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ORIGINAL COMMUNICATION

Cholic acid as a treatment for cerebrotendinous xanthomatosis in adults

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Abstract

Cerebrotendineous xanthomatosis (CTX) is an autosomal recessive disorder of bile acids synthesis. Patients may present with a variety of clinical manifestations: bilateral cataract and chronic diarrhea during childhood, then occurrence of neurological debilitating symptoms in adulthood (cognitive decline, motor disorders). Plasma cholestanol is used as a diagnostic marker of CTX, and to monitor the response to the treatment. Current treatment for CTX is chenodeoxycholic acid (CDCA), which was reported to improve and/or stabilize clinical status and decrease levels of plasma cholestanol. Rare published reports have also suggested a potential efficacy of cholic acid (CA) in patients with CTX. In this retrospective Franco-Belgian multicentric study, we collected data from 12 patients treated with CA, evaluating their clinical status, cholestanol levels and adverse effects during the treatment period. The population was divided in two subgroups: treatment-naive (who never had CDCA prior to CA) and non-treatment-naive patients (who had CDCA prior to CA introduction). We found that treatment with CA significantly and strongly reduced cholestanol levels in all patients. Additionally, 10 out of 12 patients clinically improved or stabilized with CA treatment. Worsening was noted in one treatment-naïve patient and one non-treatment-naïve patient, but both patients experienced similar outcomes with CDCA treatment as well. No adverse effects were reported from patients with CA treatment, whereas elevated transaminases were observed in some patients while they were treated with CDCA. In conclusion, these findings suggest that CA may be a suitable alternative treatment for CTX, especially in patients with side effects related to CDCA.

Keywords Cerebrotendineous xanthomatosis · Cholic acid · Cholestanol · Chenodeoxycholic acid

Introduction

Cerebrotendinous xanthomatosis (CTX: OMIM#213700) is a rare disorder of bile acid synthesis with an autosomal recessive inheritance and a prevalence estimated between 1:72,000 and 1:150,000 [1]. CTX may have different clinical manifestations including neonatal cholestasis, chronic diarrhea, bilateral cataract and learning difficulties during childhood, and later occurrence of motor disorders (from cerebellar and/or pyramidal and/or peripheral nerves dysfunctions), cognitive decline, psychosis, epilepsy and tendons xanthomas. Because of its heterogeneous phenotype, CTX is often diagnosed several years after symptom onset [2–4].

27-sterol-α-hydroxylase, a cytochrome P450 encoded by CYP27A1 gene, responsible for cholesterol oxidation and consequent generation of 27-hydroxycholesterol, is defective in CTX [5] leading to a reduced production of bile acids, especially chenodeoxycholic acid (CDCA), and to a lesser extent cholic acid (CA). As CDCA and CA physiologically have a negative feedback on 7-α-hydroxylase, the rate-limiting enzyme of bile acids synthetic pathway, in CTX 7-α-hydroxylase activity is highly enhanced. Consequently, some intermediate compounds of this metabolic pathway, i.e., bile alcohols and cholestanol, pathologically accumulate in tissues (mostly central nervous system, tendons and lens) [6, 7]. Evidence of bile alcohols urinary accumulation and increased plasmatic cholestanol levels are routinely used

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to detect CTX in suspected patients, before confirmatory genetic testing [8, 9].

Currently, the standard of care for CTX is oral bile acid supplementation with CDCA [2]. CDCA was initially preferred to CA as CTX treatment due to more intense reduced synthesis observed in CTX, and strongest negative feedback on 7-α-hydroxylase [10, 11]. Several studies have shown its efficiency in lowering cholestanol levels and stabilizing/improving neurological symptoms in CTX [4, 8], especially if treated early [12].

CA may also be considered as potential treatment for CTX, however, to our best knowledge, only three old clinical studies have investigated the effect of CA in CTX: (1) CA was successfully administered to two children having CTX, with a clinical stabilization/improvement and no side effects reported [7], (2) three adult patients showed, under CA, a clinical stabilization and a normalization of urinary bile alcohols [13], (3) a cohort of adult Dutch CTX patients treated with either CDCA ($n=13$) or CA ($n=8$), showed a similar reduction of serum cholestanol and urinary bile alcohols without a clear clinical improvement in all patients [14]. In this latter study, CA caused less adverse events compared with CDCA (nausea, diarrhea, liver dysfunction). Additionally, CDCA was found responsible for highly elevated transaminases in a neonate with cholestasis due to CTX [15].

