Efficacy of dual therapy in patients >65 years old with alanine transaminase flare during chronic hepatitis C genotype 2

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ABSTRACT

Hepatitis C virus (HCV)-related chronic hepatitis is characterized by different clinical outcomes as well as by distinct biochemical and virological patterns. According to guidelines concerning dual therapy, high rates of sustained virological response (or HCV-RNA undetectable 24 weeks after the end of antiviral treatment) has been obtained in patients with persistent HCV infection, caused by genotype 2 (CHC G2). Dual therapy (pegylated interferon plus ribavirin) might be an useful strategy not only in the treatment of younger patients (≤65 years old, that is generally considered as age limit for the beginning of the antiviral treatment) but also of older patients (>65 years old) experiencing an alanine aminotransferase (ALT) flare (with value of ALT-alanine transaminase ≥400 U/L). In fact the progress of fibrosis can advance quicker exactly during the transaminase breakthrough. We report our experience in the treatment of two Italian patients with CHC G2, one of them was a never treated (naive) woman, whereas the other was a previously treated man with several co-morbidities. Both patients presented an excellent virological response to dual therapy despite unfavorable predictive factors, such as old age (>65 years), ALT flare and possible moderate hepatic fibrosis.

Introduction

In Italy hepatitis C virus (HCV) infection prevalence ranges from 2% to 5%, its variability depends on patients' age (it is higher in patients older than 50 years) and on geographical areas considered (it is higher in South Italy). In patients with persistent HCV infection,

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genotype 1 is the most frequent, followed by genotype 2, present in about 30% of HCV seropositive individuals.[1] Chronic hepatitis C genotype 2 (CHC G2) is often detectable in older (>60 years) transfused or sporadically infected patients without a known route of transmission. Incidence rates of genotype 2 are similar in female and male sex.[2] Patients with CHC G2 sometimes show a biochemical pattern characterized by a significant increase in transaminase levels [alanine aminotransferase (ALT)], usually x3-4 upper limit normality (ULN) but they frequently exhibit normal transaminase values and are defined as persistent normal alaninoamino transferase (PNAL) subjects. In the natural history of patients with chronic HCV-related infection, caused by genotype 2, ALT flares, even reaching levels ≥10 ULN, have been reported by some Authors.[3] Patients (naive or relapser/null responders to previous treatment) experiencing these episodes may develop progressive liver fibrosis.[3] Chronic HCV-related hepatitis represents a high-risk condition for cirrhosis and hepatocarcinoma. Therefore an overall assessment of the disease has to be performed in each of these patients, with the aim to evaluate possible benefits of treatment. It is well-known that the achievement of a sustained virological response to therapy in patients with chronic HCV infection results in global survival improvement, reduced risk of liver disease progression and hepatocellular carcinoma development,[4,5] as well as diminished medical costs.[6] Nevertheless there are some clinical situations as decompensated cirrhosis, uncontrolled depression, psychosis or epilepsy and severe concurrent medical disease, that represent a contraindication to interferon therapy. HCV infection caused by genotype 2 is defined an *easy to treat* condition with

