

BMJ Open Glucocorticoids for acute urticaria: study protocol for a double-blind non-inferiority randomised controlled trial

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ABSTRACT

Introduction This study protocol describes a trial designed to investigate whether antihistamine alone in patients with acute urticaria does not increase the 7-day Urticaria Activity Score (UAS7) in comparison with an association of antihistamine and glucocorticoids and reduces short-term relapses and chronic-induced urticaria.

Methods and analysis This is a prospective, double-blind, parallel-group, multicentre non-inferiority randomised controlled trial. Two-hundred and forty patients with acute urticaria admitted to emergency department will be randomised in a 1:1 ratio to receive levocetirizine or an association of levocetirizine and prednisone. Randomisation will be stratified by centre. The primary outcome will be the UAS7 at day 7. The secondary outcomes will encompass recurrence of hives and/or itch at day 7; occurrence of spontaneous hives or itch for >6 weeks; patients with angioedema at day 7, and 2, 6, 12 and 24 weeks; new emergency visits for acute urticaria recurrences at days 7 and 14, and 3 months; Dermatology Life Quality Index at days 7 and 14, and 3 and 6 months; and Chronic Urticaria Quality of Life Questionnaire at 6 weeks.

Ethics and dissemination The protocol has been approved by the *Comité de Protection des Personnes Sud-Méditerranée II* and will be carried out in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. A steering committee will oversee the progress of the study. Findings will be disseminated through national and international scientific conferences and publication in peer-reviewed journals.

Trial registration number NCT03545464

INTRODUCTION

Acute urticaria is a common condition among patients in the emergency departments (ED) and is associated with high morbidity.^{1,2} Acute urticaria accounted for 9% of dermatologic diseases presenting at the ED¹ and for 1.3 ED admissions per day in a retrospective study.² Second-generation H1-antihistamines are the cornerstone of the management of

Strengths and limitations of this study

- This study will be the largest multicentre, double-blind randomised controlled trial ever conducted on the use of glucocorticoids during the treatment of acute urticaria and may help establish strong recommendations on treatment strategy with a high level of evidence.
- Primary outcome criteria will be used in accordance with international guidelines.
- This is the first study with a long-term follow-up.

acute urticaria with the avoidance of eliciting factors.³ Few studies have focused on adding of glucocorticoid therapy.⁴⁻⁶ But despite the controversial benefit, a short course of oral glucocorticoids is included in the treatment guidelines of acute urticaria.³ Two studies have suggested that a short course of glucocorticoids, which may be helpful to reduce disease duration and/or activity, in addition to antihistamines, improved more quickly and more completely patients with acute urticaria.^{4,5} Indeed, with days, glucocorticoids reduce mast cell number but do not inhibit mast cell degranulation.⁶ However, in a recent double-blind randomised controlled trial (RCT), the addition of prednisone to levocetirizine did not improve the symptomatic and clinical response of acute urticaria.⁷ Moreover, no long-term follow-up was investigated in these studies,^{4,5,7} although oral steroids might confer resistance to antihistamine in chronic urticaria in a prospective study in 17 patients.⁸

Given such uncertainties, there is heterogeneity among criteria for initiation of glucocorticoids that leads to discrepancies in the use of glucocorticoids as an ancillary therapeutic agent in the treatment of acute

urticaria. Ninety-three per cent of 459 Italian patients attending an ED for this condition received glucocorticoids in a retrospective study in 2011.² In another recent observational study, frequent glucocorticoid use (48% of 2701 ED visits) to treat allergic reactions or anaphylaxis was reported but no significant benefit was observed in Canada.⁹ Indeed, the authority consider an appropriate multicentre RCT involving patients with acute urticaria to be an important research priority.³ To fill this perceived need, in the current trial we compared a strategy of an antihistamine treatment without glucocorticoids with a strategy with glucocorticoids in ED patients who had acute urticaria.

