Appropriateness of Crohn’s Disease Therapy in Gastroenterological Rehabilitation

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Abstract
Background/Aims: The treatment criteria developed by the European Panel on the Appropriateness of Crohn’s Disease (CD) Therapy (EPACT) have not been applied to rehabilitation. Thus, we retrospectively evaluated appropriateness of treatments during CD rehabilitation using the EPACT website.

Methods: We included our 1-year inpatient rehabilitation patients that had been assigned the International Classification of Disease Code for CD. The appropriateness of treatment was assessed in CD categories exhibiting frequent treatment changes. Treatment plans were compared to EPACT recommendations.

Results: Charts of 337 proven CD patients (median age 42 [range 17–65] years, 250 women, median Crohn’s Disease Activity Index 140 [range –3 to 427] units) were assigned to EPACT categories. The categories ‘steroid-dependent’ and ‘steroid-refractory’ exhibited frequent treatment changes. In these 59 patients, 16 treatments (13 azathioprine, 1 methotrexate, 2 infliximab) were rated as appropriate. One certolizumab treatment was uncertain. 22 treatments with azathioprine were inappropriate (21 due to underdosing), and 93 treatments (30 mesalamine, 59 steroid, 4 budesonide) were not rated. The number of differences between treatment plans and EPACT recommendations decreased from 45 to 25 in both CD categories (p < 0.0001).

Conclusions: We introduce the EPACT website as a practical advance towards an optimal therapy in rehabilitants with steroid-dependent or -refractory CD.

Introduction

Due to the impairment of vocational performance, up to 2,000 patients with Crohn’s disease (CD) are engaged in inpatient medical rehabilitation each year in Germany. However, no data are available on the appropriateness of treatments delivered during gastrointestinal rehabilitation. Although the implementation of practice guidelines for inflammatory bowel disease is believed to reduce practice variation and may improve patients’ quality of life [1], some patients with CD still do not receive optimal quality of care.
therapy [2]. To help ameliorate this, the European Panel on the Appropriateness of Crohn’s Disease Therapy (EPACT) developed explicit, detailed and clinically specific criteria for the appropriateness of care, using the RAND/UCLA appropriateness method, in 2004 [3, 4]. These criteria have been operationalized in 569 clinical scenarios, grouped in broad clinical categories. Although the criteria were designed to be used prospectively, we were interested in evaluating the appropriateness of care in rehabilitation at baseline, retrospectively, using rehabilitation medical records. This kind of approach has been successful in a retrospective feasibility study by members of the EPACT panel in CD patients from gastroenterologist offices [5]. Therefore, we analyzed the 1-year patient charts from our inpatient rehabilitation center. The aim of this pilot study was to evaluate the feasibility of EPACT guidelines, to identify patient categories with frequent treatment changes and to assess the appropriateness of care in these patients. Moreover, we investigated whether applying the EPACT treatment recommendations has the potential to improve treatment plans in the gastroenterological rehabilitation of CD patients.

Methods

Study Population
This analysis was performed as part of a larger, ongoing project to characterize gastroenterological rehabilitation, the results of which have been presented elsewhere [6, 7]. In short, a single-center chart review was performed in a 228-bed inpatient rehabilitation center where patients with gastrointestinal diseases from all regions of Germany are rehabilitated. Almost all rehabilitants were salaried employees insured by the German Pension Insurance, Federal Office. We screened all patient charts from 2006 that had been assigned the International Classification of Disease (ICD) code K50 (Crohn’s disease). Patients with documented endoscopic, histological and laboratory signs of CD were included in the study. The study was approved by the Ethics Committee of the Bavarian Board of Physicians.

Parameters Assessed
To assess clinical types of CD manifestation and categories according to the EPACT definitions, we reviewed each medical record in terms of patient history, endoscopies, laboratory tests, pathology and radiological reports [4]. Moreover, current and past CD treatments and changes in treatments were recorded, including dosage changes, with the duration of treatment and clinical response. We used the 2008 version of the website criteria, which were based on the results of an expert meeting held in 2007 [8]. Clinical response was recorded as complete (prolonged clinical remission with or without endoscopic remission), partial (improvement without remission or transitory remission), failure (clinical non-amelioration or worsening or an adverse event) or not assessable (response was not found in the medical record). Moreover, the treatment plans that the patients agreed upon at admission and discharge were abstracted from the files.

