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A Special Terpene Combination (Rowatinex®) Improves Stone Clearance after Extracorporeal Shockwave Lithotripsy in Urolithiasis Patients: Results of a Placebo-Controlled Randomised Controlled Trial

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Key Words
Extracorporeal shockwave lithotripsy · Urolithiasis · Kidney stones · Terpenes · Rowatinex®

Abstract
Objective: To investigate the safety and efficacy of a special terpene combination in the treatment of patients with urolithiasis after extracorporeal shockwave lithotripsy (ESWL). ***Patients and Methods:*** 222 patients with clinically stable kidney or ureter stones of 0.3–2.0 cm undergoing complication-free ESWL were randomised to receive a special terpene combination (Rowatinex®; 3 × 2 capsules/day) or placebo. The study consisted of a 12-week active treatment phase and a 2-week follow-up phase. All patients had a physical examination, and diagnosis of kidney stones was made by X-ray, intravenous pyelogram or ultrasound at weeks 1, 4, 8 and 12 as well as after 2 weeks of follow-up. Stone-free status was defined as obviously successful expulsion of calculi/fragments, being without any stone. ***Results:*** In all, when compared to placebo, significantly more patients receiving the terpene combination treatment in the intent-to-treat (ITT) group [72 (67.9%) vs. 49 (50.0%); p = 0.0009] and the per-protocol (PP) group [69 (78.4%) vs. 48 (52.2%); p = 0.0004] were stone-free at the end of the study. Treatment with the terpene combination was also more effective when analysed with respect to the size of the treated stone. In addition, treatment with the terpene combination significantly reduced the median time to stone-free status from 85.0 to 56.0 days (p = 0.0061) and from 85.0 to 49.5 days (p = 0.0028) in the ITT and PP populations, respectively. Nine mild-to-moderate adverse events (AE; terpene combination group: 7 AE in 4 patients; placebo group: 2 AE in 2 patients) were assessed as drug-related. ***Conclusions:*** Treatment with the terpene combination is well tolerated and safe. The terpene combination was found to be an efficacious treatment in eliminating calculi fragments generated by ESWL as compared to placebo. The pharmacodynamic properties of the terpene combination (antilithogenic, antibacterial, antiinflammatory, spasmolytic and analgesic effects), which have been also confirmed in preclinical studies, represent a valuable alternative to the different drugs used in the treatment of urolithiasis.

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Introduction

Urolithiasis is a common condition which affects approximately 5–12% of the population worldwide [1–3]. At present, extracorporeal shockwave lithotripsy (ESWL) is the first-choice treatment for most renal stones, and success rates of more than 90% have been reported [4–6]. Interpretation of results is complicated by variable definitions of success in lithotripsy [4]. The current understanding is that stone-free should mean exactly that, and should not include those patients with asymptomatic (clinically insignificant residual stone) fragments less than 4 mm in size [7, 8]. Lithotripsy remains the treatment of choice for the majority of calculi, both renal and ureteral, although adjunctive procedures may be required for complex stones [4].

The therapeutic use of the special terpene combination Rowatinex® (an essential oil preparation composed of 31% pinene, 15% camphene, 10% borneol, 4% anethole, 4% fenchone and 3% cineol in olive oil; developed at the beginning of the second half of the 20th century and a registered drug in over 60 countries) in the supportive treatment of urolithiasis (renal and/or urethral calculi), particularly in conditions with spasm and/or inflammation associated with urolithiasis and for assistance in the expulsion of stones of the renal system, has a 50-year history in more than 60 countries all around the world.

The first clinical and preclinical investigations of Rowatinex date back as early as 1954 and 1956, respectively [9]. Since then, expulsion of stones and preventive effects on stone formation were observed as results of Rowatinex treatment in animal models of nephrocalcinosis [9–11], and it was shown also in the clinical studies and in postmarketing reports.

The aim of this multicentre, randomised, double-blind, therapeutic, parallel group trial was to demonstrate the superiority of Rowatinex over placebo with respect to the status of stone-free patients during 12 weeks of treatment after ESWL.

