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COMBINATION THERAPY OF CROHN'S ANAL FISTULAS WITH A SINGLE DOSE OF DALBAVANCIN AND NEGATIVE PRESSURE THERAPY

KOMPLEKSOWE LECZENIE PRZETOK OKOŁOODBYTNICZYCH U PACJENTÓW Z CHOROBAJĄ LEŚNIEWSKIEGO-CROHNA Z ZASTOSOWANIEM JEDNORAZOWEJ INIEKCJI DALBAWANCYNY ORAZ TERAPII PODCIŚNIENIOWEJ

ABSTRACT: Introduction The perirectal fistulas in patients with CD (Crohn's disease) lead to a significant deterioration in quality of life with a high rate of failures and recurrences after conservative and surgical treatment. Biological therapy represents a major advance in the treatment of CD. However, introduction of such treatment should be preceded with drainage of pus accompanying anal fistulas and supplementation with intravenous antibiotic therapy. **Material and methods** The study was a preliminary pilot research. The survey was entered by 4 patients suffering from active, simple or branched Crohn's anal fistulas with accompanying abscesses requiring surgical drainage. The type of fistulas was confirmed on MRI. Culture was taken every time an abscess was evacuated and a single intravenous injection of dalbavancin (Xydalba®) was administered, if viable. Subsequently, surgical debridement of fistulous tracts was performed with application of negative pressure dressings (NPWT) to evacuate discharge more effectively. After assessing wound healing, the patients were released home and recommended to continue therapy at the outpatient clinic. **Results** Rapid resolution of inflammation and decrease of infection markers was observed in all cases. None of the patients required further antibiotic treatment. The average length of hospitalization was 4 days. The healing time until the complete elimination of inflammation was on average 12 days and after an average of 14 days the patients started biological treatment. **Conclusions** Single intravenous injection of 1500 mg dalbavancin with additional application of negative pressure dressings (V.A.C. therapy) may be an effective and well-tolerated alternative treatment of infected anal fistulas in CD.

KEY WORDS: Crohn's disease, dalbavancin, NPWT, perirectal fistula

STRESZCZENIE: Wstęp Przetoki okołodbytnicze u chorych z chorobą Crohna prowadzą do znaczącego pogorszenia jakości życia. Leczenie chirurgiczne jest trudne, u części pacjentów związane z wysokim ryzykiem uszkodzenia zwieraczy. Stosunkowo dużą efektywność w terapii przetok można osiągnąć dzięki zastosowaniu leczenia biologicznego, jednakże jego wprowadzenie musi być poprzedzone eliminacją ropni i zakażenia kanału przetoki oraz okolicznych tkanek miękkich. Zabieg chirurgiczny uzupełniony dożylną antybiotykoterapią wymaga często długotrwałego pobytu szpitalnego, co opóźnia wprowadzenie leczenia biologicznego. **Materiał i metody** Badanie miało charakter obserwacyjnego badania pilotażowego. Przeprowadzono je u czterech pacjentów z rozpoznaną chorobą Crohna, z aktywnymi przetokami okołodbytniczymi oraz współwystępującym miejscowym zakażeniem tkanek miękkich i/lub ropniami wewnątrz ich kanałów. Każdorazowo oceniano charakter przetoki w MR miednicy oraz pobierano posiew z ewakuującej się wydzieliny lub ropnia. Po ocenie antybiotykowrażliwości u chorych, u których było to uzasadnione, podawano jednorazowo 1500 mg dalbawancyny (Xydalba®) i.v., po czym przetoki opracowywano chirurgicznie. Następnie zakładano opatrunek podciśnieniowy w celu zwiększenia efektywności oczyszczania rany. Po ocenie gojenia rany chorzy byli wypisywani do domu z zaleceniem dalszej kontroli rany w trybie ambulatoryjnym. **Wyniki** U wszystkich pacjentów obserwowano szybkie ustępowanie stanu zapalnego

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oraz wykładników zakażenia. Żaden z chorych nie wymagał podawania kolejnych antybiotyków. Średni czas hospitalizacji wynosił 4 dni. Czas gojenia do momentu całkowitego ustąpienia stanu zapalnego wyniósł średnio 12 dni, po średnio 14 dniach u osób badanych wprowadzono leczenie biologiczne. **Wnioski** Jednorazowa iniekcja 1500 mg dalbawancyny oraz zastosowanie terapii podciśnieniowej może być efektywną, skuteczną i dobrze tolerowaną metodą leczenia zakażonych przetok okołoodbytniczych u pacjentów z chorobą Crohna.