Types of CD Manifestation and EPACT Categories in the Study Cohort
To characterize our CD patients, we assessed all information on disease patterns present in the files and compared them to the clinical types of CD manifestations as defined by the EPACT panel (Table 1) [4]. Next, we assigned each patient to a single CD category using the definitions on the EPACT website (www.epact.ch) [8]. If the medical record contained at least one of the definition criteria for any category and included supporting documentation, this element was considered ‘present and precise’. If the medical record mentioned the item, but none of the criteria used to define the category were documented, this element was considered ‘present but imprecise’. The type of CD manifestation and the category were assumed to be valid during the whole rehabilitation procedure [9–15]. An inter-rater reliability analysis was performed to evaluate consistency between two independent raters.

Frequency of Treatment Changes and Associations with CD Categories
The treatments on admission were compared with those agreed upon by patients and the rehabilitation team during the rehabilitation. Only those resulting in documented changes in prescription of CD medication during rehabilitation entered the

Table 1. Clinical types of CD manifestations

| Clinical types of CD manifestations | Patients (out of 337) | % |
|-----------------------------------|----------------------|---|
| Luminal                           | 129                  | 38.3 |
| Fistulizing                       | 103                  | 30.6 |
| Fibrostenotic                     | 105                  | 31.1 |
| Gastroduodenal                    | 18                   | 5.3 |
| Stenotic                          | 4                    | 22.2 |
| Non-stenotic                      | 14                   | 77.8 |
| Extraintestinal                   | 71                   | 21.1 |
| Active                            | 130                  | 38.6 |
| Mild-moderate                     | 130                  | 100 |
| Severe                            | 0                    | 0 |
| Remission                         | 160                  | 47.5 |
| Medically induced                 | 103                  | 64.4 |
| Surgically induced                | 57                   | 35.6 |
| Steroid-dependent                 | 30                   | 8.9 |
| Steroid-refractory                | 17                   | 5.0 |

Different clinical types of CD manifestation may be present in one patient. Clinical types of CD manifestations were defined according to CD behavior (luminal, fistulizing, fibrostenotic), types of activity (active, remission, steroid-dependent, steroid-refractory) and the presence of gastroduodenal and extraintestinal involvement.
analysis as changed treatments. Treatment changes were defined as a new prescription or a discontinuation or dose change of a CD drug. We assessed the occurrence and kind of treatment changes and the number of patients with changed treatments in every CD category.

Assessment of the Appropriateness of Treatments before and after Rehabilitation in Steroid-Dependent and -Refractory Patients

The appropriateness of pre- and post-rehabilitation treatments was compared in patients of the EPACT categories ‘steroid-dependent’ and ‘steroid-refractory’. To evaluate the quality of our dataset, we assessed the proportion of 118 encounters (n = 59 admission, n = 59 discharge) with all elements necessary to determine the appropriateness of treatments by the EPACT criteria. The treatments prescribed in steroid-dependent and -refractory patients were checked pre- and post-rehabilitation using the EPACT website and classified as appropriate, uncertain, inappropriate or not rated (www.epact.ch) [8]. The EPACT rating was performed with or without dose criteria.

Comparison of Treatment Aims to EPACT Recommendations on Admission and Discharge in Steroid-Dependent and -Refractory Patients

Initial treatment plans and new treatment plans agreed upon during rehabilitation were compared to the EPACT recommendations. Importantly, treatment plans entered the analysis only as new in cases where there was evidence of the patient accepting the new plan. For instance, if an initial therapy plan comprised 1 mg/kg azathioprine, a new 2 mg/kg dosage plan entered the analysis as a new plan if the prescriptions proved an increased azathioprine dose was delivered during rehabilitation. Three kinds of differences between EPACT recommendations and treatment plans were defined: target dose different from EPACT recommendations; EPACT-recommended treatment not given, and treatment not indicated according to EPACT. The number of differences was compared between treatment plans on admission and discharge.

To assess the overall quantitative effect of changed treatment plans on drug delivery during rehabilitation, the doses of azathioprine and the equivalence doses of corticosteroids were compared on admission and discharge in patients persistently treated with this medication throughout the rehabilitation procedure.

