Therapeutics of urticaria: results from a hospital-based multicenter study in China

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Article

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Abstract

Background: Therapeutics of urticaria in Chinese outpatients remain to be illustrated.

Objectives: To investigate clinical treatment of outpatients with urticaria, and provide theoretical evidence for selection of medication regimens.

Methods: In this hospital-based multicenter study, urticaria outpatients filled in a questionnaire at initial visit and were followed-up (once per week, for 4 weeks).

Results: 1715 urticaria outpatients were recruited and 647 completed 4- week's follow-up. Their total UAS7 was reduced (27.44 at baseline, 16.87 in 1 week, 12.39 in 2 weeks, 7.21 in 3 weeks, 4.2 in 4 weeks). 71.8% patients recovered from urticaria (therapy was highly effective in 11%, whereas effective in 14.2%). The second-generation H1 antihistamines (sgAHs) (at conventional dose) were the most commonly prescribed drugs, with ebastine, levocetirizine and olopatadine being the leading ones (41.1%, 36.2%, and 16%, respectively). Combinations of several antihistamines (649 cases, 37.8%) at conventional dose were far more common than a single drug at escalated dose (59 cases, 3.4%). The combination of ebastine with levocetirizine was the most frequent options (18.25%, 313 cases), followed by combination of ebastine with compound glycyrrhizin (18.2%, 312 cases). The usage rates of tripterygium glycoside (19.6%), hydroxychloroquine (17.2%) and system application glucocorticoids (5.5%) in angioneurotic edema were much higher than in dermographic urticaria and chronic spontaneous urticaria.

Conclusions: This study identifies curative therapy for Chinese outpatients with urticaria. The sgAHs, especially ebastine, are the most commonly prescribed drugs. Olopatadine has fast-acting and curative effects. Compound glycyrrhizin holds potential as a versatile collaborator.

Combinations of several antihistamines at conventional dose is common.

Introduction

Urticaria is a common disease in dermatology, with an estimated incidence of 1.7% in general European adults.[1] Chronic spontaneous urticaria (CSU), manifesting as recurrent itchy wheals and/or angioedema for more than 6 weeks, affected 0.23% of general population in the United States, most of whom were women or adults ≥ 40 years of age.[2] Among Chinese adolescents, a cross-sectional study reported prevalence for chronic spontaneous urticaria as high as 2.7%.[3,4]

Chronic urticaria can substantially affect patients' quality of life (QoL), ability to perform daily tasks, and even mental health. [5] Moreover, according to ASSURE-CSU (ASSessment of the Economic and Humanistic Burden of Chronic Spontaneous/Idiopathic Urticaria patiEnts), average CSU-related out-of-pocket expense for patients reached nearly PPP$500 per year (whereas PPP$1000 in Canada). In addition, CSU considerably affected productivity, such that one in five patients took time off from work and one in four experienced reduced productivity at work. [6] All these findings indicate urgent need to improve urticaria treatment. Unfortunately, there has been little research on prescription from a dermatologist in real-world in China.

Due to unclear pathogenesis, CSU (also known as chronic idiopathic urticaria [CIU]) has been commonly managed with antihistamine therapy in clinical practice.[7] The second-generation H1-antihistamines (sgAHs) at licensed doses have been recommended as the first-line treatment for CSU based on International guideline (EAACI/GA^{2}LEN/EDF/WAO) as well as American guideline (American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology Joint Task Force).[8, 9] Among multiple types of sgAHs, dermatologists have different opinions upon prescribing in practice. In addition, few studies focused on third-line or fourth-line drugs, such as compound glycyrrhizin and tripterygium wilfordii polyglycoside. Thus, we aim to assess dermatologists' preferences for treatment options in China, and compare therapeutic effects on different types of urticaria.

Materials And Methods

Study design

This prospective multicenter study was performed from January 1 to December 31 in 2019. Ten tertiary hospitals in mainland China, with geographically dispersed uniformly, were chosen as sampling units, located in 6 provinces and municipalities including Fujian, Sichuan, Chongqing, Hubei and Liaoning provinces, as well as Beijing. All outpatients diagnosed with urticaria who consented to participate in the current study underwent a questionnaire survey and specific survey. This study had conformed to the STROBE guidelines.

