

Chronic Urticaria in Special Populations: Children, Pregnancy, Lactation and Elderly People

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Abbreviations ASST Autologous serum skin test · CU Chronic urticaria · CSU Chronic spontaneous urticaria · CNS Central nervous system · FcER-I High affinity IgE receptor · FDA US Food and Drug Administration · NSAID Non-steroidal anti-inflammatory drugs · PEP Polymorphic eruption of pregnancy · PUPPP Pruritic urticarial plaques and papules of pregnancy

Opinion statement

Chronic urticaria can occur at any age and in both sexes. Regardless of the different populations affected, a stepwise treatment approach is recommended, beginning with non-sedating antihistamines, from licensed doses to a “controlled overdose” up to fourfold, followed by a change to a different antihistamine and/or addition of a leukotriene antagonist if symptoms persist; systemic corticosteroids in short courses (3 to 7 days) can be used for exacerbations. As a third-line therapy in adults, omalizumab is now considered of choice and only in nonresponsive cases to omalizumab cyclosporin or other options should be used. First-generation H1-antihistamines are no longer recommended, either in adults, in children, in pregnant women, or in the elderly because of their high potential to cause sedation and to

impair school/work performance and vehicle driving. Among the second-generation H1-antihistamines, most of them have proven efficacy and safety, but there are important concerns for special populations with nearly every medication used in chronic spontaneous urticaria (CSU) treatment.

Children. Cetirizine is approved in children aged 6 months and older. Also, levocetirizine, ebastine, loratadine, rupatadine, and desloratadine are among the recommended medications in children <12 years old. When up-dosing is necessary, only cetirizine, levocetirizine, loratadine, or desloratadine, and only for a short time, should be used in childhood. Corticosteroids may be needed in short courses, but growth suppression is a major concern. Omalizumab is approved for CSU only in adolescents ≥12 years. Cyclosporin should be reserved for children whose CSU is resistant to other measures, and serum concentrations, renal, and hepatic function should always be carefully monitored.

Pregnancy and lactation. When eluding CSU therapy during pregnancy is not possible, non-sedating H1-antihistamines are the first choice, and most first-generation antihistamines should be avoided—especially hydroxyzine. Several second-generation H1-antihistamines are classified as FDA's pregnancy category C (risk not ruled out), and cetirizine or loratadine (category B—no risk in animal studies) are still the preferred option, as well as in breastfeeding women. Corticosteroids are not recommended in the first trimester because of a possible increased risk of cleft palate; prednisone and methylprednisolone, however, are classified as category B. Cyclosporin is classified as category C. There is little published data on the safety of omalizumab in pregnant women with CSU, but observational studies in asthmatic patients have not shown an increase in major anomalies, and it is so classified as category B.

The elderly. Potential drug-drug interactions are a major concern in the elderly because of frequent concomitant medications, and first-generation antihistamines must be especially avoided because of interactions and because of potential anticholinergic and CNS and cardiac side effects. Loratadine is not recommended due to a lower clearance rate in patients older than 65. Osteoporosis, hypertension, and metabolic side effects limit the use of systemic corticosteroids. Cyclosporin cannot be recommended in the elderly, especially if hypertension or renal impairment is present. So far, no special safety concerns have been reported with omalizumab in CSU aged patients, but in asthmatic patients, omalizumab has been associated with higher than expected reporting of arterial thrombotic events.

Introduction

The term “chronic urticaria” (CU) refers to the occurrence of itchy hives lasting for more than 6 weeks, accompanied or not by angioedema. According to international guidelines on diagnosis and management of urticaria [1•, 2•, 3•, 4•], CU can be spontaneous (formerly named idiopathic), when wheals are not triggered by identifiable factors, or inducible, when triggers are either physical stimuli—such as heat, cold, pressure applied to the skin, sunlight, exercise, water, or vibration—or contact allergens. Spontaneous and inducible urticaria can coexist in the same patient and can occur in both sexes and at any age, including infants, children,

pregnant and breastfeeding women, or elderly population. In any case, quality of life is often severely impaired.

