still unclear but they are usually higher than the ones recommended in the agents' marketing authorization. The administration of two intravenous antibiotics is, for instance, often combined with an inhaled maintenance antibiotic treatment. Inhaled antibiotics must be administered after chest physical therapy (CPT) and after having administered beta-2-agonists and rhDNase.

For *S. aureus* infections, a primary prophylactic treatment is not recommended for infants and children. For methicillin-susceptible *S. aureus* exacerbations, the recommendation is to first administer oral beta-lactams as first-line treatments with or without fusidic acid. Treatment duration is at least 14 days. For methicillin-resistant *S. aureus* exacerbations, it is recommended to administer a combination of pristinamycin and rifampicin. There is currently no recommendation for secondary antibiotic prophylaxis (or maintenance treatment) as there is no consensus on that matter.

For *P. aeruginosa* infection, it is recommended to first administer two intravenous bactericidal antibiotics (14–21 days) to patients presenting with a primary colonization (beta-lactams + aminoglycoside). Inhaled colistin may then be prescribed for 3 to 6 months. Exacerbations of patients presenting with chronic infection should be treated with a combination treatment to prevent the emergence of resistant strains: beta-lactam and tobramycin for at least 14 days. For a multidrug-resistant strain, a combined treatment with three antibiotics should be administered including oral ciprofloxacin or intravenous colistin. Although there is currently no guideline recommending such treatment, a maintenance antibiotic treatment (inhaled) administered for 28 days or IV treatments administered every three months, preferably at home, may be considered.

A significant association between previous intravenous antibiotic treatments and *M. abscessus* isolation in the lungs of CF patients has recently been reported. Such association highlights the role of a broad spectrum antibiotic treatment in the occurrence of *M. abscessus* infection [17].

1. Vaccination strategies

Pathogens can be divided into two groups: vaccine-preventable pathogens and non-vaccine-preventable pathogens. There is currently no human vaccine against most antibiotic-resistant pathogens previously mentioned. It would thus be interesting to develop a prophylactic vaccination strategy to improve the prevention of those infections. Reverse-vaccinology is interesting as it would help target antigens associated with strong vaccine effectiveness. A better understanding of the regulation of bacterial gene expression helps in developing new strategies to combat such bacteria [18].

Various vaccination strategies can be considered once a potential target is identified: conventional vaccination using a recombinant protein or vaccination using a plasmid DNA encoding the antigen.

Various pathogens may contain highly similar antigens acting as virulence factors. Those antigens could be used to ensure