Montelukast-Induced Adverse Drug Reactions: A Review of Case Reports in the Literature

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Key Words

Montelukast · Adverse drug reaction · Anti-leucotrienes · Allergy · Asthma · Hypersensitivity · Pharmacovigilance · Churg-Strauss syndrome · Toxicity

Abstract

Background: Montelukast, a leucotriene receptor antagonist, binds the cysteinyl leucotriene type 1 receptor. Montelukast is commonly prescribed to asthma patients as add-on therapy to inhaled corticosteroids. Several clinical trials emphasized that montelukast can be considered a safe drug. However, recent evidence reconsidered the benefit/risk ratio of the use of montelukast for both paediatric and adult patients. **Summary:** The present review analyzed the previously published case reports regarding montelukast-induced adverse drug reactions (ADRs). They included agitation, anxiety, depression, sleep disturbance, hallucinations, suicidal thinking and suicidality, tremor, dizziness, drowsiness, neuropathies and seizures. The immune system can be involved, in particular, cases of Churg-Strauss syndrome have been published. Furthermore, it can induce hypersensitivity reactions, including anaphylaxis and eosinophilic infiltration. In

addition, hepatobiliary, pancreatic and uropoietic disorders have been observed. Some of these cases are characterized by severe prognosis (i.e. neurological deficit and fatal hepatotoxicity). **Key Message:** The use of montelukast can be burdened by several ADRs, of which physicians should be aware in their clinical practice. A better understanding of the mechanisms causing ADRs after using montelukast could help researchers and clinicians in defining a risk-reduction strategy aimed to lessen montelukast toxicity. More accurate epidemiological studies, in order to discover risk factors favouring montelukast-associated ADRs, are demanded.

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Introduction

Montelukast sodium is a selective leucotriene receptor antagonist (LTRA) that specifically blocks the cysteinyl leucotriene type 1 (CysLT1) receptor. CysLTs (LTC 4, LTD 4 and LTE 4) are important pro-asthmatic lipid mediators binding to CysLT receptors. The CysLT1 receptor is localized in the human airways and synthesized by a variety of cells, including mast cells, eosinophils, baso-

phils and macrophages [1]. CysLTs have been correlated with the pathophysiology of asthma and allergic rhinitis [2]. Montelukast is an orally active compound with anti-inflammatory properties, which is effective in improving clinical parameters of asthmatic inflammation (i.e. respiratory function and FEV1 in clinical trials). It causes bronchodilation in addition to that produced by beta-2-stimulating drugs [3].

Asthma is a chronic immunological disorder of the lung characterized by reversible airway obstruction, airway inflammation and increased airway hyperresponsiveness to provocative challenge [4]. As many as 300 million individuals of all ages, and all ethnic backgrounds, suffer from asthma, and the burden of this disease to public health is increasing worldwide [5]. LTRAs provide an alternative treatment for asthma patients who are not controlled by, not satisfied with or refuse to take inhaled corticosteroids (ICS) therapy [6, 7]. In patients whose asthma is not controlled by ICS therapy, the addition of a second drug, rather than increasing the dose of ICS, can result in an improved control of the symptoms [8, 9].

Background

Montelukast is generally considered a safe drug with the occurrence of a few adverse drug reactions (ADRs). The overall incidence of adverse events (AEs) due to montelukast, based on clinical data, suggests that it is comparable to placebo and its use as add-on therapy does not seem to increase AEs in comparison to mono-therapy based on ICS or beta-2 stimulants [7, 10]. A review of clinical trials summarized the safety and tolerability information for montelukast evaluating data from 2,751 paediatric patients. The authors found that montelukast was well-tolerated, and the most frequent clinical AEs noticed in all treatments (placebo, montelukast and active control/usual care) in virtually all studies were upper respiratory infection, worsening asthma, pharyngitis and fever [11, 12].

