Supplemental Table 1: Recovery after each treatment period. The parameters were measured just before the treatment, at the end of the preceding washout treatment (WO-pre-tt) and after a 6-week washout post-treatment period (WO post-tt). Full recovery was obtained for the three treatments.

		Indomethacin			**Eplerenone**			**Amiloride**		
		WO pre-tt	WO post-tt	*P-value*[a]	WO pre-tt	WO post-tt	*P-value*[a]	WO pre-tt	WO post-tt	*P-value*[a]
PLASMA										
Sodium	mmol/L	139 ± 1	139 ± 1	*0.2822*	140 ± 2	139 ± 1.5	*0.2000*	140 ± 1.5	139 ± 2	*0.4183*
Potassium	mmol/L	2.8 ± 0.4	2.8 ± 0.4	*0.9057*	2.8 ± 0.4	2.8 ± 0.3	*0.8764*	2.8 ± 0.4	2.8 ± 0.4	*0.7957*
Magnesium	mmol/L	0.55 ± 0.08	0.55 ± 0.08	*0.7851*	0.55 ± 0.08	0.55 ± 0.09	*0.9824*	0.55 ± 0.08	0.55 ± 0.07	*0.8944*
Renin	mU/L	82 [62;109]	82 [62;109]	*0.4716*	78 [59;105]	80 [60 ;106]	*0.9472*	86 [64;117]	82 [62;109]	*0.8655*
Aldosterone	pg/mL	54 [40;73]	54 [40;73]	*0.7917*	54 [39;73]	57 [40;81]	*1.0000*	61 [44;85]	60 [43;85]	*0.8953*
URINE										
Sodium	mmol/24h	160 [123;208]	165 [136;200]	*0.8526*	185 [161;213]	171 [131;224]	*0.8926*	183 [155;214]	170 [145;199]	*0.4836*
Potassium	mmol/24h	106 [91;124]	103 [88;121]	*0.6761*	114 [99;132]	110 [95;127]	*0.9620*	111 [97;128]	104 [91;119]	*0.6455*
Magnesium	mmol/24h	1.5 [1.0;2.1]	1.3 [0.9;1.9]	*0.6875*	1.3 [0.9;2.0]	1.9 [1.3;2.8]	*0.1587*	1.8 [1.3;2.6]	1.4 [0.9;2.2]	*0.5219*
Creatinine	mmol/24h	10.3 [9.0;11.8]	10.2 [8.7;12.0]	*0.8164*	10.9 [9.8;12.2]	11.0 [9.8;12.4]	*0.9683*	11.0 [9.8;12.4]	10.6 [9.5;12.0]	*0.6098*

a : pre-treatment vs. post-treatment washout periods.

Supplemental Table 2. Genetic data obtained in the 33 patients included in the study.