Statistics

Data were tabulated using Microsoft Excel. For statistical analysis the SPSS™ software package (Chicago, Ill., USA) was used. Unless stated otherwise, parameters are expressed as an average ± standard deviation. As the majority of parameters were not normally distributed, the non-parametric Wilcoxon log-rank test was used for statistical comparison. We compared doses of immune modulating therapy in the same patient on admission and discharge by the matched-pairs t test. Associations between CD categories and frequencies of CD treatment changes were identified by a forward binary logistic regression analysis. Candidate variables with a p value of <0.05 in univariate analysis were considered significantly associated. To assess the inter-rater reliability, Cohen’s κ coefficient was calculated. The results are expressed as odds ratios (OR) with 95% confidence intervals (CI).

Results

Patient Characteristics

Overall, we screened 3,113 files of rehabilitants scheduled for rehabilitation in our center in 2006. Out of 355 patients with ICD K50, 337 fulfilled the predefined inclusion criteria. The median age was 42 [range 29–51] years. The study population comprised 87 men and 250 women with a median CDAI of 140 [range –3 to 427]. The inpatient rehabilitations had a median duration of 21 [range 1–43] days. The clinical types of CD manifestation, luminal (38.3%), fistulizing (30.6%) and fibrostenotic (31.1%), were almost equally represented in the study population (table 1). As the study was planned in 2007 and the charts analyzed were from 2006, physicians and patients were not aware that the aim of the study was to analyze treatments by the EPACT criteria.

Precision of Information and Inter-Rater Reliability

For the assignment to the category mild-moderate, the necessary information was present and precise in 31 of 40 patients (78%); in 31 of 36 steroid-dependent (86%); in 22 of 23 steroid-refractory (96%); in 37 of 37 fistulizing (100%); in 28 of 30 fibrostenotic (93%); in 101 of 113 requiring maintenance of medically induced remission (89%), and in 52 of 58 in the category maintenance of surgical remission (90%). The presence of necessary elements to determine treatment appropriateness by the EPACT criteria were evaluated in all 118 encounters of 59 patients assigned to the clinical categories steroid-dependent and steroid-refractory. With all elements, 68 of 72 (94%) encounters were in the category steroid-dependent, and 40 of 46 (87%) encounters involved patients assigned to the category steroid-refractory. The inter-rater reliability between two independent raters had a Cohen’s κ coefficient of 0.941 (p < 0.001) (95% CI = 0.914–0.968).

Frequency of Treatment Changes in the Cohort

Overall, 476 CD-specific treatments were identified in 337 rehabilitants. Of these, 198 (42%) treatments were changed in 162 (48%) patients during rehabilitation. The majority of treatment changes comprised modifications in drug dosage (n = 138), whereas 31 new prescriptions of CD-specific drugs were identified (table 2). From all CD categories analyzed univariately, the categories steroid-dependent and steroid-refractory were significantly associated with treatment changes. We calculated the following odds ratios, with their 95% CI, for all CD categories: mild-moderate active luminal OR = 0.87 (95% CI = 0.45–
1.69); steroid-refractory OR = 4.36 (95% CI = 1.93–9.88); steroid-refractory OR = 4.25 (95% CI = 1.54–11.73); fistulizing OR = 0.31 (95% CI = 0.14–0.68); fibrostenotic OR = 0.51 (95% CI = 0.23–1.13); maintenance of medically induced remission OR = 1.09 (95% CI = 0.70–1.72), and maintenance of surgically induced remission OR = 0.66 (95% CI = 0.37–1.18).

**Appropriateness of Treatments in Steroid-Dependent and -Refractory Patients**

We analyzed 132 treatments on admission and 137 on discharge in 36 steroid-dependent and 23 steroid-refractory patients. The rate of appropriate treatment increased from 16/132 (12%) to 23/137 (17%) during rehabilitation. All 16 initially appropriate treatments remained appropriate throughout rehabilitation. The differences remained insignificant if the EPACT rating was performed without the dose criterion. These results are shown in table 3.

