Comment of an Expert Group of the Paul-Ehrlich-Society for Chemotherapy on the benefit assessment of fidaxomicin for treatment of Clostridium difficile infections

Michael Kresken[1,2]
Lutz von Müller[3]
Béatrice Grabein[4]
Mathias Herrmann[3]
Gert Höffken[5,6]
Achim Hoerauf[7]
Peter Kern[8]
Mathias W. Pletz[9]
Emil Reisinger[10]
Oliver A. Cornely[11,12]
Andreas H. Groll[13]

1 Antiinfectives Intelligence GmbH, Rheinbach, Germany

2 Rheinische Fachhochschule Köln, Cologne, Germany

3 Institut für Medizinische Mikrobiologie und Hygiene, Universitätsklinikum des Saarlandes, Homburg/Saar, Germany

4 Klinikum der Universität München, Munich, Germany

5 Medizinische Klinik I, Universitätsklinikum Carl Gustav Carus, Dresden, Germany

6 Zentrum für Pneumologie, Allergologie, Beatmungsmedizin, Thorax- und Gefäßchirurgie, Fachkrankenhaus Coswig, Germany

7 Institut für Medizinische Mikrobiologie, Immunologie und Parasitologie, Universitätsklinikum Bonn, Germany

8 Universitätsklinikum Ulm, Germany

9 Zentrum für Infektionsmedizin und Krankenhaushygiene, Universitätsklinikum Jena, Germany

10 Universitätsmedizin Rostock, Germany

11 Klinik I für Innere Medizin, Uniklinik Köln, Cologne, Germany

12 Zentrum für Klinische Studien (ZKS – BMBF 01KN1106), Universität zu Köln, Cologne, Germany

13 Klinik für Kinder- und Jugendmedizin, Pädiatrische Hämatologie und Onkologie, Universitätsklinikum Münster, Germany

Benefit assessment of fidaxomicin for treatment of Clostridium difficile infections

Fidaxomicin (Dificlir®) has been approved by the European Medicines Agency (EMA) in December 2011 for treatment of *Clostridium difficile* infections (CDI), also known under the term *Clostridium difficile* associated diarrhea (CDAD). The recommended oral dose is 200 mg twice daily for a total of 10 days.

The compound is now available in almost all European countries. In Germany, the legally binding procedure for evaluation of the additional benefit of the prescription of fidaxomicin has been completed in July 2013. The predominant aim of this procedure is to evaluate the additional benefit of a new intervention versus existing comparable interventions, and to assess the magnitude of this benefit and its therapeutic impact. The institution responsible for this evaluation, the 'Gemeinsame Bundesausschuss' (G-BA), concluded that fidaxomicin possesses a relevant additional benefit in the treatment of patients with severe and/or recurrent courses of CDI. During the course of the evaluation procedure, the Paul-Ehrlich-Gesellschaft für Chemotherapie (Paul Ehrlich Society for Chemotherapy, PEG) submitted a commentary on the benefit evaluation to the G-BA [1]. This commentary endorsed the clinical usefulness of fidaxomicin on the basis of the existing clinical trial data and is summarized in this note.

Based on its unique mechanism of action and the lack of cross resistance to existing antimicrobial agents, fidaxomicin can be considered as a true novel antibiotic. Further therapeutic advantages include a narrow spectrum of activity leaving the intestinal bystander flora preferably unimpaired, the bactericidal mode of action against *C. difficile* and the inhibition of the organism's toxin production already at subinhibitory concentrations. The introduction of a novel antibiotic represents per se an additional benefit, since it contributes to reducing the selective pressure exerted by existing antibiotics on enteric bacteria.