the currently approved drugs and the standard of care treatment, until sofosbuvir's marketing, still includes pegylated interferon plus ribavirin for 24 weeks. Although ribavirin can be used at a flat dose of dose of 800 mg/day, patients with genotype 2 with baseline factors suggesting low response probability (*i.e.* advanced fibrosis/cirrhosis, metabolic syndrome, insulin resistance, hepatic steatosis) should receive weight-based ribavirin at the dose of 15 mg/kg. Considering dual therapy and according to the European Association for Study of Liver (EASL) guidelines,[7] the treatment's duration can be shortened and patients with CHC G2 who achieve a rapid virological response (RVR) (HCV-RNA undetectable at 4 week of treatment) and who have low baseline viral titre (<400,000 UI/mL) can be treated only for 16 weeks. If negative predictors of response are present, published evidence for equal efficacy of shortened treatment is lacking. Instead, subjects receiving dual therapy with genotype 2 and with any adverse predictor of sustained virological response (SVR), and who achieve an early virological response (EVR) (HCV RNA undetectable at 12 weeks) without RVR can be treated for 48 weeks. However, in general, satisfactory rates (reaching also 80-90%)[8] of sustained virological response to the standard therapeutic approach have been obtained in clinical trials. ALT flare rates are higher in patients with HCV G2 infection in comparison with different genotypes. These episodes are more frequent in sixty-year old subjects[9] and although the development of a flare represents a condition at elevated risk for hepatic decompensation, a good and rapid virological response to antiviral treatment has been proved.[3] Nowadays the mean age of our patients is progressively increasing and some of them with HCV genotype 2 infection present ALT flares; patients' age and co-morbidities as well as treatment-related potential side effects sometimes make the hepatologist doubtful about the real benefit that dual therapy may produce in these subjects. So, we place our hope in the introduction of the new several direct-acting antivirals (DAAs) in clinical practice, and including NS3 protease inhibitors, nucleoside/nucleotide analogues and non-nucleoside inhibitors of the RNA-dependent RNA polymerase and NS5A inhibitors, because they improve tolerability and efficacy profile of the antiviral treatment in these difficult patients allowing shorter treatments. Among them, sofosbuvir[10] is much more promising considering its high barrier to resistance and pan-genotypic antiviral effect. It is given orally, once a day and has few drug interactions. Side effects are limited and in genotype 2 sofosbuvir combined with ribavirin for 12 weeks was associated with sustained virological response in 100% of G2 HCV infected patients. Nevertheless, clinical trials using DAAs lack to include large numbers of patients with cirrhosis, comorbidities, previously non-responders and experiencing ALT flare. In conclusion, although we are waiting for these new pan-genotypic and interferon free strategies,[11] we aimed to assess the efficacy of the recommended dual therapy approach in the treatment of two patients with HCV infection, caused by genotype 2 in the *real practice*.

Case Reports

Case #1

In 2012, a 69-year old Italian woman was visited at our Department, because about one month before, she experienced a symptomatic pattern characterized by malaise with headache, dyspepsia, weight loss (approximately 4 kg) and vague abdominal pain. Routine serum biochemical tests showed a transaminase flare (ALT 999 U/L, AST 806 U/L), an increase of γ-glutamyl transferase (GGT) (296 U/L) and of α-fetoprotein (AFP) levels (273 ng/mL), with normal values of alkaline phosphatase (ALP) and total bilirubin. Values of albuminemia, glycemia, coagulation and inflammatory markers were normal. Personal history was negative for alcohol or herbal medicine intake, smoke, and risk factors for leptospirosis infection as well as for food poisoning. The woman was housewife, she had no children and she didn't take any type of medication. She lived with a HCV (+)ve sister and reported dental care in the nineties. Her past medical history was characterized by the following points: at the age of 50 years she underwent hysterotomy because of a fibroma with the casual detection of anti-HCV positivity, at the age of 65 hemorrohoidectomy and a diagnosis of osteoporosis was performed. Concerning incidental discovery of anti-HCV (+)ve, the patient never performed liver biopsy as well as neither FibroScan nor dual therapy. She only attended regular yearly biochemical liver tests (in April 2002 we observed normal transaminase values AST 30 U/L, ALT 34 U/L) with HCV low viral load-450,900 UI/mL, genotype 2a/2c) without regular clinical follow up by hepatologist because as she said *transaminases were always normal*. Furthermore she has undergone an abdomen ultrasound (US) scan 3 years before but we did not have the results of this previous test. Physical examination showed: body mass index equal to 23, hepatomegaly and palmar erythema, but no other signs or symptoms of chronic liver disease could be found. No additional signs were detected in other organs and systems. We planned an additional biochemical investigation, that showed normal values of serum creatinine and thyroid stimulating hormone (TSH). In addition, we searched blood markers of autoimmunity (AMA, ASMA, ANA, ENA, ANCA, native DNA, LKM) as well as antigen and/or antibody profiles of the most important hepatotropic viruses (HBV, CMV, EBV, HAV, HSV-1 e 2), of human immunodeficiency