A recent study has reconsidered the benefit/risk ratio in paediatric patients, suggesting that there is not sufficient proof to support therapeutic and safety advantages of anti-leucotriene use as add-on therapy in asthmatic children [13]. A Cochrane review, comparing long-acting beta-2 agonists versus anti-leucotrienes (including montelukast) in children and adults on regular treatment with ICS, stated that anti-leucotrienes caused less incidences of serious AEs compared to long-acting beta-2 agonists

[14]. Although anti-leucotrienes are generally well-tolerated, several case reports describing ADRs after the use of montelukast have been published. For this reason, it appears desirable to explore and summarize the literature to offer a helpful perspective to clinicians, which enables them to better recognize and manage montelukast-induced ADRs.

Methods

A search of the scientific literature for case reports on montelukast and ADRs published prior to March 1, 2014, has been conducted. Two investigators independently collected articles from EMBASE, PubMed, Scopus, SciFinder, Web of Science and Google Scholar. The following keywords were used (alone or in combination): montelukast sodium, montelukast, antileukotriene, anti-leukotriene, leukotriene receptor antagonist, adverse reaction, adverse event, side effect, safety profile and toxicity. Only case reports where montelukast has been administered according to the dose indicated in the summary product characteristics (SPC) and articles in English were included. In this review, the case reports are summarized according to the systems or organs involved in the ADRs. Tables 1 and 2 give a brief overview of the main features of the case reports. We only included case reports where the full text of the article was available.

Immune System Disorders

Hypersensitivity Reactions Including Anaphylaxis, Hepatic Eosinophilic Infiltration and Autoimmune Vasculitis

Churg-Strauss syndrome (CSS) is a rare form of eosinophilic vasculitis associated with asthma [15, 16]. Its incidence rate is approximately 1–2 cases per million persons per year; it may range from 0.3 to 4 cases per million persons per year [17]. The possible role of LTRA therapy in the pathogenesis of CSS is still uncertain. Several case reports and case series describe the onset of CSS in patients receiving montelukast for the management of difficult-to-control moderate-to-severe asthma.

In their article, Bibby et al. [18] examined the association between LTRA therapy and CSS in cases detected in the Food Drug Administration (FDA) Adverse Event Reporting System database. The authors concluded that LTRA therapy was a suspected cause of CSS confirmed in 114 cases. In about two-thirds, it was not possible to associate pre-existing or possible prodromal CSS to the reduction in oral or ICS therapy [18].

In individuals suffering from asthma, LTRA-induced CSS commonly presents with a wide range of clinical