Therefore, CA could be a potential therapeutic option for patients with CTX, especially CTX patients with adverse events due to CDCA. To investigate this further, we conducted a retrospective study on adult French and Belgian CTX patients who were treated by CA. We aimed at evaluating tolerance, and clinical and biological efficiency of CA in those patients.

Methods

This was a multicenter retrospective study, conducted in France and Belgium. Adult patients diagnosed with CTX and treated with CA were enrolled. Patients were identified from a French national registry of all individuals receiving CA treatment. The diagnosis of CTX was defined by suggestive clinical and radiological features, high serum cholestanol levels and, when genetic testing was performed, the presence of *CYP27A1* pathogenic variants. In the period between February and November 2018, data were collected from eight centers in France and one in Belgium through reviewing medical records and questionnaires filled in by treating clinicians, concerning demographic data and the following clinical information:

- Modalities of CA prescription (duration of treatment, posology, etc.).
- Cholestanol levels in plasma before and after introduction of CA; the measurements were normalized, as they were dosed in different laboratories with different normal ranges (with 1 equal to the upper limit of normal).
- Liver function tests (AST, ALT, gammaGT, bilirubin) before and under CA treatment (and also under CDCA when available), for which all laboratories had the same normal range.
- Clinical signs of CTX and their evolution under CA. Clinical evolution in patients treated with CA, at last follow-up, was assessed by physician judgement, in which the patient's condition was defined as "better", "stable" or "worse", compared to condition at the time of CA introduction. Subjects who went through surgery for cataract or xanthomas were not considered for this evaluation.

Some patients were treated with CDCA before CA, so we divided our population in two subgroups: the treatment-naive patients ($n=7$), who never had CDCA ($n=5$) or their switch span between CDCA and CA was superior to 100 days ($n=2$); the non-treatment-naive patients ($n=5$), who had CDCA before CA, and the switch span between CDCA and CA was less than 10 days.

A Wilcoxon signed-rank test was used as a statistic test to compare cholestanol levels means before and after CA treatment, and under CDCA versus CA.

Results

Fourteen patients treated with CA were identified for inclusion in this study. Two patients were excluded for lack of data, with 12 patients enrolled (6 males, 11 families) treated for an average of 798 ± 377 days (145–1311) (see individual data in Table 1). All patients initiated CA during or after 2014. Mean age at last follow-up was 45.25 ± 11.8 years and mean age at the time of CTX diagnosis was 32.9 years. All subjects received CA 750 mg/day, except for patients 5 (550 mg/day), 6 (600 mg/day) and 7 (500 mg/day). For all patients who had CDCA before CA except one, the switch for CA was due to CDCA supply difficulties; for patient 7, CDCA was switched to CA due to CDCA adverse events (see below).

In the subgroup of treatment-naïve patients ($n=7$, patients 1, 2, 3, 4, 5, 6, 7), five subjects (patients 1, 4, 5, 6, 7) showed a clinical improvement after introduction of CA, one remained stable (patient 3) and one (patient 2) deteriorated (increased gait difficulties and worsened peripheral neuropathy in nerve conduction study) at the point that, after 830 days of CA, and despite cholestanol normalization, she was switched to CDCA (see in Table 2 the evolution of CTX manifestations under CA for each patient). She continued to

Table 1 Demographic, clinical, biological, and MRI features of our patients

Patients	Sex	Age at diagnosis	Age at last follow-up	Cholestanol before treatment	Genetics	CA dose (mg/day)	Liver function tests under CA (AST/ALT)	MRI cerebellar vacuolation
Treatment-naive patients								
1	M	26	34	6.63	ND	750	N	no
2	F	43	45	12.5	c.193C>T / c.1183C>T	750	N	yes
3	F	29	59	ND	c.845-1G>A / c.845-1G>A	750	N	no
4	M	39	41	19.34	c.1183C>T / c.1477-2delinsCC.p?	750	N	no
5	F	56	58	9.52	ND	550	N	no
6	F	63	66	8.32	ND	600	N	no
7	M	36	39	10.4	c.1183C>T / c.1184+1G>A	500	N	no
Non-treatment-naive patients								
8	F	14	38	6.72	ND	750	N	ND
9	M	18	48	7.44	ND	750	N	ND
10	M	23	53	17.36	ND	750	1,1/1,6*	ND
11	F	31	36	9.15	c.1184+1 G>A / c.1435 C>T	750	N	yes
12	M	17	26	ND	c.1263+1G>A / c.1263+1G>A	750	N	no