Questionnaire

The questionnaire comprised of 33 questions, including demographics (gender, age, ethnicity); disease duration; comorbid conditions (such as allergic, cardiovascular, metabolic, and autoimmune diseases); family history of urticaria; food to be avoided (such as fish-prawn-crab, alcohol consumption, beef, mutton, milk, and egg); laboratory results (such as blood count, plasma allergen, routine urine, thyroid antibody, auto-antibodies and helicobacter pylori); severity of itching and quantity of wheal (at initial visit and follow-up); physician-certified diagnoses (such as CSU, dermographic urticaria, delayed pressure urticaria, and cold urticaria); current and former therapeutic schedule (dose and type of drugs).

Study objects

This study was approved by Ethics Committee of Beijing Friendship Hospital, Capital Medical University. All experiments were performed in accordance with relevant guidelines and regulations. Informed consent was obtained from each participant. The inclusion criteria included: diagnosis with urticaria and agreement to participating in this study. Exclusion criteria included outpatients with serious mental illness or organic disease, who could not cooperate with investigators; or who refused to provide informed consent. The presence of urticaria was identified by physician-certified diagnoses according to the International Classification of Diseases 10th Revision (ICD-10) codes for various types of urticaria (L500–L509) and angioedema (T783). ‘Clinical urticaria’ was defined as urticaria which caused a patient to visit hospital, subsequently to be diagnosed as a main problem by a clinician. Multiple diagnoses were allowed. All dermatologists involved in this study had abundant experience in clinical diagnosis and treatment of

urticaria; and were trained in a standardized program. After the initial visit, patients were followed-up once per week, for 4 weeks.

Clinical criteria

The treatment effect was determined based on UAS and change in wheal-and-erythema reaction or itching. The efficacy index (%) was calculated as follows: (total score before treatment-total score after treatment)/total score before treatment ×100%. An efficacy index >90% was classified as recovery; whereas 60%~90% as highly effective; 20%~60% as effective;

Statistical analysis

All statistical analyses were performed with SPSS software version 20 (IBM, Armonk, NY, USA). Continuous variables were described by mean ± standard deviation (SD) according to distribution. The normality of variables was evaluated by Kolmogorov-Smirnov test. Age was normally distributed, while the distribution of disease duration was skewed. The relationships of follow-up duration with itching degrees or quantities of wheal were analyzed by Spearman Correlation. Each drug combination was assessed by association rule algorithm. Missing data were excluded from data analyses. All tests were two-tailed with a significance level of ≤ 0.05.

Results

Previous treatment

We approached 1800 outpatients, among whom 1715 agreed to participate in this study (with a response rate of 95.3%). The patient was asked about previous treatment options at the first visit. In previous treatment, sgAHs at conventional dose (787 cases, 45.9%) were the most commonly prescribed drugs. Combinations of several antihistamines (649 cases, 37.8%) at conventional dose were far more common than a single drug at escalated dose (59 cases, 3.4%). As a non-antihistamine compound, glycyrrhizin (394 cases, 23%) was the most widely used, followed by traditional Chinese medicine (142 cases, 8.3%), glucocorticoid (87 cases, 5.1%), and tripterygium glycoside (73 cases, 4.3%). By contrast, hydroxychloroquine (8 cases, 0.5%) and cyclosporin (4 cases, 0.2%) were rarely used.

Treatment options

In general, sgAHs, in particular the 2nd-generation antihistamines, were the most commonly prescribed drugs, with ebastine, levocetirizine and olopatadine being the leading ones (41.1%, 36.2%, and 16%, respectively). Comparatively, the proportion of traditional sgAHs, such as loratadine (13.6%) and cetirizine (12.9%), had been reduced. Among the first-generation H1-antihistamines, ketotifen (7.2%) was more often applied, followed by chlorphenamine maleate (2%), diphenhydramine (1.9%) and cimetidine (1.9%). As a non-antihistamine compound, glycyrrhizin (34.3%) was the most widely used, followed by traditional Chinese medicine (9.2%) and tripterygium glycoside (8.1%). Moreover, omalizumab (0.6%) had low acceptability.