Table 1. Summary of the case reports on montelukast-induced CSS

Reference		Indication	Age, years Gender	Dosage of montelukast Duration of therapy	Concomitant therapy/-ies	ADRs	Severity of ADRs and prognosis
Anar et al., 2012 [30]		rhinitis, asthma	59, female	10 mg, 3 years	inhaled salmeterol, beclomethasone	CSS, bilateral pulmonary infiltrates, leucocytosis, eosinophilia	resolution within 2 months
Black et al., 2009 [34]		cough asthma	37, female	NR, NR	ICS, albuterol, antibiotics	CSS, pulmonary infiltrates, leucocytosis, eosinophilia, nasal polyps	resolution within 1 year
Cuchacovich et al., 2007 [23]	case 1	asthma, allergic rhinitis	68, female	10 mg once a day, 4 months	insulin, zocor otensin, Lasix, flonase, neurontin, albuterol	CSS, skin rash, dry cough, shortness of breath, chest tightness	resolution
	case 2	asthma	43, female	10 mg once a day, 1 year	prednisone	CSS, fever, generalized malaise, arthralgias, jaundice with a serum bilirubin at 3 mg/dl; liver biopsy revealed eosinophilic hepatitis	resolution
	case 3	asthma	58, female	10 mg once a day, 6 months	prednisone up to 40 mg/day, albuterol	CSS, fever, purpuric rash was present on her lower extremities; synovitis of the wrists; bilateral scleritis	resolution
Conen et al., 2004 [35]		asthma	46, male	10 mg, 2 months	ICS and intermittent salbutamol, oral prednisone	CSS, hepatojugular reflux and inspiratory crackles, depressed left ventricular function, pericardial effusion, pulmonary infiltrates, leucocytosis, eosinophilia	resolution
Currie et al., 2008 [24]		asthma	40, male	10 mg, 1 month	250 mg fluticasone/ 25 mg salmeterol (2 puffs twice daily)	CSS, respiratory symptoms, maculopapular rash, pulmonary infiltrates, leucocytosis, eosinophilia	CSS abnormalities
Franco and Artés, 1999 [31]		asthma	26, male	10 mg, 4 months	1,000 µg fluticasone daily	pulmonary eosinophilia	resolution
Girszyn et al., 2008 [25]		asthma	47, female	NR, 5 months	NR	CSS, fever, cutaneous manifestations, pain and paraesthesias, pulmonary infiltrates, leucocytosis, eosinophilia	resolution
Goransson and Omdal, 2000 [20]		asthma	46, female	NR, 4 months	prednisolone, budesonide, formoterol, terbutaline	CSS, pulmonary infiltrates, leucocytosis, eosinophilia, microscopic haematuria, hyaline, granular and erythrocyte casts, 1.6 g urinary protein, necrotizing glomerulonephritis	resolution, persistent proteinuria
Jennings et al., 2009 [26]		asthma	21, female	NR, 5 weeks	fluticasone steroid nebulizer, salbutamol inhaler	CSS, bronchiectasis, asthma and eczema, bullous vasculitic rash, pulmonary infiltrates, leucocytosis, eosinophilia, ANCA	resolution within 4 weeks
Matsui and Nishijima, 2011 [29]		asthma, rhinitis	64, female	NR, 4 months	atorvastatin	CCS with hepatitis	
Man et al., 2012 [27]		asthma	62, female	10 mg, 5 months	50/500 µg salmeterol/ fluticasone	CSS, pulmonary infiltrates, leucocytosis, eosinophilia, fever, malaise, sensory deficits in the lower extremities, diffuse musculoskeletal and thoracic pain	resolution
Michael and Murphy, 2003 [22]		asthma	68, male	NR, 3 months	beclomethasone, ipratropium, salbutamol inhalers, aspirin, nifedipine	CSS, pulmonary infiltrates, leucocytosis, eosinophilia, polyneuropathy	partial resolution, neurological deficit

Table 1. (continued)

Reference		Indication	Age, years Gender	Dosage of montelukast Duration of therapy	Concomitant therapy/-ies	ADRs	Severity of ADRs and prognosis
Mukhopadhyay and Stanley, 2001 [38]		asthma	56, male	10 mg, 6 months	1,000 µg fluticasone, 100 µg salmeterol daily, prednisolone	CSS, proteinuria, rash, leucocytosis, eosinophilia	resolution of symptoms only with prednisolone 10 mg maintenance therapy
Solans et al., 2002 [21]	case 1	CSS	54, male	10 mg, 2 weeks	10 mg/day prednisone, 100 mg/day cyclophosphamide	relapse of CSS, fever, dyspnoea on exertion, and polyarthralgia, rash, rhonchi, wheezes, scattered coarse crackles in the bases of both lungs, pulmonary infiltrates, leucocytosis, eosinophilia	resolution on 10 mg/day prednisone and 100 mg/day cyclophosphamide
	case 2	asthma	60, female	10 mg, 4 months	inhaled β agonists, inhaled steroids, oral theophylline	CSS, malaise, myalgia, polyarthralgia, progressive numbness of and pain in her lower and upper limbs, erythematous exanthema, deep tendon areflexia in the right upper limb and in both lower limbs, with flexor plantar responses, diminished sensation, rheumatoid factor, ANCA, ANA, leucocytosis, eosinophilia	partial resolution, sensorimotor sequelae
	case 3	asthma	62, female	10 mg, 10 days	salmeterol and fluticasone propionate	CSS, malaise, myalgia, swollen ankles, polyarthralgia, and palpable purpura over both legs, leucocytosis, eosinophilia	resolution
Tuggey and Hosker, 2000 [32]		asthma	72, female	10 mg, 4 weeks	750 µg fluticasone twice daily together with 50 µg inhaled salmeterol twice daily	CSS, cough and breathlessness, swollen ankles, polyarthralgia, and numbness, malaise, inspiratory crackles, expiratory wheeze, rash, pulmonary infiltrates, leucocytosis, eosinophilia	resolution
Uyar et al., 2012 [39]		asthma	18, male	NR, 6 months	fluticasone propionate and salmeterol 500/ 50 µg twice daily	CSS, cough, dyspnoea and haemoptysis, pulmonary infiltrates, leucocytosis, eosinophilia	significant improvement
Villena et al., 2000 [19]		asthma	25, female	10 mg, 5 months	fluticasone, formoterol, terbutaline	CSS, fever, rash, proteinuria, pulmonary infiltrates, leucocytosis, eosinophilia	resolution on 15 mg/day prednisone
Wechsler et al., 2000 [28]	case 1	asthma	62, female	NR, 3 months	ICS	CSS, musculoskeletal pain, weakness, sensory loss in both lower and upper extremities, rash, leucocytosis, eosinophilia	partial resolution of polyneuropathy
	case 2	asthma	25, male	NR, 7 months	high-dose fluticasone (1,720 mg/day) and salmeterol (200 mg/day)	CSS, diarrhoea, fatigue, shortness of breath, rash, bibasilar rales, occult blood, neuropathy, pulmonary infiltrates, leucocytosis, eosinophilia	partial resolution, neuropathy
	case 3	asthma	38, female	NR, 2 months	inhaled steroids and β agonist	CSS, pulmonary infiltrates, leucocytosis, eosinophilia	resolution
	case 4	asthma	63, female	NR, 6 months	880 µg fluticasone once daily	CSS, leucocytosis, eosinophilia, muscle pain, neuropathy	resolution

