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

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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

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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/82k28wzxmr/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 RCT[2] 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.

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Figure legend

Figure. Study design and dosages.

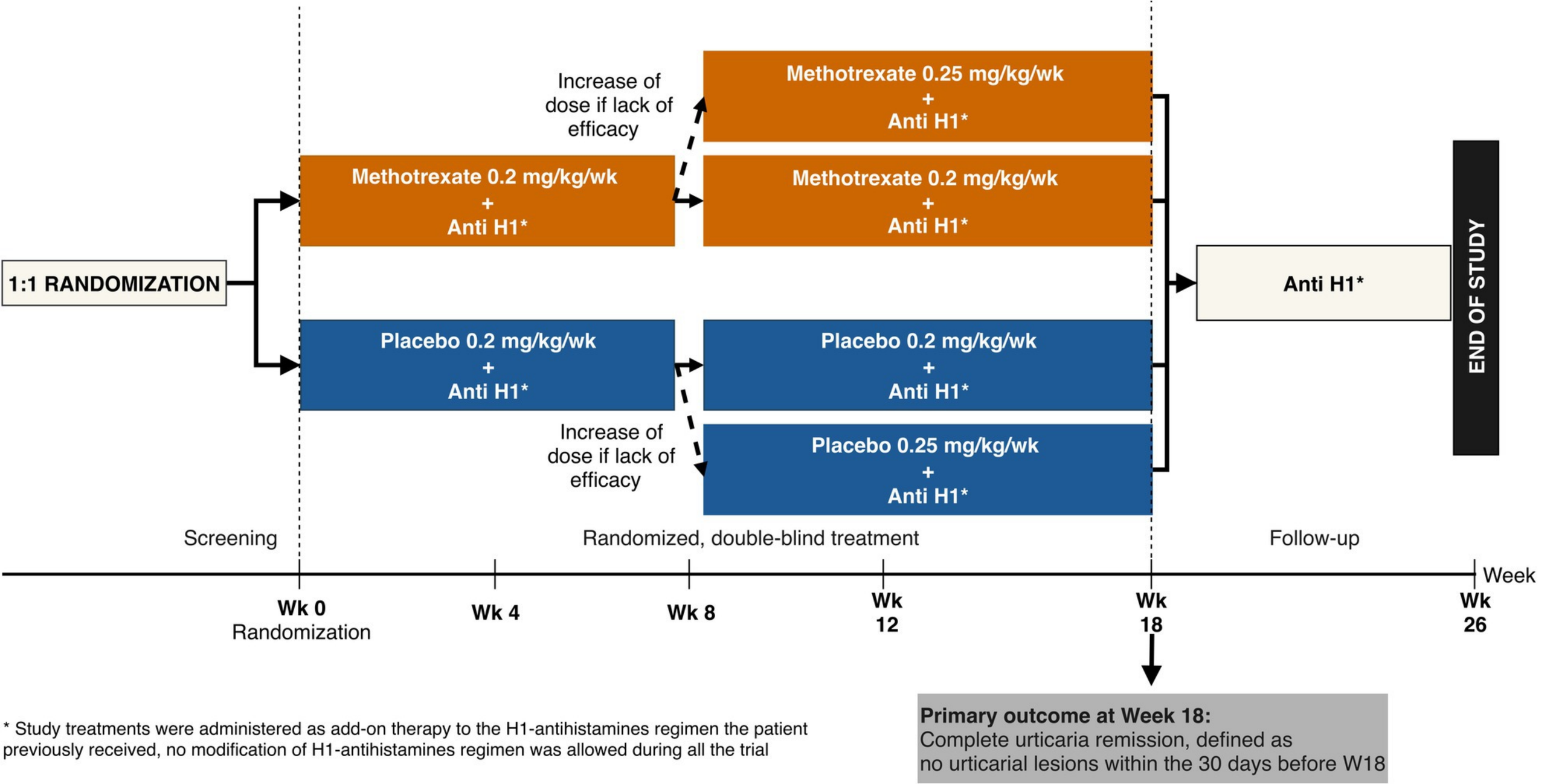
Table legend

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, *n* (%)				
Intent-to-treat analysis [1,2]	n = 38	n = 32		
	3 (7.9)	0 (0)	7.9 (-4.0 to 20.8)	p = 0.24
Complete-cases analysis [3]	n = 35	n = 31		
	3 (8.6)	0 (0)	8.6 (-3.8 to 22.4)	p = 0.24
Per-protocol analysis [4]	n = 35	n = 29		
	3 (8.6)	0 (0)	8.6 (-4.4 to 22.4)	p = 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