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ORIGINAL ARTICLE

Adherence to ursodeoxycholic acid therapy in patients with cholestatic and autoimmune liver disease

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KEYWORDS
Attitude to health;
Behavioral medicine;
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Summary
Background: Ursodeoxycholic acid (UDCA) is used for treatment of cholestatic liver diseases and may improve long-term outcome. Although treatment with this hydrophilic bile acid is virtually without side effects, medication adherence might be suboptimal due to patient misconceptions, compromising clinical outcome. Our aim was to evaluate adherence to UDCA in relation to patient beliefs about medicine and to identify potential predictors of poor adherence.
Methods: Prospective open-label study recruiting patients in treatment with UDCA from April 2016 to March 2017. Adherence was assessed both by the Sensemedic dispenser and by patient-reported adherence, during 12 weeks. Good adherence was defined as $\geq$ 80% intake. Quality of life (by SF-36) and beliefs about medicine (by BMQ) were also assessed.
Results: A total of 75 patients were enrolled (32% primary biliary cholangitis, 31% autoimmune hepatitis, 29% primary sclerosing cholangitis and 8% other conditions). Average adherence according to the medication dispenser was 92 $\pm$ 16% (range: 17—100). Eighty-nine percent of the patients exhibited good adherence and 11% poor adherence. According to the BMQ, 42% of all patients were accepting, 50% ambivalent, 8% indifferent and 0% skeptical to UDCA treatment. Poor adherence was associated with young age ($P = 0.029$) and male gender ($P = 0.021$).

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Conclusions: Despite the excellent safety profile of UDCA, still a significant number of patients are poorly adherent. Young age and male sex are associated with poor adherence. Efforts should be made to identify patients with poor adherence and to improve their compliance to therapy.

UDCA	ursodeoxycholic acid
PBC	primary biliary cholangitis
PSC	primary sclerosing cholangitis
SF-36	36-item Short-Form General Health Survey
BMQ	Beliefs about Medicines Questionnaire

Introduction

Ursodexycholic acid (UDCA) is a hydrophilic bile acid that is often used for the treatment of cholestatic liver diseases. In primary biliary cholangitis (PBC), UDCA improves serum liver biochemistry, may delay disease progression to severe fibrosis or cirrhosis, and may prolong transplant-free as well as overall survival [1]. Biochemical response to UDCA predicts long-term outcome [2]. For primary sclerosing cholangitis (PSC), evidence that shows long-term benefit of ursodeoxycholic acid is unclear and its use remains controversial [3]. Similarly, adjunctive UDCA therapy may improve liver biochemistry in patients with problematic autoimmune hepatitis, but long-term beneficial effects of this approach are unclear [4]. Beneficial effects of UDCA have also been reported in intrahepatic cholestasis of pregnancy, cystic fibrosis, progressive familial intrahepatic cholestasis type III, and chronic graft-versus-host disease [5].

It has been demonstrated that adherence could affect response to treatment in some chronic diseases such as hypertension or human immunodeficiency virus (HIV) infection [6—9]. Poor adherence to long-term treatment, especially in asymptomatic patients, is a frequent phenomenon and adherence tends to decrease over time. For example, among patients with new diagnosis of hypertension, adherence to anti-hypertensive medications after 1 year was 78% and 46% after 4-5 years [10]. For hypercholesterolemia, adherence rates after 6 months and 3 years of statins for secondary prevention of cardiovascular disease were 71% and 45%, respectively, while for primary prevention this was 65% and 35%, respectively [11]. In hepatitis B patients on nucleot(s)ide analogues [12] and in hepatitis C patients on ribavirin containing therapy [13], poor adherence is less frequent (15% and 6%, respectively), but may lead to increased risk of treatment failure.