NR = Not reported; ANCA = antineutrophil cytoplasmic antibody; ANA = antinuclear antibody.

Table 2. Summary of the case reports on montelukast-induced ADRs

Reference	Indication	Age, years Gender	Dosage of montelukast Exposure time to montelukast	Concomitant therapy/-ies	ADRs	Severity of ADRs and prognosis
Actis et al., 2007 [55]	asthma	45, female	10 mg once a day 5 years	food supplements containing <i>Citrus aurantium</i> and <i>Garcinia cambogia</i> extracts	fatal hepatitis	dead
Alkhuja et al., 2013 [50]	asthma	16, female	10 mg once a day, 24 h	250 µg fluticasone propionate/50 µg salmeterol, albuterol sulfate	parasomnia (sleep talking and sleepwalking)*	resolution
Anandan and Ibitoye, 2008 [44]	asthma	29, female	10 mg once a day, 48 h	750 mg quetiapine once a day	worsening of hallucinations in paranoid schizophrenia	resolution within 2 days
Aypak et al., 2013 [62]	asthma	31, female	10 mg once a day, 1 month	200 µg budesonide twice a day	ecchymosis [§]	resolution
Byrne et al., 2012 [48]	asthma, rhinitis	9, male	5 mg once a day, 2 years and 6 months	50 µg beclomethasone inhaler (1 puff twice daily)	sleep disturbance, parasomnia, aggressive behaviour, anxiety	resolution within 2 weeks
Callero- Viera et al., 2012 [47]	case 1 asthma	9, male	5 mg once a day, 3 weeks	salbutamol, budesonide	headache, behavioural disturbances, aggressiveness, night terror	resolution within 24 h
	case 2 asthma	14, male	5 mg once a day, 2 months	salbutamol	extreme aggressiveness	resolution within 5 days
	case 3 asthma	14, male	10 mg once a day, 3 weeks	salbutamol	behavioural disturbances, extreme aggressiveness, autolytic ideation	resolution within 10 days
	case 4 asthma	8, male	5 mg once a day, 6 weeks	salbutamol	extreme aggressiveness, behavioural disturbances, night terrors	resolution within 7 days
Cetkovska and Pizinger, 2003 [57]	asthmatic bronchitis	8, female	5 mg once a day, 5 months	N/A, no other therapies	suspected pemphigus	resolution
Harugeri et al., 2009 [52]	asthma	46, male	10 mg once a day, NR	100 µg albuterol metered dose inhaler (2 puffs), 200 µg budesonide, 6 µg formoterol	hepatitis	resolution
Herzinger et al., 2008 [60]	asthma	50, female	10 mg once a day, NR	omeprazole	urticaria [§]	resolution
Incekik et al., 2007 [54]	asthma	5, male	5 mg once a day, 2 years	N/A, no other therapies	hepatitis with fatigue, vomiting	resolution within 2 weeks
Ibarra-Barrueta et al., 2014 [45]	asthma	41, female	10 mg once a day, 2 months	efavirenz, emtricitabine, tenofovir disoproxil fumarate	sleep disturbance, vivid dreams, irritability, confusion, concentration difficulties	resolution
Kocyigit et al., 2013 [49]	asthma	13, male	NR, 24–36 h	formoterol, budesonide	hallucination, anxiety	resolution
Minciullo et al., 2004 [58]	allergic rhinitis	28, male	10 mg once a day, 5 days	fluticasone	urticaria [§]	resolution
Palodhi et al., 2012 [51]	asthma	48, male	10 mg once a day, for around 1 month	hydrochlorothiazide, triamterene, beclomethasone, salbutamol	hypertriglyceridaemia [§]	resolution
Rusmann et al., 2003 [53]	NR	76, male	10 mg once a day, 2 years	salmeterol and fluticasone, <i>Serenoa repens</i> extract, acetylsalicylic acid	hepatitis with fatigue, vomiting, icterus	resolution