virus (HIV) type 1 and 2 as well as of toxoplasma. Markers of autoimmunity were negative and we excluded the presence of acute viral or bacterial infection. In particular antigen and/or antibody pattern for HBV and HAV was as follows: HBsAg (-)ve HBsAb (-)ve HBcAb (-)ve HBeAg (-)ve HBeAb (-)ve, anti-HAV IgM (-)ve, anti-HAV IgG >1000. Levels of the most important tumor markers (CEA, CA 19.9, CA 125, CA 15.3) were normal, except α-fetoprotein. In addition serum parameters were: ferritin 1007 ng/mL, [normal value (n. v.) 12-150], transferrin 271 mg/dL (n. v. 200-375), iron 256 mcg/dL (n. v. 50-175), % transferrin saturation 66.5% (n. v. 20-45). Major genetic mutations for hemochromatosis (C282Y and H63D) were not detected as well as coeliac disease was excluded. Quantitative HCV-RNA value was equal to 359,800 UI/mL, genotype was 2a/2c, search for serum cryoglobulins was negative, IL28B rs12979860 genotype was C/C, vitamin D levels were in normal range. Abdomen US scan showed *liver with regular size (cranial-caudal diameter right lobe=11 cm), with thick and rounded liver borders, not-homogeneous ultrasound structure, without liver lesions, regular caliber of portal vein (diameter portal vein=9 mm), stretched hepatic veins, regular gall bladder without gall-stones, normal size of spleen (longitudinal diameter: 8.7 cm), no ascites*. So we concluded that a chronic liver disease with steatosis and associated fibrosis without liver lesions was present. Patient's weight loss and increase in α-fetoprotein were investigated by means of a thorax X ray and an abdominal computerized tomography (CT) scan with intravenous contrast administration. No pathological findings were observed, in particular abdomen CT confirmed the absence of liver lesions, pancreatic mass or pathological lymph nodes. Esophago-gastro-duodenoscopy (EGD) detected neither varices nor hypertensive portal gastropathy. At the beginning, we decided a clinical strategy characterized by a *watch and wait* approach. About one month after our first visit we repeated routine blood tests and we documented persistent hypertransaminasemia and progressive increase in HCV-RNA viral load and in α-fetoprotein (max detected value 1100 ng/mL). Although patient presented predictive factors of no response, such as ALT flare, older age (>65 years old) and increase in α-fetoprotein, we started dual therapy as follows: peg-interferon α-2b 80 mcg once a week s.c. (subcutaneously) plus ribavirin 200 mg 2 cpr/bid per os (oral somministration) (twice a day) (patient's body weight was 47 kg) for 24 weeks. After 4 weeks of dual therapy, we noted RVR (HCV-RNA negative) and biochemical response with normalization of transaminases (ALT 909 U/L at baseline *vs* ALT 37 U/L at week 4) and decrease in α-fetoprotein, which was again normal after 12 weeks of dual therapy. The

patient achieved complete early virological response (cEVR) (HCV-RNA negative at week 12 of treatment), end of treatment response (EOT) (HCV-RNA negative after 24 weeks of treatment) and SVR (HCV-RNA negative 24 weeks after the end of treatment) (Table 1). We performed FibroScan, only after transaminase decrease (about 4 weeks after the beginning of dual therapy) with the purpose to reduce the risk of overestimate liver stiffness. Liver stiffness measurement was equal to 13.4 kPa (IQR 1.6). The dual therapy was generally well tolerated by our patient, although she experienced arthralgia, flu like syndrome following peg-interferon administration, dry skin, intermittent cough and an episode of dysuria with suspected urinary tract infection in the absence of neutropenia. She was treated with empirical antibiotic therapy. At fourth week of treatment macrocytic anemia was detected and it was treated with Eprex 40,000 UI (epoietin α) once every two weeks (as needed) s.c. without reducing ribavirin dose. Thyroid function remained normal and markers of autoimmunity remained negative during therapy. Now the patient is fine, she underwent an efficacious HBV vaccination and continues periodic clinical, laboratory and imaging follow up at the Hepatology Department of our Institution.