Chronic spontaneous urticaria (CSU) can be autoimmune, or autoreactive, e.g., triggered by functional antibodies against self-antigens such as IgE, high-affinity IgE receptor (FcER-I), or thyroglobulin, in nearly 50 % of patients [5]. For most cases, though, a definite etiology is not identified, even if intrinsic abnormalities of basophils or mast cells are suspected [6••]. An association with other autoimmune diseases is common. For diagnostic purposes, a detailed clinical history and

laboratory testing on an individual basis are essential; however, extensive routine testing is not favorable from a cost-benefit standpoint.

For CSU treatment a stepwise approach is recommended, beginning with non-sedating antihistamines at licensed doses. If symptoms persist, most guidelines suggest increasing the dose of H1-antihistamine, changing agents, or both. When symptoms are refractory to these measures, guidelines differ somewhat as to the next steps, although most suggest the addition of an H2 antihistamine or antileukotriene agents. Systemic corticosteroids in short courses (3 to 7 days) can be used

for treatment of exacerbations. As a third-line therapy, anti-IgE monoclonal antibody (omalizumab) is presently the licensed treatment of choice [7], but if unavailable, or in nonresponsive cases, cyclosporin or other options might be used.

Since CSU can be suffered by both sexes and at any age, there is a special concern on management in specific populations such as children, elderly patients, and pregnant or breastfeeding women. This paper intends to be an updated, brief review on treatment advice in such populations according to different current guidelines.

Chronic urticaria in children

While up to 3 % of adults will develop CSU (estimated point prevalence 0.6 %) [8], the condition appears to be less prevalent in children, in which acute or recurrent urticaria (triggered by infections, physical stimuli, or allergic reactions to food and drugs) is more common than CSU [9]. When CSU occurs in pediatric ages, it is rarely a severe disease and usually remits over time, either spontaneously or after antihistamine treatment and avoidance of triggers: a quarter of children with CSU are disease-free 3 years after presentation and 96 % after 7 years [3•]. In children, underlying causes for CSU are considered the same than those in adults; a detailed clinical history and physical examination usually establishes the diagnosis, and further investigations are rarely required. Fifty to eighty percent of children with CSU have associated angioedema [3•]. Around 40 % have an autoimmune background with a positive autologous serum skin test (ASST) [10], and about 4 % have positive antithyroid antibodies [11]. There are case reports of an association between CSU and celiac disease, even improving on a gluten-free diet [12]. Other forms of food allergy should be discarded by skin tests and/or specific IgE testing. A diagnostic skin biopsy could be considered if lesions last more than 24 h, do not respond to second-line treatment, or become purpuric. The commonest cause of vasculitic urticaria in children is Henoch-Schönlein purpura [3•]. On the other hand, it is considered essential to rule out juvenile idiopathic arthritis or rare hereditary auto-inflammatory syndromes which can associate urticarial-like lesions [13].

Evidence-based data concerning clinical management in pediatric population are still limited, and most of the recommendations in current guidelines are based on extrapolation of data from adults. A general, obvious recommendation is that only those medications that have been proved to be safe and effective in the pediatric population should be used.

Diet and lifestyle

- Avoidance of known provoking stimuli (NSAID or other drugs, contact allergens, or physical stimuli: heat, cold, pressure applied to the skin, sunlight, exercise, water, vibration...)

- Pseudoallergen-free diets (without food additives, such as preservatives or dyes) are hard to plan and carry on, and the evidence of their usefulness is low [14•, 15•]
- When food allergy is suspected, it should be necessary to undertake withdrawal and rechallenge diets, always overseen by a dietician

