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REVIEW ARTICLE

A systematic review investigating the proportion of clinical images shared in prospective randomized controlled trials involving patients with atopic dermatitis and systemic pharmacotherapy

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ABSTRACT

Purpose: For individuals with atopic dermatitis (AD), interpreting scientific papers that present clinical outcomes including the Eczema Area and Severity Index (EASI) and Investigators Global Assessment may be difficult. When compared to tabulated data and graphs, images from before and after treatment are often far more meaningful to these patients that ultimately will be candidates for the treatment. This systematic review focused on determining the frequency of clinical image sharing in AD research.
Materials and methods: Conducted in accordance with PRISMA guidelines, the review concentrated on randomized controlled trials that investigated predefined and available systemic treatments for AD. The search was performed in the MEDLINE database for studies published from the inception until 21 December 2023.
Results: The review included 60 studies, encompassing 17,799 randomized patients. Across these studies, 16 images representing 6 patients were shared in the manuscripts, leading to a sharing rate of 0.3‰.
Conclusions: The almost missing inclusion of patient images in clinical trial publications hinders patient understanding. Adding images to scientific manuscripts could significantly improve patients' comprehension of potential treatment outcomes. This review highlights the need for authors, the pharmaceutical industry, study sponsors, and publishers to enhance and promote patient information through increased use of visual data.

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Atopic dermatitis; data sharing; Janus kinase inhibitor; pharmaceuticals, biologic; randomized controlled trial; skin imaging; systematic review

Introduction

Atopic dermatitis (AD) is a common inflammatory skin condition characterized by recurring eczematous lesions and severe itching, affecting individuals across all age groups and ethnic backgrounds (1,2). AD not only adds to the global burden of skin diseases but also significantly impacts the psychosocial well-being of both patients and their families (3,4).

Historically, patients with psoriasis have had more available treatment options as compared to individuals with AD. However, the last decade has seen a significant expansion in novel systemic pharmacotherapy for AD, including the introduction of biologics and Janus kinase inhibitors (JAKi) (5,6). While often very effective, these novel drugs still have ongoing patents meaning that they have a considerable impact on healthcare budgets worldwide.

In randomized prospective clinical trials involving patients with AD, the most often used primary outcomes are based on improvement of baseline Eczema Area and Severity Index (EASI) and/or variations of the Investigators Global Assessment (IGA) scale. The EASI score, evaluates the intensity of symptoms (such as redness, swelling, crusting, and scaling) and the area affected by eczema on the body. This tool is commonly used by healthcare professionals to monitor the progression or improvement of eczema over time. The IGA score is a simple, overall clinical assessment tool used by investigators to rate the severity of AD, considering factors like redness, swelling, and the area of skin affected, at a specific point in time. The score ranges from 0, clear, to 5, severe.

Shared decision making is a collaborative process in which a healthcare professional works together with a patient to reach a decision about care (7). It is generally agreed, and also stipulated in many legislations worldwide, that shared decision making should be the norm in contemporary medicine.

The majority of patients find scientific manuscripts, including scoring systems like EASI and IGA, challenging to comprehend. Furthermore, although the purpose of these manuscripts, particularly those that discuss pharmaceutical treatments, is to assess effectiveness with the goal of enhancing patient care, the format of scientific manuscripts has remained largely static for decades. Bearing this in mind, most patients and learners naturally resonate with visual aids.

The aim of this systematic review was to investigate at what proportion clinical images were shared in randomized prospective clinical trials of currently available systemic pharmacotherapy for AD.

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Materials and methods

A systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for all applicable items (8). The PRISMA checklist is available in the supplementary material (Appendix S1). Prior the initiation, the review protocol was compiled by both authors. Our predefined list of systemic treatment options was developed in accordance with the American and European guidelines for the treatment of Atopic Dermatitis (AD) (9–11).