The increasingly uncritical use of broad spectrum antibacterial agents over the past decades has greatly contributed to the rising incidence of CDI in Germany. According to data provided by the German Robert Koch-Institut (RKI), the number of hospital-acquired cases of CDI rose from 1.3/100,000 discharges in the year 2000 to 97.5/100,000 in 2006 [2]; the number of severe cases reported according to §6 of the national law for reporting and prevention of infectious diseases, 'Infektionsschutzgesetz' (IfSG), has doubled from 2008 until 2012 [3]. It was shown that nosocomial infections by *C. difficile* have become twice as common in Germany relative to those caused by methicillin-resistant *Staphylococcus aureus* (MRSA) [4]. Of note, these data do not consider the high number of unreported cases related to the lack of widely available, standardized diagnostic procedures. On the basis of the results of the European ECDIS study, the incidence of CDI has been estimated to one out of 435 hospital admissions [5]. Of additional serious concern is the epidemic occurrence of hypervirulent strains (e.g. ribotype 027) with multiple resistance against standard antibiotics (i.e., fluoroquinolones, macrolides) [6], [7].

An increasing rate of CDI was also found for the ambulatory setting, as a recent analysis of cases in the outpatient setting from England suggests. In this study, the percentage of CDI acquired outside the hospital rose from 7% in 1997/98 to 13% in 2009/10 [8]. The spread of *C. difficile* in residents of nursing and special care homes has become another important problem. According to a study from the state of Hessen, Germany, one out of 20 residents of nursing homes is colonized by *C. difficile* [9]. The most important risk factors to acquire CDI include advanced age (>65 years), the presence of a chronic underlying condition, recent hospitalization, and recent use of antibacterial agents, particularly clindamycin, fluoroquinolones, and cephalosporins [10].

The potential sequelae of severe CDI are well known: increased length of stay in the hospital, a high rate of recurrent CDI, and death. The possible economical costs are enormous. In 2006, an expert consortium composed of members of the European Centers for Disease Control (ECDC) and the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) study group for Clostridium difficile estimated the direct cost to 3 billion Euros per year for the geographic area of the European Union (E.U.) [11]. This expenditure is likely to rise given the demographic changes with an increasing proportion of elderly and old individuals.

Prior to the introduction of fidaxomicin, only two agents were available for treatment of CDI, i.e. metronidazole and vancomycin. Metronidazole, which is recommended but not formally approved for treatment of mild CDI, is almost completely absorbed from the gastrointestinal tract after oral administration; only a small fraction (6%) of a given dose is excreted via the bile fluid into the gastrointestinal tract [12]. Therefore, it cannot be assumed that therapeutically adequate concentrations of the compound can always be achieved within the colon, the primary site of replication of *C. difficile*. In addition, there is suggestive evidence that metronidazole may be metabolized by resident enterococci inside the colon [13]. In contrast to metronidazole, vancomycin is only minimally absorbed after oral administration [14]. Considering the different disposition of both compounds (low intestinal concentrations of metronidazole, high intestinal concentrations of vancomycin), there are obvious advantages favoring vancomycin for the treatment of severe and/or recurrent CDI, and these advantages are reflected in the results of several comparative clinical trials [15]. Of note, the use of both agents and particularly that of vancomycin has been identified as a risk factor for selection of vancomycin-resistant enterococci (VRE) [16].

The ESCMID study group for Clostridium difficile has recommended metronidazole for primary treatment of mild to moderate, and vancomycin for primary treatment of severe CDI [15]. However, recurrent CDI is frequent and observed at a rate of approximately 25% with either of the two agents [15]. Importantly, in phase III clinical registration trials, treatment with fidaxomicin was associated with a significantly lower rate of recurrent CDI relative to vancomycin (14.1% vs. 26.0%; 95% CI. [–16.8%; –6.8%]) [17]. Even though it was not the primary endpoint of the cited trials, this difference in recurrent CDI promises to be of high relevance for patients affected with severe CDI.

