Comparison between Vancomycin and Fidaxomicin in treatment of CDI

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Abstract

Clostridium difficile infection (CDI) has become more and more prevalent worldwide, requiring more attention from people to treat this infection. In this work, the epidemiology of Clostridium difficile infection in the world and China is demonstrated, which can contribute to a better understanding of the way of infection and patients' conditions of CDI and look for possible methods or policies to help prevent the spread of this disease. On the other hand, there is a growing demand for more reliable and efficient antibiotic treatments for CDI, of which fidaxomicin and vancomycin are regarded as the most common. This work aims to compare the chemical structures, action mechanisms, and cost-effectiveness of fidaxomicin and vancomycin to assist choices between two antibiotics for CDI patients and healthcare workers.

Keywords: Clostridium difficile infection, Clostridium difficile-associated diarrhea, epidemiology, antibiotics, Vancomycin, Fidaxomicin

1. Introduction

Clostridium difficile (C.difficile) is a gram-positive anaerobic bacterium responsible for Clostridium difficile-associated diarrhea (CDAD). CDAD is the main cause of infectious nosocomial diarrhea, and has a noticeable increase in prevalence in hospitals worldwide. [1] The reason for the high number of infections is the resistance of C.difficile to heat and various disinfectants, which enables the spores of Clostridium difficile to survive and spread in healthcare facilities. [2] Symptoms of Clostridium difficile infection varies depending on the patient, medical treatment given by hospitals or way of infection. In general, patients of CDAD have shared symptoms from mild diarrhea to severe inflammation of the colon. [3] CDI has various causes, in which antibiotic use is recognized as the most risk factor contributing to CDAD.[4] The epidemiology of Clostridium difficile infection reveals asymmetry of information in various parts of the world, appealing for more attention of government and associated organizations to distribute more resources to gain sufficient information about CDI for more comprehensive comprehension of this severe disease. Meanwhile, there have been continuous advancements in the medical treatment and management of Clostridium difficile infection (CDI), while considering the burden levied on economy in management of Clostridium difficile infection, more research is required to be done to prevent infections and benefit public health.

2. Epidemiology and comparison between two antibiotic treatments of CDI

2.1 *Epidemiology in China*

Since 2000, CDI morbidity, death, and associated expenditures have risen rapidly. [5] From my point of view, it is very essential to know about the epidemiology in order to address the problem of high level of Clostridium difficile infection effectively and efficiently. When analyzing the data that I collected, I noticed that the asymmetry of the CDI related data in different parts of the world. From my perspective, it is likely that the distribution of data has certain relations to the economy of the places. In developed countries such as Western European countries such as France, the US or Spain, there are abundant sources of reports showing the data of CDI in different parts of the country, including information about the patients, the treatment that healthcare workers decide to use on those patients, and the duration of the stay of the patients in those hospitals. The sufficient amount of information related to CDI can certainly contribute to effective treatment of this severe disease and benefit the whole population. However, in contrast, in less developed counties, the information is inaccurate or not enough for workers to take advantage of in order to get a useful conclusion about the Clostridium difficile infection in the area, including the causes, the paths where pathogens come in contact with patients, and the treatment used by workers in the hospitals. The lack of information are highly possible to become obstacles for healthcare

workers and experts to have an agreement on the solution of CDI. On the other hand, the uneven distribution of information about Clostridium difficile infection in different areas of a country due to different economic development can also lead to invalid and misleading conclusion about the CDI epidemiology in the country, and China has such problem, resulting in concern about whether the epidemiology drawn from areas that provide abundant information about CDI can conclude the real occasions in sight of a whole country.

Based on various reports about the epidemiology of CDI, while the incidence of Clostridium difficile infection has increased in industrialized nations such as Europe and the United States, the epidemiology of CDI in emerging countries such as China remains unknown. It can be attributed to the lack of CDI-related professional knowledge and clinic experience of healthcare workers in hospitals. CDI incidence varies by region, and relevant data on CDI, ranging from number of patients to length of treatments given, is generally scarce in China's central and western areas. [6] The asymmetry of clinic information is partly due to the lack of systematic training for healthcare workers towards Clostridium difficile infection. This problem requires timely solution, since only when sufficient data is collected from all regions in China, a whole picture of epidemiology in China can be comprehended, which can facilitate regional-based treatment plans to be introduced.

