Lenvatinib as First-line Treatment of Hepatocellular Carcinoma in Patients with Impaired Liver Function in Advanced Liver Cirrhosis: Real World Data and Experience of a Tertiary Hepatobiliary Center

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INTRODUCTION

Hepatocellular cancer (HCC) ranks sixth in terms of incident cases [1] and is the second most common cause of cancer-related death worldwide [2], associated with a poor 5-year survival rate of 18% [3]. Among primary liver cancers HCC is the most common, with increasing incidence throughout the world [4]. Only about 15% of patients with HCC are suitable for curative therapy (resection, ablation or liver transplantation) [5].

Lenvatinib is an oral multikinase inhibitor that targets vascular endothelial growth factor (VEGF) receptors 1-3, fibroblast growth factor (FGF) receptors 1-4, plate-derived growth factor (PDGF) receptor α, and proto-oncogenes (rearranged during transfection (RET) and tyrosine kinase receptor encoding protein (KIT) [6, 7]. A phase II trial of lenvatinib for the treatment of patients with advanced HCC demonstrated that a dose of 12 mg daily (QD) had proven a significant survival benefit as well as acceptable toxicity profiles.

ABSTRACT

Background & Aims: Lenvatinib is a multikinase inhibitor approved for systemic first line treatment of hepatocellular cancer (HCC) in patients with compensated liver cirrhosis (LC) and unaltered liver function. We aimed to evaluate the efficiency and tolerability of lenvatinib in patients with HCC in a real world setting, also including patients with advanced LC and impaired liver function.

Methods: Retrospectively, 35 patients with HCC BCLC stages B, C and D were screened. After drop-out and exclusion of patients not receiving active treatment for > 2 weeks, 28 patients (27 male; median age 64.7) with advanced HCC and LC were included in the analysis.

Results: Fourteen patients (male, median age 62.7) treated had Child-Pugh class B LC, while the other 12 patients had a good liver function Child-Pugh class A (male, median age 68.8). Two patients had advanced Child-Pugh class C LC. The patients received an escalating dosing scheme of lenvatinib up to 12 mg/d. The tolerability of lenvatinib was similar in most of the patients, with no significant difference between the subgroups. Median survival was better in patients with Child-Pugh A LC (p=0.003). More than 60% of the patients with Child-Pugh A were still on treatment at the time of data analysis with a median follow-up of 274 ± 117.5 days compared with 153 days (95%CI: 88.3 – 217.7) in patients with Child-Pugh B and 30 days in Child-Pugh C. The survival benefit correlated significantly with less impaired liver function (p=0.003).

Conclusion: Tolerability and toxicity of lenvatinib are similar in patients with Child-Pugh class A and class B LC, but patients with less impaired liver function have a better survival benefit.

Key words: systemic therapy – lenvatinib – hepatocellular carcinoma – advanced liver cirrhosis.

Abbreviations: AFP: alpha-fetoprotein; ALBI: albumin-bilirubin grade; BCLC: Barcelona Clinic Liver Cancer staging; CEUS: contrast-enhanced ultrasound; EASL: European Association for the Study of the Liver; ECG: electrocardiogram; ECOG: Eastern cooperative oncology group; FGF: fibroblast growth factor; HBV: hepatitis B virus; HCV: hepatitis C virus; HCC: hepatocellular carcinoma; KIT: Proto-oncogene encoding the receptor tyrosine kinase protein; MRI: magnetic resonance imaging; MW A: microwave ablation; ORR: objective response rate; OS: overall survival; PDGF: platelet derived growth factor; PFS: progression free survival; PS: performance status; PSC: primary sclerosing cholangitis; QD: every day; RET: rearranged during transfection gene; RFA: radiofrequency ablation; TACE: transarterial chemoembolization; TTP: time to progression; VEGF: vascular endothelial growth factor.
In the subsequent randomized multicenter phase III REFLECT trial of lenvatinib in first-line treatment of patients with advanced HCC, lenvatinib showed a comparable overall survival (OS) of 13.6 months compared to 12.3 months in patients treated with sorafenib. However, in the lenvatinib group a longer progression-free survival (PFS) of 8.9 months compared to 3.7 months in the sorafenib group was found [9]. These results concluded the non-inferiority of lenvatinib versus sorafenib in terms of OS as well as an improvement in PFS, time to progression (TTP) and objective response rate (ORR), which finally led to the approval of lenvatinib in the first line treatment of patients with HCC in 2018 [10].