Table 2. (continued)

Reference	Indication	Age, years Gender	Dosage of montelukast Exposure time to montelukast	Concomitant therapy/-ies	ADRs	Severity of ADRs and prognosis
Sabbagh and Sheikh-Taha, 2009 [61]	allergy	46, female	10 mg once a day, 1 month	10 mg ebastine	angio-oedema	resolution
Tayeb, 2013 [63]	asthma	30, female	10 mg, just 1 administration	budesonide, formoterol	urticaria, shortness of breath, lip swelling	resolution
Tedeschi, 2009 [59]	urticaria	23, male	10 mg, just 1 administration	prednisone	urticaria	resolution with azathioprine

NR = Not reported.

[§] Causality assessment: Naranjo's algorithm was 'probable'.

* Causality assessments: World Health Organization-The Uppsala Monitoring Center (WHO-UMC) was 'certain'; Naranjo's algorithm was 'probable'.

signs, including fever, malaise, arthralgias, clinical jaundice, peripheral blood eosinophilia, eosinophilic hepatitis, scleritis and arthritis [19–30]. Pulmonary involvement can be prominent, and chest radiography can show mixed alveolar-interstitial eosinophilic (80%) infiltrates in the upper lobes [31]. Anar et al. [30] also reported haemoptysis. In some patients, LTRA-induced CSS can appear as skin lesions described as generalized bullous vasculitic rash or cutaneous necrotizing vasculitis [23, 26, 32]. In one case, a woman had a necrotic lesion in the foot suggestive of CSS [33]. Two case reports suggested that montelukast can act as a trigger for glomerulonephritis, a complication of CSS [4, 20]. Some other articles reported CSS with a prevalent cardiac involvement, which is considered a bad prognostic indicator [34]; and in one case, it was reported in a patient developing progressive heart failure along with severe obstructive symptoms [35]. In other case reports, patients with CSS experienced peripheral neuropathy [22, 36], which can persist even after montelukast has been discontinued and a successive improvement of CSS [21, 22, 32]. The time elapsed between the administration of montelukast and the development of clinically evident CSS was really short in some cases, less than 7 days, while in other cases, a latency of 6 months or even years has been observed [30, 37].

According to these case reports, patients who developed LTRA-induced CSS were also receiving other therapies; corticosteroids were the most common among them in combination with beta stimulants. Many patients were on salmeterol or salbutamol plus fluticasone propionate [19, 21, 24, 26, 27, 32, 38, 39]. In some cases,

the drugs taken by the patient included salbutamol, nedocromil, theophylline and beclomethasone [31]. In another case, described by Michael and Murphy [22], the patient took beclomethasone, ipratropium and salbutamol. In the case report by Mukhopadhyay and Stanley [38], the treatment consisted of budesonide, terbutaline and prednisolone [36, 38]. One of the patients in Solans et al.'s [21] case series was also taking aspirin and nifedipine.