Several methods are used to measure adherence such as pharmacy refill claims or patients self-report. Nevertheless, pharmacy claims provide only a gross estimation of adherence, whereas patient-self-reported and especially physician-reported adherence rates are well known to overestimate adherence considerably [14]. In contrast, real time medication intake monitoring is the most reliable new methodology currently available to assess patient adherence. Currently, no studies have investigated adherence to UDCA. The aim of this study was to evaluate adherence to UDCA treatment in patient with cholestatic and autoimmune liver disease both with real time medication monitoring and patient-reported adherence and to identify potential predictors of poor adherence.

Patients and methods

Study design and population

During the study period, from April 2016 to March 2017, all consecutive patients meeting the inclusion criteria and without exclusion criteria visiting the outpatient hepatology clinic of the University Medical Center Utrecht were asked to participate. Inclusion criteria were:

- currently receiving or about to start UDCA;
- willing to participate in the study.

Age below 18 years, poor understanding of Dutch language and inability to provide written informed consent were the exclusion criteria. This study was allowed by the local Medical Ethical Committee and conducted in accordance with the guidelines of the Declaration of Helsinki and the principles of Good Clinical Practice. All patients gave written informed consent.

After written informed consent, patients received a Sensemedic medication dispenser that monitored medication intake during 12 weeks. Presence or absence of symptoms (currently or in the past) related to the disease was recorded. Patients were also asked to fill in the following questionnaires: the Short-Form 36 (SF-36) [15], the Beliefs about Medicine Questionnaire (BMQ) [16,17] and the patient-reported adherence questionnaire, both at the beginning and at the end of the 12-weeks study period. At both visits, routine laboratory tests including alkaline phosphatase (ALP), bilirubin, gamma glutamyl transferase (γGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, prothrombin time (PT), INR, full blood count and creatinine were performed. Sociodemographic characteristics (age, gender, ethnicity), medical history (comorbidities, fibrosis stages), co-medications and data on UCDA treatment (duration and dose of therapy) were gathered from patients' electronic records. Adverse events were specified both at baseline and at the end of the study. To assess the severity of adverse events we used the Common Terminology Criteria for Adverse Events (CTCAE) scale

from grade 1 (mild symptoms) to 5 (death related to adverse events) [18].

Sensemedic dispenser

The Sensemedic medication dispenser (Evalan, Amsterdam, The Netherlands) monitors medication intake real time. The patient stores the medication in the dispenser, which sends a brief wireless message through the GSM network to a server each time it is opened. This message contains information about the time of the medication event and the identification number of the dispenser. The data is collected in a central database and can be made available through a secure Internet account to authorized persons, including the investigators. Sensemedic can remind patients through SMS text messaging (sent if the patient forgets the medication) in order to enhance medication adherence. This reminder function was not activated in the current study and there was no intervention by the study team when the patient did not open the dispenser to minimize any influence of the dispenser on adherence. Based on UDCA dosing interval (at discretion of the patient and agreed at baseline to be fixed during the study period), the patient could open the dispenser 1 to 3 times daily. In case of no opening of the Sensemedic dispenser on a study day, this was classified as missed intake and registered as 0% adherence for that day. In case of expected multiple daily dosing, adherence was corrected accordingly by any registered medication events (e.g. if the dispenser was opened once in case of expected 3 doses/day, adherence of 33% that day was assumed).

