



HAL
open science

Efficacy and safety of methotrexate versus placebo as add-on therapy to H1 antihistamines for patients with difficult-to-treat chronic spontaneous urticaria: A randomized, controlled trial

Sophie Leducq, Mahtab Samimi, Claire Bernier, Angele Soria, Emmanuelle Amsler, Delphine Staumont-Sallé, Germaine Gabison, Olivier Chosidow, Nathalie Beneton, Corina Bara, et al.

► **To cite this version:**

Sophie Leducq, Mahtab Samimi, Claire Bernier, Angele Soria, Emmanuelle Amsler, et al.. Efficacy and safety of methotrexate versus placebo as add-on therapy to H1 antihistamines for patients with difficult-to-treat chronic spontaneous urticaria: A randomized, controlled trial. *Journal of The American Academy of Dermatology*, 2020, 82 (1), pp.240-243. 10.1016/j.jaad.2019.07.097 . hal-02623128

HAL Id: hal-02623128

<https://hal.inrae.fr/hal-02623128>

Submitted on 21 Jul 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Title: Efficacy and safety of methotrexate add-on therapy versus placebo for patients with chronic spontaneous urticaria resistant to H1-antihistamines: a randomized, controlled trial

Authors and affiliations

S. Leducq^{1,2,3*}, M. Samimi^{1,4*}, C. Bernier⁵, A. Soria⁶, E. Amsler⁶, D. Staumont-Sallé⁷, G. Gabison⁸, O. Chosidow⁸, N. Beneton⁹, C. Bara⁹, A. Grange-Prunier¹⁰, E. Wierzbicka-Hainaut¹¹, E. Brenaut¹², C. Droitcourt¹³, N. Raison-Peyron¹⁴, H. Bourgoin¹⁵, H. Cornillier¹, L. Machet¹, B. Giraudeau^{2,3}, A. Caille^{2,3}, A. Maruani^{1,2,3*}

**Equally contributed*

¹Department of Dermatology, University Hospital of Tours, Tours, France

²Clinical Investigation Center, INSERM CIC 1415, University Hospital of Tours, Tours, France

³Université de Tours, Université de Nantes, INSERM U1246 - SPHERE, France

⁴ISP 1282 INRA, University of Tours, Tours, France

⁵Department of Dermatology, University Hospital Center of Nantes, Nantes, France

⁶Department of Dermatology and Allergology, Hospital Tenon, Paris, Assistance Publique Hopitaux de Paris, Sorbonne Université, Paris, France

⁷CHU Lille, Service de Dermatologie et Vénérologie, F-59000 Lille, France, Université de Lille, INSERM U995 – LIRIC – Lille Inflammation Research International Center, F-59000 Lille, France

⁸Department of Dermatology, AP-HP, Henri-Mondor Hospital, Créteil, France

⁹Department of Dermatology, Hospital Center of le Mans, le Mans, France

¹⁰Department of Dermatology, Reims University Hospital, University of Reims-Champagne-Ardenne, Reims, France

¹¹Department of Dermatology, University Hospital of Poitiers, Poitiers, France

¹²Department of Dermatology, University Hospital of Brest, Brest, France

¹³Department of Dermatology, University Hospital of Rennes, Rennes, France

¹⁴Department of Dermatology, University Hospital of Montpellier, Montpellier, France

¹⁵Department of Pharmacy, University Hospital of Tours, Tours, France

Corresponding author

Dr Sophie Leducq, Department of Dermatology, CHRU Tours

Avenue de la République, 37044 Tours Cedex 9, France.

Tel: +33 2 47 47 90 80

Fax: +33 2 47 47 82 47

Email: soleducq@gmail.com

Funding sources: The study was funded by the French Ministry of Social Affairs and Health (French National Programme of Clinical Research [PHRC], 2009)

Conflict of interest: Dr Leducq, Dr Bernier, Dr Gabison, Pr Chosidow, Dr Beneton, Dr Bara, Dr Grange-Prunier, Dr Brenaut, Dr Droitcourt, Dr Bourgoin, Dr Cornillier, Pr Machet, Pr Giraudeau, Dr Caille et Pr Maruani have no conflicts of interest to disclose. Pr Samimi has received speaking fees for an educational program from BMS, Janssen, Acthelion, Abbvie. Dr Soria has received honoraria as a speaker, advisor and consultant from Novartis. Dr Amsler has received honoraria as a speaker and advisor from Novartis. Pr Staumont-Sallé has received fees as advisor and/or speaker from Janssen, Novartis, Sanofi, Pfizer, Abbvie, Lilly and has received research funding as principal investigator from Galderma, Leo Pharma, Novartis and Lilly. Dr Wierzbicka-Hainaut has received honoraria as advisor for Novartis and Sanofi. Dr Raison-Peyron has received honoraria as speaker and principal investigator from Novartis and has received equipment from Novartis.