Patients and Methods

This multicentre, placebo-controlled outpatient study was designed according to the European Association of Urology guidance [12] on active removal of stones in the kidney or the ureter by ESWL. The ESWL was performed with a Dornier Compact Delta (Wessling, Germany). In addition, the study was performed in accordance with Hungarian laws and approved by Országos Gyógyszerészeti Intézet (National Institute of Pharmacy) regulations, with the guidelines of the International Conference on Harmonisation (Good Clinical Practise), and the guidelines of the Declaration of Helsinki (2000). The Independent Ethics Committees of the participating hospitals approved the study design, and the participating patients gave their informed consent.

The study evaluated the safety and efficacy of the terpene combination Rowatinex (3 × 2 capsules/day) in patients with clinically stable kidney or ureter stone(s). Inclusion criteria were complication-free ESWL indicated by complication-free calculus, no urinary deviation, diameter of calculus smaller than or equal to 20 mm, no previous endourological intervention (e.g. nephrostoma, endosplint) before ESWL, no urinary tract obstruction, no severe untreated associated other disease, age older than 18 years, and signed informed consent. Patients were excluded if a kidney stone with complication (e.g. severe colic, anuria or severe infection of the urinary tract), pregnancy or lactation or allergy to the terpene combination or other components of Rowatinex were assessed.

The patients were treated by one and the same investigator at each centre with the treatment strategy to reach disintegration of the calculus with 3,500 impulses/shock waves or less if the stone totally disintegrated earlier. The endpoint of ESWL was to reach fragments with 4-mm or smaller size. A repeat ESWL was done in case of no spontaneous stone elimination.

Aside from analgesics (usual medication: metamizol 500 mg tablets) and spasmolytics (drotaverine HCl 40 mg injection or tablets) as needed, no other concomitant treatment of residual stones after ESWL was foreseen or permitted. If applicable, the doses of analgesics or spasmolytics were recorded in the case report form (CRF).

The primary endpoint of the study was the total elimination of the fragments of calculi generated by ESWL after 3 months of treatment (rate of stone-free patients). The stone-free status was determined by X-ray of the kidney, ureter and bladder and ultrasound. Based on these findings, and considering there was no dilatation in the urinary tract, the patient was declared symptom-free.

The study consisted of a screening phase, a 12-week active treatment phase and a 2-week follow-up phase. Following the screening phase, subjects eligible for the study who had signed the informed consent were enrolled in the 12-week active treatment phase in a randomised manner. In all, 223 patients with clinically stable kidney stones were screened at 6 centres between June 26, 2003, and December 1, 2006. As 1 patient withdrew informed consent prior to the start of treatment with the study medication, 222 patients were randomised.

All patients had physical and laboratory examinations [haemoglobin, haematocrit, red blood cell count, white blood cell count, platelet count, prothrombin (at screening only), serum calcium, blood glucose, uric acid, serum bilirubin, serum creatinine, alkaline phosphatase, aspartate amino transferase, alanine amino transferase], and urinalysis (pH, white blood cell count, red blood cell count, urine culture) and a urinary pregnancy test were performed at screening and at the follow-up visit in females of child-bearing potential. Diagnosis of kidney stones was made by X-ray of the kidney, ureter and bladder with the X-ray equipment available in the hospital, intravenous pyelogram (only at baseline) with expositions 10 and 20 min after the administration of contrast liquid and/or ultrasound with a 3.5-MHz abdominal head. The patients were questioned about their previous medical history and concomitant medications.

The administration of the terpene combination Rowatinex (manufacturer: ROWA Pharmaceuticals Ltd., Bantry, Ireland) or placebo started at the first day of the trial after ESWL in the morning. The patients were instructed to take 3 × 2 capsules per day before meals, drink 2.5 litres of liquid to achieve standard hydration and to record dates of missed doses.