H1-antihistamines

Grade of recommendation: B

As in adults, H1-antihistamines are mainstay therapy. CSU may present as early as the second year of life and this can limit the drug choice. First-generation H1-antihistamines (such as chlorpheniramine, diphenhydramine, promethazine, or hydroxyzine) are no longer recommended because of their high potential to cause sedation and anticholinergic effects, contributing to daytime sleepiness and impaired school and play performance. Among the second-generation H1-antihistamines, cetirizine (even though probably more sedating than any other [16]) has confirmed efficacy and safety and it is approved for chronic urticaria in children aged 6 months and older; however, the metabolism of cetirizine and its enantiomer levocetirizine is different in young children, where renal clearance is more rapid to that in adults, and so these drugs are advised to be taken twice daily [17••]. Also, pediatric suspensions of ebastine, loratadine, and rupatadine are available for patients from 2- to 12-year-old children, and safety of all these drugs has been well established in children [17••]. Desloratadine (the main active metabolite common to both loratadine and rupatadine) is licensed for the treatment of chronic urticaria in children from 1 year of age. Fexofenadine is also approved in the USA for urticaria in children aged ≥ 6 months, but at present, it is not licensed for children < 12 years old in Europe (Table 1). On the other hand, specific pediatric studies on efficacy in chronic urticaria with these second-generation antihistamines are lacking. If no response is achieved at licensed doses, age-adjusted dose escalation could be considered also in children, although again no trials have been performed in CSU in this specific age group. When up-dosing is necessary, only those non-sedating H1-antihistamines with proven safety at higher doses in pediatric patients (e.g., cetirizine, levocetirizine, loratadine, and desloratadine) should be used.

Corticosteroids

Grade of recommendation: D

As in adults, short courses of corticosteroids (3–5 days) may be needed during exacerbations in children, but caution is especially necessary due to adverse effects, including growth suppression. Corticosteroids are considered poorly efficient in inducible urticaria unresponsive to antihistamines and avoidance of triggers, with exception of delayed pressure urticaria [3•].

Table 1. H1-antihistamines for chronic urticaria in children

ANTI-HISTAMINES	MINIMAL AGE (Data sheet)
First-generation	6 months
Second-generation	
Cetirizine	6 months
Fexofenadine (USA)	
Desloratadine	1 year
Levocetirizine	2 years
Loratadine	
Ebastine	
Rupatadine	
Fexofenadine (Europe)	12 years
Bilastine	
Mizolastine	
Mequitazine	

Leukotriene receptor antagonists (montelukast)

Grade of recommendation: C

Leukotriene receptor antagonist montelukast has a good safety profile and can be used as an add-on therapy when antihistamines fail to control CSU symptoms. However, its evidence of effectiveness in CSU either as monotherapy or as a third-line therapy in association with antihistamines is poor in adults and children as well [18, 19].

Anti-IgE (omalizumab)

Grade of recommendation: C

Although licensed for children aged ≥ 6 years with severe allergic asthma, omalizumab is approved as add-on therapy for CSU unresponsive to H1-antihistamines only in patients aged 12 years or more. However, evidence for its efficacy and safety have been reported in small case studies in children with CSU aged <12 years resistant to first-line treatment [20, 21], at doses varying from a single 300 mg injection [22] to six injections of 150–300 mg administered monthly.

Cyclosporin

Grade of recommendation: C

Several studies in children ≥ 9 years have shown efficacy of cyclosporin as a third-line therapy in CSU unresponsive to high-dose H1-antihistamines and corticosteroids, within periods ranging from 1 to 8 weeks [23, 24]. No major side effects were detected in those studies; however, since cyclosporin

is not licensed for CSU neither in adults or children, it should be reserved for children whose CSU is refractory to all other measures, and monitoring of serum cyclosporin levels and renal and hepatic function is strongly recommended.

Chronic urticaria in pregnancy and lactation

When chronic urticaria occurs in pregnancy, their symptoms and outcome often improve spontaneously but may also worsen. Differential diagnosis is especially important during prenatal period, since the so-called urticarial dermatoses of pregnancy are much more common and can occur or coexist with CSU. The most important of these conditions are:

- *Polymorphic eruption of pregnancy* (PEP) or *pruritic urticarial plaques and papules of pregnancy* (PUPPP), seen in 1/160–300 pregnancies [4•] usually in the third trimester, as spreading red, itchy papules that coalesce to form urticarial plaques
- *Besnier's prurigo gestationis*, occurring in 1/300 pregnancies usually within second or third trimester and presenting as reddish, excoriated nodules or papules on extensor surfaces of limbs and trunk

As a general rule, considering the potential risks and benefits, clinicians should avoid any systemic treatment in pregnant women, especially during the first trimester. When avoiding CSU therapy during pregnancy is not possible, non-sedating H1-antihistamines are the first choice. Corticosteroids are not recommended in the first trimester because of increased risk of cleft palate, and cyclosporin is potentially embryotoxic. Data on omalizumab safety in pregnant women with CSU are lacking, but observational studies in asthmatic patients have not shown an increase in major anomalies.

