

## RESEARCH ARTICLE

### Randomized clinical trials related to urticaria: Bibliometric analysis from 2009 to 2019

Anant D Patil

Department of Pharmacology, Dr. D. Y. Patil Medical College, Navi Mumbai, Maharashtra, India

Correspondence to: Anant D Patil, E-mail: anantdlpatil@gmail.com

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#### ABSTRACT


**Background:** Urticaria is associated with considerable health-care costs. Randomized controlled trials (RCTs) are considered as the gold standard for evaluating efficacy in clinical research. **Aims and Objectives:** The objective of this study was to analyze RCTs in the therapeutic area of urticaria from 2009 to 2019. **Materials and Methods:** Systematic search of “PubMed” was performed using words “Study[ti] OR trial[ti] AND urticaria[ti] AND “2009” [Date – Publication]: “2019” [Date – Publication].” All retrieving articles were screened for understanding the study design. RCTs were considered for further analysis. Year-wise and indication-wise analysis of RCTs was performed. **Results:** Of 189 articles retrieved, nine articles did not satisfy the inclusion criteria. Of 180 articles, 6 (3.3%) articles were published in 2009. In subsequent years (2010–2019), the number (%) of articles published was 8 (4.4%), 9 (5%), 10 (5.6%), 12 (6.7%), 14 (7.8%) 15 (8.3%), 15 (8.3%), 20 (11.1%), 32 (17.8%), and 39 (21.7%), respectively. A total of 47 (26.11%) were RCTs. The number (%) of RCTs from 2009 to 2019 was 2 (4.26%), 3 (6.38%), 2 (4.26%), 3 (6.38%), 4 (8.51%), 5 (10.64%), 3 (6.38%), 4 (8.51%), 6 (12.77%), 7 (14.89%), and 8 (17.01%), respectively. A total of 31 (65.96%) RCTs were related to chronic spontaneous urticaria/chronic idiopathic urticaria (CSU/CIU). **Conclusion:** Analysis of articles showed that the numbers of RCTs related to urticaria are increasing over the years. CSU/CIU is the most commonly researched topic in urticaria through RCTs.

**KEY WORDS:** Randomized Controlled Trials; Urticaria; Research

#### INTRODUCTION

Urticaria is a common dermatological disorder with complex pathogenesis which presents with hives, angioedema, or both. The condition poses high disease burden and is associated with considerable health-care costs.<sup>[1]</sup> Sometimes, chronic urticaria poses a challenge for physicians in terms of diagnosis and/or treatment. Over

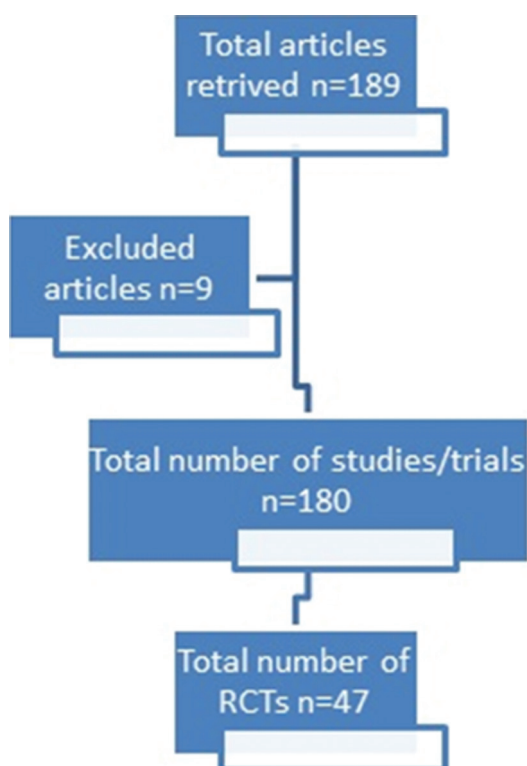
the past decade, significant scientific developments have happened globally as well as in India. A popular EAACI/GA2LEN/EDF/WAO guideline on the management of urticaria was published in 2009.<sup>[2]</sup> After a couple of years, a consensus statement on the management of urticaria by the expert dermatologists in India was published.<sup>[3]</sup> According to these guidelines and consensus documents, the second-generation antihistamines are recommended as the first-line therapy in the management of chronic urticaria. Up-dosing of the second-generation antihistamines is recommended as the second-line treatment, in those who do not respond satisfactorily.<sup>[2,3]</sup> Omalizumab has emerged as promising option. Updated guideline (2013)<sup>[4]</sup> by the EAACI/GA2LEN/EDF/WAO recommends the use of omalizumab as the third-line therapy. Later, position statement<sup>[5]</sup> for the use of