In addition, the patients were instructed to return all used and unused medication boxes and blisters at each visit as compliance was assessed by capsule count. Non-compliance was defined as taking less than 80% or more than 120% of the study medication during any outpatient evaluation period (visit to visit). Discontinuation for non-compliance was at the investigator's discretion, and was noted in the CRF. A patient was considered as having completed the study when he/she completed the week 14 visit.

At each visit the patient was asked if he/she had experienced any problems since the last visit. All adverse events (AE) were recorded in standard medical terminology on CRF. For all AE, the investigator pursued and obtained information adequate both to determine the outcome of the AE and to assess whether it met the criteria for a serious AE requiring immediate notification. Follow-up of the AE, even after the date of therapy discontinuation, was conducted if the AE persisted until the event had resolved or stabilised at a level acceptable to the investigator. The intensity of the AE was characterised as mild, moderate or severe, and the relationship to or association with the study medication in causing or contributing to the AE was characterised as unrelated, unlikely, possible, probable or highly probable.

Randomisation lists were generated centrally by the biometrical department at Rowa Pharmaceuticals Ltd., Bantry, Ireland, using the random number function of a Sharp Scientific Calculator; study medications were assigned to individual patient numbers. The study medication was delivered in blocks to the sites. At baseline, patient numbers were sequentially assigned to newly included patients by the investigators in an ascending order.

The safety-analysable population (safety population) consisted of all randomised patients who had safety data after the first dose of study drug. Note that if a patient had no AE, this defined a safety statement. The intent-to-treat (ITT) population consisted of all randomised patients with at least 1 postrandomisation (on-drug) efficacy evaluation. Patients who were stone-free after ESWL were excluded from the ITT population and any other populations to evaluate efficacy. The per-protocol (PP) population consisted of all patients of the ITT population who completed the study without major protocol violations. Protocol deviations were defined and assessed prior to unblinding in a blind data review. The evaluable population for the primary efficacy analysis in this study was the ITT population. Additional analyses in the PP or PP completer set population have been performed to evaluate the robustness of the effects which had been observed in the ITT population.

The numbers of patients with or without residual stones were compared between both treatment groups by Fisher's exact test. Continuous data were compared by two-sample Wilcoxon or t tests, further categorical data by χ^2 contingency tests or logistic regression models, fitting terms for treatment group and centre. Time to stone-free status was compared between the 2 treatment groups using Kaplan-Meier life table analysis with the log rank statistics. In addition, ESWL complications (haematuria, fever, pyelonephritis, occlusion, haematoma) and clinical symptoms (headache, vertigo, nausea, vomiting, eruption) specified in the CRF were compared descriptively.

Results

Patient Characteristics

The safety population consisted of 222 randomised patients who were treated with at least 1 dose of study medication. For 1 additional patient no postbaseline values were available because of discontinuation of the study at day 1. There were 15 patients stone-free already at the baseline visit. In addition, 1 patient had no postbaseline efficacy values due to discontinuation of the study at day 1, and 2 further patients were excluded as they had no postbaseline efficacy values after ESWL. Thus, these 18 patients were excluded from the ITT population. In the ITT population, 98 (89.1%) of the patients receiving placebo and 106 (94.6%) of the patients receiving the terpene combination were evaluable for efficacy.

There were 24 patients in the ITT population (6 patients receiving placebo and 18 patients receiving the terpene combination) that were excluded from the PP population because they dropped out before visit 5 (week 12) with no stone-free status. The PP population, therefore, consisted of 180 patients with 92 patients in the placebo group and 88 patients in the terpene combination group.

The demographic and other baseline characteristics displayed for the ITT population are given in table 1. In both treatment groups there were slightly more men (placebo: 54.1%; terpene combination: 58.5%) than women. The subjects in the terpene combination group were slightly older on average than those from the placebo group, but the difference was not significant. For 13 patients in the placebo group (13.3%) and 16 patients in the terpene combination group (15.1%), drug allergies were reported. No differences in vital signs between the treatment groups could be found at baseline. The same statement can be made for the other relevant populations.

