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Bezlotoxumab in the treatment of *Clostridioides difficile* infections: a real-life experience

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ABSTRACT

Background. Following the approval of bezlotoxumab in 2017, studies evaluating its effectiveness in prevention of *Clostridioides difficile* infection under "real-life" conditions are scarce.

Material and methods. We conducted a retrospective study developed in a large tertiary care hospital describing the use and outcomes of patients with *Clostridioides difficile* infection (CDI) treated with bezlotoxumab.

Results. A total of 16 patients were included, all of whom had an episode of CDI with high probability of recurrence and 14 of them had some kind of immunosuppression. Bezlotoxumab was effective in the prevention of CDI recurrence in 11 of the 14 cases in which follow up was possible, without significant side effects.

Conclusions. Bezlotoxumab was well tolerated and the incidence of recurrent CDI in a high-risk population for recurrence was only 21.4%.

Keywords: *Clostridioides difficile*, bezlotoxumab, treatment, recurrence

Bezlotoxumab para el tratamiento de las infecciones por *Clostridioides difficile*: experiencia en vida real

RESUMEN

Antecedentes. Tras la aprobación de bezlotoxumab en 2017, son escasos los estudios que evalúan su eficacia en la prevención de la infección por *Clostridioides difficile* en condiciones de vida real.

Material y métodos. Realizamos un estudio retrospectivo desarrollado en un hospital terciario describiendo el uso y los resultados de los pacientes con infección por *Clostridioides difficile* (ICD) tratados con bezlotoxumab.

Resultados. Se incluyeron un total de 16 pacientes, todos ellos con un episodio de ICD con alto riesgo de recurrencia y 14 de ellos con algún tipo de inmunosupresión. El bezlotoxumab fue eficaz en la prevención de la recurrencia de la ICD en 11 de los 14 casos en los que fue posible el seguimiento, sin efectos secundarios significativos.

Conclusiones. El bezlotoxumab fue bien tolerado. La incidencia de ICD recurrente en una población de alto riesgo de recurrencia, fue sólo del 21,4%.

Keywords: *Clostridioides difficile*, bezlotoxumab, tratamiento, recurrencia

INTRODUCTION

Clostridioides difficile infection (CDI) is an important cause of morbidity and mortality in hospitalized patients and it is an increasingly frequent cause of community onset diarrhea [1].

CDI has a high rate of recurrence [2], especially in patients with risk factors for recurrence such as: advanced age, prior CDI episodes, need to continue receiving antibiotics, immunosuppression (solid organ transplant, hematologic malignancy, neoplasia), infection by a hypervirulent strain (O27 ribotype), concomitant Inflammatory Bowel Disease (IBD) or having a low toxin B Ct value in PCR test [3].

Recurrence rates for patients with previous recurrent episodes of CDI reach 45% when treated with metronidazole or vancomycin [4]. Moreover, in patients with multiple recurrences, the risk of further recurrences approaches 75% [5,6]. Recurrences increase days of hospital stay, readmissions and cost [7,8]. Fidaxomicin has been shown to reduce the rate of CDI to about 10% in first episodes [9] but it is not always available, since in Spain it is financed by the Ministry of Health for second recurrences.

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Fecal microbiota transplant emerged as an effective treatment for CDI and its recurring episodes, but it is not available everywhere, it should be given with caution in some immunosuppressed patients [10-15], and it is still considered an experimental procedure after a first episode of CDI.

Bezlotoxumab is a monoclonal antibody against toxin B of *C. difficile*, that is proven to be effective in decreasing the incidence of rCDI (recurrent CDI) in randomized clinical trials [16,17]. Experience in real-life situations in the post-marketing of bezlotoxumab are still scarce [18] and we are not aware of any particular cases published in Spain.

We report our experience in a Spanish tertiary hospital with the use of bezlotoxumab in the first 16 patients at high risk for CDI recurrence.

MATERIAL AND METHODS

Study design. This was a retrospective study, carried out in a large tertiary care hospital with 1,300 beds, in the 13-month period from the date of marketing bezlotoxumab in Spain (August 2018 – September 2019). We included in this study all patients who received Bezlotoxumab during that period, in our institution.

Patients were selected for bezlotoxumab if they fulfilled the indications for the financing of bezlotoxumab in Spain [20] and, in addition, had 3 or more risk factors for rCDI: age > 65 years, prior CDI episode, incapability to stop antibiotics during the CDI episode, immunosuppression (solid organ transplant, hematologic malignancy, neoplasia), infection by a hypervirulent strain such as 027 ribotype, concomitant Inflammatory Bowel Disease or with low toxin B Ct values. All the patients had a life expectancy of more than three months.