Eligibility criteria

- *Population:* no geographic restriction was imposed.
- *Atopic dermatitis:* including all subtypes.
- *Study design:* randomized controlled trials published within the specified time frame, from the inception of MEDLINE until 21 December 2023.
- *Outcome measure:* Investigator-reported visual assessment of AD severity.
- *Study drugs:* dupilumab, tralokinumab; abrocitinib, baricitinib, upadacitinib; azathioprine, cyclosporine, methotrexate, mycophenolate mofetil.

Exclusion criteria

- Follow-up, *post-hoc* or extension investigations.
- Non-English investigations.

Information sources and search strategy

The MEDLINE (PubMed) database was searched for eligible studies published from inception to 21 December 2023. The search string employed is detailed in Appendix S2. We confined our search to MEDLINE, based on a previous review addressing a similar topic in psoriasis where all the papers ultimately selected after the screening phase were indexed in this database (12).

Selection and data collection process

Both authors independently reviewed the titles and abstracts of all the studies. Any discrepancies during the title/abstract screening phase were settled through consensus. Subsequently, both authors independently assessed all the full texts. At this stage consensus was used to resolve any conflicting opinions regarding the eligibility of studies. Additionally, both authors confirmed the data extracted from the selected studies to ensure accuracy.

Data items

Data extracted from the included studies encompassed several key elements: the first author's name, publication year, journal name, digital object identifier (DOI) link (where available), primary outcome (if specified), duration until the primary outcome (if specified), total number of patients randomized, and the count of patients and images presented in the manuscript, inclusive of all supplementary and video material. In cases where a study comprised more than one stage, only the patient numbers contributing to the primary outcome were included in the analysis. A customized data extraction worksheet was utilized to methodically collect all the aforementioned data points (Table SI).

Study risk of bias assessment

Given the dichotomous outcome focus of this review, we did not employ any quality assessment tools nor conduct tests for publication bias.

Effect measures and statistics

This review was based on a binary measure, specifically the presence or absence of clinical images. We calculated the proportion of images shared in each study and across the entire dataset. The compilation and organization of records were facilitated using three software tools: EndNote (Clarivate Analytics, Philadelphia, PA, USA), Rayyan (Rayyan Systems Inc., Cambridge, MA, USA), and Microsoft Excel (Microsoft, Redmond, WA, USA). The process of handling all publications and data extraction was conducted manually, without the use of any automation software. The original EndNote library utilized for this review can be made available upon request to the corresponding author.

Results

Of the 417 records first identified, 71 investigations were reviewed in full text. Among these, 11 investigations were excluded (13–23) (Table SII). After exclusions, 60 studies published in the time period of 1991 to 2023 were included in the analysis (Figure 1). Overall, 18 medical journals were represented (Table SIII).

When combining the 60 investigations (24–83), above, 17,799 patients were randomized. Overall, 3 investigations included patients image material in the running manuscript (26,40,79), and one additional investigation (37), shared patient images in the supplementary material (Table 1). When combining these four investigations, 16 images were shared depicting 6 patients in the manuscripts (including all supplementary text and video material) yielding an overall sharing rate of 0.3‰. One investigation included video supplement, however this recording did not include any patient images (56). The majority of patients ($n=16,259$) were randomized in trials that included EASI and/or variations of the IGA score as a primary outcome. Among these individuals, five patients (0.3‰) were depicted. The same proportion (*i.e.*, 0.3‰) was observed when combining the five medical journals that included the highest number of patients (Table 2).

Discussion

This systematic review underlines the striking scarcity of image sharing in AD-related randomized controlled trials, pointing to an almost overlooked aspect in clinical research dissemination. The vast majority (93.3%, $n=56$) of all included investigations included no patient image material and merely 0.3‰ ($n=6$) of all randomized patients ($n=17,799$) were depicted in the included manuscripts.