Aims and hypotheses

The primary aim of this study is to assess the non-inferiority of the effectiveness of an antihistamine treatment alone in comparison with an association of

antihistamine and glucocorticoid in the treatment of acute urticaria in EDs. We hypothesise that antihistamine treatment without glucocorticoid could not increase the 7-day Urticaria Activity Score (UAS7) at day 7, in comparison with the standard treatment of an association of antihistamine and glucocorticoid and would entail a lower risk of adverse events (AE). The key secondary aims are to compare the number of urticaria (hives) recurrences at day 7; the number of transitions to chronic urticaria beyond 6 weeks; the number of patients with angioedema at day 7, and 2, 6, 12 and 24 weeks; the new emergency visits for acute urticaria (hives) recurrences at days 7 and 14, and 3 months; Dermatology Life Quality Index (DLQI) at days 7 and 14, and 3 and 6 months; and Chronic Urticaria Quality of Life Questionnaire (Cu-Q2QoL) up to 6 weeks.

Table 1 Schedule of enrolment, interventions and assessments

Procedures and treatments	D0 Enrolment	D7 Dermatology visit	D14-D42-D84-D168 Dermatology visit or phone call			
	Visit 1	Visit 2 At 1 week	Visit 3 At 2 weeks	Visit 4 At 6 weeks	Visit 5 At 12 weeks	Visit 6 At 24 weeks
Inclusion and non-inclusion criteria	X					
Informed consent	X					
Randomisation	X					
Blinded treatment	X					
Levocetirizine+prednisone or placebo of prednisone						
Levocetirizine, on persistence of hives		X				
Clinical examination						
Weight	X					
Diabetes mellitus	X					
Hypertension	X	X	X	X	X	X
Angioedema	X	X	X	X	X	X
Trigger	X					
Outcome variables						
UAS7		X	X	X	X	X
Relapse of rash		X	X	X	X	X
Relapse of pruritus		X	X	X	X	X
Readmission to ED		X	X	X	X	X
Mortality		X	X	X	X	X
Gastrointestinal bleeding		X	X	X	X	X
Induced diabetes		X	X	X	X	X
Cu-Q2QoL		X	X	X	X	X
Dermatology Life Quality Index (DLQI)		X	X	X	X	X

Cu-Q2QoL, Chronic Urticaria Quality of Life Questionnaire; ED, emergency department; UAS7, 7-day Urticaria Activity Score.

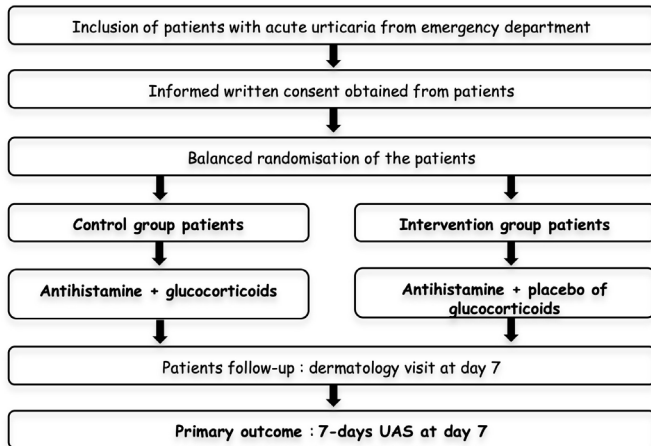


Figure 1 Flow chart of study design. UAS, Urticaria Activity Score.

METHODS/DESIGN

Design overview

The Glucocorticoids in Acute Urticaria in Emergency Department (COURAGE) trial is a prospective, double-blind, parallel-group, multicentre non-inferiority RCT in which patients with acute urticaria are allocated in a 1:1 ratio to antihistamine alone (experimental group) or to an association of antihistamine and glucocorticoid (control group). The trial design is summarised in [table 1](#). We report the study protocol according to the Standard Protocol Items: Recommendations for Interventional Trials statement.¹⁰ The flow chart of the COURAGE study is shown in [figures 1 and 2](#).