Case #2

In 2009, a 65-year old Italian man with chronic hepatitis C (genotype 2a/2c) was visited at our Department for a clinical re-evaluation of his liver disease. His past medical history included: poliomyelitis when he was a child (resolved without consequences), appendicectomy at 20 years of age, hypertension, prostatic hypertrophy and hypercholesterolemia. Home therapy included ramipril 5 mg/day, simvastatin 20 mg/day and tamsulosin 0.4 mg/day. He was a retired civil servant and a married man (wife and one daughter were in good health). He did not smoke and never drunk alcohol. No clear risk factors for HCV infection was detectable in his personal history. In 1994 he occasionally experienced a slight increase in transaminase levels (ALTx2 ULN) and a diagnosis of HCV-related chronic hepatitis was made. In that circumstance other causes of liver damage, including autoimmunity and co-infections were excluded at a different Institution (in particular serology of HBV infection was as follows: HBsAg (-)ve HBsAb (-)ve HBcAb (+)ve HBeAg (-)ve HBeAb (-)ve HBV DNA (-)ve). Then he underwent a liver biopsy, that showed a description of moderate chronic hepatitis (grading A2, staging F2 in accordance with Metavir classification). In the same year (1994) the patient underwent a 48 weeks course of interferon treatment (interferon α-2a 1 fL s.c. three times per week) without adverse events. According to his reported clinical history he

obtained a biochemical response (with normalization of transaminases), without a virological response. Then he discontinued his programmed clinical follow-up until 2009, when he was visited at our Institution. We performed an abdomen US scan that showed slight liver steatosis with possible associated fibrosis without focal lesions, gall bladder, spleen and portal vein were normal. Liver stiffness measurement (LSM) was obtained by means of FibroScan evaluation and was equal to 3.8 kPa (IQR 0.6), routine serum biochemical analysis showed normal transaminase levels (ALT 30 U/L, AST 20 U/L) with fluctuating viral load values ranging from 10^5 to 10^6 log. We suggested to start dual therapy but the patient refused, because of personal problems, so we decided to follow-up our patient with regular controls every six-months. Biochemical parameters remained stable until May 2012, when the patient was 68-years old and he was visited before the scheduled time, because he suddenly experienced abdominal pain, nausea, anorexia and asthenia. Our patient's biochemical profile was as follows: ALT 947 U/L, AST 548 U/L, total bilirubin 3.1 mg/dL (conjugated 2.1 mg/dL), GGT 888 U/L, ALP 149 U/L, albuminemia 3.0 g/dL; normal white blood cells count, AFP 26.9 ng/mL, ferritin 1079 ng/mL, transferrin 181 mg/dL, iron 133 mcg/dL, % transferrin saturation 51%, international normalized ratio 0.96, normal levels of TSH, glycemia and cholesterol; IL28B rs12979860 T/T genotype. HCV-RNA levels were equal to 4,460,000 UI/mL. Abdominal ultrasound was unchanged and EGD reported no abnormalities. On physical examination, only light jaundice without hepatomegaly was detectable. We repeated specific laboratory tests with the aim to exclude the main causes of ALT flare, and were again negative. Although patient presented predictive factors of no response, including ALT flare, older age (>65 years old), hyperbilirubinemia and ipoalbuminemia we informed the patient that an antiviral strategy with the dual therapy have to be urgently started. He accepted and therapy was administered as follows: peg-interferon α-2a 180 mcg once weekly s.c. plus ribavirin 200 mg 2 cpr/bid per os (twice a day) (patient's body weight was 53 kg) for 24 weeks. We temporarily suspended the home treatment, because of possible iatrogenic adverse effects, including transaminase breakthrough. Patient was requested to accurately monitor his arterial pressure. At week 4, we observed an evident decrease in levels of transaminases (ALT 111 U/L), bilirubin (total bilirubin 1.1 mg/dL conjugated 0.8 mg/dL), GGT (288 U/L) and ALP (106 U/L). HCV-RNA was undetectable (RVR). In that occasion, we performed a FibroScan evaluation and LSM was equal to 14.4 kPa (IQR 1.5). This patient also achieved a complete cEVR (HCV-RNA negative at week 12 of therapy), EOT (HCV-RNA negative after 24 weeks) and SVR (HCV-RNA negative 24 weeks after the end of treatment) (Table 2). The normalization of transaminases was reached only about 24 weeks after the end of treatment and home therapy was reconsidered again.

Table 1. Hemato-chemical parameters in Case #1.