Medical records for all patients receiving bezlotoxumab were reviewed. Data collected included patient demographics, underlying conditions, number of former rCDI episodes, severity of CDI episode, treatment used for previous CDI episodes, antimicrobial therapy administered concomitant to bezlotoxumab, reasons for its use, dosages, adverse events and outcomes (need for ICU admission, need for surgery due to the CDI episode, recurrence, mortality, and CDI-associated mortality).

The laboratory diagnosis of *C. difficile* was performed according to our own practice [21]. Rapid tests were performed on all samples. The rapid detection test consisted of a two-step diagnostic algorithm based on a first immunochromatographic antigen detection of glutamate deshydrogenase (GDH) and toxins A/B simultaneously (CDiff Quik-Chek Complete assay, TechLab, Blacksburg, VA) and secondly, all samples with any of the previous tests positive, were tested by a real-time PCR of the B toxin gene (Xpert™ *C. difficile* Assay, GeneXpert, Cepheid, Sunnyvale, CA). Furthermore, all samples were also tested by toxigenic culture (TC).

Definitions. A CDI episode was defined as the presence

of a positive result for toxigenic *C. difficile* testing (having found the toxin directly or indirectly) and the presence of diarrhea (3 unformed stools in 24 h) without other apparent cause.

Severity of CDI episodes was defined according to the European Society of Clinical Microbiology and Infectious Disease (ESCMID) guidelines [22].

CDI-associated mortality was defined as death, not clearly attributable to other causes, occurring within 10 days of the CDI diagnosis.

Recurrent CDI (r-CDI) was defined as CDI symptoms and positive stool sample that occurred in the first 10 to 90 days after recovery of a previous CDI episode.

The follow-up period of the patients was 90 days or until their death.

Ethical issues. Being a systematic clinical intervention, the local ethics committees approved the study, without requiring informed consent (MICRO.HGUGM.2019-021).

RESULTS

In the 13-month period from the date of marketing bezlotoxumab in Spain, 16 patients fulfilled our criteria for bezlotoxumab selection and accepted this modality of treatment in our center.

Demographic and baseline characteristics of the study population were shown in Table 1. Patients' age ranged from 54-84 years [median 69.5 years; SD 20 years] and 10 (62.5%) were female. Overall, 14 (87.5%) had some kind of immunosuppression, 3 (18.8%) were solid organ transplant recipients, 6 (37.5%) patients had a cancer and 2 (12.5%) had cirrhosis. Overall, 8 (50%) of the patients received some kind of immunosuppressive therapy.

At presentation time, the disease was mild in 7 cases (43.8%), severe in 3 (18.8%) and severe-complicated in 6 (37.5%). Of the 16 patients, 9 (56.3%) had a history of prior CDI episodes, 15 episodes/recurrences in total treated with either metronidazole (1), vancomycin (7), extended duration vancomycin (2) or fidaxomicin (5).

During the episode treated with bezlotoxumab, 14 of the 16 patients received 10 days of vancomycin as concomitant treatment and two received 10 days of fidaxomicin due to a history of vancomycin allergy. We used standard dosages of bezlotoxumab (10mg/kg) in all patients. Bezlotoxumab tolerability was good and no side effects were detected.

Two patients died due to other causes, so it was not possible to demonstrate any CDI cure. Of the remaining 14 patients, 11 did not recur during a 3-month follow up period. This resulted in a recurrence rate of 21.4% (3/14).

In the subgroup of patients with any previous recurrence, the recurrence rate was 25% (2/8, because one died). These patients had had 2 and 4 respectively recurrences previously.

Table 1 Description of patients and their results

Nº of patients	Age	Gender	Underlying conditions	Risk factors present	Immunosuppressive therapy	Episodes or Recurrences	Severity	Previous treatment	Concomitant treatment	Outcome
1	69	F	Kidney transplant	4	Tacrolimus, Everolimus, Prednisone	1	Severe	VAN		Curation
2	66	F	Micobacterium avium lung infection	3	no	4	Mild	VAN and FID	VAN	CD Recurrence
3	57	F	Oropharyngeal cancer, intestinal perforation (colostomy)	3	Radiotherapy & Chemotherapy	1	Severe-complic.	VAN	VAN	Curation
4	80	F	Leukemia, myelodyspl. syndrome, RA, knee prosthesis infection	3	Azathioprine	3	Mild	MET and FID	FID (allergy to VAN)	Curation
5	84	M	Pneumonia, dysphagia	4	no	1	Mild	VAN	VAN	27/2 exitus
6	70	F	Kidney transplant	3	Tacrolimus, mycophenolate	0	Severe	-	VAN	Curation
7	57	M	Child C Cirrhosis	3	no	0	Severe-complic.	-	VAN	Curation
8	82	M	Lung cancer	3	Nivolumab	0	Mild	-	VAN	Curation
9	59	F	Ulcerative Colitis	3	AZA, 5ASA; Adalimumab, INF, GC	0	Severe	-	VAN	Curation
10	78	M	Child C Cirrhosis	3	no	0	Severe-complic.	-	VAN	Curation
11	80	M	Sigma cancer, cardiopathy	4	no	2	Mild	VAN	VAN	CD Recurrence
12	69	F	HIV	3	Other, HIV treatment	1	Severe-complic.	VAN	VAN	Curation
13	63	M	Pancreatic cancer	3	Chemotherapy	0	Mild	-	VAN	22/07 exitus
14	76	F	Pancreatic cancer	5	Chemotherapy	1	Severe-complic.	VAN	VAN	Curation
15	81	F	Renal insufficiency, cardiopathy	3	no	1	Mild	FID	FID (allergy to VAN)	Curation
16	54	F	Renal insufficiency, liver transplant	3	Tacrolimus	0	Severe-complic.	-	VAN	CD Recurrence