**Overall Dose Change of Immune-Modulating Therapy and the Differences between Treatment Plans and EPACT Recommendations on Admission and Discharge**

In 40 of 59 patients with steroid-dependent or -refractory CD who were persistently treated with steroids, the steroid-equivalent dose decreased significantly from 81.0 ± 63 to 66 ± 52 mg, a difference of 15 mg (95% CI = 0.7–28 mg) (p = 0.04). In 35 patients treated with azathioprine throughout the rehabilitation procedure, the average dose increased significantly from 1.65 ± 0.64 to 1.85 ± 0.61 mg/kg, a difference of 0.2 mg/kg (95% CI = 0.04–0.36 mg/kg) (p = 0.014). The number of treatments different in treatment plans and EPACT recommendations decreased from 45 to 25 (p = 0.0001) between admission and discharge (table 4).

**Discussion**

Our study demonstrates for the first time that CD patients can be reliably sorted to CD categories using the EPACT website by analyzing rehabilitation charts. This finding provides independent support of an earlier retrospective, multicenter, population-based study conducted by EPACT members, who proved the feasibility of the EPACT criteria in medical records of gastroenterologist offices [5]. In contrast to that study, the luminal, fistulizing and fibrostenotic types of CD manifestation were equally represented in our patients (table 1). In this sense, we present the first evidence that meaningful application of the EPACT website may not be restricted to luminal CD, which prevails in gastroenterologist offices [5].

Interestingly, almost 80% of the steroid-dependent and -refractory patients consented to therapy changes in rehabilitation. This frequency was significantly greater than that observed in patients from other CD categories (table 2). Additionally, steroid-dependent and -refractory patients were unfit to work almost twice as often (58%) as patients in other CD categories (33%). Moreover, we showed that treatment with systemic steroids is independently associated with unfitness to work in CD rehabili-

tants [7]. These observations support the view that increasing the appropriateness of therapy in steroid-dependent and -refractory patients is an important task in rehabilitation.
In our steroid-dependent and -refractory patients, only 16 out of 132 (12%) treatments were rated as appropriate by EPACT criteria (table 3). This was considerably less than the 43% found by Guessous et al. [5] in their 7 patients with steroid-dependent or -refractory CD. However, this group rated the appropriateness of treatments irrespective of doses given. And, indeed, by instituting relaxed dose criteria, the percentage of appropriate treatments increased to 28% (table 3). Given the high number of not rated treatments, one may suspect that appropriateness could not be rated in these cases due to incomplete information extracted from the charts. However, the majority of ‘not rated’ treatments comprised steroid and mesalamine treatments (table 3). The EPACT regards these treatments as ‘not rated’ in the case of steroid-dependent or -refractory patients, referring to contradictory treatment guidelines. Furthermore, the low percentage of appropriate treatments may also reflect too few prescriptions of azathioprine, methotrexate and infliximab in our steroid-dependent and -refractory patients (table 4).

Surprisingly, only minor, insignificant changes were found between the appropriateness of treatments at the beginning and end of rehabilitation (table 3). Analyzing this largely negative result made it apparent that the majority of treatment changes (48 of 59, 81%) were dose adjustments (table 2). Although these adjustments resulted in a significant 0.2 mg/kg increment of azathioprine during rehabilitation, the ultimate 1.85 mg/kg dose fell short of the 2 mg/kg recommended by the EPACT. This observation indicates that rehabilitation programs should be optimized to overcome patients’ inhibitions about increasing the azathioprine dose to the EPACT-recommended level.

Beyond this, we asked whether the EPACT website may play a role in refining therapy plans and compared them with EPACT recommendations. Indeed, the number of inadequate dosage aims decreased from 21 to 8 during rehabilitation (table 4).

Some limitations of our study should be addressed. The retrospective and single-center design may have biased our results, which need to be corroborated in a prospective multicenter study. Although all 337 patients could be assigned to the EPACT categories with rather high precision and reliability, we restricted our further analysis of appropriateness to 132 treatments in 59 ste-