Questionnaires

The baseline and 12 weeks-end of the study questionnaires contained questions on quality of life, on patients' beliefs about medicine and on self-reported adherence. Quality of life was assessed using the validated medical outcomes study 36-item Short-Form General Health Survey (SF-36) [15]. The SF-36 is composed of 36 questions, and contains four domains in the area of physical health and four domains in the area of mental health. There are eight subscales which include: physical functioning, role physical, body pain, general health, energy/fatigue, social functioning, role emotional and emotional well-being. The mental component summary (MCS) and the physical component summary (PCS) can be computed with the scores of the eight subscales. The Scores range from 0 (lowest) to 100 (highest). A higher score generally indicates better health. The Beliefs about Medicines Questionnaire (BMQ) [16,17] consists of two sections. The BMQ-General assesses, with the aid of two 4-item scores, beliefs about the harmfulness and overuse of medicine in general. The ''BMQ Specific'' comprises two 5-item scores (necessity and concerns) assessing patients' beliefs about the necessity of a prescribed medication (UDCA in our case) for controlling their illness and their concerns about the potential adverse consequences of taking it. Examples of items from the necessity scale include ''My health at present depends on this medicine'', while an example item from the concerns scale includes ''I sometimes worry about becoming too dependent on this medicine.'' Respondents indicate their degree of agreement with each individual statement on a 5-points Likert scale, ranging from strongly disagree (1) to strongly agree (5). A mean score for each subscale is computed by dividing total scores for that scale by the number of items in the scale, giving a mean score range of 1–5 for both the Necessity Scale and the Concerns Scales. The scores can be interpreted in two ways: as a continuous scale where higher scores indicate stronger beliefs or by dichotomizing at the scale midpoint (2.5). The score can be used to categorize study participants into four attitudinal groups based on their beliefs about medicine: ''accepting'' (i.e. high necessity, low concerns), ''ambivalent'' (i.e. high necessity, high concerns), ''indifferent'' (i.e. low necessity, low concerns) and ''skeptical'' (i.e. low necessity, high concerns). ''Indifferent'' and ''skeptical'' attitudes have been reported to predict poor medication adherence in inflammatory bowel disease and depressive disorders [19,20].

Self-reported adherence was based on a personal patients' evaluation with the aid of Visual Analog Score (VAS) of how well they took their medication and expressed as a percentage at both baseline visit and at the end of the study visit. In addition, the treating physician was asked to categorize the patients, based on the cut-off of 80%, in one of three subgroups:

- poorly adherent;
- well adherent;
- uncertain, based on treating physician impression of the patient.

Statistics analysis: results are given as mean ± SD for variables with normal distribution, and otherwise as median and range. The primary endpoint of the study was the adherence to UDCA as measured by the Sensemedic dispenser during the 12 weeks' study period. Adherence was expressed as percentage and calculated using the formula: No. of expected doses − No. of missed doses)/No. of expected doses. Patients were subdivided into two groups (good adherence vs. poor adherence) using a cut-off of 80% adherence [21]. Baseline characteristics of both groups were compared using the Chi^2 test for dichotomous variables and the *t*-test or Mann–Whitney U test for continuous variables. IBM SPSS Statistics, version 20.0.0 (IBM, Armonk, New York, United States) was used for statistical analysis. Since we had not a priori information on expected adherence on UDCA therapy, we could not perform a formal power analysis. Based on experience in other hepatological patient groups with adherence according to the Sensemedic device [12,13], we included 75 patients in the study. A two-sided *P*-value < 0.05 was considered statistically significant.

Results

We asked 78 consecutive patients meeting the inclusion criteria and without exclusion criteria to participate and three of these refused to be included. A total of 75 patients were thus enrolled in the study. Baseline characteristics are given in Table 1. Primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH) were the most frequent indications for treatment with UDCA. Other diagnoses included cystic fibrosis, sarcoidosis,

Table 1 Clinical characteristics of 75 patients treated with ursodeoxycholic acid.

Female gender	54 (72%)
Age	52 ± 16 (53, 18—91)
Body weight kg	75 ± 14 (74, 47—111)
Cirrhosis	22 (29%)
Child-Pugh A	20 (92%)
B	1 (4%)
C	1 (4%)
Diagnosis	
Primary biliary cholangitis	24 (32%)
Primary sclerosing cholangitis	22 (29%)
Autoimmune hepatitis	23 (31%)
Others	6 (8%)
Years since diagnosis	9 (0—31)
No. of patients with ≥ 1 comorbidities	59 (79%)
No. of patients with psychiatric illness	6 (8%)
No. of patients with concomitant medications ≥ 1	65 (87%)
No. of concomitant medications	3 (1—14)
Duration of UDCA (months)	84 (0—276)
No. of patients on UDCA ≥ 1 year	63 (84%)
UDCA dose (mg/kg)	
≤ 10	12 (16%)
10 < × ≤ 15	50 (67%)
15 < × ≤ 20	11 (14%)
> 20	2 (3%)
Intake moments/day	
1	51 (68%)
2	18 (24%)
3	6 (8%)