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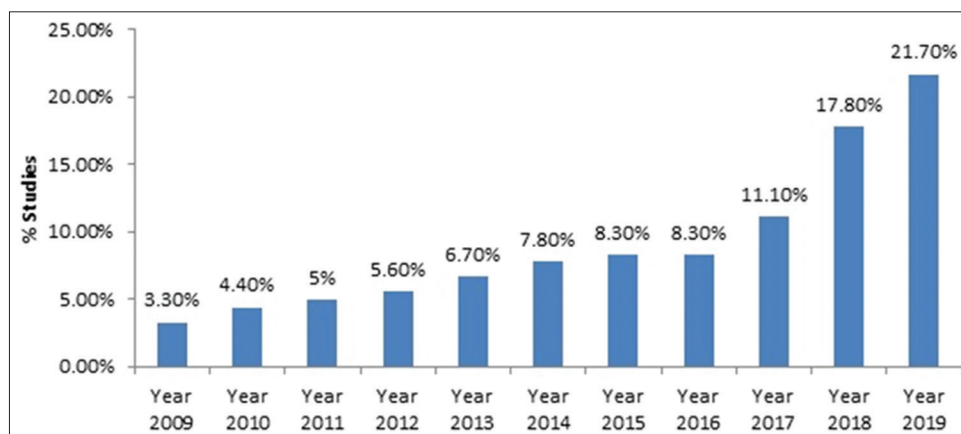
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omalizumab in Indian patients with chronic spontaneous urticaria (CSU) is published in 2016. An updated consensus statement for the diagnosis and management of urticaria in Indian patients is published recently.<sup>[6]</sup> These developments show growing interest in the research related to urticaria.

Randomized controlled trials (RCTs) are considered as the gold standard for evaluating efficacy in clinical research and guide clinicians toward decision-making in the evidence-based medicine practice.<sup>[7]</sup> A review of literature published few years back suggested a need for well-designed clinical trials with up-dosing of non-sedating antihistamines in Indian population.<sup>[8]</sup> With this background, it is relevant and important to review the available worldwide and Indian literature for RCTs related to urticaria.



**Figure 1:** Flowchart of literature search process



**Figure 2:** Year-wise distribution of studies/trials related to urticaria

## Objective

The objective of this study was to analyze the nature and trend of RCTs in the therapeutic area of urticaria.

## MATERIALS AND METHODS

Systematic literature search of “PubMed” was performed using words “Study[ti] OR trial[ti] AND urticaria[ti] AND “2009” [Date – Publication]: “2019” [Date – Publication].” Articles other than words “study” or “trial” in the title were excluded from analysis. Articles from other search engines/databases other than PubMed were not considered.

Year-wise number of articles published was calculated. All retrieving articles with above search words were screened for understanding its design. RCTs were considered for further analysis. We included articles with words randomly allocated, randomized, or randomization. Year-wise and indication-wise analysis of RCTs was performed.

## Statistical Analysis

Data for descriptive statistics are presented as frequency and percentages.

## RESULTS

A total of 189 articles were retrieved from PubMed. Of 189 articles, 180 articles were considered for further analysis [Figure 1].

Nine articles did not satisfy the inclusion criteria. The list of articles excluded from analysis was as follows; angioedema without urticaria ( $n = 1$ ), letter in a response to study ( $n = 1$ ), author’s reply ( $n = 1$ ), commentary ( $n = 2$ ), erratum ( $n = 1$ ), retracted article ( $n = 1$ ), review article ( $n = 1$ ), and urticaria in dog ( $n = 1$ ).

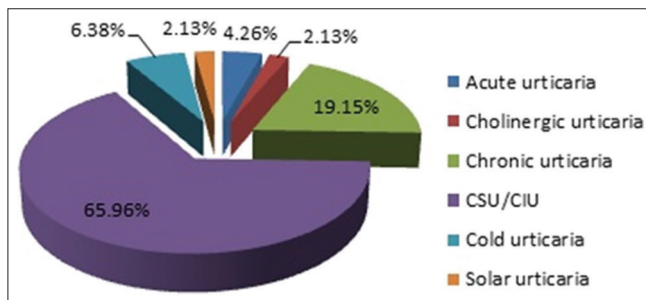
Six (3.3%) articles were published in 2009. In subsequent years (2010–2019), the number (%) of articles published was 8 (4.4%), 9 (5%), 10 (5.6%), 12 (6.7%), 14 (7.8%), 15 (8.3%), 15 (8.3%), 20 (11.1%), 32 (17.8%), and 39 (21.7%), respectively [Figure 2].

Of 180 articles, 47 (26.11%) were RCTs. A total of 31 (65.96%) RCTs were related to CSU/chronic idiopathic urticaria (CIU). Nine (19.15%) RCTs were related to chronic urticaria without mentioned of any specific subtype. Three (6.38%) RCTs were conducted in cold urticaria. Only two RCTs were related to acute urticaria. Only one RCT related to solar urticaria and cholinergic urticaria was published from 2009 to 2019 [Figure 3].