	Baseline values	One month post baseline	Pre-therapy	4th week (RVR)*	12nd week (cEVR)	24th week (EOT)°	24th week (SVR)°	Reference values
White blood cell count (10³/mcL)	5.27	4.14	3.78	5.45	3.14	3.07	6.00	4.00-11.00
Hemoglobin (g/dL)	13.9	13.5	13.4	10.5	10.2	9.8	12.8	14.0-18.0
Mean corpuscular volume (fL)	101	104	106	104	109	110	100	82.0-98.0
Platelets (10³/mcL)	170	157	124	140	157	153	180	140-440
AST (U/L)	806	408	685	33	31	27	27	10-40
ALT (U/L)	999	589	909	37	30	31	25	9-41
Total bilirubin (mg/dL)	0.8	0.6	1.2	0.7	0.4	0.3	0.4	0.2-1.2
Conjugated bilirubin (mg/dL)	0.3	0.3	0.6	0.3	0.2	0.1	0.2	0.0-0.4
GGT (U/L)	369	230	407	106	52	39	30	8-61
ALP (U/L)	109	129	163	97	71	89	60	50-136
HCV-RNA (UI/mL)	359,800	3,723,000	2,198,000	Negative	Negative	Negative	Negative	-
α-fetoprotein (ng/mL)	273	880	1100	210	12.2	7.5	7.0	0.0-10.0
INR	1.03	1.0	1.09	-	1.05	-	0.9	-
Albuminemia (mg/dL)	3.8	-	3.8	-	-	-	3.5	3.4-5.0

RVR, rapid virological response; cEVR, complete early virological response; EOT, end of treatment; SVR, sustained virological response; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyl transpeptidase; ALP, alkaline phosphatase; HCV, hepatitis C virus; INR, international normalized ratio. *Start dual therapy: peg-IFN α-2b 80 mcg once weekly s.c.+ ibavirin 200 mg 2 cpr/bid os; °End of dual therapy.

However during therapy patient showed a good control of arterial pressure and did not exhibit symptoms of prostatic hypertrophy in spite of the suspension of his α-lithic treatment. Patient experienced the following adverse effect to dual therapy: an itching eczema in the legs. He benefited by a therapy, including urso-deoxy-cholic acid at a dose of 600 mg/die and a topic steroidal cream. Now the patient is well and he continues to attend medical controls at our Hepatology Department even if transaminases are normal.

Discussion

ALT flares observed in patients with HCV genotype 2 have been associated with changes over time in the level of the hypervariable region HVR1, which carries epitopes involved in host immune control of HCV. It has been described as a situation in which there is *the loss of control* host immune response to HCV infection in these subjects, who were for a long time defined as PNAL-subjects up to the episode characterized by transaminase breakthrough. These 2 patients with hepatitis reactivation lacked serum markers of autoimmunity or acute HBV infection, did not report consumption of alcohol or herbal remedies. Both acute HCV infection and also HCV re-infection from another genotype different from genotype 2 have been excluded. Concerning the first case we underline that we considered liver biopsy unnecessary because histological report did not

change our opinion that it was necessary to start dual therapy. We correlated the increase in α-fetoprotein with the presence of ALT flare and severe hepatocyte necrosis. In the woman in post-menopausal age we used peg-interferon α-2b according to Villa's *et al.*[12] study. In the second case we observed the persistence of elevated serum transaminase and GGT levels, although HCV-RNA was undetectable in blood and we supposed that this biochemical pattern was related to an effect of *hepatic toxicity*, caused by interferon. There are some factors that affect treatment outcome in our HCV-2 patients, such as baseline HCV viremia, presence of steatosis, single nucleotide polymorphism in the interleukin 28B (IL28B) region, presence of bridging fibrosis/cirrhosis, age and gender (Table 3). Both subjects are aged >65 years old, present high/moderate fibrosis (as evidenced with FibroScan) and they do not report low viral load (HCV RNA <400,000 UI/mL) at baseline; these factors have an unfavorable impact on the results of treatment. Furthermore, the man has co-morbidities that predisposes to insulin resistance, he is an experienced previous null responder and presents unfavorable IL28B T/T. Although the woman presents favorable IL28B CC and has not co-morbidities, she is in post-menopausal age. In our patients predictors of SVR on treatment (RVR, anemia,[13] adherence to treatment) are much more important than baseline factors. In fact, for example, available evidences show that kinetic of viral load decay during treatment

Table 2. Hemato-chemical parameters in Case #2.