H1-antihistamines in pregnant and breast feeders

Grade of recommendation: B

Among the drugs prescribed during pregnancy, antihistamines are one of the commonest, either as an antipruritic agent or an antiemetic agent; and various studies on the use of antihistamines during pregnancy, including a meta-analysis of more than 200,000 women, show no increase in the teratogenic risk of these drugs in humans [25]. According to the risk categories of the US Food and Drug Administration (FDA) for use of drugs during pregnancy (Table 2), there are no oral antihistamines with a category A listing, i.e., safe in pregnant women. Among the first-generation antihistamines, chlorpheniramine,

Table 2. Drugs for chronic urticaria in pregnancy US food and drug categories and included drugs

Categories	Description	First-generation antihistamines	Second-generation antihistamines	Corticosteroids	Other drugs used in CU and/or angioedema
A No risk in controlled human studies	Well-controlled studies have failed to demonstrate a risk to the fetus in pregnancy	None			L-Thyroxine
B No risk in animal studies	Animal reproduction studies have failed to demonstrate a risk to the fetus. No adequate studies in pregnant women	Chlorpheniramine Diphenhydramine Doxylamine Azatadine Cyproheptadine	Cetirizine Loratadine Ebastine Rupatadine Levocetirizine	Methylprednisolone Prednisone	H2-Antihistamines Montelukast Omalizumab Tranexamic acid
C Risk not ruled out	Animal reproduction studies have shown some adverse effect on the fetus. No adequate and well-controlled studies in humans	Promethazine Hydroxyzine Doxepin	Desloratadine Fexofenadine Mizolastine Bilastine	Hydrocortisone Dexamethasone Deflazacort	Cyclosporine IVIg* Nifedipine Colchicine Topical steroids
D Positive evidence of risk	Positive evidence of human fetal risk based on adverse reaction data in humans, but potential benefits can outweigh potential risks	None	None	?	Other immune suppressors
X Contraindicated in pregnancy	Studies in animals or humans have demonstrated fetal anomalies or there is positive evidence of human fetal risk	None	None	?	Danazol Stanozolol
IVIg intravenous immunoglobulins					

diphenhydramine, doxylamine, azatadine, and cyproheptadine are within category B, i.e., they are safe in animal studies, without clinical studies in pregnant women. All others are considered in the category C (studies in animals may show any foetal incidence, no controlled studies in humans). Hydroxyzine is specifically contraindicated in early pregnancy in the data sheet, since it crosses the placental barrier reaching higher fetal than maternal serum levels; and in animal studies, high doses of hydroxyzine have led to embryotoxicity. In addition, a population-based study in the USA linked hydroxyzine to cleft palate in newborns [26].

The data sheets for cetirizine, levocetirizine, loratadine, desloratadine, mizolastine, ebastine, fexofenadine, rupatadine, and bilastine all recommend avoidance in pregnancy. However, the largest part of the second-generation H1-antihistamines could actually be classified as category B (no major risk in animal reproduction studies, no controlled studies in women) and be used safely [27]. In fact, there is considerable clinical experience with cetirizine and loratadine, with reassuring safety profiles at standard doses in observational studies [3•, 28], and hence, both drugs have been assigned a category B by the FDA, along with ebastine, rupatadine, and cetirizine's enantiomer levocetirizine [25] while all the rest, including desloratadine (the common major metabolite of both loratadine and rupatadine), are currently considered in category C.