Cholestanol and transaminases (normal values < 1) are showed as normalized values

ND not documented, *N* normal

*Already mildly elevated under CDCA

deteriorate after CDCA introduction, needing gastrostomy. In the subgroup of non-treatment-naive patients ($n=5$, patients 8, 9, 10, 11, 12), two were globally stable under CA (patients 8 and 12), two others had worsening behavioral disorders, but improved their gait (patients 9 and 10), one recovered from diarrhea but his gait worsened (patient 11; gait was reported to equally slowly worsen already under CDCA, before CA introduction).

Patients who received a slightly lower dose of CA (patients 5, 6, 7) clearly improved their clinical status nevertheless. Globally, all the patients improved or stabilized under CA, except the only two patients (2 and 11) who had brain MRI images of cerebellar vacuoles. The symptoms more prone to improvement were gait and cognition disorders whereas xanthomes and peripheral neuropathy, on the other hand, did not show variations under treatment. Behavioral disorders were described as "worsened" in patients 9 and 10, although this evaluation was only made by following the subjective impressions of the caregivers.

In treatment-naive patients ($n=7$) a clear and statistically significant reduction in serum levels of cholestanol with CA was observed over time (Fig. 1), from an average of 10.13 ± 5.26 to an average of 1.41 ± 0.99 (mean reduction of 86.08%, $p=0.028$), for a mean duration of treatment of 899 ± 411 days (225–1311). In non-treatment-naive patients ($n=5$), three showed low levels of cholestanol with CDCA (0.68 ± 0.37), which remained stable after switch to CA (0.5 ± 0.02; $p=0.068$), with a mean of 725.67 ± 228.67 days of follow-up (Fig. 2). For one non-treatment-naive patient (patient 11), cholestanol levels were not available under CDCA, but strongly reduced under CA, when compared to cholestanol levels before any treatment (reduction of 94.65% after 1305 days treated by CDCA then 132 days by CA). Patient 12 was not considered for monitoring the effect of CA on plasma cholestanol, because no dosage was performed after the introduction of CA.

No patient reported adverse events with CA treatment. Patient 10 showed a mild elevation of AST and ALT (already present with CDCA), while patient 8 had a normalization of liver function tests with CA, which were slightly elevated with CDCA (Fig. 3). Patient 7, who was switched from CDCA to CA due to persistent elevated transaminases (ALT 4.7N, AST 2N), had normal transaminases under CA.

Discussion

In this population of 12 adult patients affected with CTX, it was determined that CA was able to significantly reduce cholestanol levels in all treatment-naïve patients, and keep cholestanol levels unchanged in patients switched from CDCA in non-treatment-naïve patients, with clinical stabilization or improvement in 10 out of 12 patients.

However, despite the biological efficacy of CA, two correctly treated patients (#2 and #11) worsened nevertheless. Noteworthy, they were the only patients presenting MRI images of cerebellar vacuoles, which have been recently indicated as a marker of poor prognosis in CTX [16].

Table 2 Part 1—treatment-naive patients and part 2—nontreatment-naive patients

Patient ID	1	2	3	4	5	6	7
Age at first treatment	31	43	29	39	56	63	36
Duration of treatment (days)	715	830	71	1004	1311	1311	1129
Modified Rankin Scale: pre-/post-CA	2 / 1	4/5	1/1	3/2	3/2	4/4	4/2
Diarrhea	No more diarrheal episodes			No more diarrheal episodes		1 Loperamide/day → zero	4-6 diarrheal episodes/day → zero
Cataract			P		P	P	P
Cholestasis		S					
Xanthomes							
Cognitive impairment	Improvement of attention troubles	MMSE 15/30 →impossible to test because of the clear worsening of attention deficit dysarthria, dysphasia		MMSE 25/30; FAB: 15/18 → MOCA 27/30; FAB: 17/18			
Behavioral disorders							clear improvement of agressive behavior reported by caregivers
Walking disorders	100 mt: 1min45 → 1min5	Gait disorder but still able to walk → wheelchair needed			Distance walked: 150 mt → 600 mt	Few steps with two canes → improvement in deplacements, standing position assumed with support but without help	no more falls, improvement in walking stability and cerebellar syndrome (able to go back to work)
Neuropathy		EMG: Demyelinating polyneuropathy → axonal loss in lower limbs		E	E	E	S
Epilepsy				EEG: disappearance of theta activity and improvement of background activity			