Many investigators performed biopsy assessments for a more accurate diagnosis. It was confirmed that CSS may involve open lungs [24, 30, 34] and the skin [23, 38]. Summarizing the case reports, the management of LTRA-induced CSS consisted of discontinuing the use of montelukast and the uptake of systemic corticosteroids, such as mometasone [20, 32, 34, 37] and methylprednisolone [19, 21, 25, 26, 35]. Some authors managed CSS adding the immunosuppressive drugs cyclophosphamide and azathioprine to the steroids [21, 26, 32], while Villena et al. [19] treated their patient with antibiotics and methylprednisolone.

In all these cases, montelukast was the suspect medication. All patients only showed symptoms after they had started the therapy, and the symptoms seemed to remit after the medication had been withdrawn. The concomitant decrease in oral corticosteroids, while taking montelukast, in some patients suggests the possible unmasking of an underlying autoimmune pathology. In other cases, the association between montelukast and CSS seems causal, because of the chronological consequentiality of the pathology development and the remission after withdrawing the medication.

Psychiatric and Nervous System Disorders

Agitation Including Aggressive Behaviour or Hostility, Anxiousness, Depression, Disorientation, Dream Abnormalities, Hallucinations, Insomnia, Irritability, Restlessness, Somnambulism, Suicidal Thinking and Behaviour (Suicidality), Tremor, Dizziness, Drowsiness, Paraesthesia/Hypoesthesia, Very Rarely Seizures

In 2009, the FDA issued a warning regarding potential suicidality after taking montelukast and other leucotriene antagonists. However, according to a study conducted by Manalai et al. [40], there are not sufficient data to prove a link between montelukast and suicidality. A survey among 20,000 adults and children receiving this treatment showed no reports of completed suicide, and possible suicidality-related AEs were rare; furthermore, the events were similar to those seen in the control subjects [41]. Interestingly, Schumock et al. [42] conducted a regression analysis showing that the relationship between montelukast and suicidality could actually be in the opposite direction (i.e. there is a reduced risk). We found three reports in the literature about hallucinations after taking montelukast. Data collected in Sweden (in 1998–2007) indicated that having nightmares ($n = 15$) and hallucinations were the most common montelukast-induced psychiatric ADRs ($n = 48$) [43]. Another case report described a 29-year-old asthmatic woman with auditory and visual hallucinations, which stopped within 2 days after montelukast withdrawal [44]. In an HIV-positive female patient, neuropsychiatric disturbances (i.e. disturbed sleep, vivid dreams, irritability, confusion and concentration difficulties) appeared when montelukast was added to efavirenz, and they disappeared completely after montelukast withdrawal [45]. These reported symptoms might have been caused by a drug-drug interaction between efavirenz and montelukast. This explanation was supported by the inhibitory effects of efavirenz on CYP 2C9, 2C19 and 3A4 activity and by the involvement of CYP 3A4, 2C9 and 2C8 in the metabolism of montelukast [45].

Sleep disturbances, including nightmares, have not been described in clinical trials on montelukast, while several cases have been reported in post-marketing surveillance. Cereza et al. [46] reviewed 24 cases who reported nightmares, both in adults ($n = 7$) and in children ($n = 17$). Among them, 14 patients had other concomitant psychiatric symptoms, and in all these cases the suspect medication was montelukast. All these symptoms are, however, included in the SPC of montelukast [46]. Four

children, aged between 1 and 5 years, developed sleep disorders (i.e. insomnia, somnolence and night terrors) as well as behavioural and mood disorders while receiving montelukast [47]. None of them had formerly reported psychiatric disorders. Three of the 4 children expressed suicidal ideation. After montelukast withdrawal, all these symptoms disappeared [47]. A 9-year-old boy on montelukast therapy for several years experienced neuropsychiatric events consisting of sleepwalking, sleep disturbance, bruxism and anxiety worsened by stressful events [48]. Kocyigit et al. [49] reported the case of a 13-year-old patient who had visual hallucinations after starting a therapy with montelukast, which disappeared within 48 h after the cessation of drug intake. Alkhuja et al. [50] observed the case of a 16-year-old female who received montelukast for asthma. In the nights following the therapy start, the patient's mother reported daily parasomnias in the form of sleep talking and sleepwalking. Montelukast was discontinued which resulted in a disappearance of the parasomnias. After re-challenge, the parasomnias appeared again. Once montelukast was definitely discontinued, the parasomnias were never reported again [50].

