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Mixed Genotype Hepatitis C Infections and Implications for Treatment

To the Editor:

The recently licensed direct-acting antivirals (DAAs) boceprevir and telaprevir used to treat hepatitis C virus (HCV) infection act in a genotype-specific manner. The potential outcome of DAA treatment regimes on mixed HCV infections, consisting of concurrent infection with more than one HCV genotype, has not been considered. Standard genotyping methods are only capable of identifying the dominant genotype present within a mixed infection sample, leaving minor genotypes undetected. We propose that DAA treatment of mixed infections may be associated with the occurrence of genotype switching, whereby a previously undetected minority variant drug-resistant genotype expands to replace the successfully treated majority variant genotype. Such genotype switching could in some cases result in nonresponse to DAA treatment and could also be incorrectly interpreted as reinfection if genotyping is not repeated following treatment failure. As a matter of urgency, there is a need to assess the prevalence and clinical impact of mixed HCV infections.

To determine the prevalence of mixed HCV infections in a cohort of patients infected with genotype (gt) 3a (n = 47) or 1a (n = 48), we designed gt1a- and gt3a-specific primers providing partial coverage of the envelope genes E1 and E2 of HCV. Nested reverse transcription (RT) polymerase chain reaction (PCR) reactions were performed using gt1a primers with gt3a-infected samples and vice versa. Amplicons were sequenced and used to construct maximum likelihood phylogenetic trees using the MEGA 5.0 software package to confirm genotype.

The sensitivity of the RT-PCR reactions, as determined by 90% detection limits calculated from serial endpoint dilution RT-PCR and probit analysis, was nine copies/reaction. Of the gt3a-infected patient samples, 10.6% (5/47) harbored minority variant gt1a strains, whereas none of the gt1a-infected patient samples contained gt3a as a minority strain.

These findings are in keeping with other studies that found mixed HCV infections at rates of 5%-25.3%.[1-3] Further work is required to assess the impact of minority variant strains on patients treated with DAA therapy. If relapse following dual therapy for gt3 infection is associated with emerging dominance of preexisting gt1 strains, screening of baseline patient samples using genotype-specific methods could result in improved treatment strategies; for example, the prescription of triple rather than dual antiviral therapy. More work is required to assess the impact of multiple genotype infection on clinical outcome, and this work is more pressing in the DAA era.

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Unusual Oral Mucosa Damage During Telaprevir Treatment of Chronic Hepatitis C

To the Editor:

The addition of hepatitis C virus (HCV) protease inhibitor telaprevir to pegylated interferon (Peg-IFN) and ribavirin (RBV) dramatically increases the likelihood of a sustained virological response (SVR) in patients with genotype 1 HCV infection who have failed previous treatment with Peg-IFN/RBV combination.[1] The higher prevalence of cutaneous adverse reactions (CAR) of different severity was associated with the telaprevir combination treatment, in contrast to the treatment with Peg-IFN/RBV[2]; however, we could not find any published article about isolated mucosal lesions associated with the telaprevir combination treatment before this case.

A 29-year-old white male patient was referred to our department in May 2012 for reevaluation and retreatment after unsuccessful treatment for chronic HCV infection (genotype 1b). Previous treatment (PegIFN-α2b 120 μg/week plus RBV 1,200 mg/day) had achieved neither rapid nor early virological responses and was stopped after week 13 of treatment due to a low chance of SVR. The overall tolerability of this treatment was satisfactory. During the treatment hemoglobin decreased to 97 g/L, absolute neutrophil and platelet counts decreased but not below the alarm level, and no dermatological adverse events were noted. Due to advanced fibrosis and null-response to the previous treatment with Peg-IFN/RBV, the patient was enrolled in the telaprevir early access program. Triple therapy with PegIFN-α2a 180 μg subcutaneously once a week, RBV 600 mg twice daily and telaprevir 750 mg three times a day was started. Overall tolerability of the therapy was satisfactory. A rapid virological response was achieved (PCR HCV RNA was negative on the fourth week of treatment). No clinically significant hematological adverse events were noted.

At week 6 of treatment the patient complained of a tickle in his throat, but there were no skin lesions, flu-like symptoms, or fever. On the scheduled visit (week 8), vital signs were normal: weight 76.8 kg, temperature 36.8°C, blood pressure 120/70 mmHg, heartbeat 88/min. Mild hyperemia of oral mucosa plus multiple telangiectasias and erythematous lesions located on the buccal mucosa, soft palate, and back wall of the throat were found (Fig. 1A,B). Skin was normal, no regional lymph nodes were enlarged, no signs of infection were found, and the patient did not note any unusual taste