EDITORIAL

The new hepatitis C era: The guidelines are now available, reimbursement not yet...

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Berden and colleagues have taken up the challenge to guide clinicians during the use of sofosbuvir for the treatment of hepatitis C virus (HCV) as soon as its reimbursement is in place in the Netherlands.[1] Sofosbuvir is the first of more than ten new HCV direct antiviral agents (DAAs) in phase III of clinical evaluation. Many of these DAAs can be expected to get European Medicines Agency (EMA) approval within the next 24 months. It is a daunting task to keep up with the flood of new data on these DAAs. As such, a HCV treatment guideline will only be handy if it is a truly living online document that is updated as soon as another new DAA becomes EMA approved and reimbursed in the Netherlands. This is nicely illustrated by the fact that simeprevir and daclatasvir became EMA approved (but not yet reimbursed) in between the first and the second submission of this guideline to *the Netherlands Journal of Medicine*. Likewise, other tools are becoming available to assist physicians when they are confronted with a particular HCV-infected patient. The 'sustained virological response (SVR) predictor' is a useful example. It provides the best estimate of treatment success with EMA-approved drugs while taking patient characteristics (cirrhosis, genotype, interferon naive or not) into account.[2]

The benefits of these upcoming HCV treatment options are crystal clear: cure rates above 90% and very few side effects in comparison with peginterferon-based therapy. However, with the current price of € 598 per 400 mg tablet and € 50,872 for a 12-week therapy, sofosbuvir is almost 50 times(!) more expensive than gold.[3] It is not surprising that the cost-effectivity and budget impact of these DAAs will be driving a significant part of the future debate on who, when and how to treat. In high prevalence countries, such as Spain or Italy, treating all HCV-infected patients will have a huge budget impact. With this in mind, it is unfortunate that the new Dutch guideline gives very little insight into the costs of the different treatment options.

One could argue that a physician treating an individual patient should not consider costs. But what if, with the current price setting in mind, some of the suggested treatment options in the guideline can in advance be considered not cost-effective? Sofosbuvir-based HCV genotype 1 treatment is probably cost-effective for patients with significant fibrosis.[4,5] However, for HCV genotypes that are clearly more susceptible to interferon the picture is very different. Based on the new Dutch guideline, we performed a simplified cost-effectivity calculation for treatment-naive patients with genotype 3 (30% of the Dutch HCV population). Taking into account factors such as the substantial decrease in quality of life during peginterferon-ribavirin therapy, the lower cure rates in comparison with a 12-week sofosbuvir-peginterferon-ribavirin course (and therefore the need for retreatment with sofosbuvir in 30% of the patients), the costs per quality-adjusted life year (QALY) remained above 100,000 euro. The costs per QALY would increase even more if, as some physicians propose, the peginterferon-free 24-week sofosbuvir regimen is given to all. Of course, some patients are clearly interferon ineligible and should not be withhold access to interferon-free new therapies. Also, with other new DAAs to come over the next two years, supply and demand will enter the HCV market and eventually, an interferon-free treatment should become available for all patients. A true debate on the cost-effectivity of the new DAAs is urgently needed. This exercise should also clearly take into account that in certain patient populations (e.g. homosexual men or active intravenous drug users) there may well be substantial indirect cost-savings as well, through the prevention of ongoing HCV transmission.

HCV is also a very significant problem in the HIV-positive patient population in the Netherlands. Within HIV-positive patients, the majority of new HCV infections are no longer seen in (ex) intravenous drug users, but in homosexual men. In an ongoing Dutch study on acute HCV in HIV-positive men the incidence of sexually acquired

HCV is extremely high at 1.5% per year. In the ten study centres 95 (!) newly acquired HCV infections were diagnosed in the first year.[6] Breaking the chain of onward HCV transmission in this patient group may finally become possible when new DAA and peginterferon-free regimens become available and reimbursed. As such, it is unfortunate that the new guideline does not yet mention the management of HCV in HIV co-infected patients.

Berden and colleagues used the GRADE quality of evidence classification. In this form of classification a study that is a non-randomised clinical trial is per definition of low evidence (C). This may lead to very contra-intuitive gradings; in the POSITRON study, 17 patients received sofosbuvir and eight received placebo. The study was randomised and therefore received a grade B (moderate quality of evidence). When a disease, such as chronic HCV, is studied that does not cure spontaneously and 89% of the 292 patients are cured, as in the NEUTRINO clinical trial, GRADE classifies this study as grade C (low quality of evidence) just because it is a non-randomised single-arm study. It is clear that for non-randomised studies the use of the GRADE classification should be refined and is not very useful.[7]

In the light of the substantial treatment costs, well-founded answers should be given when the use of DAAs such as sofosbuvir with peginterferon (€ 53,000, SVR 92% for genotype 3), or without peginterferon (€ 102,000, SVR 94% for genotype 3) is discussed with the well-informed patient. The current article by Berden and colleagues will be helpful if the authors keep their promise and keep the guideline up-to-date.

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