Despite incomplete picture of epidemiology of CDI in China, valid conclusions can be drawn from the known data to a certain extent. In a controlled study of 800 adult patients admitted to a critical care unit in Shanghai, characterized as a major eastern city in China, it was discovered that 115 of the 800 patients had developed diarrhea, with 33 (28.70 %) of them having CDI. According to the study, the likelihood of CDI was 4.12%, which was greater than the average rate of CDI in other European nations. [7] The reason of the higher CDI percentage in China can be related to the poor training of healthcare workers towards these comprehensive infections, so the patients do not receive efficient treatment. Additionally, the hygiene of the environment of the living places of local people as well as for patients staying in the hospital is problematic, bring in high possibility for Clostridium difficile to reach and infect people, or even causing second infection for those that recover from the first CDI and stay in the hospital. Those two problems are urgent to be solve or the rate of CDI in China will possibly increase on a yearly basis, causing harm to citizens.

CDI patients are more likely than non-CDI patients to experience signs of fever and metabolic problems, and comorbidities. More CDI patients received enteral nutrition, antiviral medications, and fluoroquinolones more frequently demonstrated that antibiotics were a significant risk factor in Clostridium difficile infection. ICU stay was also considered a pathogenic factor to CDI and the usage of repeated antibiotic therapies. [8] The discovery should alert people to pay more attention to the choose of antibiotic in treating the disease. In the past, it is generally accepted that antibiotics should be control in usage when treating diseases because of the possibility of resistance of bacteria to certain antibiotics, attributing to extensive usage of antibiotics in the treatment. However, the epidemiology of Clostridium difficile infection in China reveals the second negative effect of improper antibiotics usage in treating infections—inducing another infection. Therefore, the problem associated with antibiotic usage should receive more attention and require more research into this topic, or more unexpected drawbacks of antibiotics use will be revealed in the future and lead to more difficult and severe problems to the general public.

The conclusion drawn from the epidemiology of CDI in China is that, first and foremost, it is very essential for the government to take the responsibility of introducing policies, distributing and allocating resources, such as related experts, government officers, and volunteers as well as investments to support the research financially, and encouraging various areas of the country in order to get a clear, accurate and comprehensive report of the Clostridium difficile infection of the country. With enough information about CDI, scientists and researches are able to conclude correct epidemiology of CDI in that country and hence come up with solutions to reduce the Clostridium difficile infection and benefit citizens by increasing their living standard and health condition. Additionally, there should be professional training on healthcare workers of China to enable them to fully comprehend how to treat CDI, through teaching the way of infection and various treatments available, such as different antibiotics that are able to treat the infection. At the same time, lectures and lessons can be provided by the government to increase the awareness of the Clostridium difficile infection to the general public. For instance, primary school students can have some lessons related to CDI during their school, so they can learn to avoid this disease after comprehending some information about the way of infection of the pathogen Clostridium difficile to people. Consequently, with more attention and awareness from the pubic to professional healthcare workers in the hospital, the rate Clostridium difficile infection will decrease, causing less burden on the hospitals to allocate resources in treating patients.

2.2 *Treatment of CDI*

CDI has the potential to turn fatal if without inappropriate treatment. The most common medical management of CDI are removing antibiotic causing CDI and prescribe bactericidal antibiotics. [9] Various antibiotic treatments have been proposed, including vancomycin, metronidazole and fidaxomicin. Antibiotics vary in pharmacology, pharmacokinetics, effectiveness and cost. It is extremely essential for the general public to pay attention to the choosing of antibiotic to treating the CDI. The reason is that sensible choice of antibiotic cannot only help patients and hospitals to reduce cost in treating the Clostridium difficile infection, various antibiotic may suit different kinds of patients, based on their personal occasion, the severity of the Clostridium difficile infection, the length of stay in hospital and so on. Additionally, potential problems of the choice of different antibiotics may vary, due to their different side effects. This should be included in consideration when determining which antibiotic to use in the treatment, because some of the side effects may be unaffordable for some patients, such as old people who cannot resist against some health problems due to the use of certain antibiotics, since they have poor health condition and resistance.