Presented at the 24th World Congress of Dermatology, Milan, Italy, June 10-15th, 2019

Reprints are not available from the authors

IRB approval status: 2010-018716-33

Registration on ClinicalTrials.gov: NCT01960283

EudraCT: 2010-018716-33

Section: Research letter

Manuscript word count: 498

References: 5

Figures: 1

Tables: 1

Supplemental File: 1 (Available at <https://data.mendeley.com/datasets/82k28wzxm/1>)

Keywords: chronic spontaneous urticaria, methotrexate, H1-antihistamines, immunosuppressive drug, dermatology, combined modality therapy, randomized controlled trial

Presented at the 24th World Congress of Dermatology, Milan, Italy, June 10-15th, 2019

Current guidelines for chronic spontaneous urticaria (CSU) recommend second-generation H1-antihistamines as first-line treatment and to increase the H1-antihistamines dose in case of inadequate control.¹ The third-line management includes the addition of other drugs, largely omalizumab or immunosuppressive drugs.

The aim of this multicenter randomized, placebo-controlled, two parallel-group trial was to evaluate the efficacy and safety of methotrexate (MTX) versus placebo as add-on therapy to an H1-antihistamines regimen in patients with difficult-to-treat CSU.

We included adults with CSU who previously received at least three different molecules of H1-antihistamines or H1-antihistamines with at least a double dose from 2011 to 2016 (complete description of methods is in Supplemental file 1) (<https://data.mendeley.com/datasets/82k28wzxm/1>). Patients were randomized to receive MTX orally for 18 weeks (W18) or placebo in addition to H1-antihistamines (1:1 ratio). Study design and dosages are in Figure 1. Patients and investigators were blinded to treatment assignment. The primary outcome was complete urticaria remission at W18, defined as no urticarial lesions within the 30 days before W18. Secondary outcomes included pruritus, number of outbreaks per week, duration of lesions, number of lesions on the face/neck, quality of sleep, quality of life and safety.

We included 75 patients; 39 randomized to MTX and 36 to placebo. Baseline characteristics are in a Supplemental file 2. In the intent-to-treat analysis, three patients with MTX (7.9%) and 0 with placebo showed complete remission at W18 (difference, 7.9 percentage points [95% confidence interval -4.0 to 20.8], $p=0.24$). Sensitivity analyses of the primary outcome gave similar results (Table 1). The quality of life score decreased over time, but the change from baseline to W18 did not significantly differ between the two groups, nor did secondary outcomes differ. The proportion of adverse events (AEs) was also similar. Two

serious AEs occurred with MTX but were thought not to be related to MTX. Changes to laboratory measurements were more frequent with MTX than placebo, but none were severe.

Previous studies of MTX in CSU (one double-blinded RCT² that was underpowered, and two observational studies^{3,4}) had disparate results, which might be linked to their poor level of evidence and high heterogeneity of outcomes. As in ours, MTX was given as add-on therapy to H1-antihistamines. In our study, H1-antihistamines were not always at quadruple dosage, but the regimen could not be changed during the study. We chose a hard criterion (i.e., complete remission), and the study was double-blinded to allow high-level evidence.

Immunosuppressive drugs are often used in difficult-to-treat CSU, but all drugs do not have similar properties and efficacy. MTX has immunomodulatory and anti-inflammatory effects and probably leads to reduced level of functional autoantibodies, identified in 30% of patients with CSU.⁵

The main limitation of this study is that we planned to recruit 110 patients and recruited only 75, so it may be underpowered to detect a difference in the primary outcome.

In conclusion, MTX is sometimes used as third-line therapy for CSU, but our study does not support the superiority of MTX over placebo added to H1-antihistamines for CSU.

Acknowledgements

We are indebted to Mrs. Elodie Mousset, Aurélie Darmaillacq and Christine Foulon from the Délégation à la Recherche Clinique et à l'Innovation, University Hospital Center (CHU) Tours; Carine Coffre and Michèle Carriot, Clinical Investigation Center of CHU Tours; and Stéphanie Bonte, Department of Dermatology of CHU Tours. We also deeply thank Pr Théodora Angoulvant, Pr Denis Mulleman and Pr Gérard Lorette, CHU Tours, for being members of the Data Safety Monitoring Board of the study.

References

1. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy*. 2018;73(7):1393-1414.
2. Sharma VK, Singh S, Ramam M, et al. A randomized placebo-controlled double-blind pilot study of methotrexate in the treatment of H1 antihistamine-resistant chronic spontaneous urticaria. *Indian J Dermatol Venereol Leprol*. 2014;80(2):122-128.
3. Perez A, Woods A, Grattan CEH. Methotrexate: a useful steroid-sparing agent in recalcitrant chronic urticaria. *Br J Dermatol*. 2010;162(1):191-194.
4. Sagi L, Solomon M, Baum S, et al. Evidence for methotrexate as a useful treatment for steroid-dependent chronic urticaria. *Acta Derm Venereol*. 2011;91(3):303-306.
5. Kolkhir P, Church MK, Weller K, et al. Autoimmune chronic spontaneous urticaria: what we know and what we do not know. *J Allergy Clin Immunol*. 2017;139(6):1772-1781.

Figure legend

Figure. Study design and dosages.