Patient	Sex	Status	Allele 1			Allele 1			References
			Nucleotide	Protein[§]	Exon/ Intron	Nucleotide	Protein[§]	Exon/ Intron	
1	F	Ho[1]	c.625C>T	p.Arg209Trp	5	c.625C>T	p.Arg209Trp	5	1
2	F	Ho[1]	c.625C>T	p.Arg209Trp	5	c.625C>T	p.Arg209Trp	5	1
3	F	Ho[2]	c.3077C>T	p.Thr1026Ile	26	c.3077C>T	p.Thr1026Ile	26	2
4	M	CH	c.947G>T	p.Gly316Val	7	c.2191G>A	p.Gly731Arg	18	3/4
5	F	CH	c.947G>T	p.Gly316Val	7	c.2191G>A	p.Gly731Arg	18	3/4
6	F	CH	c.1195C>T	p.Arg399Cys	10	c.2221G>A	p.Gly741Arg	18	2/1
7[$]	*F*	*CH*	*c.1195C>T*	*p.Arg399Cys*	*10*	*c.2221G>A*	*p.Gly741Arg*	*18*	*2/1*
8	M	CH	c.965C>T	p.Ala322Val	8	c.1946C>T	p.Thr649Met	16	5/6
9	F	CH	c.1805_1806del[3]c.2660+1G>A	p.Tyr602CysfsX31[3] p.? splice defect	14 22	c.2747+1G>A	p.? splice defect	23	7/8/5
10	M	CH	c.2576T>C	p.Leu859Pro	22	c.2581C>T	p.Arg861Cys	22	1/9
11	M	CH	c.1046C>T	p.Pro349Leu	8	c.1-?_964+?del[3]	p.?	1 to 7	1/5
12	M	CH	c.2221G>A	p.Gly741Arg	18	c.2581C>T	p.Arg861Cys	22	1/9
13	F	CH	c.533C>T	p.Ser178Leu	4	c.2221G>A	p.Gly741Arg	18	10/1
14	M[2]	Ho	c.2883+1G>T	p.? splice defect	24	c.2883+1G>T	p.? splice defect	24	1
15	F	CH	c.1143G>A	p.Trp381*	9	c.2981G>A	p.Cys994Tyr	26	5/3
16	F	CH	c.1336-1G>C	p.? splice defect	10	c.2581C>T	p.Arg861Cys	22	5/9
17	F	CH	c.2581C>T	p.Arg861Cys	22	c.1-?_964+?del[3]	p.?	1 to 7	9/5
18	M	CH	c.1046C>T	p.Pro349Leu	8	c.1519C>T	p.Arg507Cys	12	1/5
19[$]	*M*	*CH*	*c.2581C>T*	*p.Arg861Cys*	*22*	*c.2929C>T*	*p.Arg977**	*25*	*9/1*
20	F	CH	c.852+1G>A	p.? splice defect	6	c.1963C>T	p.Arg655Cys	16	New mutation/9
21	F	CH	c.852+1G>A	p.? splice defect	6	c.1963C>T	p.Arg655Cys	16	New mutation /9
22	M	CH	c.911C>T	p.Thr304Met	7	c.2576T>C	p.Leu859Pro	22	5/1
23[$]	*M*	*CH*	*c.1180+1G>T*	*p.? splice defect*	*9*	*c.1763C>T*	*p.Ala588Val*	*14*	*11/1*
24	M	CH	c.2576T>C	p.Leu859Pro	22	c.2993T>G	p.Leu998Arg	26	1/ New mutation
25	F	CH	c.938C>T	p.Ala313Val	7	c.2581C>T	p.Arg861Cys	22	10/9
26	M	Ho[2]	c.2576T>C	p.Leu859Pro	22	c.2576T>C	p.Leu859Pro	22	1
27	F	CH	c.56_57dup	p.Phe20Alafs*8	1	c.1-?_964+?del[3]	p.?	1 to 7	New mutation /5
28	M	CH	c.2581C>T	p.Arg861Cys	22	c.3006G>C	p.Trp1002Cys	26	9/5
29	M	Ho[2]	c.2687G>A	p.Arg896Gln	23	c.2687G>A	p.Arg896Gln	23	12
30	F	Ho[2]	c.2576T>C	p.Leu859Pro	22	c.2576T>C	p.Leu859Pro	22	1
31	M	CH	c.897C>A	p.Asn299Lys	7	c.1568C>T	p.Ala523Val	13	New mutations
32	F	CH	c.1196_1202dup	p.Ser402*	10	c.1881C>G	p.Tyr627*	15	4/5
33	F	Ho[2]	c.938C>T	p.Ala313Val	7	c.938C>T	p.Ala313Val	7	10

M: Male; F: female. [$]Patients included, not randomized**.** [§] Numbering is according to the cDNA sequence (GenBank : NM_000339.2). The A of the ATG of the initiator methionine codon is denoted as nucleotide. Mutations are described using the HGVS recommendations CH: compound heterozygous, Ho : homozygous. [1]Both parents are heterozygous [2] No deletions detected by MLPA [3]Heterozygous deletion detected par MLPA, exon1 to exon 7 deletion without breakpoint characterization. New mutation: not previously published mutation. The

following mutations were previously expressed *in vitro*: p.Arg209Trp, p.Gly741Arg, p.Pro349Leu and p.Thr1026Ile (2) ; p.Gly316Val and p.Ala588Val (13) ; p.Cys994Tyr (14) . The others were predicted to be pathogen in silico.

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Supplemental Table 3: Results of the Short Form (Health Survey (SF36) quality of life self-questionnaire at randomization and at the end of each active treatment period.

	Normal values (*)	Baseline	Indomethacin	Eplerenone	Amiloride
Physical component summary					
Physical functioning	84 ± 21	75 ± 22	70 ± 24	68 ± 21	72 ± 23
Role limitations (physical)	81 ± 32	48 ± 43	58 ± 39	50 ± 44	53 ± 36
Bodily pain	73 ± 24	53 ± 24	62 ± 25	52 ± 25	54+/- 24
General health perception	69 ± 19	45 ± 19	45 ± 20	44 ± 18	44 ± 20
Mental component summary					
Vitality	60 ± 18	37 ± 19	42 ± 22	34 ± 18	41 ± 19
Social functioning	82 ± 21	54 ± 20	65 ± 24	55 ± 28	55 ± 24
Role limitations (emotional)	82 ± 32	64 ± 44	63 ± 42	56 ± 42	59 ± 41
General mental health	68 ± 18	57 ± 15	57 ± 18	54 ± 19	56 ± 17

Physical functioning: Measurement of limitations in physical activities such as walking, climbing stairs, bending forward, lifting and significant and moderate physical effort.