Impaired liver function is one of the most important patient-related confounders that predict the outcome of systemic therapy in patients with HCC [11]. The majority of patients treated with lenvatinib in both phase II and phase III studies were included with an adequate liver function (Child-Pugh class A, 6 points) before the treatment initiation, and only few data is available on the safety and efficacy of lenvatinib in patients with advanced stages of liver cirrhosis and more impaired liver function.

In this study, we analyzed the cohort of patients that have been treated with lenvatinib for unresectable HCC in our tertiary center and outpatients’ department. We present our experience on efficacy and tolerability of lenvatinib treatment in patients with HCC and all stages of liver cirrhosis.

**METHODS**

We performed a retrospective study in our tertiary center including all patients with advanced HCC that received first line therapy with lenvatinib from December 2018 until May 2020. Therapeutic outcome in terms of efficacy as well as tolerability of the treatment was analyzed. A further subgroup analysis was performed comparing patients with preserved and impaired liver function. All data were extracted retrospectively from the medical reports and clinical information system used in our department.

The study was conducted according to the declaration of Helsinki and the guidelines of good clinical practice (ICH GCP) and was approved by the local institutional Review Board of the Medical Faculty (Nr. 20-2004-104; 16. September 2020).

**Lenvatinib treatment**

A dose of 12 mg QD lenvatinib was recommended in the case of a perfect performance status (ECOG 0, Karnofsky ≥80%), bodyweight of ≥ 60 kg, as well as an adequate liver function (Child-Pugh A) and renal clearance. With regard to the impaired liver function, performance status and bodyweight, we decided a “dosing-in” approach with 8 mg QD or even 4 mg QD with a stepwise increase up to 12 mg QD if tolerated. In cases of significant side effects that were valued not to be tolerated by the patient or that exceeded grade 2 toxicity, the dose of lenvatinib was reduced or the therapy was interrupted until symptoms had resolved to grade 1 or 2.

**Study cohort**

Between December 2018 and May 2020, 35 patients with liver cirrhosis and advanced HCC without other options for surgical or interventional local therapy were evaluated for first-line systemic therapy with lenvatinib in our department. In 5 patients, we decided against any treatment due to advanced age, reduced general condition as well as individual fear of side effects or expected reduction in quality of life. Two patients opted for another systemic treatment option. Finally, 28 patients received lenvatinib treatment and were included in our analysis.

Hepatocellular carcinoma was diagnosed either by histology (fine needle biopsy or prior surgery) or by identification of the typical hallmarks of HCC in at least two imaging techniques, obtained by multiphasic computerized tomography (CT), dynamic contrast-enhanced magnetic resonance imaging (MRI) or contrast-enhanced ultrasound (CEUS) according to the European Association for the Study of the Liver (EASL) Clinical Practice Guidelines 2018 criteria [12].

The severity of the liver cirrhosis was assessed using the Child-Pugh classification system. For the stratification of HCC, staging purposes and estimation of prognosis, the Barcelona Clinic Liver Cancer (BCLC) staging system was applied. In respect to liver function and prognosis, the albumin-bilirubin (ALBI) score was calculated. Previous surgery or interventional treatment by radiofrequency ablation (RFA), transarterial chemoembolisation (TACE), irreversible electroporation (IRE) or microwave ablation (MWA) were documented as well (Table I).

The baseline assessment included the Eastern Cooperative Oncology Group (ECOG) and Karnofsky performance status, weight, past medical history, physical examination and routine laboratory tests, including liver, renal and thyroid function tests, blood count, coagulation status and concentration of AFP. Baseline staging procedures included the identification of liver lesions and extrahepatic tumor manifestations using CT scan, MRI and/or CEUS.

**Assessment of tumor response and tolerability of treatment**

Follow-up visits were scheduled on a regular basis every 3 to 4 weeks for clinical management including evaluation of side effects, liver and renal function tests, blood count, inflammation markers, thyroid function tests and urine test for proteinuria. Staging CT scans or MRI and AFP were performed every 3 months to evaluate the tumor response. An increase in tumor size of more than 20% compared to baseline or one or more new lesions was considered to be consistent with tumor progression. A reduction in the tumor size of at least 20% or a constant tumor size compared to baseline was considered to be consistent with response or stable disease, respectively.