### Table 3. Appropriateness of treatments on admission and discharge in patients of the EPACT categories steroid-dependent and steroid-refractory (n = 59)

| CD category       | Drug                      | Appropriate admission | Uncertain admission | Inappropriate admission | Not rated admission |
|-------------------|---------------------------|------------------------|---------------------|-------------------------|---------------------|
| Steroid-dependent | Mesalamine                | 19                     | 20                  |                         |                     |
|                   | Steroid                   | 36                     | 36                  |                         |                     |
|                   | Topical                   | 1                      | 1                   |                         |                     |
|                   | Azathioprine/5-mercaptopurine | 6 (22)                | 12 (24)             | 17 (1)                  | 13 (1)              |
|                   | Methotrexate              | 1 (1)                  | 1 (1)               |                         |                     |
|                   | Infliximab and immunosuppression | 1 (1)                | 1 (1)               |                         |                     |
|                   | Certolizumab              | 1 (1)                  | 1 (1)               |                         |                     |
| Steroid-refractory| Mesalamine                | 11                     | 10                  |                         |                     |
|                   | Budesonide                | 3                      | 3                   |                         |                     |
|                   | Steroid                   | 23                     | 22                  |                         |                     |
|                   | Azathioprine/5-mercaptopurine | 7 (12)                | 8 (16)              | 5 (0)                   | 8 (0)               |
|                   | Methotrexate              |                        |                     |                         |                     |
|                   | Infliximab and immunosuppression | 1 (1)                | 1 (1)               |                         |                     |
| Total             |                           | 16 (37)                | 23 (43)             | 1                       | 1                   |

Numbers in parentheses represent EPACT ratings irrespective of dose criterion.

All 59 patients could be reliably assigned to their EPACT categories. In 50 patients the information available from the charts was present and precise, while it was present and imprecise in 9 patients. Treatments with mesalamine, budesonide or steroids are assigned to ‘not rated’ in the EPACT chapters for steroid-dependent or steroid-refractory patients.
roid-dependent or -refractory patients, due to the pre-defined study aims. However, this number of treatments and patients analyzed in our study still compares favorably to the 7 steroid-dependent or -refractory patients studied by the EPACT group to date [5]. Despite a possible single-center bias, the documentation of rehabilitation has been standardized by nationwide guidelines [16]. Therefore, rehabilitation charts should contain the same kind of information irrespective of center attitudes. In addition, only 34% of our patients were male, suggesting a gender bias. However, in two earlier studies from German inpatient rehabilitation centers, 29% of 610 and 36% of 334 CD patients were male [17, 18]. Furthermore, our patients may not be representative of the average CD patient, as we almost exclusively studied beneficiaries of the German Pension Insurance, Federal Office, which insures salaried employees and not manual laborers. However, as the quality of medical treatment relates to socio-economic status, we assume that treatment quality may be even worse in the average CD patient population. Another source of bias could have been the lack of completeness of the EPACT-relevant information in rehabilitation charts. However, we found no meaningful differences between the presence and precision of information in this and earlier studies [5].

In conclusion, we observed a high frequency of treatment changes during the rehabilitation of steroid-dependent and -refractory patients. Despite this, the percentage of treatments rated as appropriate remained below 20%, even after rehabilitation. In contrast, differences between treatment plans and EPACT recommendations declined significantly. Therefore, future studies should address strategies to increase the appropriateness of treatments in these patients by reducing steroid and mesalamine treatments and fostering the implementation of non-steroidal immune-modulating therapies such as azathioprine or methotrexate, if indicated. To achieve this, we recommend the prospective evaluation of the EPACT website as a powerful tool to stimulate and guide dialogue between physicians and CD patients, toward an optimization of treatment during and after rehabilitation.

Table 4. Differences between treatment plans and EPACT recommendations on admission and discharge in patients of the EPACT categories steroid-dependent and steroid-refractory (n = 59)

| Treatment       | Admission | | Discharge | | |
|-----------------|-----------|-----------|-----------|-----------|-----------|
|                 | target dose different from EPACT recommendations | EPACT-recommended treatment not given | treatment not indicated according to EPACT | target dose different from EPACT recommendations | EPACT-recommended treatment not given | treatment not indicated according to EPACT |
| Azathioprine    | 21        | 14        | 1         | 8         | 8         | 1         |
| 5-Mercaptopurine| 1         |           |           |           |           |           |
| Methotrexate    | 6         |           |           |           |           |           |
| Infliximab      | 2         |           |           |           |           |           |
| Overall         | 21        | 23        | 1         | 8         | 16        | 1         |

Treatments with mesalamine, budesonide or steroids are assigned to 'not rated' in the EPACT chapters for steroid-dependent or steroid-refractory patients. *p < 0.0001, Mann-Whitney U test for independent variables.

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