Based on the importance of the choice of antibiotics in treating Clostridium difficile infection, the government are obliged to help the general public to decided which antibiotic to use in the treatment, by providing enough information and encourage the healthcare workers to communicate with the patient before the antibiotic is used. Also, there should be policies restricting hospital staff to choose the antibiotic treatment regardless of the conditions of the patients but based on the economical benefit for themselves, for some expensive antibiotics with poor curing effect and are hence not preferable choice for patients can lead to more income of the healthcare workers. This phenomenon requires much attention from the government to solve with, or more and more patients will fail to receive efficient and useful treatment from Clostridium difficile infection in the hospital, leading to poor health condition and much heavier burden on the social resources, or even worthening the economy due to the individualistic decisions made by healthcare workers.

2.3 *Chemical description of vancomycin and fidaxomicin*

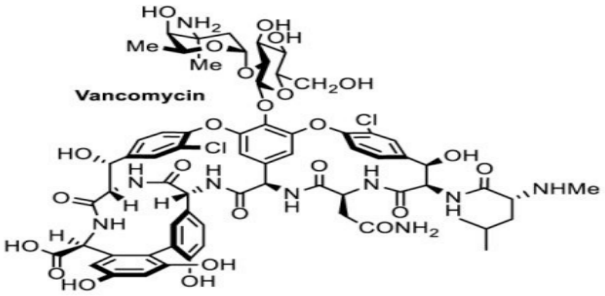

Fig.1 Structure of vancomycin [10]

2.4 *General introduction of Vancomycin*

Vancomycin is a bactericidal glycopeptide antibiotic commonly used in treatment of gram-positive bacteria related infections, including methicillin-resistant Staphylococcus aureus (MRSA). The chemical structure of Vancomycin is shown in the figure1. It is regarded as the first-line agent with a broad spectrum of antibacterial activity. It was isolated in the early 1950s at the first time at Eli Lilly and was approved for clinical use in 1958. [10] The comprehensive characteristic structure of vancomycin, with various cyclic peptide units with different ether linkages, was verified and established 25 years after its clinical use. Due to the high ability of dealing with infections, vancomycin is used only when there is no available or effective antibiotic in treating the disease.

However, nowadays, the resistance of pathogens or bacteria towards vancomycin treatment becomes an urgent problem worldwide. The problem can be attributed to the chemical structure of the vancomycin, or the improper amount of usage of vancomycin by healthcare workers in the hospital. The increase in Vancomycin-resistant pathogens stresses the need for further modification on the structure of Vancomycin to address the issue, which is a rather efficient way to solve the problem of bacterial resistance of the antibiotic. However, the method is relatively costly and require more insight into this field to enable it to be used regularly.

2.5 *Action mechanism of Vancomycin*

Vancomycin prevents bacterial infection by preventing the formation of the cell walls of bacteria, which is considered as an important step in the metabolism of the bacteria for their survival. Vancomycin molecules are able to bind to D-Ala-D-Ala, as shown in the figure2. They sequester further addition of substrate to complete the formation of transpeptidase, so the lipid intermediate II are not able to incorporate into the polysaccharide cell wall backbone due to no place available for further substitution. [10] In this way, the cell wall of bacteria cannot be successfully formed, leading to the death of the bacteria. The ability

to kill bacteria by inhibiting the process of cell wall formation enables vancomycin to have a broad spectrum towards many pathogens and hence high efficiency in curing various infections, thereby being regarded as the antibiotic as last resort.

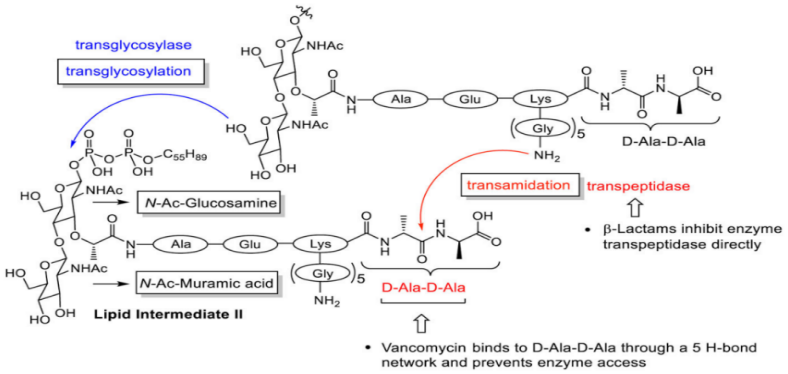

Fig.2 Binding of Vancomycin to D-Ala-D-Ala [10]