**Statistical analysis**

All data were obtained retrospectively from the medical data base of the clinic information system, entered in a clinical data base (Microsoft Excel 2016, Microsoft Corp.) and statistically analyzed (Microsoft Excel 2016, Microsoft Corp; SPSS version 25). Continuous variables are summarized as median and range, categorical variables as absolute and relative frequencies. Patient survival, TTP and PFS were visualized using Kaplan-Meier curves and differences were evaluated using the Log-rank test. Multivariable analysis of OS was
performed by Cox proportional hazard regression analysis. All statistical analyses were two-sided and p-values < 0.05 were considered statistically significant. The Crosstabs analysis was used to evaluate the tolerability of treatment and differences in the liver function at the beginning and end of therapy, and the statistical significance was evaluated using the t-test. The correlation between the ALBI score and OS was analyzed using descriptive statistics, regression analysis and the Pearson correlation test.

**RESULTS**

**Baseline characteristics**

The baseline characteristics of the 28 study patients under the treatment with lenvatinib are summarized in Table I. The median age of the patients was 64.7 ± 12.0 years and the vast majority of the patients were men (96%, n=27). Forty-two percent of patients presented with diffuse multifocal HCC (BCLC B, n=12), 50% had extrahepatic spread or vascular invasion (BCLC C, n=14) and 8% had advanced liver cirrhosis Child C with or without metastases (BCLC D, n=2). The mean values for bilirubin, albumin and prothrombin time are presented in Table I. Of the included patients, 12 (43%) had minimal to moderate ascites and none had hepatic encephalopathy.

**Treatment response and efficacy**

The evolution of the study cohort in respect to treatment discontinuation due to side effects or alteration of ECOG performance status, tumor progression with consecutive change of therapy or death are displayed in Fig. 1. During the observation time we documented the time of treatment switch to a second-line therapy due to tumor progress, time of treatment discontinuation (without switching to another therapy) due to pronounced side effects, severe infections or decrease of ECOG performance status > 3 and time of death. Five patients were lost to follow-up within the observation period. The treatment duration with lenvatinib was ≥ 4 weeks in 23 patients (82%), ≥ 8 weeks in 17 patients (61%), ≥ 12 weeks in 14 patients (50%) and ≥ 24 weeks in 8 patients (29%). Median treatment duration for all patients was 11 (± 21.5) weeks. At the time of data analysis, 6 patients were still undergoing active treatment with lenvatinib (median time 35 ± 21.8 weeks). The therapy with lenvatinib was discontinued due to documented progressive disease during the observation period in 6 patients (21%). Second-line therapies and further therapeutic options that were initiated included sorafenib, regorafenib and ramucirumab. In 9 patients (32%) discontinuation of the treatment was necessary due to altered ECOG performance status (ECOG > 3) or septic complications, mostly within the first 4-12 weeks of treatment.

Response rates are presented in Table II. Fourteen 55% patients (55%) on active treatment showed stable disease or response in scheduled CT- or MRI scan at week 12, 8 patients (29%) at week 24. At the time of data analysis, of the 6 patients still receiving treatment, of which 3 were at week ≥ 40. The median TTP in patients with Child-Pugh A class was 212 days (95%CI: 65.5–358.5) and in patients with Child-Pugh B, 91 days (95%CI: 42.8–139.2).

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**Table I. Patients’ characteristics.**

| Characteristic                          | Value     |
|-----------------------------------------|-----------|
| Age, years                              | 64.7 (range 31-86) |
| Gender (male/female)                    | 27/1 (96%) |
| BCLC-Staging                            |           |
| A                                       | 0 (0%)    |
| B                                       | 12 (42%)  |
| C                                       | 14 (50%)  |
| D                                       | 2 (8%)    |
| Extrahepatic spread and/or vascular invasion |         |
| Yes                                     | 15 (54%)  |
| No                                      | 13 (46%)  |
| ECOG PS score                           |           |
| 0                                       | 6 (21%)   |
| 1                                       | 14 (50%)  |
| 2                                       | 8 (29%)   |
| 3                                       | 0 (0%)    |
| Previous treatment                      |           |
| Surgery                                 | 6 (21%)   |
| TACE                                    | 20 (71%)  |
| RFA                                     | 6 (21%)   |
| MWA                                     | 8 (29%)   |
| IRE                                     | 12 (43%)  |
| Liver function                          |           |
| Child-Pugh Classification               |           |
| Child A                                 | 12 (42%)  |
| 5 points                                | 4         |
| 6 points                                | 8         |
| Child B                                 | 14 (50%)  |
| 7 points                                | 5         |
| 8 points                                | 4         |
| 9 points                                | 5         |
| Child C                                 | 2 (7%)    |
| ALBI-Score                              |           |
| Grade 1                                 | 1 (4%)    |
| Grade 2                                 | 18 (64%)  |
| Grade 3                                 | 9 (32%)   |
| Bilirubin (mg/dl)                       | 1.2 (0.3 – 8) |
| Albumin (g/l)                           | 29.9 (16.2 – 40) |
| Protrombin time (%)                     | 79.5 (45 – 100) |
| Ascites (n)                             | 12 (43%)  |
| Hepatic encephalopathy (n)              | 0         |
| Etiology                                |           |
| Alcohol                                 | 4 (14%)   |
| Positive HBsAg                          | 4 (14%)   |
| Positive anti-HCV                       | 4 (14%)   |
| NASH                                    | 8 (29%)   |
| PSC                                     | 1 (4%)    |
| Unknown                                 | 7 (25%)   |