The number (%) of RCTs from 2009 to 2019 was 2 (4.26%), 3 (6.38%), 2 (4.26%), 3 (6.38%), 4 (8.51%), 5 (10.64%), 3 (6.38%), 4 (8.51%), 6 (12.77%), 7 (14.89%), and 8 (17.01%), respectively [Figure 4].

## DISCUSSION

Urticaria is one of the most common clinical conditions encountered by the dermatologists in their clinical practice. In most cases, the primary care physicians are the first point of contact for patients with urticaria. Today, in the era of evidence-based medicine, decisions of the treatment are mostly guided by the available evidence. In this study, with a systematic approach of literature search, we analyzed all studies/trials



**Figure 3:** Distribution of randomized controlled trials based on the type of urticaria



**Figure 4:** Year-wise distribution of randomized controlled trials related to urticaria

related to urticaria with focus on RCTs reported in PubMed from 2009 to 2019. We selected articles from 2009 because the EAACI/GA2LEN/EDF/WAO guideline<sup>[2]</sup> on the management of urticaria was published in this year. Articles published thereafter until the date was included in the analysis. In this article, we provided year-wise and indication-wise analysis of RCTs related to urticaria in nutshell. Overall analysis suggested considerable rise in the number of studies related to urticaria over the years. There was a linear trend of rise in number of studies related to urticaria over the years. Compared to 2009, in 2019, there has been 6.5-fold rise in the number of studies related to urticaria (3.3% vs. 21.7%). Out of all article retrieved, close to one-fourth studies was RCTs which suggest interest of researchers in generating robust clinical data related to diagnosis and management of urticaria. Rise in number of studies paralleled with number of RCTs over the years. Of 47 RCTs<sup>[9-55]</sup> related to urticaria, only two were related to acute urticaria. One was a study protocol for glucocorticoids in acute urticaria,<sup>[9]</sup> whereas the second was comparison of levocetirizine plus prednisone versus levocetirizine alone in the treatment of acute urticaria.<sup>[10]</sup> We could retrieve three RCTs related to cold urticaria<sup>[11-13]</sup> and one RCTs related to solar urticaria and cholinergic urticaria each. According to our analysis, CSU or CIU is the most studied indication related in the field of urticaria. Although guidelines are in place for the management of chronic urticaria, many patients do not respond to the treatment. Moreover, due to complex pathophysiology of chronic urticaria demands research targeting different mechanisms involved in the disease. It is, thus, imperative to the study alternative treatment options. With this background, several therapies have been evaluated. The therapies of urticaria evaluated through RCTs included antihistamines (including rupatadine, levocetirizine, cetirizine, desloratadine, loratadine, bilastine, and olopatadine),<sup>[12-25]</sup> mizolastine and proteoglycan,<sup>[26]</sup> methotrexate add on,<sup>[27]</sup> azathioprine with cyclosporine,<sup>[28]</sup> levocetirizine plus montelukast,<sup>[29]</sup> cetirizine plus ranitidine,<sup>[24]</sup> sedating antihistamine,<sup>[30,31]</sup> atorvastatin plus antihistamine,<sup>[32]</sup> dapsone,<sup>[33]</sup> methotrexate,<sup>[34]</sup> omalizumab,<sup>[11,35-44]</sup> and hydroxychloroquine.<sup>[45]</sup> Other therapies evaluated were Chinese herbal medicine,<sup>[46]</sup> diamine oxidase supplementation,<sup>[47]</sup> Jumihaidokuto,<sup>[48]</sup> quilizumab,<sup>[49]</sup>

phototherapy using narrowband ultraviolet B and psoralen plus ultraviolet A,<sup>[50]</sup> acupuncture,<sup>[51]</sup> Vitamin D,<sup>[52]</sup> miltefosine,<sup>[53]</sup> levamisole,<sup>[54]</sup> and autologous whole blood and autologous serum injections.<sup>[55]</sup> These results suggest that antihistamines are the most commonly evaluated pharmacotherapeutic agents in the management of chronic urticaria. Omalizumab is a promising agent which is evaluated thoroughly for its efficacy and safety in the treatment of chronic urticaria. It has been studied in CSU,<sup>[30,36,38,39,43]</sup> solar urticaria,<sup>[42]</sup> cholinergic urticaria,<sup>[35]</sup> as well as cold urticaria.<sup>[11]</sup>

This study provides significant insights into the researchers and academicians on different types of RCTs conducted in the field of urticaria. Our study has some limitations. We did not search databases other than “PubMed;” hence, RCTs published in other journals not indexed with “PubMed” are not included in this analysis. This may induce some bias in our reporting the results.

## CONCLUSION

Analysis of RCTs from 2009 to 2019 shows a trend of increase in number of RCTs in the therapeutic area of urticaria. Germany and India rank first and second, respectively, in contribution to the RCTs in the therapeutic area of urticaria.

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