

Management of Chronic Spontaneous Urticaria in the Elderly

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Abstract The guidelines for the management of urticaria in adults and children have been revised and updated recently. However, there are few data in the literature concerning several aspects of this disease in the elderly (e.g., epidemiology, etiopathogenesis, clinical aspects, association with co-morbidities, efficacy and safety profiles of treatments, and management strategies). This is an obvious deficiency in the data, as this disease causes a deterioration in quality of life, affecting the quality of sleep, everyday life habits and activities, and inducing severe disability. Chronic spontaneous urticaria (CSU) can also be associated with internal, infectious, autoimmune, or neoplastic diseases. It is therefore necessary to pay particular attention to these clinical issues through appropriate clinical examinations. At the same time, the specific features of medications used to treat CSU in the elderly should be carefully evaluated, as its pharmacological treatment raises a number of problems related both to the clinical condition of the patient and to concomitant diseases, as well as to the polypharmacotherapy, which is common in older subjects

and may cause safety problems because of the drug interactions. Non-sedating new-generation antihistamines are the mainstay treatment of CSU for the elderly. The efficacy and safety of alternative treatment options have not been assessed in the geriatric population with CSU; corticosteroids and cyclosporine (ciclosporin) should be used by this population with extreme caution. Similarly, there are no data regarding the actual safety profile of the new-generation antihistamines at higher doses than those recommended in elderly patients.

Key Points

Data concerning chronic spontaneous urticaria (CSU) in the elderly are lacking in the literature, although the disease induces severe disability and deterioration in quality of life.

In the elderly, CSU can be associated with internal pathologies such as infectious, autoimmune and neoplastic diseases, or atopic dermatitis.

Polypharmacy is prominent in the elderly, and should be taken into account in the treatment of CSU in the elderly, as it can induce drug interaction due to the various co-morbidities and changes in pharmacokinetics and pharmacodynamics.

The mainstay treatment for CSU in the elderly consists of new-generation non-sedating antihistamines. Alternative treatment options have not been systematically evaluated in elderly patients with CSU. Corticosteroids and cyclosporine (ciclosporin) could be used with extreme caution in cases resistant to therapy.

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1 Introduction

The knowledge of the etiology and pathogenesis of chronic spontaneous urticaria (CSU) has been considerably updated recently and its classification has been subjected to rearrangements resulting in the revision of its nomenclature. This upgrade process is the result of a joint initiative of the Dermatology Section of the European Academy of Allergy and Clinical Immunology (EAACI), the Global Allergy and Asthma European Network (GAALen), the European Dermatology Forum (EDF), and the World Allergy Organization (WAO); the guidelines have been accepted, shared, and published [1, 2]. Summing up, urticaria is characterized by the sudden appearance of wheals and/or angioedema. Urticaria is initially classified as either an acute or chronic form, depending on whether the duration is, respectively, less or more than 6 weeks [3]. Moreover, chronic urticaria can be divided into two groups depending on whether it takes place spontaneously (CSU) or it is induced by a specific physical or environmental stimulus (inducible urticarias). The previously used term chronic idiopathic urticaria should therefore be abandoned and substituted by CSU to avoid confusion [3, 4]. Urticaria pigmentosa (cutaneous mastocytosis), urticarial vasculitis, familial cold urticaria, and angioedema due to C1-esterase inhibitor deficiency are no longer considered subtypes of urticaria: these were all historically related to urticaria but have a pathogenic basis that is completely different.

In the last 20 years much progress has been made in the identification of possible pathomechanisms of CSU. Among others, one of the most studied pathomechanisms is autoreactivity, including autoimmunity mediated by functional histamine-releasing autoantibodies directed against the high-affinity IgE receptor. The autologous serum skin test (ASST) is a screening test for autoreactivity; if positive, this test suggests the presence of circulating histamine-releasing factors of any type, and not only of functional autoantibodies [3].

The aim of this work is to provide guidelines for urticaria in elderly patients, in whom multiple critical points require special precautions. In particular, as the elderly take a large number of drugs because of co-morbidities, they can have safety problems. Therefore, it is difficult to establish a therapy for them without inducing adverse effects as a result of changes in the pharmacodynamics and pharmacokinetics.

2 Epidemiology and Presentation of the Disease

According to Zuberbier et al. [5], who analyzed the epidemiology of urticaria in across-sectional epidemiological study, it has been calculated that its incidence has reached 8.8 % for all types, with a prevalence of 1.8 % for the

chronic forms; women had an increased risk of urticaria (70.3 vs. 29.7 %) and angioedema was present in 33.3 % of cases. However, there are very few studies that deal specifically with urticaria in elderly patients. Some authors have emphasized the role of drug-induced urticaria in the geriatric population [6]. In the elderly, the commonest chronic urticarial form is likely to be CSU, as inducible urticarias are less common, being more frequent in adolescents and young adults. Precise information regarding CSU prevalence in the elderly is still lacking.