We specifically analyzed three major types of urticaria: dermographic urticaria, chronic spontaneous urticaria and angioneurotic edema. The therapeutic options for urticaria outpatients were summarized in Table 1. Vast majority patients with dermographic urticaria (98.7%), chronic spontaneous urticaria (97.8%) or angioneurotic edema (96.3%) were given drugs at standard doses. None of them had a high proportion of lean-to double doses drugs (1.3%, 2.2%, 3.7%, respectively). When comparing three types of urticaria, no regular patterns of prescribing H1-antihistamines and H2-antihistamines were identified. For non-antihistamines, the usage rate of tripterygium glycoside (19.6%), hydroxychloroquine (17.2%) or system application glucocorticoids (5.5%) in angioneurotic edema, respectively, was much higher than others. However, the usage rate of compound glycyrrhizin (20.2%) or traditional Chinese medicine (4.3%) was relatively lower.

Table 1 Therapeutic options in major types of urticaria outpatients by clinical reality

Medicine	Dermographic urticaria (N=615) Yes (n, %)	Chronic Spontaneous urticaria (N=1396) Yes (n, %)	Angioneurotic edema (N=163) Yes (n, %)	*P*
Second-generation H1-antihistamines				
Ebastine	233 (37.9)	586 (42)	37 (22.7)	<0.001
Levocetirizine	194 (31.5)	508 (36.4)	32 (19.6)	<0.001
Olopatadine	98 (15.9)	244 (17.5)	18 (11)	0.099
Desloratadine	29 (4.7)	71 (5.1)	9 (5.5)	0.897
Loratadine	135 (22)	206 (14.8)	77 (47.2)	<0.001
Cetirizine	88 (14.3)	174 (12.5)	17 (10.4)	0.331
Fexofenadine	39 (6.3)	162 (11.6)	13 (8)	0.001
Acrivastine	54 (8.8)	82 (5.9)	32 (19.6)	<0.001
Mizolastine	7 (1.1)	25 (1.8)	5 (3.1)	0.218
First-generation H1-antihistamines				
Ketotifen	34 (5.5)	91 (6.5)	6 (3.7)	0.294
Diphenhydramine	12 (2)	32 (2.3)	3 (1.8)	0.852
Chlorphenamine Maleate	10 (1.6)	20 (1.4)	7 (4.3)	0.028
Cyproheptadine	8 (1.3)	15 (1.1)	3 (1.8)	0.669
Promethazine	3 (0.5)	2 (0.1)	3 (1.8)	0.003
H2-antihistamines				
Cimetidine	14 (2.3)	23 (1.6)	1 (0.6)	0.316
Ranitidine	1 (0.2)	6 (0.4)	5 (3.1)	<0.001
Alternative treatment options				
Compound glycyrrhizin	212 (34.5)	511 (36.6)	33 (20.2)	<0.001
Traditional Chinese medicine	76 (12.4)	145 (10.4)	7 (4.3)	0.011
Tripterygium glycoside	44 (7.2)	127 (9.1)	32 (19.6)	<0.001
Hydroxychloroquine	29 (4.7)	36 (2.6)	28 (17.2)	<0.001

System Application Glucocorticoids	10 (1.6)	15 (1.1)	9 (5.5)	<0.001
Omalizumab	2 (0.3)	7 (0.5)	0 (0)	0.59
Montelukast sodium	2 (0.3)	9 (0.6)	1 (0.6)	0.668

A total of 1715 patients were included, a single drug or combination were generally acceptable.

Drug combination

As a whole, combinations of ebastine with levocetirizine were the most common treatment options (18.25%, 313 cases), which almost identical to combinations of ebastine with compound glycyrrhizin (18.2%, 312 cases). Surprisingly, combination of sgAHs and fgAHs is not used frequently, most of which is levocetirizine and ketotifen (2.5%, 43 cases). And similarly, proportion in combination of sgAHs and H2-antihistamines wasn't high. Compound glycyrrhizin seems to show potential as a versatile collaborator, which was the first choice for drug combinations (Table 2).

