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An overview of reports on montelukast

Introduction

Montelukast (Singulair®) was approved for the market in November 1998 for *treatment of asthma, as combination therapy, and for patients with light to moderate forms of chronic asthma that can not be adequately controlled by inhalation corticosteroids or short-term ß-agonists. Montelukast is also indicated in asthma prophylaxis, if exercise-induced bronchoconstriction is the main factor.* Montelukast is an orally active substance, which binds with high affinity and high selectivity to the cysteinyl leukotriene-receptor CysLT1. Cysteinyl leukotrienes (leukotriene C4, D4 and E4) are pro-asthma mediators that bind to cysteinyl leukotriene receptors in the bronchi and induce several respiratory effects, including bronchoconstriction, secretion of mucus and cell locomotion of blood eosinophils. Montelukast can improve respiration function by antagonising the cysteinyl leukotriene-receptor CysLT1. Lung function improvements are maintained on chronic administration and are associated with reductions in a variety of asthma symptom scores [1-3].

The following adverse events have been reported in association with montelukast (table1)[1]:

Table 1: ADRs mentioned in the SPC, separated by system and organ class and by origin from either (pre-) clinical studies or post-marketing surveillance.

S&O Class	clinical studies	post-marketing
Body as a whole:	*common:* abdominal pain, asthenia, tiredness, fever, trauma	asthenia, tiredness, influenza, malaise, oedema, allergic reaction including anaphylaxis, angioneurotic oedema, rash, urticaria, pruritus
Nervous system	*very common:* headache *common:* dizziness, insomnia	dizziness, insomnia, abnormal dreams (including nightmares), drowsiness, hallucination, irritability, restlessness, and seizure
Gastrointestinal tract:	*common:* diarrhoea, dry mouth, dyspepsia, infectious gastroenteritis, toothache, nausea	diarrhoea, dry mouth, dyspepsia, vomiting
Cardiovascular:		increased bleeding tendency, bruising, palpitation
Respiratory:	*very common:* cough, pharyngitis *common:* stuffed up nose, sinusitis, influenza	
Musculoskeletal:		arthralgia, myalgia
Furthermore:	Churg-Strauss syndrome is mentioned under 'special warnings'	

Montelukast has been approved for almost 3 years. We give an overview of reported adverse events, including the Dutch reports from the MAH.

Reports

Until 19 September 2002, Lareb received 38 reports from health professionals (including one report from the marketing authorisation holder) representing 52 suspected adverse reactions (ADRs) on montelukast (see Table 1).

Four of these reports were classified as serious:
One report of a paediatrician concerning a possible anaphylactic reaction characterised by facial oedema, rash, coughing and fatigue in a 4-year old boy, occurring 2 days after starting montelukast 5 mg daily for asthma. As concomitant medication formoterol and budesonide inhalation were used. Montelukast was discontinued and patient was treated with prednisone and clemastine, after which symptoms significantly improved. Laboratory examination revealed an increased IgE: 209 kU/l (ref 0-60 kU/l). Complement factors C3 1.02 g/l (ref. 0.83-1.56 g/l); C4 0.26 g/l (ref. 0.16-0.40 g/l) and eosinophils $0.17*10^9$/l (ref.0.04-0.4 $*10^9$/l) were within the normal range.

Table 1. Distribution of the Lareb-reported ADRs associated with the use of montelukast.

System Organ Class (MedDRA)	*n*
Eye disorders	1
Gastrointestinal disorders	6
General disorders and administration site conditions	3
Infections and infestations	1
Investigations	2
Metabolism and nutrition disorders	1
Musculoskeletal and connective tissue disorders	3
Nervous system disorders	6
Psychiatric disorders	5
Reproductive system and breast disorders	1
Respiratory, thoracic and mediastinal disorders	4
Skin and subcutaneous tissue disorders	16
Vascular disorders	3
Total number of adverse drug reactions	52

The second serious report concerned a 20-year-old female who died as result of pulmonary embolism 8 weeks after starting montelukast for asthma. The reporters considered the causal relationship with the use of montelukast uncertain.
The third report concerns of a 45-year-old female who was admitted to a hospital for treatment of her asthma. Some hours after starting montelukast, she developed fatigue, malaise and rigors for which prolongation of the hospital admission was necessary. The medication was discontinued and she recovered.
Finally, the MAH reported a 28-year-old man, who used montelukast 10 mg od for the treatment of asthma. Concomitant medication included fluticasone propionate. Four days after the start with montelukast, he experienced urticaria and was hospitalised. He was treated with terfenadine. The use of montelukast was discontinued but the urticaria persisted.

The reported ADRs most frequently belonged to the system organ class: skin and subcutaneous tissue disorders. The ADRs in this system organ class included alopecia, angioneurotic oedema, face oedema, periorbital oedema, pruritus, purpura, rash, psoriatiform rash, vesicular rash, increased sweating and urticaria.

Other sources of information

Literature

Articles and reviews on the efficacy and safety of use of montelukast in asthma management in clinical studies generally reveal the same ADRs as referred to in the SPC [4-7].

Databases

In September 2002, the WHO database contained 2,784 ADRs on montelukast. ADRs that were disproportionately over-presented were: Churg Strauss syndrome (Reporting Odds Ratio 759; 95%CI 978-1259), asthma (ROR 16; 95%CI 20-25), bronchospasm aggravated (ROR 10;95%CI 16-24), eosinophilia (ROR 8.97 (95%CI 11-14) and vasculitis (ROR 7.6;95% CI 9.9-12.9). These reported adverse events may all be indicative of a Churg Strauss syndrome or, in the event of respiratory disorders, also may be confounded by indication.

Conclusion

In general the reports on montelukast received by Lareb and the WHO show a spectrum of adverse reactions comparable to those mentioned in the SPC.
Most of these unlabeled ADRs were
reported only once to Lareb. All system and organ classes in table 1 with n=1 refer to unlabeled

ADRs (vision blurred, urinary tract infection, appetite increased and priapism). Two unlabeled ADR's were reported twice: alopecia and weight increase.
There are no signs of (frequently reported) unexpected adverse events.

References

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