A retrospective population-based cohort study carried out in Taiwan using the National Health Insurance Research Database enrolled a total of 12,720 patients with chronic urticaria from 1996 until 2008 [7]. Of the total number of patients, 25.1 % were in the age group from 60 to 79 years and 3.4 % were older.

Magen et al. analyzed the clinical and laboratory features of 1,598 adult patients with CSU [8], 9.4 % of whom were older subjects who tended to have fewer wheals, lower rates of angioedema, less frequent association with dermographism, and a lower frequency of ASST positivity. Unlike in the younger patients, the group of older patients showed a minor dominance of women, with a nearly equal distribution among the sexes. Laboratory data showed no difference between older patients and younger adults with CSU. Nevertheless, a higher prevalence of hypertension, diabetes mellitus, chronic renal failure, Hashimoto's thyroiditis, and malignancies was detected in the elderly.

Another work took into account the possible correlation between urticaria/angioedema, co-morbidities, and polypharmacy in the elderly population [9]. It was suggested that the presence of concomitant diseases, especially thyroid diseases, is responsible for an equal increase in urticaria/angioedema in both elderly and younger patients. Although no correlation has been proved between age and symptoms, it has been pointed out that in older patients suffering from multiple illnesses (three or more co-morbidities treated with at least two drugs) there was a higher risk of CSU, and the correlation was still stronger when the patients were receiving multiple medications. In fact, both the number of prescribed drugs and age increase the potential drug-drug interaction due to interference with drug metabolism and pharmacodynamic problems. In this respect it is well-known that one of the main aspects of the reduced homeostatic mechanisms in the elderly is the impairment of kidney and liver function [10]. This risk may also be linked to the possibility that some drugs can determine an immunological or a non-immunological activation and degranulation of mast cells or may induce the release of proinflammatory mediators, such as bradykinin, which can determine angioedema [11]. This is also the case for aspirin (acetylsalicylic acid) as well as other NSAIDs, which are commonly used by the elderly and can

exacerbate CSU. Furthermore, the polypharmacy, equally frequent in older subjects, can favor the development of adverse drug reactions through pharmacokinetic and pharmacodynamic interactions between different active principles. The geriatric patient shows a progressive depletion of various functional metabolic processes and an increased sensitivity to stimulation of the immune system, as well as multiple functional changes secondary both to age and coexisting pathologies.

According to Ventura et al. [9], CSU due to infections appeared to be more common in the elderly, especially the forms related to *Helicobacter pylori* and those related to the sensitization to the parasitic nematode *Anisakis simplex*. Since the study was conducted in an area where the infestation with *Anisakis* has reached levels of endemicity due to the particular eating habits of the population, it is not surprising that the exponential spread of the infestation in the various age groups of the population has become responsible for the increase in CSU symptoms [12]. In addition, clinical observations have highlighted the age-related progressive loss of the structural integrity of the organs in frail elderly. Therefore, systemic diseases, including neurologic, hepatic, renal, and hematologic disorders, should be taken into account in geriatric patients with allergic diseases, including CSU [13]. Some cases of hives from neoplastic diseases, especially leukemias, breast cancer, and prostate cancer, should be considered in the elderly population. This is particularly relevant in the light of recent reports that have found an increased association of chronic urticaria with cancer, especially hematological malignant tumors [7]. In contrast, previous data tended to deny such an association [14]; it remains quite controversial and needs further investigation. In one study [7] the relative risk of cancer in patients with chronic urticaria varied by age but was higher among those aged from 20 to 39 years than in the general population. The risk of non-Hodgkin lymphoma was greater among the hematologic cancers. Findings derived from the Mayo Clinic's electronic database revealed that the diagnosis of hematologic malignancy was particularly frequent in patients with chronic urticaria and coexisting monoclonal gammopathy of undetermined significance (MGUS) [15]. In the same study [15], patients presenting a new diagnosis of chronic urticaria at an older age (>56 years) were more likely to have underlying MGUS. A case series of four female patients with occult papillary carcinoma of the thyroid who developed chronic urticaria which subsided after tumor removal seems to suggest a direct relationship between the two entities [16].

Autoimmune diseases are frequent co-morbidities in CSU, particularly Hashimoto's thyroiditis, which was found to affect patients with positive ASST more commonly [17]. Female patients with chronic urticaria had a significantly higher incidence of rheumatoid arthritis, Sjögren syndrome,

celiac disease, type 1 diabetes mellitus, and systemic lupus erythematosus, mostly diagnosed during the 10 years after the diagnosis of chronic urticaria [18].