Study setting and population

Participants will be prospectively recruited among patients admitted to an ED, in 12 French centres belonging to the French Society of Emergency Medicine. Eight French departments of dermatology and two French departments of internal medicine are participating in the follow-up of patients. There are reference centres that belong to the Urticaria Group of the French Society of Dermatology, to the reference centres for bradykinin-mediated angioedema and to the GA²LEN Urticaria Center of

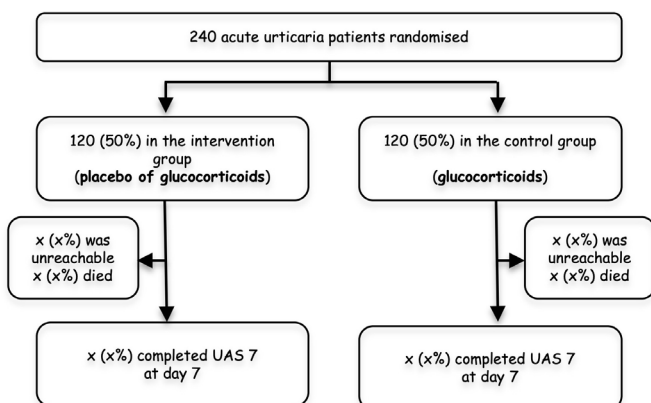


Figure 2 Flow chart of patients. UAS, Urticaria Activity Score.

Box 1 Eligibility criteria

Inclusion criteria

- ▶ Adult patients aged 18 or above, admitted to an ED.
- ▶ Isolated spontaneous urticaria (acute hives).
- ▶ Acute urticaria (hives) with angioedema without laryngeal oedema.
- ▶ Obtain patient's consent and social security affiliation.

Non-inclusion criteria

- ▶ Pregnancy or breast feeding.
- ▶ Acute hives with anaphylaxis.
- ▶ Bradykinin angioedema.
- ▶ Angioedema without urticaria (hives).
- ▶ Laryngeal oedema with urticaria (hives).
- ▶ Corticosteroid administration in the previous 5 days visiting the ED.
- ▶ Antihistamines greater than one tablet per day in the previous 5 days visiting the ED.
- ▶ Other treatment for urticaria: omalizumab, montelukast, cyclosporin A.
- ▶ Chronic urticaria before acute urticaria diagnosis.
- ▶ Other skin disease (atopic dermatitis, eczema, bullous pemphigoid, acute exanthematous pustulosis).
- ▶ Diabetes mellitus.
- ▶ Gastrointestinal ulcer.
- ▶ Refusal to participate.
- ▶ Known allergy to the study drugs or formulation ingredients.
- ▶ Hypersensitivity to lactose.
- ▶ Known renal failure defined by creatinine clearance <10 mL/min or cardiac failure defined by ejection fraction <40%.
- ▶ Contraindication to glucocorticoid.
- ▶ Psychotic states still uncontrolled by treatment limiting the participant's compliance with the research.

ED, emergency department.

Reference and Excellence for two centres. Their mission is to improve access to diagnosis and therapy for patients with urticaria, acute and chronic. All study centres have medical and paramedical teams with experience in the field of urticaria, and all implement a therapeutic education programme based on guidelines for treatment and for prophylaxis of recurrent attacks.³ Patients will be considered eligible for randomisation if they fulfil all of the inclusion criteria and none of the exclusion criteria, as defined in [box 1](#). A strategy where an association of antihistamine and placebo of glucocorticoid is initiated immediately after randomisation will be compared with a strategy where an association of antihistamine and glucocorticoid is initiated.

Interventions

Patients eligible for inclusion will be assigned to one of the two groups: (1) patients assigned to control group will receive glucocorticoid treatment; and (2) patients assigned to interventional group will receive placebo of glucocorticoid. In both groups, patients received antihistamine and stayed minimally for 1 hour in the ED.