Patient ID	8	9	10	11	12
Age at first treatment	21	33	38	31	17
Duration of treatment (days)	975	629	543	761	145
Modified Rankin Scale: pre-/post-CA	2 / 2	1 / 1	1 / 1	1/1	1 / 1
Diarrhea				No more diarrheal episodes	
Cataract	E		P	P	P
Cholestasis	S	S	S	S	
Xanthomes			P		
Cognitive impairment					
Behavioral disorders					E
Walking disorders				Cinetic cerebellar syndrome → cinetic and static cerebellar syndrome	
Neuropathy		S	S		S
Epilepsy					

Table 2 (continued)

Clinical evolution of patients treated with CA

Qualitative and quantitative data concerning the clinical evolution under CA are reported in appropriate boxes when possible. Modified Rankin Scale: 0 = no symptom; 1 = no significant disability, able to carry out all usual activities, despite some symptoms; 2 = slight disability, able to look after own affairs without assistance, but unable to carry out all previous activities; 3 = moderate disability, requires some help, but able to walk unassisted; 4 = moderately severe disability, unable to attend to own bodily needs without assistance, and unable to walk unassisted; 5 = severe disability requires constant nursing care and attention, bedridden, incontinent; 6 = dead

Green improvement, yellow stabilization, red worsening, grey symptom not present, pink not evaluable, *E* evolution not known, *S* no data about the presence or not of this symptom, *P* post-surgery, *MMSE* Mini Mental State Examination, *FAB* frontal assessment battery, *MOCA* Montreal Cognitive Assessment

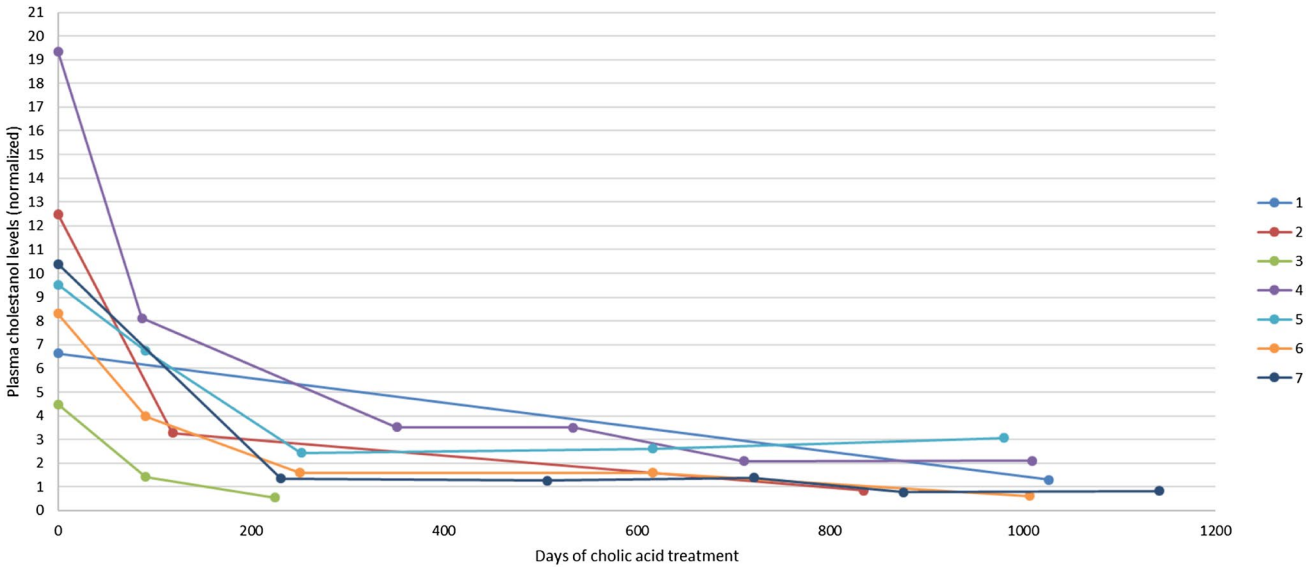

Fig. 1 Plasma cholestanol levels over time in treatment-naïve patients (from #1 to #7) treated with CA

Otherwise, they did not show any other significant clinical or biological difference (such as CA posology, duration of the treatment, clinical features or cholestanol levels in plasma), when compared to good responders to CA treatment. The delay between the onset of neurological symptoms and the first administration of the treatment (which is known to be another marker of poor prognosis) was not strictly analyzed in our patients, due to lack of data. Furthermore, as previously reported, this study confirmed that there is no strict correlation between plasma cholestanol levels and neurological symptoms evolutions in CTX [17, 18].