The frequent coexistence of a psychiatric co-morbidity has recently been underlined [19, 20] and contributes to worsen the already poor quality of life (QOL). Recent evidence has shown the devastating effects of urticaria on QOL. In particular, according to O'Donnell et al. [21], the impact of urticaria on QOL is comparable to the health status of patients with coronary artery disease. This detrimental aspect has been examined by means of a specific QOL questionnaire developed for chronic urticaria which explores physical, emotional, social, and practical aspects correlated to this condition [22]. A comparison with patients with respiratory allergy showed that chronic urticaria had a more pronounced impact on health status. The patients with chronic urticaria showed significantly lower scores in physical functioning, role physical, bodily pain, and general health, as well as a worse satisfaction profile in many aspects of daily life [23]. Thus, although CSU is only sometimes the symptom of a serious systemic disease, it creates a condition of severe disability.

In a recent paper, Ban et al. [24] reported that in the elderly with urticaria there is a high prevalence of atopic dermatitis (AD) compared with non-elderly. The prevalence of AD was equal to 37.8 versus 21.7 %, respectively ($p = 0.022$). Disorders of the skin barrier are found in subjects suffering from AD and this event determines the colonization of *Staphylococcus aureus*, the degraded ceramide of which penetrates the skin barrier and determines IgE sensitization.

3 Diagnosis

The diagnosis of CSU in the elderly does not differ from that in younger patients [1, 25, 26]. The international guidelines recommend a routine patient evaluation, which should comprise a thorough history and physical examination. In CSU, the drug history should be stressed (especially for aspirin and ACE inhibitors). Moreover, extended laboratory and instrumental tests should be based on the patient history and clinical symptoms.

4 Treatment of Chronic Spontaneous Urticaria (CSU): General Principles and Special Considerations for the Elderly

Generally, the treatment of urticaria should, whenever possible, firstly consider the avoidance of eliciting factors. However, despite several efforts directed at identifying the potential causal/triggering factors, the search for such

factors is unfortunately unsuccessful in most cases of CSU, which therefore remain without an apparent cause [25]. The objectives of symptomatic treatment of CSU are primarily the reduction of itch severity and the control of development of wheals and/or angioedema, thus in parallel improving the impact on QOL.

According to the international guidelines [1, 27], the therapeutic management of CSU consists of a step-wise approach, with sequential steps to be implemented according to the clinical response. As the majority of CSU manifestations are mediated by the activity of histamine through the interaction with H₁ receptors, it is obvious that H₁ antihistamines have a fundamental therapeutic role. Antihistamines act as inverse agonists that combine with and stabilize the H₁ receptor, favoring its inactive conformation. Most antihistamines, especially the most recent ones, have been shown to exert direct or indirect anti-inflammatory effects, leading to the downregulation of antigen presentation, synthesis of proinflammatory cytokines, expression of adhesion molecules, mediator release, and chemotaxis [28, 29]. Most of these effects were found to occur with high drug dosages; it can partially explain the utility of antihistamine up-dosing in cases that do not respond to standard doses. Traditionally, antihistamines can be distinguished into first-generation drugs that can cause sedation and impairment of cognitive and psychomotor functions, and second-generation antihistamines (sg-AHs) that are relatively non-sedating.

In brief, the international guidelines for management of CSU recommend sg-AHs as first-line treatment because of the extremely positive efficacy and safety profiles, as documented by several randomized controlled trials (RCTs) [1]. In the absence of a satisfactory response to licensed dosages of sg-AHs, it is currently advised to increase the dose of the same sg-AH up to four times. In patients who remain refractory to sg-AHs at both conventional and higher dosages, the next step consists of the combination of the sg-AH at a standard dose with a third-line drug represented (without order of preference) by cyclosporine (ciclosporin), montelukast, or omalizumab. It is advisable to use a short-term corticosteroid therapy (up to 10 days) for the management of severe disease exacerbations, although no well-designed RCTs exist (low strength of recommendation) [1].

Alternative drugs (i.e., anticoagulants, dapsone, mycophenolate, methotrexate, intravenous immunoglobulins, and others) have very weak levels of recommendation because of the limited evidence documenting their efficacy in CSU [30, 31]. As a consequence, their use can be considered only in selected severe refractory cases and safety issues should be carefully assessed, especially in the elderly.

It is surprising to note that in the above-mentioned therapeutic algorithm, antihistamines and omalizumab are the only drugs indicated for the treatment of CSU at the

moment, whereas all the other treatment approaches are not formally approved for CSU. Regarding efficacy in CSU—apart from sg-AHs—there is high-quality evidence based on the availability of RCTs in cyclosporine [32, 33] and omalizumab [34–36]. Montelukast, whose usage is off-label for CSU, has only been considered slightly effective in CSU, due to the available (low-quality) evidence [1]. Moreover, sg-AH up-dosing is another off-label approach. The available data have suggested that a greater proportion of patients can obtain clinical benefit from this option without safety or tolerability problems [37]. Thus, based on the existing data, the safety and efficacy of this treatment strategy have been evaluated in very few studies in CSU, using increased doses of some agents, and rarely with a dosage fourfold higher than the manufacturers' recommended dosages. The response does not seem univocal and to date the most convincing results from CSU studies with doses increased by up to four times have been obtained with levocetirizine and desloratadine [38].