Experimental arm

In ED: placebo of prednisone 1 mg/kg once orally, without exceeding a maximum of six tablets. At home:

placebo of prednisone 40 mg (two tablets) once per day for 3 days orally.

Control arm

In ED: prednisone 20 mg; 1 mg/kg once orally. At home: prednisone 40 mg: two tablets of 20 mg once per day for 3 days orally.

Both groups

In ED: levocetirizine 5 mg orally. On persistence of hives at 30 min, levocetirizine 5 mg orally, once renewable. At home: levocetirizine 5 mg twice daily for 7 days (D1–D7). On persistence of hives, levocetirizine 10 mg twice daily for 7 more days (D8–D14). After D14, the choice of second-generation H1-antihistamines and adjunctive medication (omalizumab, cyclosporin A) administered to support first step treatment was left to the discretion of the treating dermatologist physician. Glucocorticoids are not allowed.

Trial outcomes

Primary outcome

The primary outcome is the UAS7 at day 7, which is validated in French.

UAS is a daily combined score of severity of itch and number of hives. Each component of the UAS is scored on a scale of 0–3. The two scores are added together for a daily total of 0–6. The daily UAS ranges from 0 to 6 points, depending on the number of wheals (0–3 points) and the intensity of pruritus (0–3 points).

Wheals: 0: none; 1: <20; 2: 20–50; 3: >50.

Pruritus: 0: none; 1: mild; 2: moderate; 3: severe.

UAS will be collected in a follow-up visit at day 7 by a dermatologist coinvestigator thanks to the patient's notebook.

Secondary outcomes

Secondary outcome variables include the following:

1. Recurrence of hives at day 7 and/or recurrence of itch at day 7.
2. Occurrence of spontaneous wheals and/or itch for >6 weeks.
3. Patients with angioedema at day 7, and 2, 6, 12 and 24 weeks.
4. New emergency visits for acute urticaria recurrences at days 7 and 14, and 3 months.
5. DLQI at days 7 and 14, and 3 and 6 months.
6. Cu-Q2QoL at 6 weeks.

Randomisation, sequence generation and allocation concealment

Eligible patients are consecutively randomly allocated to one of the two treatment arms, termed 'intervention group' without glucocorticoids (with placebo of glucocorticoids) and 'control group' with glucocorticoids. A computer-generated randomisation is performed with stratification according to centre in a 1:1 ratio. Block randomisation was used to minimise imbalances between arms.

Numbered closed boxes containing the treatments are stored in the pharmacy. The pharmacy will give the two lowest numbered closed boxes to the ED physician. After inclusion criteria checking by the ED investigator, he takes the lowest numbered closed boxes and assigns it to the patient. Boxes will be numbered according to the randomisation list. This process defines the randomisation.

The number of experimental units per block will be kept confidential to avoid prediction of future patient's allocation. Only the independent statistician and the computer programmer who will implement the sequence assignment will have access to the randomisation list.

Blinding

Participants, investigators and statisticians will be blinded to the allocated treatment. Blinding will be ensured by the use of placebo of prednisone that is strictly identical to the prednisone (conditioning, tag, semblance, odour and flavour). Moreover, none of the emergency physicians enrolling patients are members of dermatology unit that will involve in the follow-up visit. Only emergency situation or end of the study could allow the unblinding. In most cases, discontinuation of the treatment should be sufficient. Only the pharmacist involved in the study and the research assistant have the randomisation list. The study statistician will be blinded to the groups.

Statistical methods

Sample size calculation

Patients will be randomised into one of two groups: (1) intervention group receiving antihistamine alone; (2) control group receiving antihistamine combined with prednisone. According to Mathias *et al*,¹¹ the minimal important difference (MID) for the UAS7 ranged from 9.5 to 10.5. In order to be conservative, we considered a non-inferiority margin largely lower than MID and equal to 5, and an SD around 13 for UAS7 and a 10% attrition rate. Under these conditions, we will be including 120 patients per group to allow an 80% power to demonstrate non-inferiority using a CI approach (95% two-sided equivalent to one-sided type I error of 2.5%).