Significant amounts of antihistamines are excreted in breast milk, but based on the large body of evidence, none of the antihistamines is excreted in an appreciable quantity so as to have any adverse effects on the infant. Even so, antihistamines should only be used during lactation when the potential benefits compensate the possible damage to the infant. Among the first-generation antihistamines, chlorpheniramine is considered of choice, even if it has been related with infant drowsiness and poor feeding [3•]. Among the second-generation H1-antihistamines, data on drug concentration in breast milk are available for loratadine/desloratadine and terfenadine/fexofenadine, suggesting that they are almost completely cleared from breast milk [28]. The pharmacokinetics of loratadine and its metabolite desloratadine in breast milk were studied in six lactating women after a single oral dose of 40 mg of loratadine (fourfold the standard dose); the highest concentration of loratadine and its major metabolite desloratadine in breast milk was estimated to be 1.1 % of the daily dose given to the mother [29]. The pharmacokinetics of fexofenadine (the acid metabolite of terfenadine) in breast milk were studied in four lactating women taking 60 mg of terfenadine twice daily, and the maximum infant dose of fexofenadine based on its highest concentration in breast milk was estimated in 0.45 % of the daily maternal dose [30]. Therefore, considering the minimal exposure of a nursing infant to the drugs through breast milk, maternal use of cetirizine [3•], loratadine, desloratadine, or fexofenadine [28] in standard therapeutic doses is thought to be compatible with breastfeeding.

Corticosteroids in pregnancy and lactation

Grade of recommendation: D

Systemic corticosteroids may be required in short courses during severe exacerbations of urticaria during pregnancy, but concerns have been raised on different areas [4•, 27]:

- The use of corticosteroids in the first trimester of pregnancy is associated to increased risk of cleft palate [4•, 31].
- There is a potential risk of neonatal adrenal insufficiency—although considered very low when steroids are given in short courses, due to the quick maternal metabolism of prednisolone into inactive metabolites by placental 11- β -hydroxysteroid dehydrogenase [4•, 32].
- Low birth weight in the offspring as a result of systemic corticosteroids given to the mother has been reported in multiple animal studies and can occur in human full-term infants as well [33].
- Corticosteroids can exacerbate gestational diabetes and pregnancy-induced hypertension and facilitate preterm delivery from early rupture of membranes [4•].

Notwithstanding these worries, prednisone and methylprednisolone have been classified as FDA's category B, according to current data sheets, while the rest are assigned to category C (Table 2).

Concerning lactation and systemic corticosteroids, it has been estimated that a nursing infant would ingest less than 0.1 % of the maternal given dose of prednisolone, which is equivalent to <10 % of endogenous cortisol production; therefore, systemic corticosteroids appear to be safe during breastfeeding [32, 34].

Omalizumab in pregnant women and nursing infants

Omalizumab has been recently assigned to pregnancy category B by the FDA [35], since animal studies have failed to reveal embryotoxicity or teratogenicity, although data in human pregnancy are limited. An observational study of pregnant asthmatic women exposed to >1 dose of omalizumab within 8 weeks prior to conception, or at any time during pregnancy (the EXPECT study), has been published recently [36••], with no apparent increased prevalence in the newborn of major anomalies, prematurity, or low birth weight, with respect to other studies in this asthma population. In an anecdotic case of a woman who consented to be treated with omalizumab for CSU during two consecutive pregnancies, no apparent foetal toxicity was reported either [37].

With respect to lactation, there are no available data on omalizumab excretion into human milk, but previous studies on monkeys have demonstrated milk levels that were 1.5 % of maternal blood levels [35]. The effects in the nursing infant are unknown. In the EXPECT observational study [36••], 98 infants were exposed to omalizumab while breastfeeding, with a median omalizumab exposure duration of 3.9 months, without incidences. Nonetheless, omalizumab can again be recommended during pregnancy or lactation only when potential benefit prevails over the unknown risks.

Chronic urticaria in the elderly

The elderly population is increasing worldwide and a growing percentage of the general population is in the over 65 age group. In spite of healthy lifestyles and the improvement of medical therapeutics, the number of geriatric patients suffering from chronic conditions, including chronic urticaria, is expected to rise. CU in this population is of special concern due to the physiological changes of the aging itself, the prevalence of comorbid conditions, the frequency of polymedication, and the potential drug-drug interactions.