Categorical variables are given as number (%) and continuous variables as mean ± SD and/or median (range).

Table 2 Baseline laboratory test results of 75 patients treated with ursodeoxycholic acid.

Total bilirubin (μmol/L)	17 ± 23 (11, 5—155)
ALP (U/L)	181 ± 139 (138, 47—700)
GGT (U/L)	136 ± 174 (73, 11—770)
AST (U/L)	50 ± 34 (36, 19—170)
ALT (U/L)	52 ± 51 (33, 5—279)
Albumin (g/L)	41 ± 6 (42, 6—50)
Platelet count (× 10^9/L)	233 ± 99 (227, 28—508)
Prothrombin time	14 ± 2 (13, 12—29)

Results are given as mean ± SD and/or median (range); ALP: alkaline phosphatase; GGT: γ-glutamyl transferase; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

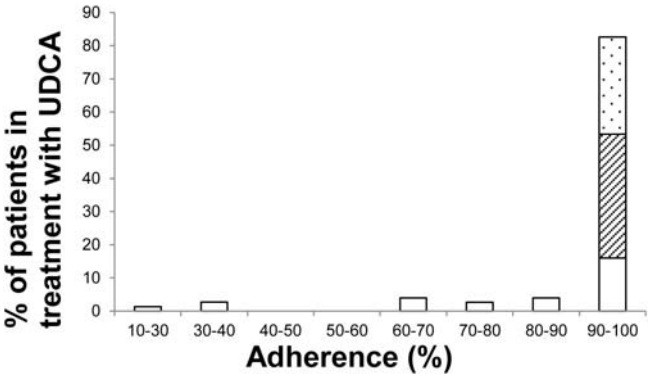

Figure 1 Medication adherence according to Sensemedic dispenser in 75 patients during 12 weeks of treatment with ursodeoxycholic acid. The bar indicating 90—100% adherence is divided into a white open part (90—94% adherence: 16% of all patients), a part with slanting stripes (95—99% adherence: 37%) and a part with dots (100% adherence: 29%). UDCA: ursodeoxycholic acid.

biliary pancreatitis, choledocholithiasis, progressive familial intrahepatic cholestasis (PFIC) type III and low-phospholipid-associated cholelithiasis (LPAC). The majority of the patients were female. Almost all patients came from the Netherlands and had been treated with UDCA since more than a year. Of the 22 cirrhotic patients, 20 (92%) had a well-compensated cirrhosis (Child-Pugh Score A). 21 patients (28%) had symptoms or signs of the disease (including, fatigue, pruritus, jaundice) during the study period. Fifty-four patients (72%) were previously or currently asymptomatic. The number of patients with psychiatric comorbidities was low (6 patients, 8%), generally with depression. Baseline blood test results are given in Table 2.

Adherence

During the 12 weeks' study period, the average adherence according to the Sensemedic medication dispenser was 92 ± 16% (median 98%: range 17—100%: Fig. 1). According to the 80% cut-off based on the dispenser, 67 patients (89%) had good adherence, while 8 (11%) were poorly adherent. The mean self-reported adherence at baseline visit, was 95 ± 13% (median 100%: range 10—100%) and 93 ± 13% (median 99: range 30—100) at the end of the study. In the subgroup of 8 patients with poor adherence, the adherence according to the dispenser and the patients-reported adherence were (for each individual patient) 35% and 50%, 63% and 90%, 65% and 80%, 68% and 100%, 76% and 80%, 79% and 80%, 17% and 10%, and 30% and 0%, respectively. The treating physician categorized 56 patients (75%) in the good adherence group, 4 patients (5%) in the poor adherence group and 14 patients (19%) in the uncertain group (data on a patient not available).