Role limitations because of physical health problem: Measurement of discomfort, due to the physical condition, in daily activities; measurement of limitations in certain activities or difficult to achieve them.

Bodily pain: Measurement of the intensity of the pain and inconvenience.

Vitality: Self-assessment of vitality, energy, fatigue.

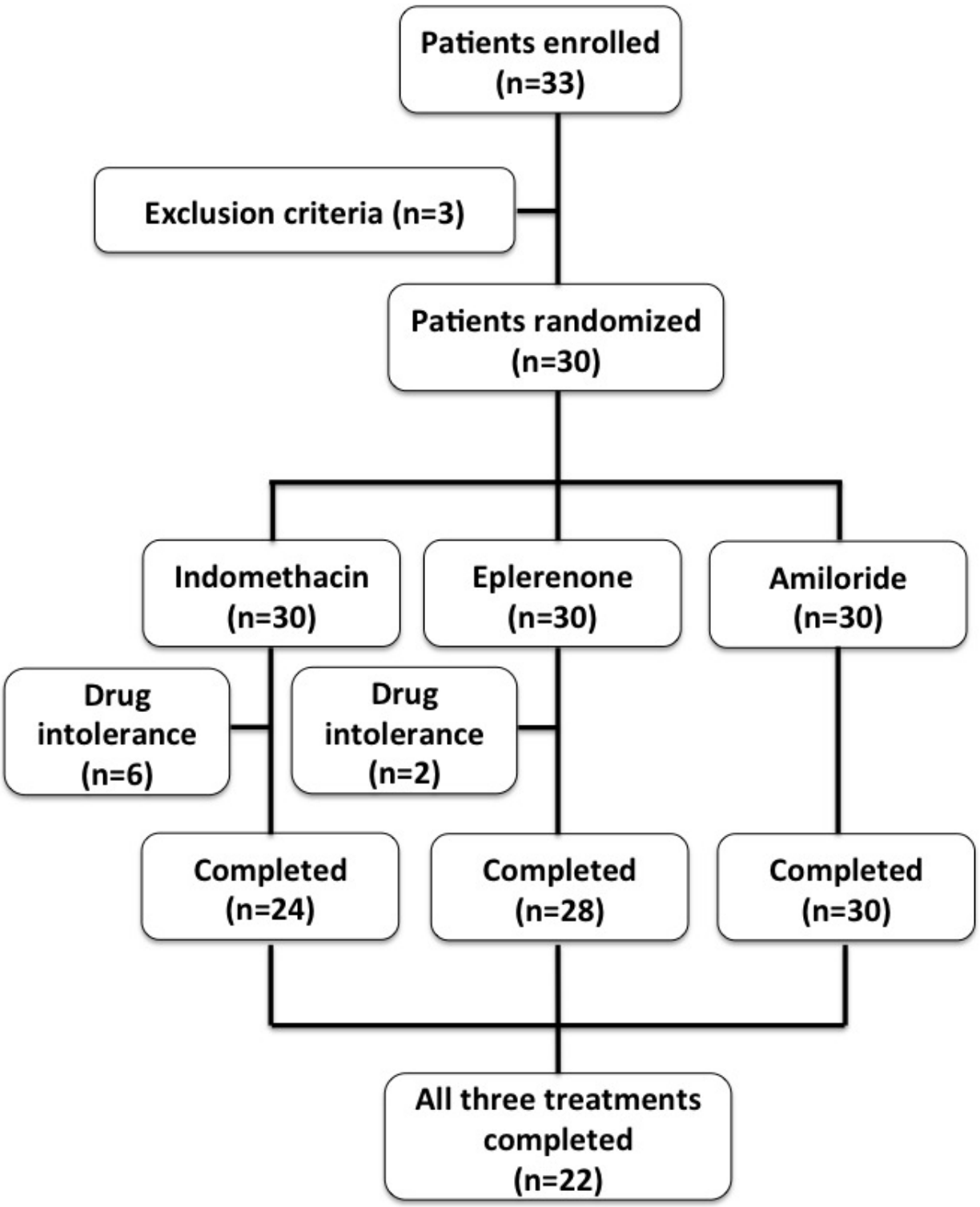
Social functioning: Measurement of limitations in social activities due to physical problems and mental health.