Several studies have investigated the clinical presentation of urticaria in the elderly [38–40]. Considered altogether, these studies find neither difference in the prevalence of CU between geriatric and adult patients or in its natural course largely unpredictable. It is usual to find higher pruritus scores in the elderly—given that itching is a common, multifactorial condition in aged patients. There is nearly an equal distribution in both sexes and a lower incidence of angioedema than in the rest of the adult population. Likewise, a lower occurrence of skin autoreactivity and a lesser amount of concomitant physical urticarias have also been reported in this age group.

The evaluation of urticaria in the geriatric population must focus on a detailed medical history with special emphasis on medications and exclusion of causal medical conditions. Underlying causes of chronic urticaria can be identified in up to 25 % in this age group [39•]. Polymedication is common in geriatric patients, and may frequently cause adverse drug reactions such as recurrent urticaria, among other unwanted side effects. On the other hand, CU may be the initial clinical manifestation of a systemic illness, including autoimmune conditions or malignancies; additional studies should be directed by positive findings during the initial evaluation. Allergy to fish nematodes (*Anisakidae*) can be associated to acute or recurrent urticarias in some endemic areas such as Japan or Spain [41], especially in the elderly. Psychosocial factors can be a common aggravating feature [42].

Obviously, the use of medications for CU in elderly patients may be considered when the potential benefits outweigh the potential risks. Treatment should begin, as in every other situation, with second-generation, non-sedating H1-antihistamines as first-line therapy. First-generation antihistamines must be especially avoided because of interactions and potential adverse effects. Systemic corticosteroids can be used for exacerbations in short courses, but osteoporosis and metabolic side effects are major concerns in geriatric patients. Cyclosporin cannot be recommended in the elderly, especially if hypertension or renal failure coexists. Although no especial safety concerns have been informed with omalizumab in CU aged patients, higher than expected arterial thrombotic events have been reported in asthmatics treated with omalizumab [43•].

Diet and lifestyle

- Avoidance of known provoking triggers (NSAID or other drugs, contact allergens, or physical stimuli)
- Patient education and reassurance on the likelihood of remission within 1 year and successful management in the majority of patients at any age
- Appropriate management of associated depression, anxiety, or mood disorders

H1-antihistamines

Grade of recommendation: B

Second-generation, non-sedating H1-antihistamines are recommended as a first-line therapy. Particularly in elderly patients, first-generation antihistamines are to be avoided due to central nervous system (CNS) adverse effects, including the risk of domestic falls or traffic accidents, and also due to anticholinergic side effects such as urinary retention, constipation, blurred vision, or glaucoma, or even dementia by a cumulative effect, according to a recent report based on a prospective cohort study [44].

In addition, dose selection must be considered carefully due to possible interactions with concomitant medications. Cetirizine and levocetirizine are eliminated by urine, mainly unchanged, and their doses have to be adjusted according to glomerular filtration rate. A lower clearance rate of loratadine [45] and rupatadine [46] in elderly patients (compared to the normal patient population) has also been reported but not of their common major metabolite desloratadine [47]. Apart from these, there are no published pharmacokinetic studies for most antihistamines in this population; even so, dose adjustment is recommended for the majority of 2nd-generation antihistamines in the elderly if hepatic or renal insufficiency is present.

Moreover, many first-generation and some second-generation antihistamines are able to inhibit certain potassium ion channels in the myocardium essential for repolarization, thus elongating QTc intervals in ECG and predisposing to ventricular arrhythmias; therefore, it is necessary to take into account, especially in the elderly, possible interactions with other drugs that can lengthen QTc interval, such as antibiotics (macrolides, fluoroquinolones), antidepressants, antiarrhythmic agents, or others.

Concerning the addition of an H2-antihistamine, a meta-analysis concluded that there is insufficient evidence to give a recommendation at any age [48]. Most of the studies suggest that the potential benefit may be due to drug interaction, rather than a true synergistic effect. Again, this concern can be especially important in the elderly because of the frequent polypharmacy. Likewise, when up-dosing is necessary, potential benefits and potential risks must be balanced, and only those non-sedating H1-antihistamines with proven safety at higher doses should be used.