In addition, medical history data at baseline showed that due to the initial disease, the most frequently mentioned medical histories were renal, urinary and reproductive system disorders. As regards the occurrence of previous stones and their chemical composition, no previous stones were reported by 57.5% of the patients in the terpene combination group and by 42.9% in the placebo group. The chemical composition was not known for most of the patients with previous stones.

Stone Characteristics and Treatment Parameters

The kidney side affected by treated stones was slightly more frequently the right (55.9%) than the left (44.6%). The distribution of positions was fairly similar in both treatment groups, even if a slightly higher rate of occur-

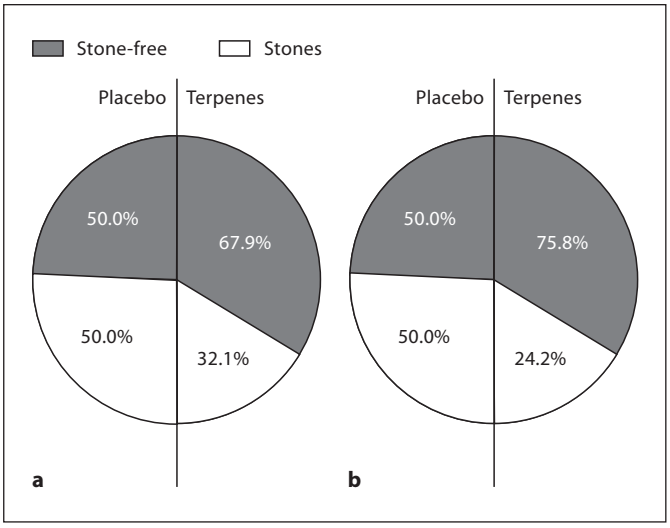

Fig. 1. Rate of patients with stone-free status within 12 weeks after ESWL in the ITT (**a**) and PP completer set populations (**b**).

rence in the lower calyx was observed for the terpene combination group. In summary, the highest number of patients had treated stones in the lower calyx (about 20%) (table 1). Ureteral stones in the ITT population were present at screening in 19 (17.9%) and 15 (15.3%) of the patients in the verum and the placebo group, respectively.

No difference in the size of treated stones was observed between both treatment groups (table 1). This is also true for the largest stone size after ESWL, i.e. at day 1, where the residual stone measurement by ultrasound revealed a median of 5.0 mm (range: 2–34 mm) and 4.0 mm (range: 2–24 mm) and a mean ± SD of 6.2 ± 5.1 mm and 5.5 ± 4.2 mm for the patients receiving placebo and the terpene combination, respectively.

Overall, there were slightly less real numbers of shockwaves in the terpene combination group when compared to the placebo group (2,968 ± 708.4 vs. 3,068 ± 646.8). Consequently, there were no significant differences between both treatment groups with respect to the number of ESWL treatments ($p = 0.9719$, Student's t test) and maximum intensity of ESWL ($p = 0.5740$, Student's t test). In addition, a higher rate of patients receiving placebo was treated with ESWL under anaesthesia (24.5 vs. 17.0%).

In the ITT population, treatment compliance was 92.8 ± 15.1% (range: 24.4–142.9%) and 98.2 ± 57.6% (range: 24.7–666.7%) in the patients receiving placebo and the terpene combination, respectively. Overall, treatment compliance was considered to be very good.