2.6 *General introduction of fidaxomicin*

As shown in the figure3, fidaxomicin is a narrow-spectrum macrocyclic antibiotic characteristic by an 18-membered lactone ring. Fidaxomicin is a relatively new drug compared with vancomycin, since the former was approved in use in 2011, while the latter was approved to be use as an antibiotic in 1958. This chemical is derived from the fermentation product of Dactylosporangium aurantiacum and Actinoplanes deccanensis, which is named lipiarmycin56,57, tiacumicin B58,59, OPT-8060,61, PAR-10162 or difimicin63. Fidaxomicin is generally taken orally by patients, after which the original chemical compound in fidaxomicin will react and change to a substance called OPT-1118, through possible processes such as hydrolysis with gastric acid or by enzymatic activity of intestinal microsomes64 in human body. [11] When hydrolyzed, fidaxomicin forms its active metabolite, OP-1118, which has an antibacterial activity 8-16 times lower than fidaxomicin. [12]

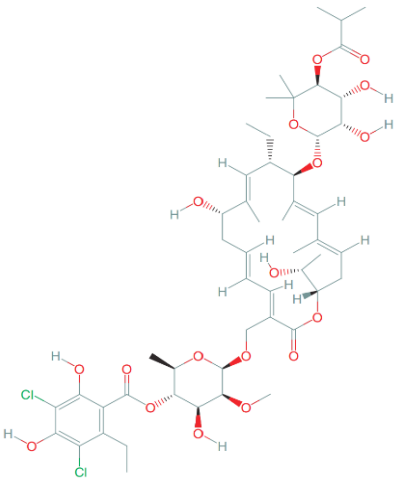

Fig.3 Chemical structure of Fidaxomicin [12]

2.7 *Action mechanism of fidaxomicin*

The bactericidal effect of fidaxomicin and OP-1118 against C.difficile based on the mechanism of inhibiting the transcription of RNA in the bacteria. As shown in the figure 4, there is the complete process of the initiation of transcription in bacteria. When fidaxomicin bonds to the sigma subunit on RNA polymerase in bacteria, promoter recognition is interrupted and hence the precursor step in RNA synthesis, separation of DNA strands, inhibited. [12] Thus, the synthesis of protein in bacteria as an essential part of activities for life is prevented, leading to the death of bacteria. The action mechanism of fidaxomicin makes it possible for it to kill bacteria with high efficiency and hence leading to satisfying curing result towards infections.

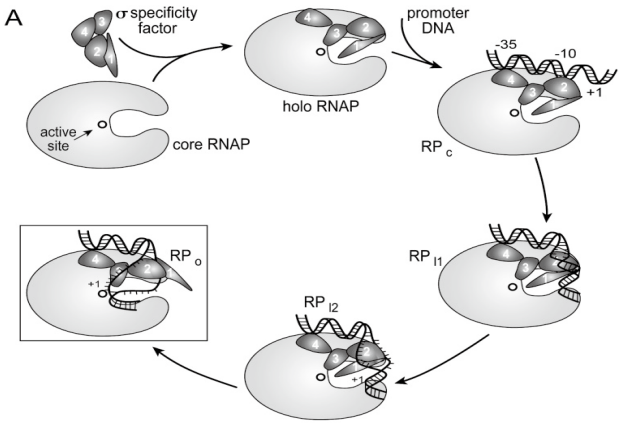

Fig.4 Transcription initiation pathway in bacteria [13]