Statistical hypotheses and rules

The present study is a non-inferiority study. Considering that the primary endpoint is a severity score, the hypotheses for non-inferiority in this situation are:

$$H_0 : D = mC - mT \leq -\delta \quad H_A : D = mC - mT > -\delta$$

where $\delta > 0$ is the non-inferiority margin of clinical interest and mC or MT is the mean (or median depending on the statistical distribution) in the control or test group. All tests will be two sided at a 5% significance level. No adjustment is necessary in this study.

Population analysed

Intention-to-treat (ITT) population analysis includes every patient assigned to a treatment strategy and kept in this group during the analysis, even if they deviated from their assignment of treatment after randomisation

and who have signed an informed consent form. When patients withdraw consent during the clinical trial, data collected before withdrawal remain part of the study unless the subject does not consent in writing.

Per protocol (PP) set as defined as all patients randomised and treated without non-adherence to treatment protocol will be performed. Predefined major non-adherences are:

- ▶ Missing data for the primary efficacy endpoints.
- ▶ Use of treatment other than attributed by randomisation or treatment crossovers other than predefined.
- ▶ Inclusion in another clinical study.
- ▶ Other major protocol violations can be defined during a data blind review meeting.

Despite early recommendations preferred PP population for non-inferiority analyses, it has been recognised that both PP and ITT can induce specific bias in non-inferiority trials. The consensus is now to consider that non-inferiority should be demonstrated in both ITT and PP populations.

Disposition of patients, patient status and patients excluded from ITT and PP populations will be summarised by treatment group. Descriptive statistics for primary reason for patient's withdrawal will also be presented by treatment group as well as a list of these patients sorted by treatment group.

Reasons for dropouts in each treatment group will be displayed. A detailed list of dropout patients will also be provided. The investigator must make every effort to contact subjects who withdrew early or lost to follow-up. Attempts to contact such subjects must be documented in the subject's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter). Subjects will not be replaced.

In the ITT population missing values will be imputed by multiple imputation technique.

Statistical analysis

Data will be analysed using SAS software V.9.3 or higher. No interim analysis is planned for this study. A flow chart will describe the number of eligible patients, and the number of patients effectively included in the study and in each of the two groups. Continuous variables will be summarised using the number of observations, mean, SD, minimum, maximum, 25%, 50% and 75% quartiles and the two-sided 95% CIs. Means, medians, minimum, maximum and SDs will be presented to one further decimal place.

There will be counting of the absolute and relative frequencies (percentages) for categorical variables. Percentages will be rounded to one decimal place and there may be occasions where the total of the percentages does not equal to 100% exactly.

Primary outcome analysis

As recommended by the European Medicines Agency (EMA) guidelines, the primary analysis will be based on the calculation of 95% two-sided CI of the difference of

the UAS7 in the tested group and the control group. The demonstration of non-inferiority will be accepted in the lower limit of this CI which is larger than the non-inferiority margin equal to -5 . The statistical distribution of the score will be assessed for normality using graphical methods and Shapiro-Wilk test, and in case of non-normality an exact CI will be used. Based on guidelines for non-inferiority trials the hypothesis will be considered as demonstrated if the ITT and PP analyses are concordant.

Secondary outcome analyses

All secondary criteria corresponding to the incidence of event or composite events will be compared by χ^2 test or Fisher's exact test.

Specific quality of life index (DLQI) will be analysed using Mann-Whitney test.

The number (%) of patients with serious AEs will be summarised by body system organ class.

A statistical analysis plan describing in details all the statistical procedures will be written before database freezing.

Patient and public involvement

Patients participated in the development of the research question. Tolerance and comfort of treatments are major elements of care since patients do their consultations in reference centres which ensure the optimal management of their patients. The burden of the treatment and disease is a major concern which permitted to establish the design of the trial through the feedback during routine care. For example, our design of the study included evaluation of patients' DLQI at days 7 and 14, and 3 and 6 months, and Cu-Q2QoL at 6 weeks. Results of the trial will be made available to all participants via ClinicalTrials.gov as well as by email notification to the associations of patients.

