IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Leukotriene receptor antagonists in patients with asthma[1]

Executive Summary

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Executive summary

Background

The Federal Joint Committee commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a benefit assessment of leukotriene receptor antagonists (LTRAs) in patients with asthma within the framework of the approval of LTRAs in Germany. (The only LTRA approved in Germany at the time of commissioning was montelukast).

Research question

The aims of the investigation were:

- The comparative benefit assessment of long-term treatment with montelukast vs. placebo or another anti-asthmatic agent (in each case as add-on therapy to inhaled corticosteroids, ICS) in patients with mild to moderate persistent asthma.
- The comparative benefit assessment of monotherapy with montelukast vs. placebo or another anti-asthmatic agent in patients with exercise-induced asthma.

The focus of the assessment was on patient-relevant therapy goals.

Methods

A systematic literature search was conducted in the databases MEDLINE (1966 to August 2005), EMBASE (1980 to August 2005), and CENTRAL (August 2005). Reference lists of relevant secondary publications (systematic reviews, HTA reports, and meta-analyses) were also searched, as well as study registries and publicly accessible regulatory documents.

Randomised controlled trials (RCTs) were included that compared montelukast/ICS with ICS monotherapy or ICS plus an alternative additional anti-asthmatic agent in patients with mild to moderate persistent asthma. The minimum study duration was 12 weeks. The assessment also included RCTs that compared montelukast monotherapy with placebo or another anti-asthmatic agent in patients with exercise-induced asthma; there was no restriction in study duration.

The literature screening was conducted by 2 reviewers independently of one another.

After the assessment of study quality, the results of the individual studies were collated and presented according to therapy goals and outcomes. Where feasible and meaningful, data on the different outcomes were summarised in a quantitative manner in a meta-analysis.

IQWiG's preliminary benefit assessment, the preliminary report, was published on the IQWiG website (www.iqwig.de), and interested parties were invited to submit written comments.

Substantial comments were discussed in a scientific debate and the final report was subsequently produced.

Results

The literature search identified 15 trials for the assessment of mild to moderate persistent asthma (including 2 paediatric trials), and 4 trials for the assessment of exercise-induced asthma (including 1 paediatric trial). With regard to study and publication quality, 10 of these trials showed major deficiencies, 3 showed minor deficiencies, and 6 showed none.

Mild to moderate persistent asthma: montelukast/ICS vs. ICS monotherapy

In patients with insufficiently controlled asthma, montelukast/ICS combination therapy offered advantages compared with ICS monotherapy with an equivalent ICS dosage.

There was better control of asthma symptoms with montelukast/ICS than with ICS monotherapy. This applied to daytime as well as nocturnal symptoms (measured by means of symptom scores). The rate of asthma-free days with montelukast/ICS was higher than with ICS monotherapy (66% asthma-free days vs. 42% asthma-free days, NNT per additional asthma-free day: 10). With regard to asthma-related nocturnal awakenings, the studies showed that the rate of such awakenings was reduced more with montelukast/ICS (1 night per week) than with ICS monotherapy (1 night per 2 weeks). The percentage of patients who experienced nocturnal awakenings was also lower with combination therapy (26% vs. 32%).

The proportion of days with exacerbations was lower with montelukast/ICS than with ICS monotherapy (Laviolette 1999: 13% vs. 18%; Vaquerizo 2003: 3% vs. 5%). In 1 study, the proportion of patients with exacerbations was lower with montelukast/ICS than with ICS monotherapy (6 % vs. 12%). In another study with a small sample size, the proportion of patients with exacerbations after reduction of the ICS dose to 25% of the baseline dose was comparable for both treatment options (2 vs. 3 patients).

Data on asthma-related hospital admissions and outpatient medical consultations were not provided in the studies.

Patients' assessments of quality of life and asthma status were comparable for both treatment options.

Adverse events rates reported in the publications and study reports were comparable for patients receiving montelukast/ICS and those receiving ICS monotherapy.

In 1 study, it was shown that with montelukast/ICS the ICS dose (with maintenance of symptom control) could be reduced more with montelukast/ICS than with ICS monotherapy (by 47% vs. 30%). A further study also showed a small advantage for montelukast, and 2 other studies showed no difference in the possibility of reducing the ICS dose through the addition of montelukast. However, with regard to the research question investigated, these 3 studies showed relevant methodological deficiencies. Conclusions cannot therefore be drawn

from the studies as to whether the reduction of the ICS dose achieved in the first study might result in a reduction of ICS-related adverse effects.

Mild to moderate persistent asthma: montelukast/ICS vs. salmeterol/ICS

Combination therapy including salmeterol showed advantages regarding efficacy vs. combination therapy including montelukast. However, with salmeterol/ICS there were indications of a possibly higher risk of adverse effects than with montelukast/ICS.

Most study results on asthma symptoms demonstrated an advantage in favour of salmeterol/ICS compared with montelukast/ICS. In 1 study, results for daytime symptoms were comparable for montelukast and salmeterol; another study showed comparable results concerning asthma-related nocturnal awakenings. Concerning symptom-free days, differences of 4% to 14% more symptom-free days (1 additional symptom-free day per 2 weeks) were reported in favour of salmeterol/ICS. The proportion of symptom-free nights was between 6% to 8% greater with salmeterol/ICS than with montelukast/ICS. Nocturnal awakenings were reduced by 0.06 and 0.23 nights per week with salmeterol/ICS compared with montelukast/ICS.