BCLC: staging; Barcelona clinic liver cancer staging, ECOG PS status: Eastern Cooperative Oncology Group performance status, TACE: Transarterial chemoembolization; HBsAg: hepatitis B-virus surface antigen, HCV: hepatitis C virus; NASH: nonalcoholic steatohepatitis; PSC: primary sclerosing cholangitis; *Percentage of male subjects.
Fig. 2 illustrates the PFS for the analyzed patients in respect to the Child-Pugh class. Similar to the TTP, the median value for PFS in the Child-Pugh A group was 212 days (95%CI: 76-347) and in the Child-Pugh B group 92 days (95%CI: 90-93).

The OS rates are illustrated by Kaplan-Meier curve in Fig. 3. In patients with Child-Pugh class A liver cirrhosis, the median survival of the patients after starting the treatment with lenvatinib could not be statistically generated due to the fact that more than 60% of these patients were still alive at the time of data analysis, after a median follow-up time of 274 ± 117.5 days. In patients with altered liver function Child-Pugh class B, the median survival was 153 days (95%CI: 88.3 – 217.7). Patients with severe reduced hepatic function (Child-Pugh class C) that were treated in the cohort documented a median survival of 30 days and no clinical benefit. The calculated one-year survival rate for patients with Child-Pugh A was 59.3% and for Child-Pugh B was 26.9%. The survival benefit was statistically significant correlated with less impaired liver function (p=0.003). Regarding the liver function, the ALBI-score at baseline was not associated with OS (p=0.673, Pearson correlation test). A subgroup analysis of patients with liver cirrhosis Child-Pugh class B revealed that patients with 7 points had a similar OS as patients with Child-Pugh class A. At the time of analysis, 56% of these patients were still on treatment and the primary endpoint was not reached. In contrast, patients with Child-Pugh class B 8 points had a reduced OS of 153 days (95%CI: 13.8-292.2; p=0.001).

Liver function under treatment with lenvatinib

The liver function in patients with liver cirrhosis according to the Child-Pugh score was Child A in 12 (42%) patients, Child B in 14 (50%) patients and Child C in 2 (7%) patients. After 4 weeks of treatment, the liver function was unchanged in all of the patients (excluding the unknown data of those lost to follow-up). At the end of therapy with lenvatinib, a patient progressed from Child-Pugh B to Child-Pugh C and a patient from Child-Pugh A to Child-Pugh C (after 9 weeks of treatment), and another patient from Child-Pugh A to Child-Pugh B (after 17 weeks of treatment). One patient had after an improvement of the liver function from Child-Pugh B to Child-Pugh A after 74 weeks of treatment. The difference between the Child-Pugh scores at the beginning and at the end of therapy was statistically not significant (p=0.265, t-test).

During the treatment with lenvatinib, none of the patients presented with complications such as variceal bleeding, spontaneous bacterial peritonitis, hepatorenal syndrome or hepatic encephalopathy. Nevertheless, the 3 patients mentioned above, whose Child-Pugh status progressed under treatment (from Child-Pugh A to Child-Pugh B, from Child-Pugh A to Child-Pugh C and from Child B to Child-Pugh C, respectively) presented with clinical worsened liver function and increased values of bilirubin and/or ascites.