Those two patients who neurologically worsened under CA showed a similar trend of decline with CDCA, administered either before (patient 11) or after (patient 2) CA, suggesting that patients who do not respond to CDCA are unlikely to respond to CA, and vice versa. However, interestingly, patient 11, despite its global clinical aggravation, clearly improved diarrhea under CA, which was not the case with CDCA.

Except for these two patients (#2 and #11), all the other patients, treatment-naïve or not, stabilized or clearly improved under CA, advocating for the capability of CA to have the same positive effects as those already demonstrated by CDCA.

CA seems to be a potential safe and well-tolerated treatment, with no adverse events reported so far in literature [7, 13–15, 19] and in the current study, whereas CDCA can be the source of persistently elevated transaminases. However, definitive conclusions about compared adverse events between CA and CDCA need much more observational data, as only sporadic cases of CTX patients treated with CA have been published so far.

In conclusion, current data support the possible importance of CA as an alternative treatment for CTX patients taking CDCA that develop related adverse events. Further studies could be useful to confirm potential efficacy and safety of CA treatment in CTX, especially compared to CDCA.

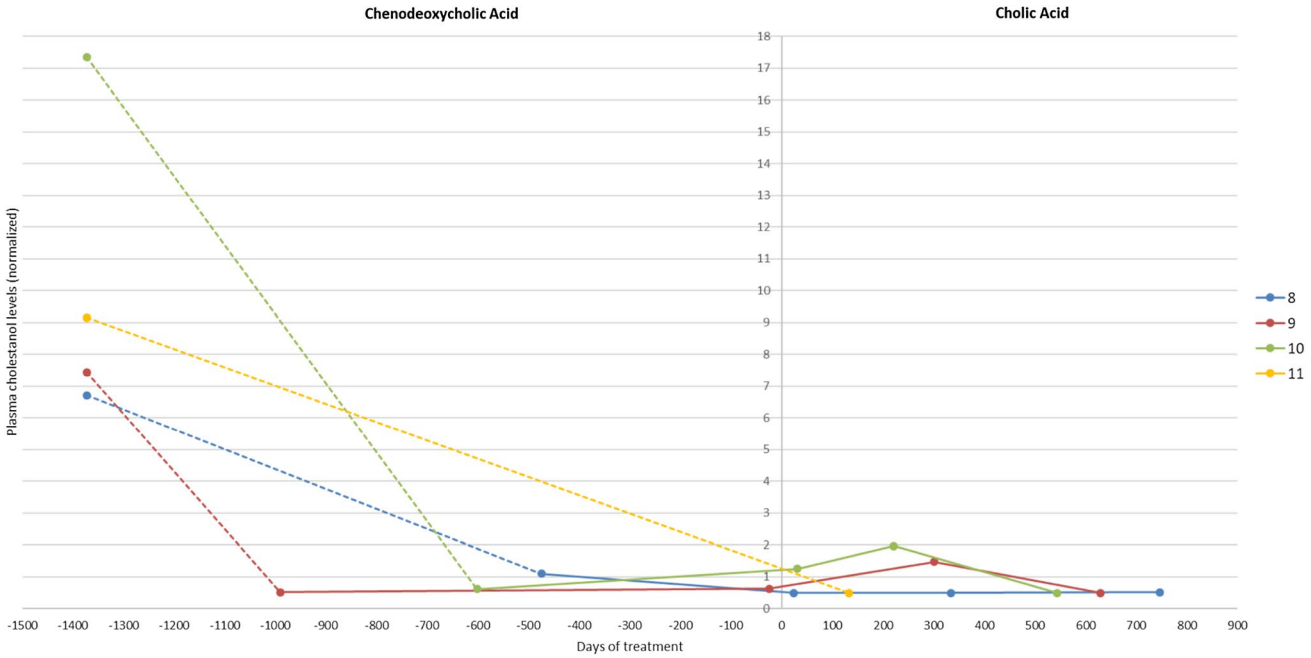

Fig. 2 Plasma cholestanol levels in patients previously treated with CDCA (< 10 days switch between CDCA and CA; from #8 to #11). Zero is the time of CA introduction. Lines are dotted when the period of time between the two points is larger than represented here