Role limitations because of emotional problems: evaluation of discomfort due to psychological problems in daily activities; time spent on less important work, sloppy work.

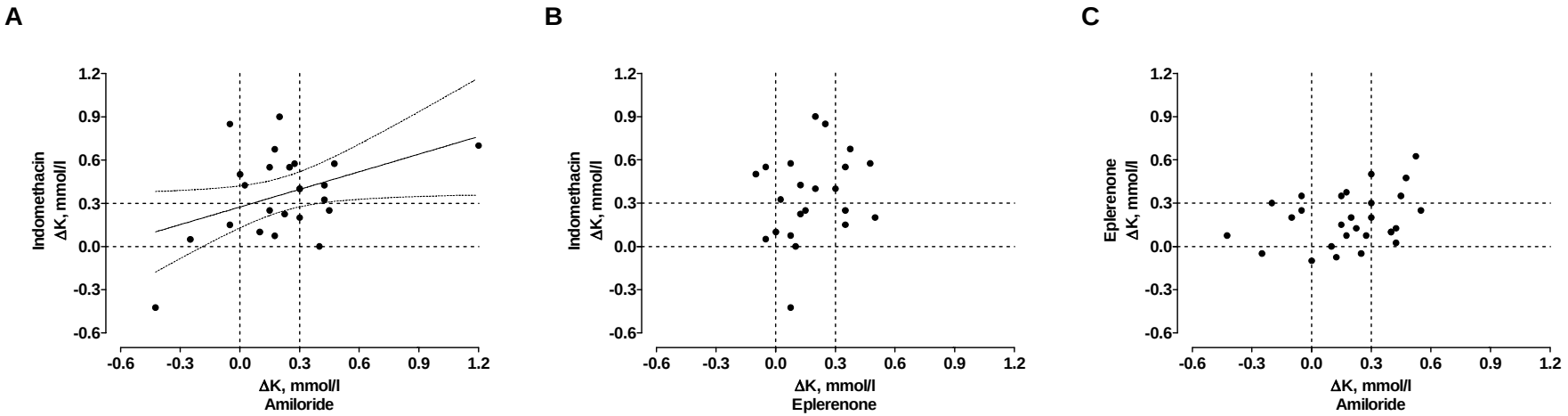
Mental health: Self-rated mental health: anxiety, depression, well-being (happiness?).

(*) Normal values are those available for established in a French population of 209 healthy subjects (Leplege, A, Ecosse, E, Verdier, A, Perneger, TV: The French SF-36 Health Survey: translation, cultural adaptation and preliminary psychometric evaluation. *Journal of clinical epidemiology,* 51**:** 1013-1023, 1998.)

Supplemental Figure 1: Flow chart of the study



Supplemental Figure 2: Correlations between treatment-induced changes in plasma potassium concentration (ΔK mmol/L). The correlation between responses to indomethacin and amiloride was significant (panel A, r^2=0.1713, 0.0444). The correlation between responses to indomethacin and eplerenone (B panel) and between responses to eplerenone and amiloride (C panel) were not significant.



DETAILED METHODS

Participants

Eligible patients were men and women aged 18 to 60 years diagnosed with genetically proven GS at five tertiary French hospitals. Patients had either homozygous (n=8) or compound heterozygous for point mutations or large rearrangements in the *SLC12A3*gene (n=27) (see supplemental Table 2). Exclusion criteria were: known intolerance to the study drugs, significant cardiac arrhythmia, no contraception in women of child bearing potential, pregnancy, or an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2. All patients gave written informed consent before participating in the study. The protocol (ClinicalTrials.gov Identifier: NCT01146197) was approved by the "Comité de Protection des Personnes", Paris-Île de France III, France.

Design of the study

This was a seven-period, three-treatment, open-label, randomized, crossover study with blind end-point evaluation. The initial baseline assessments were performed after a 2- to 6-week washout period to stop any COX inhibitor (2 weeks) or potassium-sparing diuretic (6 weeks) effects. Patients were then randomly assigned to sequentially receive slow release indomethacin, eplerenone or amiloride for 6 weeks each in addition to oral potassium and

magnesium supplementation. Each active period was intercalated with a 6-weeks washout period during which the potassium and magnesium supplementation was maintained.