Dosage and tolerability of lenvatinib

During the observation period, the increase of the dosage up to the maximum of 12 mg QD was possible in 13 patients (46.4%), of which the majority were with Child-Pugh A (83.3%). Due to side effects of the therapy and alteration in performance status with consecutive lower tolerability, in 15 patients (53.6%) the dosage increase was not possible, and they received a dose of 4 mg QD, 8 mg QD or 10 mg QD. In 5 patients, the initial dose of 12 mg QD or 8 mg QD was reduced after 2 weeks, 4 weeks, 8 weeks and 16 weeks respectively due to fatigue, joint or muscle pain, mucositis or leukopenia (toxicity grade 1-2). In 2 patients, a treatment pause of 2 to 6 weeks was necessary due to mucositis or leukopenia (toxicity grade 3). After the side effects resolved to a toxicity grade 0-2, the treatment was continued with a lower dose.
Discontinuation of lenvatinib treatment due to adverse events with grade 4 toxicity with consecutive alteration of the ECOG performance status ≥ 3 at week 4, was necessary in 2 patients (7%), after 8 weeks in 5 patients (18%) and after 12 weeks in 8 patients (29%).

Table III shows the most frequent adverse events during treatment with lenvatinib in association with the Child-Pugh classification. The most frequent adverse event in all patients was fatigue (79-100%), irrespective of the Child-Pugh classification. Most frequent adverse events in patients with liver cirrhosis Child-Pugh A was mild proteinuria (50%), leukopenia (17%), joint or muscle pain (17%), mucositis (17%) and emesis (17%). In patients with liver cirrhosis Child-Pugh B most prevalent adverse events were mild proteinuria (43%), loss of appetite (29%), weight loss (21%) and joint or muscle pain (14%). Infections during the observation period occurred in 2 patients (17%) with Child A cirrhosis, in 5 patients (36%) with Child B cirrhosis and in 1 patient (50%) with Child C cirrhosis. All differences between the groups were statistically not significant.

**DISCUSSION**

The prognosis of patients with advanced HCC is still very poor, especially in the case of impaired liver function. Liver cirrhosis itself reduces further life expectancy, and in case of decompensated cirrhosis this reduction is dramatic even without HCC. Lenvatinib demonstrated a significant survival benefit and good tolerance in patients with HCC in the phase III randomized non-inferiority trial (REFLECT) [9]. However, this trial was restricted to patients with well-preserved liver function with liver cirrhosis Child-Pugh class A, and only very little experience has been gained regarding the systemic therapy with lenvatinib in patients with more advanced stages of cirrhosis and impaired liver function. This however does not reflect our daily clinical practice, with patients presenting with stages beyond Child-Pugh class A and compensated but impaired liver function.

**Table III.** Adverse reactions during the treatment with lenvatinib

| Toxicity (all grades) | N of patients (%) |
|-----------------------|-------------------|
|                       | Child-Pugh class A (n = 12) | Child-Pugh class B (n = 14) | Child-Pugh class C (n = 2) |
| Fatigue               | 10 (83)            | 11 (79)               | 2 (100)                  |
| Loss of appetite      | 1 (8)              | 4 (29)                | 1 (50)                   |
| Infection             | 2 (17)             | 5 (36)                | 1 (50)                   |
| Weight loss           | 1 (8)              | 3 (21)                | 0                        |
| Joint or muscle pain  | 2 (17)             | 2 (14)                | 1 (50)                   |
| Mucositis             | 2 (17)             | 0                     | 0                        |
| Vomiting              | 1 (8)              | 2 (14)                | 0                        |
| Emesis                | 2 (17)             | 1 (7)                 | 0                        |
| Diarrhoea             | 0                  | 1 (7)                 | 0                        |
| Leukopenia            | 2 (17)             | 0                     | 0                        |
| Epistaxis             | 1 (8)              | 0                     | 1 (50)                   |
| Hand-foot syndrome    | 0                  | 1 (7)                 | 0                        |
| Hypertension          | 1 (8)              | 1 (7)                 | 0                        |
| Proteinuria           | 6 (50)             | 6 (43)                | 1 (50)                   |
| Albuminuria           | 5 (42)             | 4 (29)                | 0                        |
| Other side effects    | 1 (8)              | 2 (14)                | 1 (50)                   |
In this retrospective study, we report our single-center, real-world experience of lenvatinib for systemic treatment of advanced HCC also in advanced stages of liver cirrhosis and impaired liver function. Dependent on the liver function, we analyzed the treatment response and efficacy as well as the safety profile and occurrence of adverse events.