The risk of an exacerbation was increased with montelukast/ICS vs. salmeterol/ICS. The differences observed varied substantially between studies: from an increased relative risk of 5% in Bjermer 2003 to a 3-fold increased risk in Nelson 2000. Overall, advantages in favour of salmeterol were more pronounced in the 12-week trials than in the 48-week trials. A meta-analysis showed a statistically significant advantage for salmeterol in pooled 12-week trials (RR 2.03; 95% CI 1.23 to 3.37) and a non-statistically significant advantage for salmeterol in pooled 48-week trials (RR 1.12; 95% CI 0.96 to 1.30).

No differences between therapy options were shown in the number of hospital admissions. Data on outpatient medical consultations were inconclusive. In 1 study the number of outpatient medical consultations was comparable. In 2 studies, patients in the montelukast/ICS group consulted a physician more frequently than in the salmeterol/ICS group; in 1 study, this difference between groups was statistically significant. A meta-analysis of outpatient medical consultations in the 48-week trials showed an increased risk of 21% for a medical consultation in patients receiving montelukast. This result was not statistically significant (RR 1.21; 95% CI 0.99 to 1.48).

In 1 study, patients' assessment of quality of life was comparable for both treatment groups; in another study, quality of life was assessed more positively in the salmeterol/ICS group than in the montelukast/ICS group. However, only a slight difference between groups was shown, and the clinical relevance of this advantage for salmeterol is unclear. One study showed higher treatment satisfaction in the salmeterol/ICS group than in the montelukast/ICS group.

To a large extent, the available data on adverse events showed a similar safety profile between treatment groups. However, in some cases there were indications of more adverse effects with salmeterol/ICS than with montelukast/ICS. However, the relevance of these observations

cannot be judged from the available data. In the individual trials, the following differences were observed: in Bjermer 2003 the rate of serious adverse events was 7.4% (n=55) in the salmeterol/ICS group and 4.6% in the montelukast/ICS group (n=34). In Ilowite 2004, 4.2% patients (n=31) in the salmeterol/ICS group and 2.4% patients (n=18) in the montelukast/ICS group discontinued the study due to adverse events. In Bjermer 2003, adverse events causally related to the study drug were reported by the investigators in 10.0% of patients (n=74) in the salmeterol/ICS group, and in 6.3% of patients (n=47) in the montelukast/ICS group. In Ilowite 2004, adverse events possibly causally related to the study drug were reported by the investigators in 10.0% of patients (n=73) in the salmeterol/ICS group and in 8.6% (n=64) in the montelukast/ICS group. A meta-analysis of data on serious adverse events showed comparable rates for therapy options in the pooled 12-week trials; however, in the pooled 48-week trials, statistically significantly more serious adverse events occurred in the salmeterol/ICS group vs. montelukast/ICS. A meta-analysis of the rate of study discontinuations due to adverse events showed an advantage in favour of salmeterol/ICS in the pooled 12-week trials, and an advantage for montelukast/ICS in the pooled 48-week trials. None of these differences were statistically significant.

No data on patients' physical capacity were available from the studies included. With regard to their design and duration, the studies were not suitable for the investigation of the impact of the therapy options on asthma-related mortality and all-cause mortality. Statements on these outcomes are therefore not possible.

Results from paediatric trials

Overall, the data situation is insufficient for the benefit assessment of montelukast/ICS therapy in children with mild to moderate persistent asthma.

Only limited data on exacerbations, adverse events, or the potential reduction of the ICS dose were available from the 2 studies identified that compared montelukast/ICS with ICS monotherapy.

In Karaman 2004, 1 exacerbation in the montelukast/ICS group was reported. Further information on exacerbations was not available.

In the study by Phipatanakul 2003, the ICS dose could be reduced in the montelukast/ICS group (whilst maintaining symptom control), whereas the dose was increased in the ICS monotherapy group. More patients discontinued ICS in the montelukast/ICS group than in the ICS/placebo group. None of these differences were statistically significant.

The adverse event rates were comparable for the treatment options investigated.

Exercise-induced asthma

One small study in adults showed that patients' physical capacity was better after montelukast therapy than after placebo. No data were available on the efficacy of montelukast in children with exercise-induced asthma.

The overall adverse event rate for montelukast monotherapy and placebo was comparable in the studies available. This applied to adults (Bronsky 1997) and children (Kemp 1998). However, when interpreting these results one needs to consider that patients in both studies were treated for only 2 days. In Leff 1998, the rate of study discontinuations in the montelukast and placebo groups was also comparable.

Conclusion

The benefit of combination therapy with montelukast/ICS vs. ICS monotherapy (in an equivalent ICS dosage) has been demonstrated for the short-term treatment (up to 16 weeks) of adolescents and adults with mild to moderate persistent asthma

An additional benefit of montelukast (under consideration of desired and undesired effects) when compared with other add-on treatment options (only salmeterol was assessed) has not been demonstrated in adolescents and adults with mild to moderate persistent asthma.

There are indications of a benefit of montelukast monotherapy in adolescents and adults with exercise-induced asthma.

In children, the benefit of montelukast/ICS combination therapy in mild to moderate persistent asthma and montelukast monotherapy in exercise-induced asthma has not been demonstrated.

Key words: asthma, exercise-induced asthma, leukotriene receptor antagonist, montelukast, systematic review.