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Kate Moore via NICE Docs

From [redacted]

23 March 2015

Dear Sir or Madam

Re: Ledipasvir-sofosbuvir for treating chronic hepatitis C [ID742] – Appraisal Consultation Document

The Royal College of Physicians (RCP) plays a leading role in the delivery of high quality patient care by setting standards of medical practice and promoting clinical excellence. We provide physicians in the United Kingdom and overseas with education, training and support throughout their careers. As an independent body representing over 30,000 Fellows and Members worldwide, we advise and work with government, the public, patients and other professions to improve health and healthcare.

The RCP is grateful for the opportunity to respond to the above ACD consultation. In doing so, we have liaised with the British Society of Gastroenterology (BSG) and wish to fully endorse their submission. We would also like to make the following comments on behalf of our experts in genito-urinary medicine.

There are a number of specific comments that we would urge the committee to take into consideration for the Final Appraisal Determination:

1) Whilst we applaud the Committee's decision to 'allow' treatment for HIV/HCV co-infected patients along the recommendations made for HCV mono-infected patients, we would like to point out that preliminary results from the ION-4 study are now available [1]. This large single-arm study in treatment-naïve and treatment-experienced genotype 1 co-infected patients suggests similarly high sustained virological response (SVR) rates with 12 weeks of ledipasvir-sofosbuvir as those seen for mono-infected patients.

2) A large meta-analysis presented at the American Association for the Study of Liver Diseases (AASLD) Liver Meeting 2014 showed SVR was associated with large reductions in all-cause mortality, hepatocellular carcinoma (HCC) and need for transplantation; these benefits were similar in HCV mono-infected and HIV/HCV co-infected groups. In fact, the numerical reduction in 5-year all-cause death associated with SVR was greater for those who were co-infected (co-infected: 1.3% with SVR *vs* 10.0% without; mono-infected: 4.5% with SVR *vs* 10.5% without SVR) [2].

3) A separate cost-effectiveness analysis for co-infected patients is crucial. These patients have faster progression to end-stage liver disease, even in the era of effective HIV treatment [3]. Therefore, it is likely that the analyses presented here may not be applicable to co-infected patients and that 12 weeks of treatment may have demonstrated cost-effectiveness in *all* subgroups of genotype 1 co-infected patients (treatment-naïve, experienced, non-cirrhotic and cirrhotic patients).

4) We stress most emphatically to the Committee that to intimate that HCV treatment benefit in HIV co-infected patients may be offset by HIV-related mortality (paragraph 4.23) is *incorrect.* There is good-quality data from the UK [4] that with effective antiretroviral therapy, life expectancy in this group of patients approaches or equals that of the non-HIV-infected adult population.

5) Patients with HIV do have a reliable marker of adherence, which is suppressed plasma viraemia on HIV therapy.

6) There are a number of other issues that affect HIV-positive individuals disproportionately:
    a. Onward transmission: there is a well-documented, and on-going, epidemic of acute HCV in HIV-positive men who have sex with men (MSM) driven by high-risk sexual practices and recreational drugs (including injecting and intranasal use as a route of transmission). The benefits of successful HCV treatment in terms of 'treatment as prevention' are likely, therefore, to be greater in co-infected individuals. A recent analysis highlights the marked reduction in years of potential infectivity with earlier *vs* delayed HCV treatment in a co-infected population [3].
    b. Immune activation, inflammation and comorbidities: HIV is associated with an increased risk of age-related co-morbidities, driven in part by HIV-related immune activation and inflammation. HCV and, in particular, HCV-related cirrhosis further increase markers of inflammation and immune activation [5–7] in co-infected patients, another argument to treat HCV earlier.
    c. Overlapping co-morbidities: HIV is associated with earlier onset of co-morbidities classically associated with HCV including neurocognitive impairment, lymphoma and metabolic abnormalities. It is possible that earlier HCV treatment will yield an even greater benefit in terms of co-morbidities in co-infected patients.
    d. Transplant failure: liver transplant outcomes for co-infected patients are worse than for those with HCV only, making deferral of HCV treatment until fibrosis is advanced a riskier strategy for co-infected patients [8].
    e. Hepatotoxicity of antiretrovirals (ART): co-infection with HCV significantly increases the risk of ART-related hepatotoxicity, requiring more frequent monitoring, switching and use of more expensive agents.

7) We strongly urge NICE to appoint clinical experts versed in the management of co-infected patients for future appraisals.

8) We are disappointed that whilst the Committee chose to 'approve' IFN-free treatment for genotype 1 treatment-naïve patients, those patients with genotype 4 disease will have to wait until progression to cirrhosis before being able to access IFN-free therapy. The cost-effectiveness analyses may support this view; however, this is a relatively small group of patients in absolute numbers, and therefore, total treatment cost to the NHS. In addition, this group has over-representation from HIV co-infected people and individuals from ethnic minorities. We would urge reconsideration to approve IFN-free treatment for this subgroup of patients.

Yours faithfully

Dr [redacted]

References

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