Table 2 The proportion of urticaria patients treated with combination of glycyrrhizin and other drugs

Drug combined with compound glycyrrhizin	No*. of patients (%)
Ebastine	312 (18.2)
Levocetirizine	263 (15.3)
Olopatadine	163 (9.5)
Ebastine and levocetirizine	136 (7.9)
Traditional Chinese medicine	103 (6.0)
Tripterygium glycoside	70 (4.1)
Ketotifen	55 (3.2)

* N total= 1715 patients

Clinical manifestations during follow-up

A total of 647 urticaria outpatients completed 4-week's follow-up. The total urticaria activity score 7 (UAS7) showed a significant downward trend (27.44 at baseline, 16.87 in 1 week, 12.39 in 2 weeks, 7.21 in 3 weeks, 4.2 in 4 weeks). At the first week of follow-up, total efficacy indicator was 38.5%, with traditional Chinese medicine, olopatadine, and compound glycyrrhizin being the leading ones (58.4%, 55.2%, and 54.2%, respectively). At the end of follow-up, drugs with an efficacy index >90% included ebastine, compound glycyrrhizin, traditional Chinese medicine, loratadine and olopatadine. The USA7 for various drugs were summarized in Table 3.

Table 3 UAS7 for various drugs during follow-up

Medicine	UAS7 at baseline	UAS7 1 week	UAS7 2 weeks	UAS7 3 weeks	UAS7 4 weeks
Ebastine (N=239)	28.3	15.3	8.4	4.5	2.6
Compound glycyrrhizin (N=227)	33.2	15.2	9.4	5.2	3.1
Traditional Chinese medicine (N=120)	36.3	15.1	9.9	5.8	3.4
Loratadine (N=41)	25.4	13.8	6.5	2.7	1.9
Levocetirizine (N=211)	26.9	14.9	9.6	5.1	3.0
Olopatadine (N=146)	33.7	15.1	8.4	5.1	3.0
Tripterygium glycoside (N=41)	29.2	18.6	12.8	8.5	5.3
Ketotifen (N=58)	28.8	15.3	8.2	5.8	4.0

Patients enrolled had completed 4-week's follow-up, a single drug or combination were generally acceptable.

Discussion

Our study provides epidemiological evidence on drugs for urticaria. This finding was based on functional mechanism of health care system in China, which was completely different from Western countries. In this study, almost all patients sought help from dermatologists in the first place, because of lack of general practitioners and family doctors. Even acute urticaria patients were treated by dermatologists, rather than emergency departments. Globally, antihistamine therapy is the most commonly applied in clinical practice at present. In our survey, with popularization and wide utilization of the sgAHs, the fgAHs displayed obvious signs of decline. A similar drug administration pattern was reported by Rimoldi M *et al.* who found that the second-generation H1-antihistamines at the registered dose were the most common treatment in Italy.[10] By contrast, in Poland, more than one-third of physicians chose the first-generation sedative H1-antihistamines and systemic steroids either alone or in combination as the initial therapy.[11] Approximately 20% of German specialists (mainly dermatologists and allergists) applied the first-generation H1-antihistamines or steroids as the first-line treatment for CU.[12] Treatment choice was closely associated with the specialist's knowledge of current guidelines. Both EAACI/GA2LEN/EDF/WAO and Chinese guidelines suggested the 2nd-generation H1-antihistamines over the 1st-generation H1-antihistamines for chronic urticaria (evidence-based and consensus-based).[8, 13] However, these guidelines differ with regards to the second-line treatment, where the international guideline recommended escalated dosing sgAHs up to 4-fold after a maximum for 2 weeks, whereas the Chinese guideline recommended to change the current type of sgAH, multi-sgAH combination, along with the first-generation H1-antihistamine, or mono-sgAH up dosing regimens with informed consent.[13] Except for ebastine, no other sgAHs definitely doubled the dose in medicine instruction, which explained why it had been extensively applied.

Taking into account different types of urticaria, we noticed that tripterygium glycoside, hydroxychloroquine as well as systemic steroids were prescribed more often in angioneurotic edema than in others, which might reflect physician's conviction that this variant of urticaria was more difficult to control by standard regimen. Non-hereditary angioedema (AE) with normal C1 esterase inhibitor (C1INH) can be presumably bradykinin- or mast cell-mediated, or of unknown cause.[14] Differentiating histamine-mediated versus bradykinin mediated angioedema is essential, as therapy or response to therapy is quite different.[15] In Chinese guidelines for urticaria, tripterygium glycoside, system application glucocorticoids, and/or omalizumab were added as the third-line treatment. Tripterygium wilfordii Hook F (TwHF) is a vital Chinese herb belonging to Celastraceae family, with anti-inflammation, anti-anaphylaxis, and immunosuppression effects.[16] It has been reported by Liu et al. [17] and Yao et al. [18] that tripterine, a primary component in TwHF, inhibited degranulation of mast cells and histamine release. Active ingredients in TwHF are toxic components that may be harmful to liver, kidneys, reproductive tissues, and immune system. Because of side effects, TwHF is often used clinically for treating complicated autoimmune and inflammatory diseases in China, such as rheumatoid arthritis,[19] diabetic nephropathy,[20] purpura nephritis, [21] and urticaria.[22, 23] Except for omalizumab and ciclosporin A, which both have restrictions due to high cost, alternative protocols, such as combinations of sgAHs with tripterygium glycoside, are based on clinical trials lack of supporting evidence. In this study, efficacy index of tripterygium glycoside (36.3% in 1 week) was lower than other drugs (Table 3), indicating that tripterygium glycoside was not outstanding and dominant. A large sample-size, multi-center, high-quality clinical study is required to verify efficacy and safety of tripterygium glycoside in angioneurotic edema and urticaria.