In recent years, the introduction of biologics and JAKi has greatly improved treatment outcomes for patients with AD, particularly those with moderate to severe disease. In contrast with the innovative development of new systemic pharmacotherapies, the way in which randomized controlled trial data is presented has largely remained the same. Digitalization has facilitated data

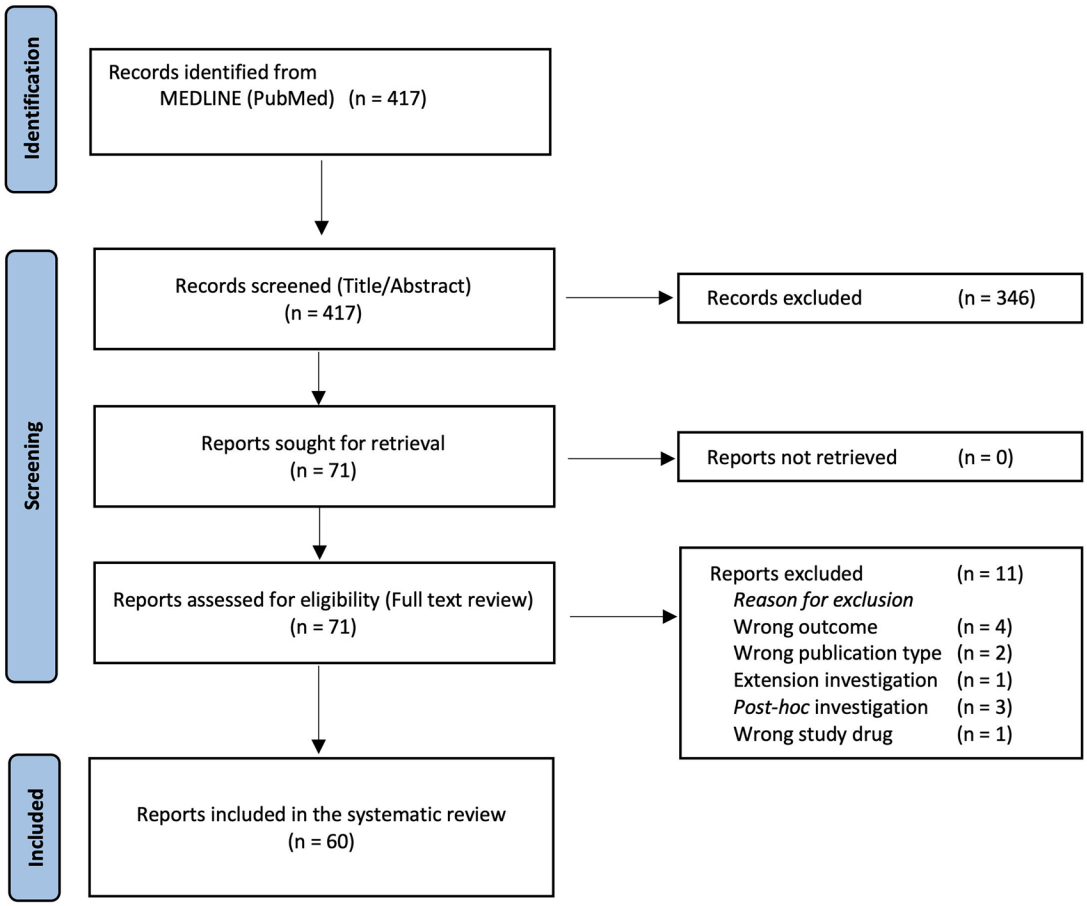

Figure 1. PRISMA flow chart. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1. List of investigations ($n = 4$) with included patient images in running manuscripts and supplements.

