Sofosbuvir: Indication of added benefit for specific patients

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The drug sofosbuvir has been available since January 2014 as a treatment for chronic hepatitis C infection. In an early benefit assessment pursuant to the Act on the Reform of the Market for Medicinal Products (AMNOG), the German Institute for Quality and Efficiency in Health Care (IQWiG) has now examined whether the new drug offers added benefit in comparison with the appropriate comparator therapy.

The dossier submitted by the drug manufacturer provides indications of added benefit for non-pretreated patients infected with the virus of genotype 2. However, the extent cannot be quantified. There were no suitable data in the dossier for patients who are infected with other virus types (genotype 1 and 3 to 6) or who are coinfected with HIV.

An addition to previous standard drug therapy

Hepatitis C viruses attack the liver and can trigger inflammation there. If this becomes chronic, cirrhosis can develop and liver function progressively deteriorates. Moreover, the risk of liver cancer increases. Sofosbuvir inhibits the reproduction of hepatitis C viruses and is administered in addition to the drugs peginterferon alfa and ribavirin, which are already on the market; in certain cases it is administered in addition to ribavirin alone. According to the approval, treatment duration differs for the individual patient groups.

The dual combination of peginterferon alfa and ribavirin is the current treatment standard; in genotype 1, this also applies to a triple combination with boceprevir or telaprevir (triple therapy) in most patients.

The Federal Joint Committee (G-BA) therefore specified peginterferon alfa and ribavirin as appropriate comparator therapy, and, in genotype 1, triple therapy as additional option.

No adequate analyses for most virus types

The manufacturer presented no adequate analyses for infection with type 1 and type 3 to 6 viruses and for HIV coinfection. It analysed results from studies in which the respective comparator therapy was tested in at least one study arm and compared these in a "historical" comparison.

It included both randomized controlled trials (RCTs) and one-arm studies on the sofosbuvir side, but only RCTs on the comparator side. It justified this by claiming that it wanted to reduce the number of hits of its literature search. However, the database for the comparison was different because of this and the comparison itself was therefore unsuitable. A first literature search by IQWiG showed that a number of studies were not considered in the dossier.

One direct comparative study on genotype 2

The situation was different for genotype 2: Here, the manufacturer cited an open-label RCT (FISSION), in which treatment-naive (i.e. non-pretreated) adults with genotype 2 and 3 hepatitis C infection were investigated. In the intervention arm, they received 12 weeks of sofosbuvir plus ribavirin, and in the control arm, they received 24 weeks of peginterferon alfa plus ribavirin.

Hence sofosbuvir was administered in compliance with the approval only for the therapeutic indication genotype 2; and, as a result, only these data were evaluable for the benefit assessment. For genotype 3, the Summary of Product Characteristics (SPC) specifies a treatment duration of 24 weeks. The manufacturer itself did not consider the FISSION study in its dossier for patients with genotype 3.

High risk of biased results

Overall, IQWiG assessed the risk of bias of the FISSION study as high. The main reason was that the manufacturer only included those participants in the analysis who had received at least one dose of the medication they were randomized to. However, particularly in the control arm, where not the new drug, but conventional drugs were administered, some patients refused to have their planned treatment.

This is a general problem of open-label studies, where it is known who receives which treatment. This poses the risk that patients discontinue the study prematurely depending on which treatment they were randomized to. This compromises the aim of randomization: the comparability of the treatment groups. This is exactly what happened in the FISSION study, which may lead to (highly) biased results.

Mortality and quality of life: added benefit not proven

As no deaths occurred in the FISSION study in the therapeutic indication genotype 2, there could be no differences between the treatment groups, and therefore no proof of added benefit, in the outcome "mortality". This also applies to health-related quality of life, but in this case because the dossier contained no evaluable data for this outcome.

Advantage in sustained virologic response

Instead of the patient-relevant outcome "development of hepatocellular carcinoma (HCC)", the manufacturer used sustained virologic response (SVR). It could show that there was a statistically significant group difference in favour of sofosbuvir. IQWiG conducted its own sensitivity analyses because of the high risk of bias. It tested how the effects changed when missing values were imputed with different strategies. The researchers found out that the result in favour of sofosbuvir was robust.

Valid surrogate for incidence of liver cancer

SVR is not itself a patient-relevant outcome and cannot be equated with "cure", and there are no studies in which SVR is validated as a surrogate outcome in accordance with the usual criteria employed by IQWiG. Nevertheless, the Institute accepts SVR here as a surrogate for the reduced incidence of liver cancer. This is because it is currently accepted that patients with no detectable hepatitis C virus in the blood are at lower risk of liver cancer. However, it is unclear how many cases of liver cancer can in fact be prevented by sofosbuvir.

For the outcome "secondary diseases", IQWiG therefore recognizes an indication of a benefit for sofosbuvir.

No quantitative conclusion on harm possible

The data on side effects contained in the dossier could only be assessed to a limited extent. The manufacturer presented these data on the basis of the proportions of patients with at least one event. However, this type of analysis is only suitable to a limited extent because the observation period of the patients was different in the two study arms.

Severe adverse events only occurred once in each of the two study arms. A statistically significant difference in the outcome "treatment discontinuation due to adverse events" in favour of sofosbuvir was not robust in the sensitivity analyses performed by IQWiG. With regard to side effects, IQWiG therefore considers the added benefit as not proven.

Overall positive effect remains

For treatment-naive patients with genotype 2 chronic hepatitis C, an overall positive effect of sofosbuvir in comparison with the appropriate comparator therapy remains with regard to serious secondary diseases. The extent of this added benefit – which was determined with the surrogate "SVR" – is non-quantifiable, however, because it is unclear how often the development of liver cancer can in fact be prevented. With regard to side effects, an assessment was only possible to a limited extent. Greater harm from sofosbuvir is unlikely, however, so that it would not be justified to downgrade the added benefit.

G-BA decides on the extent of added benefit

The dossier assessment is part of the overall procedure for early benefit assessments supervised by the G-BA. After publication of the manufacturer's dossier and IQWiG's assessment, the G-BA conducts a commenting procedure, which may provide further information and result in a change to the benefit assessment. The G-BA then decides on the extent of the added benefit, thus completing the early benefit assessment.

More information: An overview of the results of IQWiG's benefit assessment is given by a German-language executive summary. In addition, the website www.gesundheitsinformation.de, published by IQWiG, provides easily understandable and brief German-language

information on sofosbuvir.

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