Table 1. Demographic, baseline and treated stone characteristics (ITT population)

	Placebo	Terpene combination	Total
Demographic data			
Gender			
Male	53 (54.1)	62 (58.5)	115 (56.4)
Female	45 (45.9)	44 (41.5)	89 (43.6)
Total	98	106	204
Age, years			
Median	48	51.0	50
Range	18–78	18–82	18–82
Characteristics of treated stones (ITT)			
Right side	59 (60.2)	55 (51.9)	114 (55.9)
Position			
Upper calyx	7 (7.1)	5 (4.7)	12 (5.9)
Lower calyx	19 (19.4)	26 (24.5)	45 (22.1)
Middle calyx	14 (14.3)	11 (10.4)	25 (12.3)
Pyelum-PU passage	10 (10.2)	9 (8.5)	19 (9.3)
Size, mm			
Median	8.0	7.0	8.0
Range	3–20	3–19	3–20
Left side	40 (40.8)	51 (48.1)	91 (44.6)
Position			
Upper calyx	7 (7.1)	7 (6.6)	14 (6.9)
Lower calyx	16 (16.3)	24 (22.6)	40 (19.6)
Middle calyx	9 (9.2)	7 (6.6)	16 (7.8)
Pyelum-PU passage	4 (4.1)	8 (7.5)	12 (5.9)
Size, mm			
Median	6.5	6.5	6.5
Range	3–20	2–17	2–20

The table shows the numbers and percentages (in parentheses) of patients/stones in each group and in total. The chemical composition was only known for 44 patients. PU = Proximal ureter.

Efficacy

At the end of the double-blind study period (i.e. at week 12), significantly more patients receiving the terpene combination in the ITT and the PP populations were stone-free when compared to the placebo group (fig. 1).

In table 2 the cumulative numbers of stone-free patients in the placebo and the terpene combination groups are given for the ITT, PP and PP-completer set population. It can be seen that the rates of stone-free patients were significantly higher ($p = 0.0009$, $p < 0.0001$ and $p = 0.0004$, respectively) in the terpene combination group compared to the placebo group (see all 3 populations).

Survival distribution function analyses revealed that the terpene combination significantly reduced the me-

Table 2. Number of stone-free patients (cumulative)

ITT	Placebo			Terpene combination		
	ITT (n = 98)	PP (n = 92)	PP (CS) (n = 74)	ITT (n = 106)	PP (n = 88)	PP (CS) (n = 66)
Day 1–week 1	14 (14.3)	14 (15.6)	9 (12.2)	22 (20.8)	21 (23.9)	15 (22.7)
Day 1–week 4	29 (29.6)	28 (30.4)	19 (25.7)	47 (44.3)	44 (50.0)	28 (42.4)
Day 1–week 8	42 (42.9)	41 (44.6)	31 (41.9)	59 (55.7)	56 (63.6)	39 (59.1)
Day 1–week 12	49 (50.0)	48 (52.2)	37 (50.0)	72 (67.9)	69 (78.4)	50 (75.8)
Day 1–week 14	53 (54.1)	52 (56.5)	41 (55.4)	76 (71.7)	72 (81.8)	53 (80.3)

Values in parentheses denote percentages. CS = Completer set.

Table 3. Number of stone-free patients stratified by size and position of treated stone (ITT/PP)

Size	Placebo		Terpene combination	
	ITT (n = 98)	PP (n = 92)	ITT (n = 106)	PP (n = 88)
≤8 mm	35 (55.6)	35 (57.4)	55 (73.3)	53 (82.8)
>8 mm	14 (40.0)	13 (41.9)	16 (53.3)	15 (65.2)
Total	49 (50.0)	48 (52.2)	71 (67.6)	68 (78.1)

Number and percentage (in parentheses) of patients in each treatment group stratified by size or position.

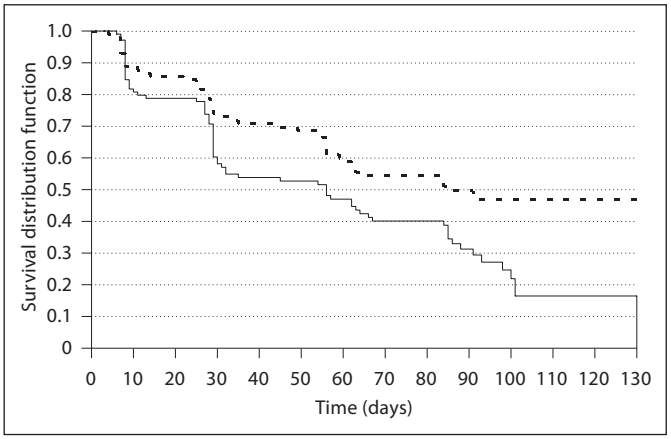

Fig. 2. Survival distribution functions of the PP population. Dashed line: placebo; solid line: terpene combination group (log rank test: p = 0.0028).