One of the most relevant problems in the elderly is the presence of limited information concerning the safety/efficacy ratio of treatments in this population. Older subjects are not included among the special populations in urticaria management guidelines [1]. It is likely that only a minority of subjects randomized in RCTs of CSU corresponds to older patients. Moreover, clinical trials tend to exclude older people because of co-morbidities (i.e., neurodegenerative disorders, renal insufficiency, or hepatic disturbances) and concomitant therapies, which are instead common characteristics of people treated in 'real life'.

Co-morbidities may increase the number of medications taken by older individuals, increasing the risk for drug-disease and drug-drug interactions. Polypharmacotherapy is a widespread and growing phenomenon in the elderly [39]. The potential for drug interactions is proportionally correlated with age and with the number of drugs prescribed and it increases the possibility of adverse events (AEs) [40]. Physiologic modifications associated with aging (e.g., the reduction of homeostatic mechanisms, alterations in renal function and metabolic liver efficiency, or absorption and distribution of the drugs) may also increase this risk [13, 41]. Mental status changes and fall risk are important aspects for the geriatric population. Older people are particularly sensitive to the hypotensive or sedative effects of medications [10].

5 Safety of CSU Treatment Options

5.1 Second-Generation Antihistamines

Several studies, including long-term RCTs, have evaluated the safety and efficacy profile of sg-AHs in the population.

Table 1 Liver metabolism and drugs interactions of new-generation histamine H₁ antihistamines

Drug	Liver metabolism	Most relevant data on interactions with drugs and alcohol
Bilastine	Absent (no effects on CYP activity in vitro)	P-gp inhibitors or substrates (increase of bilastine plasma concentrations) ^a ; grapefruit and possibly other juices, other OATP1A2 substrates or inhibitors (reduction of bilastine bioavailability/plasma concentrations) ^a No additive effect of bilastine 20 mg with alcohol on psychomotor performance, or with lorazepam 3 mg for 8 days on sedation
Cetirizine	No extensive first passage (two-thirds excreted unchanged in urine)	At therapeutic dose, no clinically significant interactions with alcohol (although caution is suggested) CNS sedatives Repeated doses of theophylline 400 mg od (slight decrease of cetirizine clearance)
Desloratadine	Enzymatic pathway not well known (no inhibition of CYP3A4 in vivo and CYP2D6 in vitro)	No clinically relevant interactions observed so far. No interference with grapefruit juice ^b No influence in potentiating the deleterious effect of alcohol on psychomotor abilities
Ebastine	Extensive first passage (CYP3A4)	CYP3A4 inhibitors
Fexofenadine	Marginal	Ketoconazole or erythromycin (two to threefold increase of fexofenadine plasma concentrations) ^c ; grapefruit, apple, or orange juices (reduction of fexofenadine bioavailability) ^d ; rifampicin (influence on fexofenadine renal clearance); antacids containing aluminium and magnesium (decrease of fexofenadine bioavailability, if taken 15 min before)
Levocetirizine	Limited (<14 % of the dose)	Lack of specific studies with drugs (including CYP3A4 inducers). Significant drug interactions unlikely Alcohol and CNS sedatives (caution is suggested, because of the risk of CNS effects in susceptible individuals)
Loratadine	Relevant first passage (CYP3A4 and CYP2D6)	Potential interactions with all CYP3A4 and CYP2D6 inhibitors (causing increased loratadine blood concentrations) No additive effect with alcohol on psychophysical performances
Mizolastine	Extensive (glucuronidation and also CYP3A4)	Potent CYP3A4 inhibitors or substrates (caution required; moderate increase of mizolastine concentrations with ketoconazole and erythromycin) No additive effect with alcohol on sedation or vigilance
Rupatadine	Extensive pre-systemic (almost complete, primarily through CYP3A4)	CYP3A4 inhibitors or grapefruit juice (concomitant administration not recommended) CNS sedatives (interactions cannot be ruled out) HMG-CoA reductase inhibitors (statins) (some of which are metabolized through CYP3A4; asymptomatic increases of CPK reported) Marginal effects of rupatadine 10 mg with alcohol on psychomotor tests; increase of alcohol-induced alterations with 20 mg

Most data in this table has been derived from the relevant Summary of Product Characteristics

CPK creatine phosphokinase, CYP cytochrome P450, OATP organic anion-transporting polypeptide, od once daily, P-gp P-glycoprotein

^a Bilastine is a substrate for P-gp and OATP in vitro and in vivo

^b Desloratadine is neither a substrate nor an inhibitor of P-gp

^c This effect appears to be without clinical relevance in terms of safety and may result from both increased gastrointestinal absorption and a reduction in biliary excretion and gastrointestinal secretion

^d Fexofenadine is a P-gp and OATP substrate

The most important pharmacological aspects of the sg-AHs used for CSU are summarized in Table 1 (liver metabolism and drug interactions) and Table 2 (warnings, including for use in the elderly, or in the case of kidney or liver insufficiency) [39, 41].