The sales price of the manufacturer in E.U. countries for one package with 20 tablets of Dificlir®, which corresponds to the recommended treatment of one tablet twice daily for 10 days, accounts for € 1,500. Given the considerably higher cost for a treatment course with fidaxomicin in comparison to a treatment course with vancomycin, the primary target population for fidaxomicin should for now be restricted to patients with carefully defined disease characteristics. Fidaxomicin is approved for treatment of CDI but this new compound clearly has no indication in patients with mild CDI and in patients with CDI and toxic megacolon. As the clinical benefit of fidaxomicin relative to vancomycin in patients with severe CDI is not founded on a better response rate but on a reduced rate of recurrent CDI, the primary target populations for fidaxomicin treatment are patients with severe CDI at risk of recurrent CDI and those with multiple recurrences. Considering the compounded cost of recurrent CDI, the use of fidaxomicin in these settings appears justified. In either way, a treatment course with fidaxomicin should always be considered before less well evaluated, non-standardized treatment approaches such as fecal microbiota transplantation are employed. Surrogate markers for identification of patients with high risk for recurrent CDI thus far do not exist and thus, a standardized stratification of patients with severe CDI in the alternative treatments, i.e. fidaxomicin and vancomycin, is not yet feasible. Apart from a proactive approach to hospital hygiene also the different treatment options may contribute to minimize *C. difficile* load in hospitals. Each hospital has to decide which patient groups are predisposed to particularly high recurrent CDI rates on the one hand and a high risk of nosocomial spreading on the other hand. These groups of high risk patients need to be characterized; however, clinical parameters and laboratory markers that allow for a reliable stratification of patients who will benefit from fidaxomicin remain still to be identified based on microbiological and clinical criteria. Additional well designed clinical trials evaluating the superiority of fidaxomicin to vancomycin in defined high risk patient groups will help to delineate the full clinical benefit of fidaxomicin in daily practice.

Notes

Competing interests

MK, GH, AH, PK and ER declare that they have no competing interests. LvM, BG and MWP received lecture honoraria from Astellas. MH received a honorarium for advisory activity from Astellas. OAC has received research grants from Astellas and Optimer, is a consultant to Astellas and Optimer, and received lecture honoraria from Astellas. AHG is a consultant to Astellas and received lecture honoraria from Astellas.

References

1. Paul-Ehrlich-Gesellschaft für Chemotherapie e.V. Fidaxomicin: Stellungnahme der PEG zum Nutzenbewertungsverfahren des G-BA. Übermittelt am 6. Mai 2013.
2. Vonberg RP, Gastmeier P. Clostridium-difficile-assoziierte Diarrhö: Zunehmende Inzidenz in Deutschland. Epidemiol Bull. 2008 Apr 11;(15):119. Available from: https://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2008/Ausgaben/15_08.pdf?__blob=publicationFile

3. Weiss B. Schwer verlaufende Clostridium-difficile-Infektionen: IfSG-Surveillancedaten von 2011 und 2012. Epidemiol Bull. 2013 Jun 24;(25):233-7. Available from: https://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2013/Ausgaben/25_13.pdf?__blob=publicationFile

4. Mock M, Halfmann A, Herrmann M, von Müller L. Aktuelles zur Epidemiologie von Clostridium difficile – Bericht aus dem Konsiliarlabor C. difficile. Epidemiol Bull. 2013 Jun 24;(26):241-4. Available from: https://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2013/Ausgaben/26_13.pdf?__blob=publicationFile

5. von Müller L, Halfmann A, Herrmann M. Aktuelle Daten und Trends zur Antibiotikaresistenzentwicklung von Clostridium difficile [Current data and trends on the development of antibiotic resistance of Clostridium difficile]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2012 Nov;55(11-12):1410-7. DOI: 10.1007/s00103-012-1556-6

6. Meyer E, Gastmeier P, Weizel-Kage D, Schwab F. Associations between nosocomial meticillin-resistant Staphylococcus aureus and nosocomial Clostridium difficile-associated diarrhoea in 89 German hospitals. J Hosp Infect. 2012 Nov;82(3):181-6. DOI: 10.1016/j.jhin.2012.07.022