In our patient cohort, a median OS rate in patients with preserved liver function (Child-Pugh class A) could not be statistically obtained due to the fact that more than 60% of the patients with Child-Pugh A cirrhosis were alive at the time of data analysis (median follow-up time 274 ± 117.5 days). For patients with impaired liver function with Child-Pugh class B liver cirrhosis, OS rates dropped to 153 days (95% CI: 88.3 – 217.7). Within the very heterogeneous group of patients with Child-Pugh class B, patients with less impaired liver function and 7 points were very similar to patients with Child-Pugh class A in regard to response and overall survival during treatment with lenvatinib. Although a small subgroup, 56% of the patients were still on treatment and the primary endpoint was not reached. The survival benefit was statistic significantly correlated with less impaired liver function (p=0.003, Log Rank test). Due to the fact that in our cohort of patients, the analyzed data was obtained over a period of 13 months and the majority of patients with Child-Pugh A were alive after this observational period, our results are in this regard similar to the results obtained from the prospective, randomized data in REFLECT (13.6 months; 95%CI: 12.1-14.9).

In our daily clinical routine as well as in the study, we adapted the recommendations for dosage not only to the patient’s weight but also to the ECOG performance status and the liver function, starting generally with a lower dose to verify the tolerability, and increasing the dose after 2-4 weeks according to the clinical evolution of the patient. Some of the patients did not tolerate the weight-adapted dose of lenvatinib but remained stable with a lower dose for a longer period of time, which suggests that also a lower dose has a potential benefit in patients with advanced HCC. In more than half of the patients (54%), the dosage of lenvatinib with the recommended 12 mg QD was not possible due to tolerability and side effects or alteration in performance status. The median treatment duration for all patients was 11 (± 21.5) weeks in which the tumor remained stable also with a lower dose, suggesting that also a lower dose can have a potential benefit in patients with advanced HCC. This finding was reported by others as well [13]. However, further data is needed to establish a concrete correlation between each possible dose and survival benefit.

Overall, the tolerability of lenvatinib was good to moderate and very similar in patients with Child-Pugh class A and B, which is similar to the results of other studies in this regard [14, 15]. The most frequent adverse event in our patients was fatigue (79-100% of patients), followed by proteinuria (43-50% of patients), infections (17-50% of patients), appetite loss, and weight loss. In contrast to other studies as well as with REFLECT, we did not observe hypertension or diarrhea as most common, predominant adverse events [9, 16, 17]. Besides that, in our cohort of patients, the therapy with lenvatinib did not statistically influence the Child-Pugh class during the treatment.

We are aware of the shortcoming of this unicentric, retrospective study with a rather small sample size. Further information and real-world data will be obtained by clinical registries that are about to come in the future. Prospective studies on further sequential therapies in second or third line will probably never be conducted due to impaired liver function and the small therapeutic window in these patients. The therapeutic setting will be further mainly influenced by the development of immune checkpoint inhibitors and the introduction of combination therapies [18].

CONCLUSIONS

Taken together, our data does not support the use of lenvatinib in patients with liver cirrhosis and severely impaired liver function. Nevertheless, patients with compensated liver cirrhosis Child-Pugh B can be treated with caution, especially Child-Pugh B with 7-8 points. Doing so, shorter survival rates but also heterogeneity of this group of patients has to be taken into consideration.

Lenvatinib is similarly tolerated in patients with liver insufficiency Child-Pugh A and Child-Pugh B, but patients with less impaired liver function (Child-Pugh A) have a better survival benefit.

Conflicts of interest: K.W. received support for scientific presentations and scientific advisory activities by: Abbvie Germany, Bristol-Myers Squibb, Falk Foundation, Gilead Sciences, GMP Orphan, Intercept, MSD Sharp&Dohme, Roche Pharma. A.K. received fees for scientific presentations and scientific advisory activities by Roche Pharma AG, Eisai GmbH, Abbvie Germany AG, Janssen-Cilag GmbH, Boston Scientific Corp. L.-S.C and M.M-S. none to declare.

Authors’ contributions: L.-S.C., A.K. conceived and designed the study, analyzed the data. L.-S.C. collected the data and wrote the draft. A.K., K.W., M.M.-S. revised the manuscript. All the authors approved the final version to be published and agreed to be accountable for all aspects of the work.

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