In these articles, both adults and children seem to develop psychiatric symptoms after the intake of the medication. In every patient, the symptomatology seems to become less with the discontinuation of the therapy with montelukast within few hours. Although anti-leucotrienes are safe drugs, these symptoms have to be monitored especially in children.

Hepatobiliary Disorders and Pancreatic Disorders

Increased ALT and AST Levels, Very Rarely Hepatitis (Including Cholestatic, Hepatocellular and Mixed-Pattern Liver Injury)

Palodhi et al. [51] observed the case of a male patient who developed hypertriglyceridemia and associated lipid profile abnormalities after taking montelukast. He had also been receiving salbutamol inhalation since childhood. Montelukast was withdrawn immediately, and his triglyceride values reached a level close to baseline after 4 months [51]. A 46-year-old male with uncontrolled asthma on inhaled albuterol and formoterol with budesonide was commenced on montelukast. Montelukast was discontinued due to suspected hepatocellular liver injury. His liver test results improved and returned to normal 55 days after drug cessation. A causality of this ADR was 'probable', based on the Council for International Organizations of Medical Sciences or Roussel Uclaf

Causality Assessment Method (CIOMS or RUCAM) and Naranjo's algorithm [52]. Russmann et al. [53] observed an AE in a 76-year-old man characterized by fatigue, vomiting and icterus, with elevated aminotransferase, bilirubin and alkaline phosphatase levels. His therapy had consisted of salmeterol, fluticasone and *Serenoa repens* extract for 4 years and acetylsalicylic acid for 9 years. He had no alcohol history; and his viral, serological and auto-antibody tests were negative. After suspending montelukast and *Serenoa repens*, his status improved and the laboratory values normalized. A liver biopsy and lymphocyte transformation test were performed: positive with montelukast [53]. Notably a 5-year-old asthmatic patient suffered from fatigue, nausea, vomiting and abdominal pain due to hepatotoxicity caused by montelukast [54]. Actis et al. [55] described a 45-year-old woman who began complaining about nausea, vomiting and malaise after having received montelukast for 5 years. One week before this episode, she had received a 1-week treatment with two dietary supplements for weight control, and one of these contained *Garcinia cambogia*. She subsequently died, and her death was related to fatal hepatitis. A relationship and potential synergy between the food supplement and montelukast were suspected as the cause of hepatotoxicity [55]. A 22-year-old male patient experienced unusual weight gain and severe abdominal pain after 2 months of therapy with montelukast. The clinical and laboratory findings revealed the presence of an acute pancreatitis, hypercholesterolemia and severe hypertriglyceridemia. Clinical recovery followed montelukast discontinuation. Naranjo's algorithm suggested that the association could be considered as 'probable' [56].

Hypertriglyceridemia can be detrimental not only for individuals with a cardiovascular risk profile but also for healthy subjects, so blood values should be monitored in every patient on montelukast therapy.

Skin and Subcutaneous Tissue Disorders

Angio-Oedema, Bruising, Erythema Nodosum, Pruritus, Rash and Urticaria

There is a case report on an 8-year-old girl with a 2-month history of widespread erythematous and bullous eruptions, mostly affecting her lower extremities. The girl had a 2-year history of chronic asthmatic bronchitis. Montelukast had been initiated 5 months before the onset of the skin lesions; the authors suspected pemphigus [57].

Our group [58] reported on the case of a 28-year-old man with allergic rhinitis and moderate persistent asth-