Risk factors for rCDI: age > 65 years, prior CD episode, antibiotic use during standard of care, immunosuppressed (solid organ transplant, hematologic disease, neoplasia), patients infected by a hypervirulent strain such as 027 ribotype, concomitant Inflammatory Bowel Disease or with low toxin B Ct values.

Gender: (F: Female & M: Male); Episodes or recurrences: Episodes or recurrences before the use of bezlotoxumab; VAN: vancomycin; MET: metronidazole; FID: Fidaxomicin

DISCUSSION

A preliminary experience with bezlotoxumab in a population at very high risk of CDI recurrence showed high rates of cure and very good tolerance.

CDI the most frequent cause of nosocomial diarrhea and an important cause of morbi-mortality in hospitalized patients. CDI usually occurs in severely ill patients, after antibiotic pre-prescription due to proven or suspected infections.

CDI risk of recurrence is a concerning problem. While antibiotics such as vancomycin or fidaxomicin are used to treat CDI, fecal microbiota transplant (FMT) and bezlotoxumab may have a role in preventing recurrences.

Possible benefits of the use of bezlotoxumab are that it could be available in every hospital and may be offered also to

patients with contraindications for FMT or those who refuse FMT.

Bezlotoxumab has been financed in Spain for patients with high risk of recurrence.

Therefore, we selected a population with particularly high risk of r-CDI, prioritizing patients in which 3 or more risk factors were present [23].

For this purpose, we designed a score so we could choose patients for treatment with Bezlotoxumab while the hospital acquires its own experience with this monoclonal antibody.

The recurrence rates in people with risk factors for CDI reported in previous studies are up to 21-75% [24,25]. Our study, showed that in patients with 3 or more risk factors for rCDI, the rates of recurrent episodes was 21.42%, and therefore probably complies with the reduction of rCDI rates from

the clinical trial [17] (bezlotoxumab 16.5% vs. placebo 26.6%; $p=0.0001$). In patients with some prior recurrence, recurrence rate in the bezlotoxumab group decreased to 25%. It is important to highlight that the patients who suffer the rCDI had had 2 and 4 respectively recurrences previously, so it is probably not the best clinical scenario to use bezlotoxumab. Tolerability was excellent in all cases.

To the best of our knowledge, there are only two publications describing real-life use of bezlotoxumab, none of them from Spain. The study by Oksi et al. described their experience with 46 patients from 5 hospitals in Finland and observed a recurrence rate of CDI of 27% (78% had three or more known risk factors for recurrence of CDI) [18], and Hengel et al described 200 patients receiving bezlotoxumab, 15.9% of whom experienced a rCDI [19].

Some limitations of our study need to be considered: Firstly, it was performed in only one institution with a limited sample size; and secondly, it does not have a population to compare recurrence rates.

Despite these limitations, in our experience bezlotoxumab proved to be a clinically effective drug for avoiding recurrences of CDI. The current data provide a starting point for performing future clinical trials to study the recurrence rate of CDI when using three different treatment options: 1) fidaxomicin, 2) vancomycin followed by fecal microbiota transplant (FMT), or 3) the combination of vancomycin with bezlotoxumab.

In conclusion, real-world experience on bezlotoxumab efficacy seems to be promising. All of our patients had 3 or more risk factors for CDI and 87.5% (14) of them were immunosuppressed. Bezlotoxumab was effective in the prevention of CDI recurrence in 78.57% (11/14) of the cases without side effects observed.

Bezlotoxumab could be an effective alternative for those patients who refuse FMT, those who may have contraindications to it, or in hospitals where it is not available.

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CONFLICTS OF INTEREST

Emilio Bouza, Patricia Muñoz, Maricela Valerio, Martha Kestler and María Olmedo have received fees for scientific advice or participation in scientific meetings of Astellas and MSD.

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