Sofosbuvir/velpatasvir in CHC: Hint of added benefit in two of ten subindications

October 17 2016

The drug combination sofosbuvir/velpatasvir (trade name: Epclusa) has been approved since July 2016 for the treatment of patients with chronic hepatitis C (CHC). In an early benefit assessment, the German Institute for Quality and Efficiency in Health Care (IQWiG) has now examined whether the combination has an added benefit for the patients. In the assessment, a distinction was made regarding type of virus (genotype 1 to 6) and liver status (without cirrhosis, with compensated cirrhosis, and with decompensated cirrhosis). According to the findings, an added benefit in comparison with the respective appropriate comparator therapy was not proven for eight of ten research questions because no suitable study data were available. There was a hint of considerable added benefit for one research question, and a hint of a non-quantifiable added benefit for another one.

Research question based on virus type and liver status

Hepatitis C is caused by infection with an RNA virus, of which there are several genotypes. One of the factors determining treatment is whether patients already have cirrhosis and whether this cirrhosis is compensated or decompensated—i.e. whether the liver tissue not yet affected can still maintain the functioning of the organ or not.

The Federal Joint Committee (G-BA) therefore distinguished eight groups of patients, two of which it divided further into subgroups, resulting in a total of ten research questions to be investigated. The appropriate comparator therapies consisted of other antiviral therapies in

nine subindications, and in best supportive care, i.e. best possible, individually optimized treatment to alleviate symptoms and improve the quality of life, for patients with genotype 2 to 6 and decompensated cirrhosis.

Hint of considerable added benefit in virus genotype 2

Data from the ASTRAL-2 study, in which the antiviral treatment in both arms lasted 12 weeks, were available for patients without cirrhosis or with compensated cirrhosis infected with genotype 2 viruses. According to the approval of sofosbuvir, treatment in the comparator arm could have been extended to 24 weeks, however. The informative value of the results was limited by the fact that this option was not used and by the lack of analyses on the outcome "sustained virologic response" 24 weeks after the end of treatment: Only data on virologic response 12 weeks after the end of treatment were submitted.

There were no statistically significant differences between the study arms in the outcome categories "mortality" and "health-related quality of life". Regarding morbidity, sustained virologic response is considered to be a sufficiently valid surrogate for the patient-relevant outcome "liver cell cancer". In this outcome, there was a hint of an added benefit of the new combination for men, but not for women. A hint of lesser harm of the new combination in the total study population was shown for two side effects - fatigue and psychiatric disorders. Hence overall, there is a hint of considerable added benefit of sofosbuvir/velpatasvir in comparison with the appropriate comparator therapy in this subindication.

Virus genotype 3: hint of non-quantifiable added benefit

The ASTRAL-3 study, which was conducted in participants infected with genotype 3 viruses, compared 12-week treatment with the new drug combination with a 24-week antiviral comparator therapy. The different treatment durations in the study arms were accompanied by different observation periods. As a result, the data on many outcomes could not be meaningfully interpreted. In addition, only data recorded 12 weeks after the end of treatment were submitted on the important outcome "sustained virologic response" also in this case, although analyses on a follow-up period of 24 weeks would have been possible. As a result, no more than hints could be derived.

The new drug combination had an advantage over the comparator therapy in sustained virologic response. There were hints of lesser harm in the outcome "discontinuation due to adverse events"; no conclusions were possible for other outcomes. Overall, this resulted in a hint of an added benefit of the new drug combination, which is non-quantifiable, however.

Historical comparisons and consideration of individual study arms unsuitable

The drug manufacturer only submitted unadjusted historical comparisons for patients infected with genotype 1 viruses and for patients without cirrhosis infected with genotype 4 viruses. Based on these comparisons, conclusions on the added benefit would only be possible if the observed effects were so large that they could not be caused by systematic bias alone. Such so-called dramatic effects were not present in this case.

For the remaining four subindications, the manufacturer submitted data on the new drug combination, but not on the corresponding appropriate comparator therapies. Based on this, no added benefit could be derived

for the research questions of the benefit assessment.

Overall, an added benefit of sofosbuvir/velpatasvir in comparison with the appropriate comparator therapies is not proven for eight of ten subindications. There is a hint of an added benefit in two subindications.

G-BA decides on the extent of added benefit

The dossier assessment is part of the early benefit assessment according to the Act on the Reform of the Market for Medicinal Products (AMNOG) supervised by the G-BA. After publication of the dossier assessment, the G-BA conducts a commenting procedure and makes a final decision on the extent of the added benefit.

More English-language information will be available soon (Sections 2.1 to 2.13 of the dossier assessment as well as easily understandable information on informedhealth.org). If you would like to be informed when these documents are available, please send an e-mail to info@iqwig.de.

More information: www.iqwig.de/en/projects-resul … -35a-sgb-v.7604.html

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