	Pre-therapy values	4th week (RVR)*	12th week (cEVR)	24th week (EOT)°	24th week (SVR)°	Reference values
White blood cell count (10³/mcL)	6.78	4.05	3.85	2.71	7.14	4.00-11.00
Hemoglobin (g/dL)	16.1	13.1	12.6	12.8	16	14.0-18.0
Mean corpuscular volume (fL)	94	95	94	94	94	82.0-98.0
Platelets (10³/mcL)	174	239	138	111	191	140-440
AST (U/L)	548	88	105	115	35	10-40
ALT (U/L)	947	111	122	116	33	9-41
Total bilirubin (mg/dL)	3.1	1.1	0.3	0.8	0.7	0.2-1.2
Conjugated bilirubin (mg/dL)	2.1	0.8	0.1	0.2	0.2	0.0-0.4
GGT (U/L)	888	288	438	191	40	8-61
ALP (U/L)	149	106	102	113	84	50-136
HCV-RNA (UI/mL)	4,460,000	Negative	Negative	Negative	Negative	-
α-fetoprotein (ng/mL)	26.9	12	7.8	-	3	0.0-10.0
INR	0.96	0.9	0.9	0.9	0.98	-
Albuminemia (g/dL)	3.0	3.1	3.5	3.5	4.0	3.4-5.0

RVR, rapid virological response; cEVR, complete early virological response; EOT, end of treatment; SVR, sustained virological response; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyl transpeptidase; ALP, alkaline phosphatase; HCV, hepatitis C virus; INR, international normalized ratio. *Start dual therapy: peg-IFN α-2a 180 mcg once weekly s.c.+ribavirin 200 mg 2 cpr/bid os; °End of dual therapy.

Table 3. Predictor factors of sustained virological response in chronic hepatitis C genotype 2.

Predictors pre-treatment (baseline) of SVR to P/R in CHC G2						Positive predictors on treatment of SVR to P/R IN CHC G2	
Virus			Host			Virus	Host
Predictive factor	Positive	Negative	Predictive factor	Positive	Negative	RVR	Full adherence to the schedule treatment (≥80% of scheduled pegylated IFN-α and ribavirin doses for ≥80% of the treatment period)
Viral load at baseline	LVL (<400,000 UI/mL)	No LVL UI/mL)	Age	<40 years old	≥40 years old		
			Gender	Female	Male		
			Female gender	Fertile	Postmenopausal		
			L 28B rs12979860	CC	CT/TT		
			Staging	≤F2	F3-F4		Treatment related anemia
			Ethnic group	Caucasian	Afro-American		
			Hepatic *non-viral* steatosis	Absent	Present		
			Insulino-resistance (obesity, metabolic syndrome)	Absent	Present		
			Co-infection (+HIV/HBV)	Absent	Present		
			Co-factors liver damage (alcohol, iron)	Absent	Present		
			Previous virological outcome (if patient experienced)	Relapser	Non responder Virological breakthrough		

SVR, sustained virological response; P/R, peg-IFN+ribavirin; CHC G2, chronic hepatitis C genotype 2; LVL, low viral load; RVR, rapid virological response; HBV, hepatitis B virus.

(and the presence of RVR) is probably a more important factor than only genetic assessment.[14] In both cases we concluded the normality of transaminases did not suggest the absence of fibrosis as showed by Puoti *et al.*[15] in the ISAAC study (Italian prospective Study of the Asymptomatic C Carriers). Furthermore, according to PROPHESYS study[16] dual therapy was well-tolerated in our experience even if two treated patients were older than 65 years. In fact, there are some evidences from literature of a good SVR rate in patients with infection HCV genotype 2 even in aged subjects.[17]

Conclusions

We report cases of 2 patients experiencing ALT flare during chronic hepatitis C caused by genotype 2 in subjects >65 years old, who had been previously defined as subjects with PNAL levels. Even if new drugs for HCV infection treatment are now under study, we would like to stress the efficacy and good tolerability of dual therapy in these patients and the hepatologist's key role in suggesting the dual therapy approach also in patients with PNAL levels to avoid probable ALT flare and progress in liver fibrosis. Furthermore, regular medical controls are very important also in patients with persistent HCV infection and normal liver tests.

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