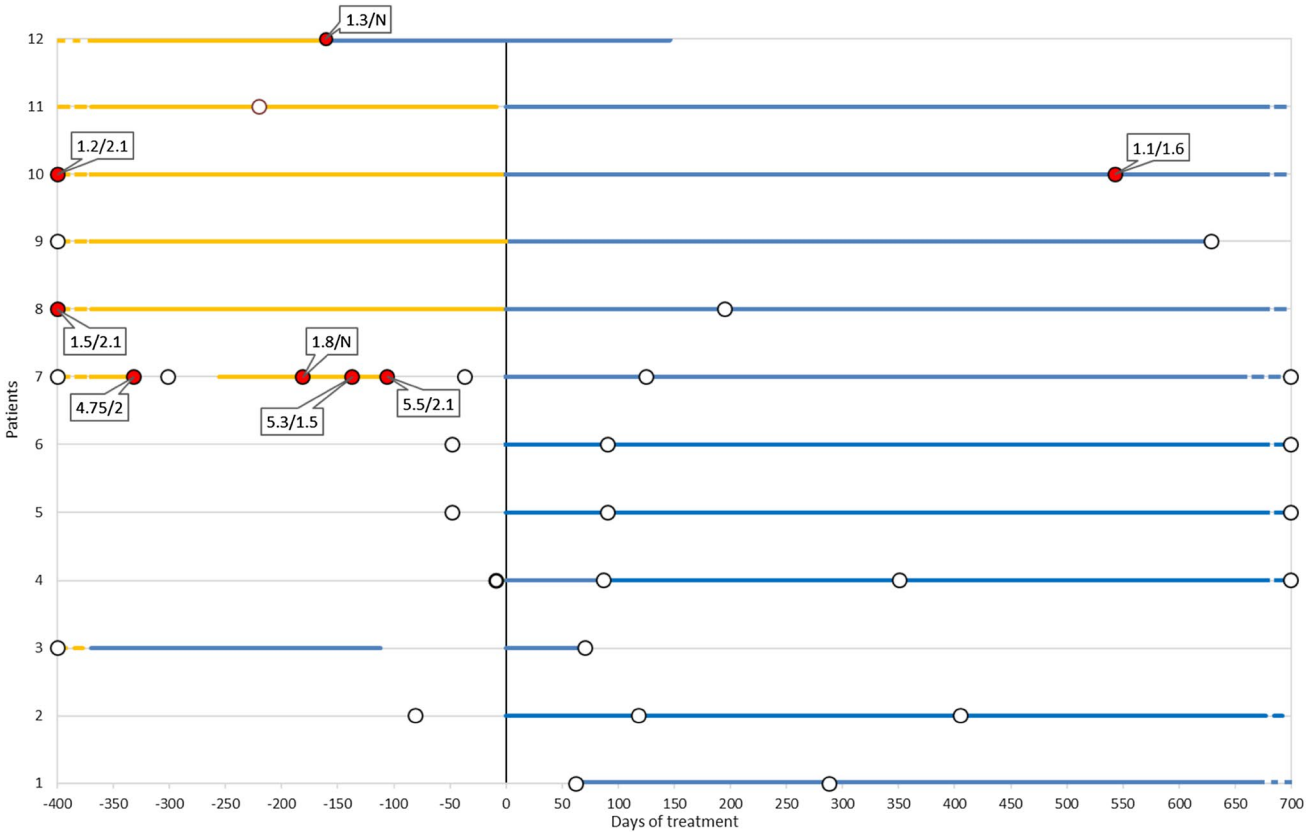

Fig. 3 ALT/AST over time in our population. Blue lines represent periods of treatment with CA; orange lines represent periods of treatments with CDCA. Dots are the transaminases dosages: the white ones resulted normal, the red ones resulted high. Serum AST/ALT levels are only shown if high (i.e., 4.75/2 in patient 11 means ALT 4.75 times the upper normal limit and AST 2 times the upper normal limit)

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Compliance with ethical standards

Conflicts of interest YN: honorarium for speeches from Amicus, Actelion, Orphan Europe, Grants for research from Actelion, Leadiant Pharmaceuticals.

Ethical approval This study has been approved by the appropriate ethics committee.

Informed consent All patients gave their informed consent prior to their inclusion in the study.

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