dian time to stone-free status from 85.0 to 56.0 days (log rank test: p = 0.0061) and from 85.0 to 49.5 days (log rank test: p = 0.0028) in the ITT and PP populations, respectively (fig. 2).

The terpene combination was more effective when analysed with respect to the size of the treated stone (table 3). In both subgroups (≤8 or >8 mm), an efficacy of the terpene combination was demonstrated even more pronouncedly in the PP group (table 3). In addition, the terpene combination seemed to be more effective in stones in the upper and lower left and right calyx.

Pain Measured by Visual Analogue Scale

The analysis of the course of pain during the study showed that pain at baseline was very mild and statistically not significantly different when comparing the terpene combination to placebo (ITT: 2.1 ± 2.6 vs. 2.1 ± 2.3). Due to this floor effect, no differences between the 2 treatments could be detected.

Adverse Events

In the terpene combination group, 25 AE [of which 3 (2.7%) were classified as serious] were reported in 15 patients (13.4%), and in the placebo group, 27 AE [of which 1 (0.9%) was classified as serious] were reported in 12 patients (10.9%). Seven mild-to-moderate AE occurring in 4 patients (3.6%) were assessed as drug-related in the terpene combination group [diarrhoea (n = 3), nausea, vomiting, headache, vertigo], and 2 mild AE [diarrhoea (n = 2)] in 2 patients (1.8%) of the placebo group.

The serious AE were deep vein thrombosis (vascular disorders), nephrolithiasis (renal and urinary disorders) and pyelonephritis (infections and infestations) in the terpene combination group, and 1 case of renal colic (renal and urinary disorders) in the placebo group. All events except the case of pyelonephritis were assessed as

Table 4. Number of ESWL-independent complications during the treatment phase

	Placebo		Terpene combination	
	ITT (n = 98)	PP (n = 92)	ITT (n = 106)	PP (n = 88)
Headache	2	2	3	2
Vertigo	1	1	2	1
Nausea	4	4	5	3
Vomiting	2	2	3	3
Eruption	1	1	–	–
Other	6	6	4	3
Sum	8	8	10	7

severe. The case of renal colic was reported as 'unlikely' to be related to the study drug; all other serious AE were documented as 'not' related to the study drug. The deep vein thrombosis and the case of nephrolithiasis were reasons for premature discontinuation of the trial. In conclusion, the tolerability of Rowatinex was excellent. Only 2 and 3 patients in the placebo and the terpene combination groups in the ITT population (PP: 2 vs. 1) experienced ESWL complications, respectively. Observed ESWL complications were haematuria, fever, pyelonephritis and occlusions. See table 4 for ESWL-independent complications during the treatment phase.

Discussion

The therapeutic efficacy of ESWL in the treatment of urinary stones is generally accepted and success rates of more than 90% have been reported [4, 13, 14]. However, the evaluation of the results of ESWL – usually assessed as the rate of stone-free patients – depends on the initial size, consistency and location of the stone, the history of urolithiasis, the presence of pyuria before ESWL, the fragment size after ESWL and the spontaneous clearance rate for fragments after ESWL [7].

ESWL had revolutionised the treatment of kidney stones. Regarding the outcome of the ESWL, the shockwave rate is to be considered appropriately. Improved ESWL efficiency occurs at slower shockwave rates [14]. Explanations for this phenomenon include decreased acoustic impedance mismatch, improved production of cavitation bubbles and improved bubble dynamics [14]. In the present study, the modal number of ESWL was higher in the terpene combination group, and fewer patients receiving the terpene combination were treated at a lower ESWL intensity when compared to the placebo group. Despite favouring placebo where a lower ESWL intensity may have increased the rate of stone-free patients, a significantly greater success was observed in the patients treated with the terpene combination.