Compared to the first-generation medications, these agents are highly selective for the H₁ receptor and have a

better side effect profile. They are minimally or non-sedating because of their poor penetration in the blood–brain barrier. H₁ receptor occupancy in the CNS was negligible for fexofenadine and at most moderate for cetirizine, with values up to 30 %, using above-label doses of 20 mg [42, 43]. Therefore, sg-AHs have a low probability of causing CNS effects. Nevertheless, some of them, such as cetirizine

Table 2 New-generation histamine H₁ antihistamines: recommendations in the elderly, in case of renal and hepatic insufficiency, and special warnings

Drug	Elderly	RI	LI	Special warnings/additional comments
Bilastine	No dose adjustment necessary. Limited clinical data. No differences in pharmacokinetics, efficacy, and safety in phase II and III studies	No dose adjustment required Increase of plasma concentrations and AUC, however, within the safety margins	No dose adjustment required	The concomitant use of P-gp inhibitors to be avoided in pts with moderate-to-severe RI or with renal problems treated with high doses No cardiotoxicity even at high doses
Cetirizine	Dose adjustment not required if renal function is normal	No data about efficacy/safety. Dose adjustment according to renal function (CL _{CR}). Contraindicated in severe RI ^a	No dose adjustment (required only if RI is associated). Increased half-life and reduced clearance in chronic liver diseases after a single dose of 10 or 20 mg	Caution in pts with or at risk of seizures No cardiotoxicity even at high doses Overdose symptoms may include CNS or anticholinergic effects (reported also with a dose fourfold higher than the standard dose) No cardiotoxicity even at very high doses. Absence of relevant clinical events with repeated doses up to 45 mg
Desloratadine	Not specified	Caution suggested in severe RI	Dose adjustment not required	Caution in pts with known cardiac risk ^b Absence of relevant clinical events with high doses (up to 100 mg/day). Clinical and ECG monitoring recommended in case of overdose
Ebastine	No different pharmacokinetics	Dose adjustment not required (to be used with caution)	Caution in pts with case of mild-to-moderate LI (without exceeding 10 mg/day). Contraindicated in severe LI	No cardiotoxicity even at very high doses. Overdose associated with dizziness, somnolence, fatigue, and xerostomia No cardiotoxicity Overdose symptoms include somnolence
Fexofenadine	No dose adjustment necessary. Attention because of limited data	No dose adjustment necessary.	Attention because of limited data	No cardiotoxicity even at very high doses. Overdose associated with dizziness, somnolence, fatigue, and xerostomia No cardiotoxicity Overdose symptoms include somnolence
Levocetirizine	Dose adjustment required in case of moderate-to-severe RI	Dose adjustment according to renal function (CL _{CR}). Contraindicated in severe RI ^a	No dose adjustment required	No cardiotoxicity (including effects on ECG, cardiac function and pacemaker intrinsic activity, and during long-term treatment). Overdose associated with an increased frequency of somnolence and anticholinergic effects
Loratadine	No dose adjustment required. No changes in pharmacokinetics of loratadine and its metabolites	No dose adjustment required	Caution in severe LI (reduced initial doses recommended). In alcohol-related liver disorder, increase of AUC and C _{max} in parallel with LI severity	Other contraindications: (1) concomitant use of systemic azole antifungals and macrolide antibiotics or drugs able to prolong the QT interval ^c ; (2) relevant heart disorders, history of symptomatic arrhythmias, or clinically significant bradycardia; (3) QT interval prolongation or hypokalemia. Recommended periodic monitoring of diabetics or pts susceptible to electrolyte disturbances and to arrhythmias, and monitoring of QT and cardiac rhythm for at least 24 h in case of overdose
Mizolastine	Possible susceptibility to sedative action and to the potential effect on cardiac repolarization	Not specified	Increase of AUC Contraindicated in severe LI	

Table 2 continued

Drug	Elderly	RI	LI	Special warnings/additional comments
Rupatadine	No dose adjustment required (increase of AUC, concentrations and C_{max} without clinical consequences). Caution because of limited data (a greater sensitivity cannot be excluded)	Not recommended because of the lack of clinical experience		No change in QT/QTc and ECG at very high doses. However, caution suggested in pts with known QT prolongation, uncorrected hypokalemia, pro-arrhythmic conditions (i.e., clinically significant bradycardia), acute myocardium ischemic disease

Most data in this table has been derived from the relevant Summary of Product Characteristics
AUC area under the concentration–time curve, *CL_{CR}* creatinine clearance, *C_{max}* maximum plasma concentration, *LI* liver insufficiency, *P-gp* P-glycoprotein, *pts* patients, *QTc* corrected QT interval, *RI* renal insufficiency

^a *CL_{CR}* <10 mL/min or dialysis

^b QT prolongation, hypokalemia, or treated with drugs than can prolong QT interval or inhibit cytochrome P450 3A4, such as systemic azole antifungals and macrolide antibiotics