ma who developed generalized urticaria 5 days after starting on montelukast and inhaled fluticasone. His symptoms disappeared 1 day after the suspension of both drugs. Two months later, after the resumption of montelukast and fluticasone, the patient developed urticaria again with eyelid angio-oedemas, which were successfully treated with intravenous betamethasone, achieving complete remission. The patient resumed only inhaled fluticasone without any further adverse reactions [58]. Tedeschi [59] reported the case of a patient with no IgE-mediated chronic urticaria, exacerbated by various medications including montelukast. Cyclosporine and azathioprine controlled the patient's symptoms [59]. Another case of montelukast-induced urticaria, in a 50-year-old woman, was described by Herzinger et al. [60]. A 46-year-old woman with a history of severe allergies and angio-oedemas had an acute angio-oedema episode. The patient was on ebastine 10 mg daily, montelukast 10 mg daily and vitamins and reported that since she had started montelukast 1 month prior, she had experienced three similar episodes, the first occurring 5 days after starting the drug [61]. There is a case report on a 31-year-old woman with a history of allergic rhinitis and asthma, who experienced severe bruising on her lower extremities after starting montelukast. De-challenge and subsequent re-challenge of montelukast confirmed the connection between the drug and lesions. The authors excluded a traumatic origin, concomitant CSS and food allergy, and the skin biopsy revealed unspecific inflammatory signs [62]. Tayeb [63] reported the case of a young woman who developed the following recurrent symptoms after taking montelukast: lip swelling, maculopapular skin rash and shortness of breath. The author performed a desensitization procedure to the anti-leucotriene [63].

Dermatitis and urticaria are frequent adverse reactions against drugs and they have been reported with montelukast, too.

Uropoietic System

Haematuria

Xie et al. [64] observed montelukast-induced haematuria in a 58-year-old female patient. Her gross haematuria improved 7 days after montelukast withdrawal. Two weeks later, her renal function returned to normal [64].

Haematuria and glomerulonephritis can be considered one aspect of an unexpected immune response triggered by the intake of montelukast and resulting in a sub-clinical CSS.

Discussion

Montelukast is, in general, a well-tolerated drug, both in adult and paediatric patients. Safety data provided by clinical trials highlight no substantial difference in AEs to placebo. The most common AEs observed in these trials were: headache, gastrointestinal disorders, fatigue, pharyngitis, upper respiratory tract infection and rash [65–67]. However, clinical trials are often conducted in highly selective patient subgroups, this must be taken into account when drawing conclusions from the SPC of montelukast.

Several case reports describe montelukast-induced CSS. This rare vasculitis presents a broad range of clinical manifestations, sometimes characterized by a severe prognosis and permanent sequelae. CSS affects especially adult patients of both genders. Unfortunately, to date, the mechanisms underlying the onset of CSS are not fully understood.

In the analyzed case reports, CSS repeatedly appears to occur when usual corticosteroid therapy is gradually tapered or discontinued [22]. Some authors advanced the hypothesis of a decreasing corticosteroid dose unmasking an underlying CSS [28, 39]. We suggest that more appropriate epidemiological studies on the role of montelukast in the pathogenesis of CSS are needed. Neuropsychiatric disorders and sleep disturbances, which affect the paediatric population more often, exert a negative impact on patients' quality of life, although most of them had a clinical resolution after montelukast discontinuation. Currently, the pharmacological mechanisms causing neuropsychiatric alterations are not clear.

Evidence of the presence of CysLT1 in the brain suggests that the pathway of CysLT receptors is more complex than it was initially supposed. Various pre-clinical experiments, exploring the function of this pathway in

the central nervous system, reveal an over-expression in the reparative process occurring during particular pathological conditions [68]. Even though studies on children are lacking, it could be hypothesized that, in susceptible paediatric patients, blocking CysLT1 by its specific antagonists can cause neuropsychiatric adverse reactions.

Montelukast can cause hepatobiliary and pancreatic dysfunction. Notably, it has been described in a case of fatal hepatotoxicity; however, in this case it was not possible to describe the mechanism triggering hepatotoxicity. Interestingly, various experimental models of drug-induced hepatotoxicity in rats showed a protective effect of montelukast [69].

Conclusion

In the light of the present review, it appears clear that montelukast administration can be burdened by several ADRs, of which physicians should be aware in their clinical practice, taking into account that the administration of montelukast, along with concomitant therapies, could increase the risk of drug-drug interaction. A better comprehension of the mechanisms causing ADRs related to this anti-leucotriene could help researchers and clinicians to define a therapeutic strategy aimed to reduce montelukast toxicity. Furthermore, it is desirable to conduct more accurate epidemiological studies on large populations in order to definitively discover risk factors favouring montelukast-associated ADRs.

Disclosure Statement

The authors of the present article declare that they have no conflicts of interest.

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