SŁOWA KLUCZOWE: choroba Leśniowskiego-Crohna, dalbawancyna, NPWT, przetoki okołoodbytnicze

INTRODUCTION

Anal fistulas continue to be a challenge in everyday surgical practice. Infection of Hermann's anal glands is the most common origin of the fistulous disease. That is to say, retention of feces in the anal crypts is responsible for infection of these glands. Next, increased pressure within the anal canal forces feces into the perianal or perirectal and finally the subcutaneous tissues resulting in abscess/fistula formation [1]. In turn, anal fistulas in the course of an anal fissure or Crohn's disease (CD) develop from fissures or ulcers penetrating each layer of the anal canal wall [2, 3]. There is still a high rate of failures and recurrences following both medical and surgical treatment of Crohn's anal fistulas. What is more, multiple surgical interventions may result in damage to the anal sphincter with subsequent anal incontinence. Biological therapy represents a major advance in the treatment of CD. However, introduction of such therapy should be preceded with drainage of any collection of pus accompanying anal fistulas. Standard surgical intervention and prolonged intravenous administration of antibiotics with long hospitalization delays introduction of biological therapy [4, 5].

MATERIAL AND METHODS

The preliminary survey was entered by 4 patients suffering from active, simple or branched Crohn's anal fistulas with accompanying abscesses requiring surgical drainage. The type of fistulas was assessed on examination under anesthesia and on MRI. In turn, activity of the fistulous disease was evaluated with blood count, C-reactive protein (CRP) and procalcitonin (PCT) levels. If cultures of the fistulous discharge showed infection of methicillin-resistant *Staphylococcus aureus* (MRSA) sensitive to dalbavancin (Xydalba®), the patients were given a single intravenous injection of that antibiotic at the dose of 1500 mg. Afterwards, trimming of external orifices, incision of abscesses accompanying fistulas and debridement of fistulous tracts were performed in an operating theater. It was followed by application of negative pressure dressings (V.A.C. therapy) used to

evacuate discharge more effectively. The dressings were in turn changed in an out-patient care setting, on average once or twice, every third or fourth day and removed after 7–10 days if the inflammatory process receded.

RESULTS

Rapid resolution of the inflammatory process and significant drop in acute-phase proteins were observed in the investigated group of patients. They were left on a single dose regimen of dalbavancin and no change of antibiotic was necessary. V.A.C. was changed twice in 3 patients and once in one patient. The average length of hospitalization was 4 days. Full healing that was confirmed either by absence of discharge or drop in inflammatory markers was achieved on average in 12 days. All patients began biological therapy after two weeks. They remain under observation to assess the late outcomes of combination therapy of anal fistulas with accompanying pus collections.

DISCUSSION

The incidence of anal fistula is 2–10 per 100 000 per year of the population in European studies. Men are twice to seven times as likely to be affected, mostly between the third and fourth decade of life, with a peak at the age of 39 [1, 5]. Anal fistulas occur in 21–54% of patients suffering from CD. On average, 41% of the patients with Crohn's colitis and only 12% of those with small bowel inflammation develop anal fistulas. There are more complex anal fistulas with accompanying abscesses requiring surgery and antibiotic therapy in CD compared to non-Crohn's anal fistulas [6–8]. There is still a high rate of failures and recurrences after treatment of Crohn's anal fistulas, therefore diverting colostomy or abdominoperineal resection of the rectum are still performed in almost half of the patients with recurrent, intractable perianal abscesses and fistulas, anal or rectal strictures and irreversible damage to the anal sphincter. It is also worth mentioning, that costs of therapy increase due

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to long-term hospitalization, multiple surgical procedures, antibiotic therapy, absence from work and social problems [3, 9, 10]. Taking into consideration the above-mentioned conditions, modern treatment of Crohn's anal fistulas should be based on biological therapy preceded with incision and drainage of concomitant abscesses or perianal phlegmon and complementary administration of antibiotics [5, 7, 11–13]. If possible, that treatment should be undertaken in an out-patient care setting in order to avoid unnecessary costs related to hospitalization [14]. Complementary administration of antibiotics, which control extensive induration of the perianal skin remaining after surgery, relies today in most cases on ciprofloxacin and metronidazole. Good clinical outcomes result from the fact that the colon is the source of primary perianal infection in the patients. Such preparations should be maintained for at least 6 to 10 weeks [8, 13, 15]. However, there is a risk of superinfection with methicillin-resistant *Staphylococcus aureus* in the patients with chronic Crohn's anal fistulas. An alternative to antibiotics against MRSA, administered at hospitals might be dalbavancin. It is a new-generation lipoglycopeptide, which belongs to the same class as vancomycin, however with a better penetration into the skin and a higher efficacy against Gram-positive microorganisms. Finally, a single dose of the antibiotic is superior to a double-dose [8]. Standard management of Crohn's anal fistulas with concomitant pus collections based on incision and drainage with multiple change of dressings and on prolonged intravenous administration of antibiotics require a long hospital stay and result in increased costs. Introduction of dalbavancin and V.A.C. might be an alternative to traditional methods of therapy [8, 14].

CONCLUSIONS

1. Incision and drainage of pus collections accompanying Crohn's anal fistulas combined with a single intravenous injection of dalbavancin at the dose of 1500 mg is an effective and well tolerated method of treatment.

2. Application of negative pressure therapy in a selected group of patients makes discharge evacuation more effective.
3. The proposed protocol shortens hospitalization time and consequently implementation of biological therapy.

CONFLICT OF INTEREST: All Authors confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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