^c Include, e.g., class I and III anti-arrhythmic drugs

and loratadine, potentially induce sedation when recommended doses are exceeded [28]. A dose-dependent relationship in the occupancy of brain H₁ receptors was shown for cetirizine [44] and in animal models also for levocetirizine [45]. In an RCT of CSU patients, rupatadine caused somnolence in 4.29, 5.41, and 21.43 % with daily doses of 5, 10, and 20 mg, respectively (vs. 2.9 % in the placebo group) [46]. Sg-AHs do not usually exacerbate the CNS effects of coadministered alcohol or other CNS-active substances, although caution is recommended for administration of alcohol with either cetirizine or levocetirizine (Table 1). A study in healthy volunteers found greater impairment in cognitive and psychomotor performances with cetirizine 10 mg or rupatadine 20 mg taken with alcohol than with the alcohol alone, while rupatadine 10 mg did not affect the effect of alcohol [47]. A higher propensity for the sedative action of mizolastine in the elderly has been hypothesized, as declared in the Summary of Product Characteristics (SPC).

No clinically significant cardiac effects have been reported for most sg-AHs, even at high doses [28, 41]. However, it has been reported that older individuals are more susceptible to the potential effect of mizolastine on cardiac repolarization, which is contraindicated in patients with relevant heart disorders and pro-arrhythmic conditions (Table 2). In such circumstances, caution is suggested in the SPC for rupatadine and ebastine.

The pharmacokinetics of these newer antihistamines have been studied in healthy adults, the elderly, and subjects with impaired hepatic or renal function. Looking at the general pharmacological profile of sg-AHs (Tables 1, 2) [39, 41], these drugs show some peculiarities that have to be taken into account for the selection of the most appropriate molecule. Some of these medications are metabolized, sometimes with the involvement of the cytochrome P450 (CYP) enzyme system in their first pass through the liver, which may lead to drug–drug interactions (Table 1). No dosage adjustment is required in the elderly for most drugs, but as a general rule the dose of drugs with extensive liver metabolism should be adapted in patients with liver dysfunction; a reduced initial dosage is often preferred in the elderly because of a slower metabolism, while the dose should be adjusted according to the renal function in the case of medications that are excreted through the kidneys [48]. For bilastine and fexofenadine, no dose adjustment is suggested in patients with renal or hepatic insufficiency; instead, rupatadine is not recommended for patients with renal or hepatic insufficiency because of limited experience.

The safety of sg-AH up-dosing has not been systematically evaluated in the older population. It is unknown if this option would be similarly safe with each molecule of the sg-AH class. Sedation may be dose-dependent in some

instances and a few patients, including older ones, may be particularly susceptible to the sedative action of minimally sedating agents. Moreover, it cannot be ruled out that up-dosing could cause risks in some patients, especially in elderly patients with renal, hepatic, and/or cardiac disorders.

5.2 Alternative Treatments

Concerning the third-line therapy for CSU, the studies specifically examining the effect of montelukast in the elderly are limited. The cumulative data appear reassuring regarding the safe use of montelukast in this age group, even though sporadic cases of acute hepatitis and Churg-Strauss syndrome have been described in older patients [48–50]. An association between the risk of such events and age has not been confirmed [50]. It should be noted that a post hoc analysis performed in a nationwide population-based cohort in Sweden revealed a significant association of montelukast use with a lower risk of recurrent myocardial infarction in male subjects [51]. This seems to reinforce the importance of the leukotriene pathway in determining the atherosclerotic risk [52]. Clearance of leukotriene receptor antagonists is decreased in the elderly and montelukast can interact with a wide range of drugs that inhibit or induce the CYP3A4, CYP2C8, or CYP2C9 systems [13] (Table 3). Dose adjustments are not necessary in either the elderly or in patients with renal failure or mild-to-moderate liver insufficiency.

Cyclosporine has well-known dose-dependent and time-dependent AEs that require careful monitoring, including effects on blood pressure and renal function [53]. It should be used with extreme attention in the elderly, who are at higher risk of developing AEs. Elderly patients should be monitored with particular care, since a decline in renal function also occurs with aging. Most available pharmacokinetic data in the elderly do not reveal any major differences from the drug disposition detected in younger individuals [54]. A more recent pharmacokinetic study in elderly kidney transplant patients has, however, demonstrated that the clearance of cyclosporine decreased with increasing age and that old patients had a significantly larger proportion of the whole blood cyclosporine concentration located in T lymphocytes [55]. Therefore, selection of the cyclosporine dose for an older patient should be made with caution and it should be started at the lowest limit of the therapeutic range. Cyclosporine has multiple drug interactions that can create relevant problems in the management of old patients on polytherapy (Table 3). Age was not shown to have an impact on cyclosporine–drug interactions in adult transplant patients, as such interactions did not show differences between 60- and 75-years-old and younger transplant patients [56].