First author	Year	Journal	Primary outcome	Time to primary outcome	Number of randomized patients	Number of patients depicted in manuscript[a]	Number of patient images in manuscript[a]	Proportion of depicted patients[a]	Digital Object Identifier link
Bemanian et al. (26)	2005	*Iran J Allergy Asthma Immunol*	SCORAD	N/A	14	1	2	7.1%	N/A
Gooderham et al. (37)[b]	2019	*JAMA Dermatol*	IGA	12 weeks	267	3	9	1.1%	https://doi.org/10.1001/jamadermatol.2019.2855
Gutermuth et al. (40)	2022	*Br J Dermatol*	ΔEASI 75	16 weeks	277	1	2	0.4%	https://doi.org/10.1111/bjd.20832
Wollenberg et al. (79)	2021	*Br J Dermatol*	ΔEASI 75 + IGA	16 weeks	1596	1	3	0.6‰	https://doi.org/10.1111/bjd.19574

Notes: Journal abbreviations: *Br J Derm: British Journal of Dermatology; Iran J Allergy Asthma Immunol: Iranian Journal of Allergy, Asthma and Immunology; JAMA Dermatol: Journal of the American Medical Association Dermatology.* Primary outcome abbreviations: EASI: Eczema Area and Severity Index; EASI 75: 75% improvement of the EASI value as compared to baseline; IGA: Investigators Global Assessment; NA: not available or not available.
[a]Running manuscript and all supplementary material combined.
[b]Image material were made available in supplementary material.

collection including imaging, compilation, and dissemination to the potential benefit of patients, healthcare providers, and the pharmaceutical industry. This review pinpoints that these opportunities have largely been overlooked when it comes to presentation of clinical trial data that is accessible and comprehensible for patients.

In a proposal published in 2016, The International Committee of Medical Journal Editors (ICMJE) stated that there is an ethical obligation to responsibly share data generated by interventional clinical trials because participants have put themselves at risk (84). In 2017, the ICMJE listed the inclusion of data sharing statements in the clinical trials registration phase as a requirement (85). While sharing of deidentified individual-patient data from clinical trials is now considered the norm, the requirements unfortunately do not explicitly mention sharing image data.

Medical scientific articles in peer-reviewed journals are primarily aimed at healthcare providers and researchers, but as patients and patient advocacy groups are becoming integral contributors to standard care practices, we believe that they must be included among the target readers. One way to meet this demand has

Table 2. Proportion of depicted patients in the five journals with most randomized patients.

Journal	Number of investigations	Number of randomized patients	Number of patients depicted in running manuscript	Number of patient images in running manuscript	Number of patients depicted in supplements[a]	Number of patient images in supplements[a]	Proportion of depicted patients[b]
Br J Dermatol	19	5657	2	5	0	0	0.4‰
Lancet	9	5076	0	0	0	0	0%
JAMA Derm	7	2516	0	0	3	9	0.10%
N Engl J Med	3	2424	0	0	0	0	0%
J Am Acad Dermatol	5	1092	0	0	0	0	0%
	43	16,765	2	5	3	9	0.3‰

Note: Br J Dermatol: British Journal of Dermatology; J Am Acad Dermatol: Journal of the American Academy of Dermatology; JAMA Dermatology: Journal of the American Medical Association Dermatology; N Engl J Med, New England Journal of Medicine.
[a]Including video supplements.
[b]Including both running manuscript and any supplementary material.

been to add plain language or capsule summaries for laypersons in original reports. Today, when the online open-access journal is the preferred medium for publication of original data, submission of supplementary material that supports the findings is often encouraged by the editorial offices. For randomized clinical trials, images illustrating disease distribution at the initial visit and the follow-up visits would be highly relevant as supplementary material. We are confident that visual amendments can play a crucial role in involving patients more closely. Enhancing patients' comprehension of the potential treatment effects is expected to significantly improve their ability to make informed decisions together with their dermatologist.