Slow release indomethacin was given at a dose of 75 mg o.d. for 6 weeks in combination with a proton pump inhibitor (omeprazole 20 mg/day) for gastric protection. This dosage regimen was based on the low indomethacin doses (≈ 1 mg/kg) currently used in Bartter syndrome [16] and preliminary reports in GS. [15]

Amiloride was uptitrated weekly from 10 mg o.d. to 15 mg o.d. and then to the maximum dose of 20 mg o.d. administered for 4 weeks. This dose of 20 mg amiloride has previously been shown to reverse the hydrochlorothiazide-induced hypokalemia and to increase plasma magnesium concentration more effectively than 100 mg spironolactone in healthy volunteers. [17]

Eplerenone was uptitrated weekly from 50 mg o.d. to 100 mg o.d. and then to the maximum dose of 150 mg o.d. administered for 4 weeks. Since eplerenone is ≈75% less potent than spironolactone [18], the selected dose was 150 mg based on the healthy volunteer study mentioned above. [17]. The amiloride and eplerenone doses could be down-titrated if symptomatic hypotension occurred.

The oral potassium and magnesium supplementation doses were adjusted for each patient during the first 6-week washout period to maintain plasma K concentration at either ≥ 2.8 mmol/L or 0.2 to 0.4 mmol/L above their usual plasma K concentration. The mean dose

of slow release potassium chloride was 4.0±1.7 g, and that of magnesium element was 226 ± 77 mg /day. Thereafter, the dose was kept constant throughout the study.

Randomisation

The randomisation sequence was generated by computer without stratification, using randomised blocks of small size and permutation of treatments within each block. Investigators, patients, and research staff were blinded to the randomisation list.

Study evaluations

Biochemical, hormonal, hemodynamic, and safety assessments were performed after each 6-week washout and active treatment periods. Blood was sampled at ≈ 09:00 a.m. in fasting conditions after the patient rested for one hour in a semi-recumbent position. Seated blood pressure (BP) and heart rate (HR) was measured at home with a validated electronic device (OMRON M6®, Omron Co., Kyoto, Japan) as described previously. [19] In addition, we assessed quality of life using the Short Form Health Survey (SF36) self-administered questionnaire adapted for the French population [36] at randomization and the end of each active treatment period.

Laboratory methods

Biochemical and hormone measurements were performed blind to the randomization sequence in a centralized laboratory. Plasma and urinary electrolytes and creatinine were measured as described previously.[20] Estimated GFR was calculated by the

Modification of Diet in Renal Disease(MDRD) formula.[21] Plasma renin and aldosterone concentrations were measured as described previously.[22]

Statistical analysis

The primary objective of the study was to determine whether slow release indomethacin would significantly increase the plasma potassium concentration compared to the control period, defined as the first 6-week period following the 2- to 6-week washout period. Using a within-patient standard deviation (SD) of 0.3 mmol/L, we calculated that 30 patients were needed to detect a 0.3 mmol/L difference in plasma potassium concentration between the indomethacin and control period with 80% power and 5% alpha error for a two-tailed test.The secondary objectives were to compare the potassium- and magnesium-sparing effects as well as the hemodynamic and hormonal effects and tolerability of the three study drugs.

Patients with a clinically significant treatment-induced increase of at least 0.3 mmol/L in plasma potassium concentration were considered as full responders, those with 0.10 to 0.29 mmol/L increases were intermediate responders and those with less than 0.10 mmol/L increases were non responders.

Since eight patients had to stop one of the study drugs for intolerance leading to a missing period for each of these patients (see results), data were analyzed by an ANOVA for a crossover designon the on-treatment population who actually received all three study

drugs (n=22/30).[23] The model included treatment, sequence, and period as fixed effects and subject nested within sequence as the random effect. When the F test was significant (P<0.05), and when there was no period, sequence or carryover effect, paired comparisons were made between treatments by Holm's method.[24] The assumptions of ANOVA (homogeneity of variance and normality) were checked for each variable and natural logarithmic transformation was applied where appropriate. We also performed an analysis restricted to plasma potassium concentration using paired t-tests comparing 6-week on-treatment vs. pre-treament values on all data sets of valid periods of treatments. Correlations were estimated using Pearson coefficients. SAS software version 9.3 (SAS Institute Inc., Cary, NC, US) was used for statistical analyses. Data are expressed as geometric means with 95 % confidence intervals (CI) or medians (interquartile range, IQR) for non-normal parameters and as means ± one SD for normally distributed data. Two-sided P values of <0.05 were considered to be significant.