The pivotal phase III studies with omalizumab in CSU enrolled patients up to 75-years-old. The studied populations were probably composed of only a minority of patients aged 65 years or older, who were specified to be 4–9 % in one study [34] and 3.7–5.2 % in another study [36] among the omalizumab-treated groups. In another study [35], omalizumab proved effective with no relationship to the patient's age, although specific details were not reported. The literature contains sporadic reports of older patients with difficult-to-treat CSU and/or chronic inducible urticaria treated with omalizumab; in one case the highest age was 82 years [57]. At present specific data are not available on omalizumab treatment in older patients with CSU or other diseases. A study examined the influence of patient age on the results of add-on treatment with omalizumab in patients with severe allergic asthma recruited in two German post-marketing surveillance trials [58]. No differences in safety and efficacy were detected between patients who were 50 years or older patients and those younger than 50 years. Based on the available information, dose adjustment is not recommended in the case of impaired renal or hepatic function, although caution is suggested, and no dose change seems to be necessary in the elderly. The clinical experience with omalizumab in CSU is still very limited, and unknown aspects include the optimal long-term treatment strategies and duration. The safety and tolerability profile of omalizumab appears to be favorable. Cases of thrombocytopenia and arterial thrombotic events have recently been reported [59, 60], although more studies are needed to define the exact correlation with the treatment.

5.3 Safety Issues Related to Glucocorticoids and First-Generation Antihistamines

There is general agreement that systemic corticosteroids should be used only for short periods and at the lowest effective dose during CSU exacerbations, and current guidelines do not recommend long-term use of glucocorticoids in urticaria because of the risk of AEs [1]. However, systemic corticosteroids are still prescribed for CSU [61, 62]. Old age may be a risk factor for particular corticosteroid-associated AEs, such as memory impairment, diabetes, cataract, and osteoporosis [13]. An increased risk of peptic ulcer has been observed in corticosteroid users who were receiving NSAIDs concomitantly [63]; it should be remembered that these drugs are commonly used by old people (including aspirin for cardiovascular prevention).

Despite current recommendations against the use of first-generation antihistamines [1], these drugs are still commonly used to treat CSU [62]. First-generation antihistamines cross the blood–brain barrier at once and impair neurotransmission by histamine at H₁ receptors in the CNS.

Table 3 Liver metabolism and most relevant drug interactions of montelukast and cyclosporine (ciclosporin)

Drug	Liver metabolism	Most relevant data on drug interactions	Special notes
Montelukast	Extensive. Predominant involvement of CYP2C8, with marginal role of CYP3A4 and CYP2C9	Absence of clinically relevant interactions between montelukast 10 mg and theophylline, prednisone, prednisolone, digoxin, and warfarin Caution in case of concomitant administration of CYP3A4, CYP2C8, and CYP2C9 inducers (e.g., phenytoin, phenobarbital, rifampicin) Relevant alterations on the metabolism of drugs metabolized through CYP2C8 (rosiglitazone, repaglinide) are not expected No dose change of montelukast recommended during use of gemfibrozil or other CYP2C8 inhibitors, but the potential risk of ADRs should be considered (increased montelukast AUC induced by gemfibrozil). Relevant interactions with less potent CYP2C8 inhibitors (i.e., trimethoprim) not expected. No change of montelukast AUC with itraconazole	Reduction of plasma concentrations of theophylline only with very high doses of montelukast (20–60 times higher than standard dose) Decrease of montelukast AUC by 40 % induced by phenobarbital In vitro, montelukast is a potent inhibitor of CYP2C8, but inhibitory effects were not shown in vivo In vitro, montelukast is a substrate of CYP2C8, and with lesser extent of CYP2C9 and CYP3A4 Gemfibrozil is an inhibitor of both CYP2C8 and CYP2C9, while itraconazole is a potent CYP3A4 inhibitor
CSA	Extensive. At least 25 metabolites identified from bile, feces, blood, and urine	CSA may increase plasma concentrations of several co-medications that are substrates of CYP3A4 or P-gp or both Compounds that decrease CSA absorption such as orlistat should be avoided CSA may reduce the clearance of digoxin, colchicine, prednisolone, HMG-CoA reductase inhibitors (statins), aliskiren, repaglinide, NSAIDs, sirolimus, etoposide, and other drugs CSA may increase the risk of toxic effects of digoxin and statins (myopathy), as well as of colchicine (especially in patients with renal dysfunction) CSA may increase the plasma concentrations of repaglinide CSA should not be used with potassium-sparing diuretics. Caution in the case of a potassium-rich diet, coadministration of potassium-sparing drugs (e.g., ACE inhibitors, angiotensin II receptor antagonists), or potassium-containing drugs Concomitant use of NSAIDs is associated with additive decreases in renal function Nifedipine should be avoided when gingival hyperplasia develops During CSA treatment, vaccination may be less effective The administration of live vaccines should be avoided	CSA is metabolized by CYP3A (particularly CYP3A4) and is a substrate of P-gp Risk of myopathy with statins, and myopathy and neuropathy with colchicine Risk of hypoglycemia Risk of hyperkalemia Control of potassium levels in these situations Close monitoring of clinical status and serum creatinine. Use of lower doses of NSAIDs Frequent occurrence of gingival hyperplasia during concomitant administration