7. Bauer MP, Notermans DW, van Benthem BH, Brazier JS, Wilcox MH, Rupnik M, Monnet DL, van Dissel JT, Kuijper EJ; ECDIS Study Group. Clostridium difficile infection in Europe: a hospital-based survey. Lancet. 2011 Jan 1;377(9759):63-73. DOI: 10.1016/S0140-6736(10)61266-4

8. Jen MH, Saxena S, Bottle A, Pollok R, Holmes A, Aylin P. Assessment of administrative data for evaluating the shifting acquisition of Clostridium difficile infection in England. J Hosp Infect. 2012 Mar;80(3):229-37. DOI: 10.1016/j.jhin.2012.01.001

9. Arvand M, Moser V, Schwehn C, Bettge-Weller G, Hensgens MP, Kuijper EJ. High prevalence of Clostridium difficile colonization among nursing home residents in Hesse, Germany. PLoS One. 2012;7(1):e30183. DOI: 10.1371/journal.pone.0030183

10. Brown KA, Khanafer N, Daneman N, Fisman DN. Meta-analysis of antibiotics and the risk of community-associated Clostridium difficile infection. Antimicrob Agents Chemother. 2013 May;57(5):2326-32. DOI: 10.1128/AAC.02176-12

11. Kuijper EJ, Coignard B, Tüll P; ESCMID Study Group for Clostridium difficile; EU Member States; European Centre for Disease Prevention and Control. Emergence of Clostridium difficile-associated disease in North America and Europe. Clin Microbiol Infect. 2006 Oct;12 Suppl 6:2-18. DOI: 10.1111/j.1469-0691.2006.01580.x

12. Fachinformation Flagyl® 400 mg. Stand Dezember 2011.

13. Nagy E, Földes J. Inactivation of metronidazole by Enterococcus faecalis. J Antimicrob Chemother. 1991 Jan;27(1):63-70. DOI: 10.1093/jac/27.1.63

14. Fachinformation VANCOMYCIN ENTEROCAPS® 250 mg. Stand Dezember 2012.

15. Bauer MP, Kuijper EJ, van Dissel JT; European Society of Clinical Microbiology and Infectious Diseases. European Society of Clinical Microbiology and Infectious Diseases (ESCMID): treatment guidance document for Clostridium difficile infection (CDI). Clin Microbiol Infect. 2009 Dec;15(12):1067-79. DOI: 10.1111/j.1469-0691.2009.03099.x

16. Ajao AO, Harris AD, Roghmann MC, Johnson JK, Zhan M, McGregor JC, Furuno JP. Systematic review of measurement and adjustment for colonization pressure in studies of methicillin-resistant Staphylococcus aureus, vancomycin-resistant enterococci, and Clostridium difficile acquisition. Infect Control Hosp Epidemiol. 2011 May;32(5):481-9. DOI: 10.1086/659403

17. Fachinformation DIFICLIR 200 mg Filmtabletten. Stand Januar 2013.

Corresponding author:
Prof. Dr. Michael Kresken
Antiinfectives Intelligence GmbH, Campus Hochschule Bonn-Rhein-Sieg, Von-Liebig-Straße 20, 53359 Rheinbach, Germany, Phone: +49(0)2226-908-912, Fax: +49(0)2226-908-918
michael.kresken@antiinfectives-intelligence.de

Please cite as
Kresken M, von Müller L, Grabein B, Herrmann M, Höffken G, Hoerauf A, Kern P, Pletz MW, Reisinger E, Cornely OA, Groll AH. Comment of an Expert Group of the Paul-Ehrlich-Society for Chemotherapy on the benefit assessment of fidaxomicin for treatment of Clostridium difficile infections. GMS Infect Dis. 2013;1:Doc07.
DOI: 10.3205/id000007, URN: urn:nbn:de:0183-id0000077

This article is freely available from
http://www.egms.de/en/journals/id/2013-1/id000007.shtml

Published: *2013-11-19*