Ticagrelor: Considerable added benefit for specific patients

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Since the start of 2011, the active ingredient ticagrelor can be prescribed in Germany in addition to acetylsalicylic acid (ASA) to avoid blood clots in patients with acute ischaemia of the cardiac muscle. The German Institute for Quality and Efficiency in Health Care (IQWiG) has now examined whether ticagrelor offers advantages to patients with acute coronary syndrome (ACS) in comparison with conventional drugs. This is the first co-called "early benefit assessment" that IQWiG has performed on the basis of a dossier provided by the manufacturer, in accordance with the new legal regulations.

The Institute has come to the conclusion that ticagrelor provides considerable added benefit to patients with "mild" myocardial infarction without the typical changes in the ECG (NSTEMI), as well as to patients with unstable angina pectoris, by reducing the risk of death and myocardial infarction. However, there is no corresponding proof for "severe" myocardial infarction (STEMI), in which there are usually characteristic changes in the ECG.

IQWiG assesses, G-BA decides

The company AstraZeneca developed the drug and introduced it to the German market at the start of 2011, under the trade name of Brillique®. On 1 January 2011, the German Act on the Reform of the Market for Medicinal Products (AMNOG) came into force, which lays down that new pharmaceuticals should regularly be subjected to a benefit

assessment. For this purpose, the pharmaceutical company must submit a dossier containing proof of the added benefit, in comparison to the "appropriate comparator". The latter is specified by the Federal Joint Committee (G-BA).

The G-BA is responsible for the overall process, but can commission IQWiG to assess the manufacturer's dossier - as happened with ticagrelor. IQWiG then issues a recommendation as to how the added benefit is to be classified. After the commenting procedure, the G-BA reaches a formal decision on this added benefit. The assessment is only then complete.

Advantages in mortality and myocardial infarction

The G-BA specified clopidogrel as the appropriate comparator for the therapeutic indication of unstable angina pectoris or NSTEMI. On the basis of data from the PLATO study, the manufacturer could demonstrate that ticagrelor offers advantages to patients for this therapeutic indication. There were fewer deaths with ticagrelor than with clopidogrel. There were also fewer myocardial infarctions with ticagrelor, although it was not clear to what extent these were relevant to the analysis, i.e. were perceptible, myocardial infarctions.

No proof that severe bleeding events are more frequent

Drugs that inhibit parts of the blood clotting system generally also increase the risk of bleeding. However, severe bleeding events were no more frequent during treatment with ticagrelor than during treatment with clopidogrel. On the other hand, there was proof of more harm from ticagrelor with respect to study discontinuations due to adverse events and shortage of breath (dyspnoea).

Added benefit of intermediate category in patients with unstable angina pectoris and NSTEMI

After considering the individual results, IQWiG has classified the added benefit of ticagrelor in comparison with clopidogrel as being "considerable" in patients with unstable angina pectoris or NSTEMI. The legislator has classified three different degrees of added benefit - "minor", "considerable" and "major" in order to determine its extent. However, according to the legal requirements, the highest category should be reserved for drugs which give "persistent great improvement, which has not previously been seen". In other words, it must be regarded as a breakthrough in the treatment of the disease.

No proof of added benefit for patients with STEMI

The dossier failed to provide proof that ticagrelor is of added benefit for patients with STEMI. In patients whose coronary arteries had been expanded with a balloon catheter (PCI) after a STEMI, the comparison with prasugrel (another coagulation inhibitor) showed no advantages for ticagrelor. No informative data were provided by the manufacturer for patients who had only been given drug treatment after a STEMI or who had received a bypass operation. One reason for this was that AstraZeneca deviated from the appropriate comparator which the G-BA specified for the therapeutic indication "STEMI". In the opinion of IQWiG, AstraZeneca has not adequately justified this deviation, given that it was even partially inconsistent with the approval status of the coagulation inhibitors.

The law demands that benefits and harms should be balanced

According to the Institute's Director, Jürgen Windeler, "Myocardial

infarctions and deaths are rarer with ticagrelor than with clopidogrel. However, there is also proof of more harm, such as increased dyspnoea. It is difficult to balance these advantages and disadvantages. Value judgements play a role here and to date there is no generally accepted scientific method for striking such a balance."

Nevertheless, IQWiG has to do this, as the legislator explicitly demands that a benefit assessment according to AMNOG should contain an overall conclusion, including a conclusion on the extent of the added benefit. According to Windeler, IQWiG has explained how they have arrived at the assessment of the different outcomes and how they have come to the overall conclusion. They explicitly wish this to be viewed as a suggestion. Not only the results, but also the methods could be discussed during the commenting procedure at the G-BA. They hope and wish that the procedure IQWiG has used in the case of ticagrelor will encourage scientific debate.

Patients and external experts involved

Both patients and external experts are regularly involved in the assessment of dossiers by IQWiG. Because of time limitations, this is mostly done by post. Medical advisors, generally specialists, and representatives of affected patients are sent questionnaires. This allows them to provide information about what they consider to be the important points for the treatment of the specific disease.

Practicable and transparent procedure

At the end of September 2011, IQWiG transmitted the dossier assessment to the G-BA, which then published it on 4 October 2011 - together with the manufacturer's dossier - and initiated the commenting procedure. It is planned that the G-BA will complete the assessment

within three months of the publication. According to Thomas Kaiser, Head of the Department of Drug Assessment: "It is a real milestone, also internationally, that not only the IQWiG assessment is being published, but that the manufacturer has to disclose all relevant data. This is one reason why international experts are so interested in the early benefit assessment."

In IQWiG's opinion, the AMNOG procedure has passed its first practical test. Jürgen Windeler summarizes: "It is practicable and can be implemented in detail. The legal specifications have turned out to be appropriate. The first assessment certified that the drug shows added benefit and this demonstrates that the anxieties which have been expressed again and again by the pharmaceutical industry are unjustified. AMNOG does not present a threat to Germany as a site for industry."

Provided by Institute for Quality and Efficiency in Health Care

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