ADRs adverse reactions, AUC area under the concentration–time curve, CYP cytochrome P450, CSA cyclosporine, P-gp P-glycoprotein

Positron emission tomography analyses have shown that these medications occupy more than 70 % of the CNS H₁ receptors. This potentially leads to several AEs, such as drowsiness, sedation, somnolence, fatigue, dizziness,

headache, decreased reaction time, dyskinesia, confusion, and agitation (older patients may experience paradoxical excitation and agitation), with potential impairment of the cognitive function, memory and psychomotor performance,

and increased risk of falls [28, 64, 65]. The possibility of activation of epileptogenic foci has also been described [38]. Impairment of CNS function is produced even by the standard or low doses of first-generation antihistamines, and has been documented also with bedtime administration (the so-called ‘hangover’ in the following morning) because of the long elimination half-life of these medications [64]. The elderly can be particularly susceptible to CNS effects, as are people with a small body mass, hepatic or renal dysfunction, or those with a pre-existing CNS disorder [65, 66]. In fact, the administration of first-generation antihistamines in the elderly has been associated with an increased risk of impaired CNS function, inattention, disorganized speech, altered consciousness, or delirium [67, 68]. This increased risk in the geriatric population can also be linked to the frequent association with cognitive, often subclinical, impairment, the presence of histamine neurotransmission disruption in individuals with neurodegenerative diseases, as well as the slower elimination of the drugs and the common coadministration of CNS-active drugs, such as benzodiazepines [68].

First-generation antihistamines have poor receptor selectivity. Non-antihistamine activity is another source of concern, particularly in older individuals, who are more prone to anticholinergic effects. Such effects include urinary hesitancy, urinary retention, constipation, dry mouth, dry eyes, papillary dilatation, dizziness, impaired coordination, and memory dysfunction, whereas the α -adrenergic blockade may be responsible for arrhythmias, peripheral vasodilatation, and postural hypotension [69]. These AEs may lead to falls or to the aggravation of concomitant diseases, such as prostatic hypertrophy, bladder neck obstruction, narrow-angle glaucoma, and heart disease.

Moreover, there are very few prospective clinical pharmacological studies of the older antihistamines in the elderly, or in people with impaired hepatic or renal function, and few studies about their interactions with other drugs, foods, or herbal products. The long-term safety of these drugs has never been investigated systematically. For all of these reasons, first-generation antihistamines should be avoided in older subjects and have been included in the American Geriatrics Society updated Beers list of potentially inappropriate medications for older adults [70].

6 Conclusions

The purpose of this article is to contribute to the promotion of the concept of healthy aging and to revise the main aspects of CSU in the elderly. CSU often occurs in the elderly, causing itch, irritability, insomnia, and a reduced

QOL. Appropriate diagnostic protocols should be applied in order to recognize this disease, which is often under diagnosed and possibly underestimated. It is important to understand the pathogenic mechanisms in order to rule out concomitant medical or autoimmune pathologies, which can themselves cause hives, and in order to prevent secondary forms caused by drug administration. In the management of the disease it is recommended to avoid causative or triggering factors, if possible. Patient history and clinical examinations are very important for the identification of such factors and should act as a basis and a guide for extended diagnostic testing.

When medications to control CSU symptoms are prescribed to older patients, attention should be paid to potential drug–drug interactions and to the impact of the drug treatment on co-morbidities. The therapy must include drugs that do not cause adverse effects to patients or further worsen their co-morbid status. Non-sedating antihistamines are considered the mainstay treatment for CSU and should also be the preferred treatment in the elderly. However, despite the overall good safety of sg-AHs, the selection of the molecule should take into consideration the risk of mild sedative effects as described for a few agents—especially with high doses—and the presence of coexisting disorders; the SPCs for some medications carry special warnings regarding patients with cardiac problems and kidney or liver failure. It is always appropriate to use drugs that do not interfere with the activity of the CYP system. Information concerning the tolerability of sg-AH up-dosing in the elderly is lacking, so it is necessary to conduct further studies on this topic, as well as on the safety profiles of alternative treatment approaches (e.g., omalizumab) in elderly CSU patients. The experience derived from patients with respiratory allergy suggests that montelukast is generally safe in the geriatric population. Short-term treatment with corticosteroids and cyclosporine should be used with extreme caution, paying attention to the patient’s clinical condition and contraindications. After careful scrutiny of the available data, we conclude that the use of first-generation antihistamines should be avoided for the routine management of CSU in the elderly.

The literature review indicates that there are several areas of CSU in the elderly that deserve further research, especially in reference to epidemiology, clinical presentation, association with co-morbidities, impact on QOL, efficacy, and the safety of the different treatment options.

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