The so-called clinically insignificant residual fragments have the potential to cause obstruction and are important risk factors for stone recurrence and regrowth. Secondary procedures are advised to be applied selectively to those patients who have significant symptoms of obstruction associated with the residual stone [8]. El-Nahas et al. [13] determined the predictors of clinical outcome of residual fragments after ESWL in 99 male and 55 female patients (mean age: 43.1 years), with residual fragments of $\leq$5 mm, for >3 months after ESWL for renal stones. Stone-free status, regrowth of fragments and persistence of fragments of the same size were present in 21 (13.6%), 52 (33.8%) and 81 (52.6%) of the patients, respectively. Significant independent predictors of a clinically significant outcome were fragment size of $\geq$4 mm and history of recurrent stone disease ($p < 0.001$). According to the authors, the term 'clinically insignificant residual fragments' is not appropriate for all patients with post-ESWL fragments as 48.7% of the patients in their study had fragments that became clinically significant. In addition, the authors concluded that fragments of 4–5 mm and recurrent stone disease predict clinical significance [13]. They confirmed earlier findings by Khaitan et al. [15], who revealed an about 50% rate of previously 'insignificant' residual stones becoming clinically significant with one more complication.

Therefore, it is important to define stone-free status as really stone-free and not to include clinically 'insignificant' residual stones of $\leq$4 mm. Obviously, stone size or surface determines also the rate of immediate complications after ESWL leading to surgical measures in the follow-up treatment. The median size at baseline in the present terpene study was between 6.5 and 8.0 mm, which corresponds to rather small fragments after ESWL.

The terpene combination was statistically superior to placebo, with a difference of 17.9% in the rate of patients with stone-free status in the ITT population (67.9% in the terpene combination group vs. 50% in the placebo group). Based on this difference, the number needed to treat was 5.6, which is clinically relevant. The more favourable efficacy of the terpene combination was even more pronounced in the PP population, with 26.12% more responders and a clinically highly significant number

needed to treat of 3.8. From the Kaplan-Meier analyses, the median time for patients to become stone-free was 56 days in the terpene combination group and 85 days in the placebo group. This difference of approximately 1 month was statistically significant ($p = 0.0061$). The analysis of the numbers of stone-free patients with an initial size of the treated stone of ≤ 8 or >8 mm showed no difference in efficacy of the terpene combination, which was clearly superior compared to placebo in both subgroups, but more pronouncedly so in patients with smaller stones at baseline.

The results with the terpene combination in the present study are in line with those of a previous open, non-controlled prospective study evaluating whether the terpene combination (Rowatinex capsules; Rowa Pharmaceuticals Ltd.) facilitates the elimination of stone fragments or debris generated by ESWL. Out of 50 patients (28 men, 22 females; age range: 22–80 years; average age: 44 years), 30 (60%) and 41 (82%) of the patients on day 14 and on day 28, respectively, became stone-free. On day 28, 2 patients (4%) had small stone fragments without any symptoms, and 7 patients (14%) had retained residual stones that were either >5 mm in size or caused complaints. The fate of the stones was monitored by X-ray examination and ultrasound scan and the dilatation of the urinary tract was assessed by ultrasound technique as a measure of the magnitude of the problem of passage [16].