Trial status

Not recruiting.

Trial ethics and dissemination

Legal obligations and approval

The sponsor was *Assistance Publique-Hôpitaux de Paris* (AP-HP, Clinical Research and Innovation Department). AP-HP obtained prior approval from the *Comité de Protection des Personnes (CPP) Sud-Méditerranée II* (No 218A17) for its clinical trial COURAGE. AP-HP obtains authorisation from the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) after sending CPP approval and summary of the study protocol (No MEDAECNAT-2018-09-00012). The Declaration of Helsinki and the Good Clinical Practice guidelines will be respected by the trial. The coordinating investigator can make an amendment after submission to the sponsor, and approval from the CPP and ANSM. It is after the respect of these different stages that the amendment will be implemented.

Data collection and quality control

Investigators complete a case report form (paper and electronic case report form (e-CRF)) at each patient visit to the ED and a medical file. The person in charge of follow-up will be a dermatologist who completes a medical file and a case report form.

In the ED, the section 'acute episode' of the e-CRF is completed by the investigator of the participating centre visited by the patient. The e-CRF is then handed on to the study coordinator who will organise the follow-up telephone interviews with the patient included in the protocol. At week 1, the patient will be followed up in dermatologist's consultation. The follow-up at weeks 2, 6, 12 and 24 will depend on the evolution of hives and/or itch.

Patients will be evaluated by follow-up visit by the dermatologist after obtaining informed consent. Patients will record their results—pruritus score and number of skin lesions—in a paper/notebook. The DLQI and the Cu-Q2QoL will be recorded at each follow-up interview.

There will be three medical data sheets to be centralised by the scientific director:

1. A data sheet completed at the initial ED visit.
2. A data sheet completed at 7-day follow-up visit.
3. A data sheet completed at 14 days, 6 weeks, 12 weeks and at 24 weeks of follow-up visit.

All precautions to ensure confidentiality of information relating to drug treatments of the study, to study participants and their identity and to results of the trial are taken by persons responsible for the quality control of clinical studies in accordance with Article L.1121-3 of the French Public Health Code and with the conditions set out in Articles 226-13 and 226-14 of the French Criminal Code that governs the professional secrecy. An anonymisation of all data collected will be carried out and these will be sent to the sponsor by the investigators. No names and addresses of the participants will be shown. The sponsor will ensure that each subject has agreed in writing for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

Primary endpoint, secondary endpoints and safety assessment should be collected by the investigators even in any case of premature withdrawals and try to document their reason(s). The use of data collected prior to the date of premature exit or withdraw of consent is possible, except if the participant refuses in writing.

Safety considerations

During this research, AEs (serious and non-serious AEs) need to be reported to the sponsor. The investigator will report serious and non-serious AEs in the 'Adverse events' section of the e-CRF. The following events are foreseen and expected serious AEs: hypertension and gastrointestinal bleeding.

These serious AEs are simply recorded in the case report form:

- ▶ *Normal and natural course of the condition:*

- Relapse of hives or relapse of pruritus is possible after 2 weeks of the last tablet.
- Readmission (for relapse of hives or pruritus) to the ED can be necessary.
- ▶ *The following serious AEs are related to prednisone and reported in the Summary of Product Characteristics (SmPC) of prednisone:*
 - Hypokalaemia defined by value less than the limit lowest normal=3.0 mmol/L.
 - Cardiac insufficiency defined by symptoms occurring after mild or moderate effort.
 - Hyperglycaemia defined by fasting glucose value >160–250 mg/dL.
 - Agitation defined by mild or moderate mood alteration.

Dissemination of results

Results of the therapeutic trial will be presented in national and international meetings and in peer-reviewed journals. The results of the trial will be relevant to emergency physicians who manage patients with acute urticaria and potentially modified international guidelines for management of acute urticaria.