Table legend

Table 1. Analysis of the primary efficacy outcome

	Methotrexate	Placebo	Difference in proportions (%) (95% CI)	P value
Complete remission of urticaria at week 18 (W18) defined as no urticarial lesion within 30 days before W18, <i>n</i> (%)				
Intent-to-treat analysis ^{1,2}	<i>n</i> = 38 3 (7.9)	<i>n</i> = 32 0 (0)	7.9 (-4.0 to 20.8)	<i>p</i> = 0.24
Complete-cases analysis ³	<i>n</i> = 35 3 (8.6)	<i>n</i> = 31 0 (0)	8.6 (-3.8 to 22.4)	<i>p</i> = 0.24
Per-protocol analysis ⁴	<i>n</i> = 35 3 (8.6)	<i>n</i> = 29 0 (0)	8.6 (-4.4 to 22.4)	<i>p</i> = 0.24

The primary outcome was compared by Fisher exact test.
Data were self-reported by patients in a daily diary.

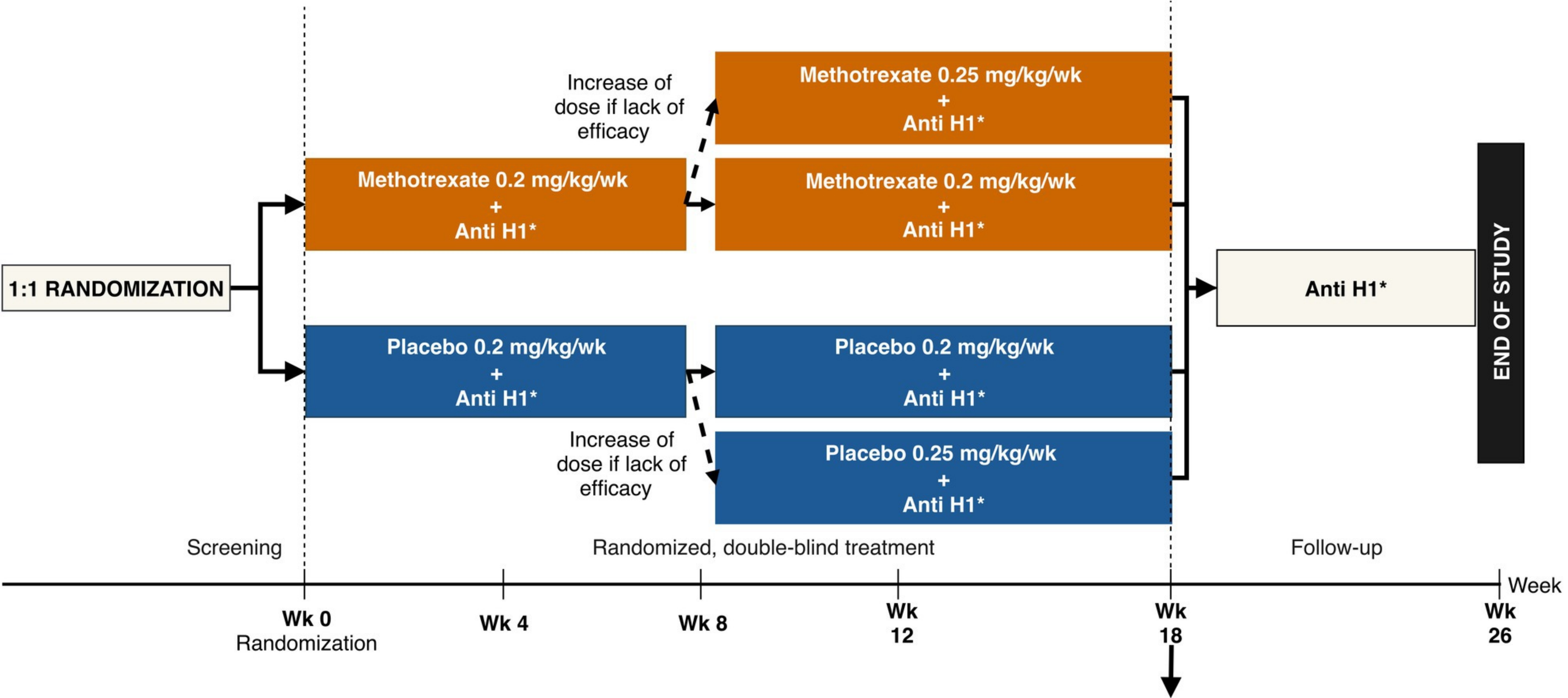
Legend

¹ imputation by failure

² all patients recruited were included in the analysis on the basis of the treatment group to which they were randomly allocated and regardless of whether they received a different treatment, except for patients who withdrew consent before W18 (time of primary outcome).

³ missing excluded

⁴ only patients who completed the protocol for the treatment to which they were originally allocated were included (patients in the placebo group who received methotrexate, patients in the methotrexate group who discontinued methotrexate, patients who withdrew consent and patients who were lost to follow-up were excluded).



* Study treatments were administered as add-on therapy to the H1-antihistamines regimen the patient previously received, no modification of H1-antihistamines regimen was allowed during all the trial

Primary outcome at Week 18:
 Complete urticaria remission, defined as no urticarial lesions within the 30 days before W18