2.8 *Comparison between vancomycin and fidaxomicin treatment for CDI*

The effectiveness of fidaxomicin and vancomycin in treating Clostridium difficile infection is generally

the same, although each antibiotic has different action mechanisms, targets and pharmacokinetics towards the pathogen Clostridium difficile. It is very worth noticing that due to the higher cost of fidaxomicin, healthcare workers generally do not regard fidaxomicin as a preferrable choice as antibiotics treatment to CDI compared to vancomycin when they choose between two antibiotics. It is estimated that fidaxomicin treatments in place of vancomycin ones for CDI patients will increase $1105 at the hospital level and $14 per treated CDI patient in revenue. [14] When considering singly the cost of drug, it is likely that the majority of patients will determine to use vancomycin to treat Clostridium difficile infection as the effectiveness of the two kinds of antibiotics are the same. However, recent studies have revealed that fidaxomicin is a more cost-effective drug for patients and hospitals than vancomycin through strong evidence provided by experiments. The reason is that fidaxomicin is more effective in preventing recurrences of CDI than vancomycin. The cost of readmission is therefore significantly reduced, offsetting the higher cost of drug. In a study conducted with 46 readmitted patients receiving oral vancomycin and 49 receiving fidaxomicin, readmission costs for vancomycin-treated patients were $454,800 for 183 days of stay and $196,200 for fidaxomicin-treated ones for 87 lengths of stay. The average cost per patient was $6,333 for vancomycin group and $3,286 for fidaxomicin group, proving that fidaxomicin treatment was more cost-effective than vancomycin treatment. [15] The reason for the significant capability of fidaxomicin to inhibit recurrence of Clostridium difficile infection still requires researches to carry out more investigations to confirm. Notwithstanding the unknown reasons for this advantage of fidaxomicin prior to vancomycin, the ability to prevent further recurrence or second infection of Clostridium difficile infection is essential because of the key benefits brought by the decrease in rate of infection to patients, hospitals and the central government. If patients choosing fidaxomicin can avoid getting Clostridium difficile infection a second time, they can have better health and get rid of higher economic burden levied by the higher length of stay in the hospital and longer medical care for this disease. For hospitals, there can be more available resources, ranging from doctors, nurses to facilities, for more patients with various diseases, which can benefit the society. The reason for which is that there may be fewer patients requiring for extra stay in the hospital because of being attacked by Clostridium difficile infection a second time. Additionally, government has the obligation to invest in public hospital through public taxation. If there is less occurrence of multiple cases of Clostridium difficile infection, which means the public hospital will have to serve less patients and hence have lower cost in management, the government are able to distribute resources to other fields, such as more scientific investigations towards varieties of diseases and possible treatments, which will benefit the economy in a certain extent.

3. Conclusion

Clostridium difficile infection (CDI) is a severe disease with an increase in rate of incidence worldwide, which is responsible for Clostridium difficile-associated diarrhea (CDAD), regarded as a threat to the health of people worldwide and levy great burden on the global economy. The causes of Clostridium difficile infection vary. It is generally believed that the use of antibiotic in treatment is a potential cause of Clostridium difficile infection. The epidemiology of Clostridium difficile infection is studied, which can contribute to better comprehension of Clostridium difficile infection as well as seeking for efficient and cost-effective method to control the rate of infection. According to analysis of the data of Clostridium difficile infection worldwide, it is observed that there is a clear asymmetry in the data related to Clostridium difficile infection in different parts of the world. Specifically, China as a typical developing country has ineligibly asymmetry in Clostridium difficile infection-related information proved by local governments and associated organizations. Data of Clostridium difficile infection is generally abundant in more developed areas such as the Southern part of China, while vital data is still lack for Clostridium difficile infection in other areas in China, therefore preventing researchers to gain a whole picture of the infection of this disease and then search for efficient solution to prevent further spread of such severe disease. Vancomycin and fidaxomicin as two typical and prevailing antibiotics used as treatment for Clostridium difficile infection are compared in several aspects in this work. Although the mechanism of action for each antibiotic is different, the ability for vancomycin and fidaxomicin to treat Clostridium difficile infection is similar. However, fidaxomicin has better performance in preventing second infection of this disease, which can lead to many benefits arose from shorter hospital stay of patients. Fidaxomicin is hence considered to be a more cost-effective treatment towards Clostridium difficile infection when compared with vancomycin. The reason why fidaxomicin has higher capability to prevent reinfection of Clostridium difficile infection is still unsure and requires more research to confirm the reason. More researches are worth carrying out and require more attention and support because

with more thorough comprehension of the mechanism of fidaxomicin preventing further infection, antibiotic can be further improved through chemical modification and hence provide more efficient and effective treatment towards Clostridium difficile infection, benefiting the whole society.

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