Questionnaires

SF-36 and BMQ scores at baseline visit are given in Table 3. In the SF-36, mental health summary was higher than the Physical Health Summary, suggesting that the disease especially impacts physical activities. One patient did not fill in the specific part of the BMQ questionnaire. In the remaining patients, according to the BMQ questionnaire, 65% of them believed that, in general, doctors prescribe too many medications, while 41% believed that this could be harmful. The BMQ specific questionnaire indicated that 42% of all patients were accepting, 50% ambivalent and 8% indifferent,

Table 3 Baseline social characteristics, quality of life and attitude to medications in 75 patients in treatment with ursodeoxycholic acid.

Quality of life (SF-36) score	
Physical functioning	79 ± 20
Social functioning	75 ± 27
Role functioning/physical	63 ± 44
Role functioning/emotional	79 ± 36
Emotional well-being	77 ± 18
Energy/fatigue	57 ± 22
Body pain	75 ± 24
General health	50 ± 21
Physical health summary	66 ± 21
Mental health summary	72 ± 21
Beliefs about Medicine Questionnaire (BMQ) *n* of patients	
General harm[a]	31 (41%)
General overuse[a]	49 (65%)
Specific attitude towards UDCA	
Accepting	31 (42%)
Ambivalent	37 (50%)
Indifferent	6 (8%)
Skeptical	0 (0%)
Country of origin	
The Netherlands	68 (91%)
Other European country	2 (3%)
Non-European country	5 (6%)
Marital status	
Single	12 (16%)
Married/in a relationship	53 (71%)
Divorced	4 (5%)
Widow(er)	6 (8%)
Employment status	
Student	3 (4%)
Paid employee	42 (56%)
Retired	12 (16%)
Disabled	6 (8%)
Household	5 (7%)
Volunteer	4 (5%)
Searching for a job	2 (3%)
Rentier	1 (1%)
If employee	
Mean number hours/week	33 ± 12

Categorical variables are given as number (%) and continuous variables as mean ± SD. NL: the Netherlands; EU: European country; non-EU: non-European country; UDCA: ursodeoxycholic acid; SF-36: study 36-item Short-Form General Health Survey; BMQ: Beliefs about Medicines Questionnaire.

[a] Patients with an average score > 2.5 on the subscale.

as far as UDCA use was concerned. No patient was classified as skeptical to UDCA. So, of all patients, 92% had a strong belief that UDCA is highly necessary for their health, but at the same time 50% were worried about the possibility to become addicted to this medication and/or to experience adverse events. Both SF-36 and BMQ questionnaires were not significantly different at baseline and (results not given) after 12 weeks.

Predictors of poor adherence

In Table 4, the subgroups with good vs poor adherence are compared. We found an association between age and poor adherence. In particular, younger age appeared associated with poor adherence ($P = 0.029$). Also being male was associated with poor adherence ($P = 0.021$). The type and stage of the disease, the number of comorbidities and co-medications, whether the patient was (previously or currently) symptomatic or not, the number of daily UDCA pills, the duration of treatment and whether side effects were perceived or not, were not different between both subgroups. Of note, diarrhea (the most frequent side effect: in 14% of patients) was according the patients' own definition, without formal criteria, and may well have been only once daily loose stools. Also, socio-economic status and personal attitude towards UDCA did not differ between both subgroups. SF-36 mental health summary and BMQ general overuse tended to be higher in the subgroup with good adherence, and physician estimation of adherence had some merit to identify poor adherence, but differences between good adherence and poor adherence groups for these items failed to reach statistical significance (Table 4).