DISCUSSION

Antihistamine is the cornerstone of treatment of acute urticaria and oral glucocorticoid is often used to reduce disease duration and activity. Because of several drawbacks regarding its potential AEs (short-term relapse and/or resistance to antihistamine in chronic urticaria), oral glucocorticoids may not be the best drug to maintain the beneficial effects obtained by antihistamine treatment. Moreover, this study could show the interest of using the oral route and second generation of antihistamines in patients with acute urticaria while they often receive a first-generation antihistamine intravenously in EDs.

This trial is, to the best of our knowledge, the first RCT that will appropriately assess the use of glucocorticoids in patients with acute urticaria. To date, the only data available on glucocorticoids in this indication have been obtained from three previous studies with controversial results and with methodological limitations.^{4 5 7} Two old studies found that a short burst of glucocorticoids in addition to antihistamine could be beneficial to patients with acute urticaria.^{4 5} In the first prospective, randomised, double-blinded, placebo-controlled study, the addition of glucocorticoid (prednisone: 40 mg/day for 4 days) to antihistamine treatment (hydroxyzine: 100 mg/day) improved the efficacy (with a reduction in an itch score on a 10-point visual analogue scale) and reduced the course of acute urticaria.⁴ In this study, the principal limitations were the lack of long-term follow-up since follow-up was only 5 days and the use of unusual primary endpoint.⁴ The second study was non-randomised, non-double-blinded, non-placebo-controlled study and included 109 patients with acute urticaria in which symptoms resolved earlier with glucocorticoid (prednisone: 50 mg/day for 3 days)

than with antihistamine (loratadine: 10 mg/day for 3 days).⁵ Recently, a prospective, double-blind randomised (in a 1:1 ratio to receive levocetirizine plus prednisone burst, 40 mg orally once daily for 4 days, or levocetirizine plus placebo of prednisone) controlled monocentre trial enrolled 100 patients aged 18 years or older who had acute urticaria. The addition of a glucocorticoid to antihistamine was not superior to antihistamine alone for relieving itching (62% of the patients in the prednisone group had an itch score of 0 vs 76% of those in the placebo group (Δ -14%; 95% CI -31% to 4%)) of acute urticaria.⁷ Fifteen (30%) patients in the glucocorticoid group and 12 (24%) patients in the placebo group reported one or more relapses (Δ 6%; 95% CI -11% to 23%).⁷ This study does not support the addition of glucocorticoid to H1-antihistamine as first-line treatment of acute urticaria without angioedema. Principal limitations of this study were the non-use of the UAS7 as primary endpoint (and the use of itching score at 2 days after the ED visit), the monocentric nature of the study and the absence of long-term follow-up.⁷

Strengths and limitations

This is the largest prospective multicentre RCT comparing standard treatment regimen which comprises an association of glucocorticoid and antihistamine to antihistamine alone in patients with acute urticaria. Moreover, very strict treatment regimen will be used to ensure that all centres will apply the same treatment with a long-term follow-up.

The main limitation of our trial should be noted. Our results do apply to selected patients and cannot be generalised to all patients with acute urticaria. Patients with anaphylaxis and angioedema without urticaria which is more often mast cell mediated are not included in this study.

In conclusion, the COURAGE trial is an investigator-initiated RCT empowered to test the hypothesis that antihistamine alone in comparison to standard association of glucocorticoid and antihistamine may not decrease the UAS7 at 7 days in patients with acute urticaria and might mainly decrease the number of short-term relapses and of chronic urticarias induced by glucocorticoids.

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Disclaimer The funding source had no role in the design of the trial and will have no role in its execution, in the analysis and interpretation of data, or in the decision to submit results for publication.

Competing interests None declared.

Patient consent for publication Obtained.

Ethics approval The protocol has been approved by the Comité de Protection des Personnes (CPP) Sud-Méditerranée II (No 218A17).

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