Sharing deidentified clinical images of AD from interventional trials can also serve other important purposes. Visual representation, in addition to the scoring systems recommended for clinical trials by the Harmonizing Outcome Measures for Eczema (HOME) taskforce, aids external validation of the treatment effects (86). Clinical images hold a predominant position in the field of dermatology education, serving as a fundamental tool for teaching and learning. Readily available sets of images depicting different AD phenotypes in different patient populations and the response to treatment can be used in the training of healthcare professionals, medical students as well as for patient education. It is important to consider that skin phototypes affects the visual manifestations of active AD as well as the post-inflammatory state (87). For instance, hyperemia is not always perceived as red but rather as purple or brown in melanin-rich skin types. This limits the applicability of erythema as a scoring item in systems such as EASI or the SCORing of Atopic Dermatitis (SCORAD) index. Clinical trials with global recruitment could therefore provide valuable images of AD phenotypes in different skin phototypes, in active disease and remission, to improve healthcare providers' clinical assessment.

Another potential ancillary use for large sets of images of atopic skin is in the development of machine learning (ML) algorithms to aid management of AD. It is highly conceivable that ML algorithms, which incorporate the baseline clinical phenotype together with patient metadata, could significantly aid physicians in pinpointing the most efficacious treatment options for the individual patient. Clearly, this approach has the potential to circumvent the traditional trial-and-error method, offering a more streamlined and precise pathway to optimal patient care.

We report an exceptionally low sharing rate of clinical images. Investigating the reasons for this was outside the scope of this review. One reason could be medicolegal regulations for clinical trial procedure and patient privacy. Another likely reason is a lack of clinical images to share. While standardized photography is an integrated part of patient follow-up in real-world dermatology it is currently not an established method for assessment and follow-up in clinical trials. Different aspects of this were previously discussed (12). In addition, AD has a relapsing course with rapid fluctuations, which makes representative documentation with photography more challenging than for other skin diseases such as psoriasis.

Collecting clinical images would be an additional task for investigators but could prove rewarding. Images of selected body parts illustrating treatment progress could most often be used in publications without exposing the patient's identity. As a service to readers, editorial offices have restrictions on the amount of data that is presented in the running manuscript, but including online supplementary files is usually encouraged. To maintain an overview for readers, only a minority of patient outcomes in trials can be presented with clinical images even in such supplementary files. This in turn introduces a risk for "cherry picking" (i.e., selection bias). Accessibility to all available image material for all patients could partly help resolve this issue.

While the comprehensive design of a system for managing clinical images collected in clinical trials falls outside the scope of this review, we envision such a system as an open-access, unified, authenticated, and secure database. Ideally this platform would garner universal support from the pharmaceutical industry, healthcare providers, academic institutions, and publishers. An interface with intuitive design would be essential for such a system. Image data should be collected in a standardized manner, specified in the trial protocol, to protect patient integrity. Moreover, the online platform should feature a user-friendly navigation system to ensure that patients, healthcare providers, and other stakeholders can maximize its utility.

The limitations of this study include that the search was confined to MEDLINE. The reason for this is explained in the Materials and Methods section. Investigations published in other languages than English were excluded and could potentially differ in the sharing rate of clinical images although we considered this unlikely. Also, it is likely that all pivotal clinical trials for new systemic pharmacotherapy for AD are published in English. It is possible that there are other subsets of publications on AD (apart from case reports) that contain more clinical images.

In the era of new systemic pharmacotherapy, online image-based communication, and increased demand for patient participation in clinical decision-making, we report an almost non-existent inclusion of patient images in published clinical AD trials. Patients who commit to participation in clinical trials devote considerable time and effort to improve future care. We believe that they would like to share appropriately anonymized images to illustrate treatment effects. We welcome a discussion on how

clinical images can be used in the execution and communication of clinical trials to the benefit of patients, healthcare providers, sponsors, and healthcare authorities.

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MA: With no relation to the present manuscript, Mikael Alsterholm has received speaker honoraria and/or been in advisory boards for AbbVie, Almirall, Eli-Lilly, Essity, LEO Pharma, Pfizer, and Sanofi-Genzyme, and is/has been an investigator for AbbVie, LEO Pharma, and Sanofi-Genzyme.

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