In addition, a benefit of the terpene combination Rowatinex over placebo was already demonstrated in one prospective, randomised, double-blind, placebo-controlled study in patients with ureterolithiasis [17], from which a subset of data had been published in advance [18]. The goal of the study by Engelstein et al. [17] was to assess the value of Rowatinex in both spontaneous expulsion of ureteral stones and/or disappearance of pretreatment dilatation of the collecting system, indicating stone expulsion. For this purpose, a total of 87 patients suffering from acute renal colic caused by ureterolithiasis were studied. The patients were reported to be prospectively and double-blindly randomised to receive either the terpene combination (n = 43; age: 26–74 years) or placebo (n = 44; age: 26–75 years), 4 capsules 4 times a day. Intramuscular injections of 75 mg diclofenac, 30 mg pentazocine or pethidine HCl (1 mg/kg bodyweight) were used for pain management. A significantly greater average stone diameter at baseline was noted in the terpene combination group compared to the placebo group (4 vs. 2.6 mm; $p = 0.015$). Twenty-six calculi in the terpene combination group and 20 in the placebo group were expelled ($0.01 > p > 0.001$) and 9 ureteral dilatations disappeared following terpene treatment compared to 6 in the placebo group ($0.05 > p > 0.025$). The terpene combination group showed an overall higher success rate than the placebo group (81 vs. 59%; $0.025 > p > 0.01$), and despite the larger average diameter of calculi, the overall stone expulsion rate was significantly higher in the terpene combination group. It was considered that early treatment with Rowatinex for patients with ureteral stones is indicated before other more aggressive measures are considered. The efficacy of the terpene combination Rowatinex in the alleviation of symptoms associated with nephrolithiasis/urolithiasis had previously also been described in open studies [19, 20].

These early findings on the clinical efficacy of the terpene combination in a wide variety of symptoms associated with illnesses of the kidney and the urinary tract collecting system rely on the antilithogenic, antibacterial, antiinflammatory, spasmolytic and analgesic activities of the special terpene combination of Rowatinex, which have been confirmed in preclinical experiments. These preclinical studies demonstrated primary pharmacodynamic effects with a consistent picture of the inhibition of stone formation [9–11, 21, 22]. The findings of an antilithogenic influence on renal oxalate lithogenesis are of particular importance since most of the renal or ureteral stones are composed of calcium oxalate aggregates and, therefore, inhibition of stone formation originating from clinically insignificant residual stones generated by ESWL might increase the long-term success rate of ESWL. In addition, Rowatinex showed antibacterial effects against a variety of pathogens (i.e. *Bacillus subtilis, Escherichia coli, Proteus vulgaris, Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus faecalis, Enterococcus, Salmonella* Typhi, *Saccharomyces cerevisiae 2*) [23–25].

The spasmolytic activities of Rowatinex and of its single terpenes like camphene, 1,8-cineole and borneol were seen with the classical methods for showing antispasmodic efficiency in smooth muscle preparations (intestine, bladder, aorta) of guinea pigs, cats and rabbits [26], and correspond to the findings in toxicity studies representing effects like vasodilatation and hyperaemic status [9]. Together with the antiinflammatory and analgesic properties (i.e. by 1,8-cineole, anethole [27, 28]) the pharmacodynamic spectrum of the special terpene combination of Rowatinex mirrors the clinically important pathophysiological changes in patients with nephro-/urolithiasis with spasm, inflammation, pain and infection, especially if it is considered that the excreted terpene

glucuronides are still active, impeding further complications in the ureter and lower urinary tract. In summary, the properties of Rowatinex represent a valuable drug used in the pro- and metaphylaxis of urolithiasis. In relation to α-blockers (e.g. tamsulosin), which have shown to support the stone expulsion especially of ureteral stones with a diameter of >5 mm [29], the advantages versus control in the rate of stone-free patients and time to stone-free status are comparable. However, since Rowatinex has spasmolytic and antiinflammatory properties, it is more similar to the combination of α-blocker and corticosteroid.

Overall this is the first randomised, double-blind, placebo-controlled multicentre study demonstrating the superiority of the terpene combination as compared to placebo with respect to the rate of stone-free patients and the time to stone-free status during 12 weeks of treatment after ESWL. Treatment with the terpene combination was well tolerated and safe; furthermore, the therapy with Rowatinex was cheap since the daily costs were about EUR 0.8 for the daily dose of 3 × 2 capsules. The terpene combination was found to be an efficacious treatment in eliminating calculi fragments generated by ESWL as compared to placebo.

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