Discussion

In this study we assessed adherence to UDCA treatment in 75 consecutive patients with cholestatic liver diseases, using real-time medication monitoring and patient-reported adherence. Our main finding is that 11% of the patients treated with UDCA exhibited poor adherence according to the Sensemedic dispenser. Real time medication intake monitoring such as performed in the current study, is probably the most reliable tool available to assess adherence. This approach has also the advantage to improve adherence through SMS text messages, if the patient forgets to take the medication [22,23]. In the current study, we did not use the SMS reminder option to avoid potential influence on adherence during the study period. Although patient-reported adherence is less precise, this approach may be valuable in clinical practice, when real time medication intake monitoring is generally not available. In the current study, 6 of 8 patients with poor adherence (75%) were correctly identified by patient-reported adherence (considering the Sensemedic dispenser as gold standard). Also, physician estimation of poor adherence appears to have some merit: 3 of 8 patients with poor adherence according to the dispenser were thought by the treating physician to be certainly or possibly poorly adherent (Table 4). Nevertheless, sensitivity of physician estimation appears low. Most important is that the physician discusses the issue of adherence routinely during outpatient clinic visits, with the right approach (e.g. avoiding to ask ''whether the medication is taken well'' (the answer will always be ''yes''), but instead to ask ''whether the patient ever forgets to take the medication'' (thus giving the patient the opportunity for an honest answer without losing his self-esteem). UDCA has an excellent safety profile and it is associated with, at most, mild side effects (notably, loose stools) and has few interactions with other drugs [24]. Nevertheless, according to the results of the BMQ questionnaire, 50% of all patients are worried

Table 4 Comparison of clinical and medication characteristics in patients with good or bad adherence, according to the cut-off of 80%, during 12 weeks of ursodeoxycholic acid treatment.

	Adherence ≥ 80%($n = 67$)	Adherence ≤ 80% ($n = 8$)	*P*-value
Male gender	16 (24%)	5 (62%)	0.021
Marital status: married	48 (72%)	5 (62%)	0.591
Country of origin: NL vs. EU vs. non-EU	61 (91%)—2 (3%)—4 (6%)	7 (88%)—0 (0%)—1 (12%)	0.703
Presence of cirrhosis	20 (30%)	2 (25%)	0.776
Any comorbidities	53 (79%)	6 (75%)	0.789
Any medications	58 (87%)	7 (87%)	0.942
UDCA ≥ 1 year	57 (85%)	6 (75%)	0.463
Alcohol use	25 (37%)	2 (25%)	0.493
Age (years)	53 ± 16	41 ± 10	0.029
Diseases			0.882
Primary biliary cholangitis	22 (33%)	2 (25%)	
Primary sclerosing cholangitis	19 (28%)	3 (38%)	
Autoimmune hepatitis	21 (31%)	2 (25%)	
Others	5 (8%)	1 (12%)	
Laboratory results			
Total Bilirubin (μmol/L)	15 ± 17	30 ± 51	0.093
ALP (U/L)	175 ± 134	227 ± 183	0.322
GGT (U/L)	130 ± 159	187 ± 277	0.380
AST (U/L)	50 ± 34	53 ± 35	0.834
ALT (U/L)	52 ± 52	49 ± 39	0.884
Diarrhea	9 (14%)	0 (0%)	0.316
Side effects score[a]	2 ± 4	1 ± 2	0.335
SF-36_physical health	66 ± 22	66 ± 18	0.999
SF-36_mental health	73 ± 21	59 ± 22	0.081
BMQ general harm[a]	29 (43%)	2 (25%)	0.321
BMQ general overuse[a]	46 (61%)	3 (28%)	0.080
BMQ specific attitude[b]			0.576
Accepting	29 (44%)	2 (25%)	
Ambivalent	32 (48%)	5 (63%)	
Indifferent	5 (8%)	1 (12%)	
Skeptical	0%	0%	
Intake moments			0.675
1	45 (67%)	6 (74%)	
2	17 (25)	1 (13%)	
3	5 (8%)	1 (13%)	
Treatment indication			0.790
Primary prophylaxis	14 (21%)	1 (12%)	
Previous symptoms	34 (51%)	5 (63%)	
Current symptoms	19 (28%)	2 (25%)	
Physician estimation[c]			0.073
Good adherence	51 (76%)	5 (63%)	
Bad adherence	2 (3%)	2 (25%)	
Doubtful	13 (19%)	1 (12%)	
Not personally known	1 (2%)	0	