Leukotriene receptor antagonists (montelukast)

Grade of recommendation: C

As stated before, montelukast has been used as an add-on therapy in CSU when antihistamines fail, but evidence of its effectiveness is poor, either as monotherapy or in association with antihistamines [18, 19]. Anyhow, its safety profile is high and there is no need of dose adjustment in the elderly [49].

Corticosteroids

Grade of recommendation: D

Only recommended in short courses (up to 5–7 days) followed by tapering regimes during severe exacerbations of urticaria, especially if accompanied by angioedema or in urticaria-vasculitis. Hypertension, osteoporosis, and metabolic side effects are major reservations in geriatric patients.

Cyclosporin

Grade of recommendation: C

Cyclosporin is not licensed for CSU, and because of hypertension and nephrotoxicity [50] as main concerns, its use in geriatric patients should be reserved to the most recalcitrant cases, unresponsive to all other measures. On the other hand, polypharmacy may have specific relevance for elderly patients treated with cyclosporin since this agent is a substrate of both CYP3A and P-glycoprotein [51], both of which are important in the elimination of many commonly used drugs, including antihistamines.

Anti-IgE (omalizumab)

Grade of recommendation: B

Omalizumab is licensed as add-on therapy for CSU unresponsive to H1-antihistamines in adolescents and adults. In elderly patients with CSU, data are limited, as are data on omalizumab pharmacokinetics in the aged asthmatics [52]. Population pharmacokinetic modeling suggests that, in the treatment of patients with CSU, there is no need for dosage adjustment based on age, race/ethnicity, sex, body weight, baseline IgE levels, autoantibodies to FcεRI, or concomitant therapies [53]. Moreover, no especial safety issues have been informed with omalizumab in CSU elderly patients. However, in asthmatics treated with omalizumab a higher than expected rate of arterial thrombotic events (overall cardiovascular death and stroke) have been reported

[43•]. Therefore, the use of omalizumab in aged patients with cardiovascular risk factors must be taken with all safety precautions.

Conclusions

The stepwise treatment approach recommended for chronic urticaria, with second-generation H1-antihistamines as a cornerstone, raises some important concerns in special populations.

First-generation H1-antihistamines are no longer recommended, either in adults, in children, in pregnant women, or in the elderly because of their potential to cause sedation and to impair school/work performance and vehicle driving.

Cetirizine, levocetirizine, ebastine, loratadine, rupatadine, and desloratadine are among the recommended second-generation antihistamines in children <12 years old. When up-dosing is necessary, only the safest drugs, and only for a short time, should be used in childhood. Corticosteroids may be needed in short courses, but growth suppression is a major worry. Third-line therapies such as omalizumab or cyclosporin are not approved for CSU in children <12 years.

If avoiding therapy during pregnancy is not possible, non-sedating H1-antihistamines are the first choice, and among them, cetirizine or loratadine are still the preferred option, as well as in breastfeeding women. Corticosteroids use in the first trimester increases risk of cleft palate. Cyclosporin is also potentially teratogenic. There is little published data on the safety of omalizumab in pregnant women with CSU, but observational studies in asthmatic patients fail to find an increase in major anomalies, prematurity, or low birth weight.

Polypharmacy and potential drug-drug interactions are the greatest concern in the elderly, overall when up-dosing is necessary. Loratadine is not recommended due to a lower clearance rate in patients older than 65. Osteoporosis, hypertension, and metabolic side effects limit the use of systemic corticosteroids. Cyclosporin is also limited by hypertension or renal impairment. So far, no special safety concerns have been reported with omalizumab in CSU aged patients, but the use of omalizumab must be taken with all safety precautions in every patient with concomitant cardiovascular risk factors.

Compliance with ethical standards

Conflict of interest

Dr Jáuregui Presa declares to have acted as lecturer, writer, and/or medical advisor for Novartis Spain, Faes Farma, Pfizer Spain, Menarini Spain, and Sanofi-Genzyme. Drs. Navajas Rodríguez, Ramos Bareño, Gamboa Setién, Urrutia Etzebarria, and Antépara Ercoreca declare to have no conflict of interest in this work.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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