Interestingly, this study provides preliminary evidence that compound glycyrrhizin holds potential as a versatile collaborator, which has been widely used in combination with a variety of drugs. The oral compound glycyrrhizin is a preparation composed of glycyrrhizin, cysteine hydro- chloride, and glycine. Primary active component is glycyrrhizic acid, an active substance found in licorice.[24] Glycyrrhiza glabra (Fabaceae) commonly known as liquorice is considered to possess carminative, antimicrobial, hypolipidemic, anti-atherosclerotic, antiviral, antiulcerogenic, hepatoprotective, cardio- protective, immunomodulatory, antimutagenic, anti-pyretic, and anti-inflammatory activities.[25] Broad anti-inflammatory activity of glycyrrhizin is mediated by interaction with lipid bilayer, thereby attenuating receptor-mediated signaling. In China, although not recommended in guidelines, compound glycyrrhizin has been widely used to treat urticaria with high clinical efficacy as an anti-allergic and anti-inflammatory agent. compound glycyrrhizin has minor adverse effects, including hypertension, hypokalemia, and pseudo-aldosteronism. In particular, glycyrrhizin in conjunction with conventional therapy has been used in clinical practice, especially for severe clinical symptoms, however, supporting evidence for such practice has not been evaluated systematically. In our survey, combination has achieved better therapeutic effect (efficacy index of 54.2% in 1 week, whereas 90.7% in 4 weeks). To our knowledge, few high-quality studies have been published on efficacy evaluation of compound glycyrrhizin in urticaria. Further research is required to determine acceptable long-term efficacy and safety of compound glycyrrhizin in urticaria patients.

In general, urticaria patients obtained good clinical outcome in response to single or in combination regimen. After 4-week followed up, 71.8% of patients recovered from urticaria, 11% was highly effective, and 14.2% was effective. Patients with more severe symptoms were often treated with a combination regimen, such as

an antihistamine drug in combination with compound glycyrrhizin or traditional Chinese medicine. In the current study, patients on olopatadine, who had the highest starting USA7 scores (33.7), showed a high first-week efficacy indicator (55.2%) with an efficacy index of > 90% at the end of follow-up. Previous studies on olopatadine and levocetirizine have shown that urticaria activity score (UAS) and urticaria total severity score (TSS) values declined significantly over the treatment period, however, the reduction was greater with olopatadine.[26] Mild to moderate urticaria could be controlled by standard application, while severe urticaria could be managed by a standard application of olopatadine, however, levocetirizine might need an additional dose to control severe urticaria.[27] The booklets of medicine instruction indicate that olopatadine is more suitable for poor first-line treatment, attributed to the highest starting USA7 scores. Compared with other sgAHs, olopatadine has fast-acting and curative effect, especially during the first week.

Conclusions

In conclusion, this study provides a profile of therapeutics of urticaria in Chinese outpatients, which demonstrates curative effects. The sgAHs at conventional dose, especially ebastine, have been the most commonly prescribed drugs. Olopatadine has fast-acting and curative effect. Compound glycyrrhizin holds potential as a versatile collaborator.

Declarations

Competing Interests The authors declare that there are no conflict of interests.

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Author Contributions Xin Wang and Lin-Feng Li performed the experiments and drafted the manuscript. Xiao-Dong Shi performed data analyses. Yi-wei Shen prepared Tables 1–3. All authors reviewed the manuscript.

Availability of data and materials The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

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