Results are given as number (%) and mean ± SD; NL, the Netherlands; EU: European country; non-EU: non-European country; UDCA: ursodeoxycholic acid; ALP: alkaline phosphatase; GGT: γ-glutamyl transferase; SF-36: study 36-item Short-Form General Health Survey; BMQ: Beliefs about Medicines Questionnaire. Calculated by sum up the Score of each side effect.

[a] Patients with an average score > 2.5 on the subscale.

[b] One patients not fill in the BMQ specific part.

[c] One patient not well known by the physician.

about adverse events due to UDCA and to become addicted to this drug. In other chronic diseases it has been shown that indifferent or skeptical attitudes towards medication are important predictors of non-adherence [19,20,25,26]. Poor adherence seems to occur less frequently in patients on UDCA treatment than in patients with other chronic (asymptomatic) diseases. For example, adherence rates after 6 months and 3 year of statins for secondary prevention of cardiovascular disease were 71% and 45%, respectively, while for primary prevention this was 65% and 35%, respectively

[11]. Similar results were obtained for anti-hypertensive medication, with adherence rates of 78% after 1 year and 46% after 4.5 years [10]. In our study, we found no clear association between presence/absence of disease-related symptoms (currently or in the past) or perceived side effects and adherence. Of note, poor adherence was associated with younger age, which is in line with some other chronic conditions such as HIV [27] and HBV [28]. Also, being male was associated with poor adherence. No other demographic or treatment-related predictors of non-adherence could be identified.

Our study has some limitations such as the relatively limited number of included patients Therefore, we are cautious to not to draw final conclusions on magnitude of the non-adherence problem. Also, subgroup analysis could be prone to type II errors. Also, the study period was relatively short. Medication intake monitored for 12 weeks may, in theory, not be indicative of adherence changes over long time periods. Furthermore, although the cut-off of 80% is often used to distinguish subgroups with good adherence vs poor adherence [21], this cut-off is rather arbitrary. Another possible limitation of our study could be that adherence rates may have been influenced by participation in a study and by the use of the medication dispenser. One would intuitively expect, that if there would be any influence of study participation, adherence would be improved during the study period, with worse adherence in real-life setting, thus emphasizing the importance of adherence in clinical practice. Furthermore, one could hypothesize that opening of the medication dispenser is no guarantee for medication intake by the patient. In addition, absence of a signal indicating opening of the dispenser does not have to indicate non-adherence. However, it has been shown that mismatches between electronic detection of opening of the medication dispenser and actual dosing are rare [29,30].

Conclusion

The majority of our patients exhibited good adherence to UDCA therapy, but there is still a significant number of patients, which are poorly adherent. Efforts to improve adherence should be made. Physicians could spend more time and pay more attention to explain the tolerability and safety profile of UDCA treatment. Additional tools such as electronic devices with SMS text messaging, if necessary, could further improve adherence.

Authors' contribution

M.C.L., L.A., F.I.L., J.vdB., K.vE. contributed to study conception and design, acquisition of data, final interpretation of data, drafting and revising of the article and final approval.

J.dB., J.A. contributed to study conception and design, drafting and revising of the article and final approval.

C.vE. contributed to the study conception and design, final interpretation of data, drafting and revising of the article and final approval.

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Disclosure of interest

The authors declare that they have no competing interest.

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