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A scoping review of nucleic acid therapies for inflammatory skin diseases

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ADMINISTRATIVE INFORMATION

Support - University of Liverpool.

Review Stage at time of this submission - Data analysis.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 December 2024 and was last updated on 18 December 2024.

INTRODUCTION

Review question / Objective The key objective was to understand: (a) Which nucleic acid technologies have been evaluated for inflammatory skin diseases? (b) What inflammatory skin conditions are these therapies targeting? (c) What stage of research (preclinical, clinical trials) are these studies currently at?

Background Inflammatory skin diseases, including both drug-induced reactions (such as Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), acute generalized exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS)) and chronic conditions (such as atopic dermatitis, psoriasis, hidradenitis suppurativa, eczema, seborrheic dermatitis), constitute significant global health challenges, leading to high healthcare burdens and substantial morbidity and mortality (1). Many of these diseases are characterised by immune system dysregulation and persistent inflammation, manifesting in classic inflammatory signs—heat, pain, redness, swelling, and impaired function. The inflammation is usually driven by the activation of the innate and adaptive immune system via the production of pro-inflammatory cytokines(2, 3). Currently available treatments are mostly supportive and lack targeted mechanisms thereby limiting their effectiveness and causing adverse effects, particularly for drug-induced conditions like SJS/TEN (4). The medical treatment for SJS/TEN include immunoglobulins, ciclosporin (5, 6), systemic corticosteroids like dexamethasone (7, 8), and TNF inhibitors like etanercept (9-11). Also, the treatments for psoriasis include topical therapy (emollients, creams, lotion, gel, ointments, solution), phototherapy (broad - or narrow-band

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ultraviolet B light or PUVA (psoralen and ultraviolet A light)), and systemic therapy (methotrexate, ciclosporin, apremilast, etanercept, adalimumab, etc) (12) but they are non-targeted therapies. Similarly, the treatments for atopic dermatitis are for symptomatic relief. They include creams and ointments containing corticosteroids, phototherapy and systemic medications like Janus kinase inhibitors (eg, ruxolitinib) and biologics (13).

Recent advances in nucleic acid-based therapies have opened potential opportunities for more targeted and efficacious treatments. While some nucleic acids, such as mRNAs are already in clinical use (e.g, mRNA vaccines), many others such as DNA, microRNA, small interfering RNA (siRNA), circular RNA (circRNA), short hairpin RNA (shRNA), piwi-associated RNA (piRNA), RNA interference (RNAi), antisense oligonucleotides are still under investigation for their ability to modulate immune responses and target specific inflammatory pathways(14-19). [Given that poor skin penetration is one of the major challenges in utilisation nucleic acids for topical treatment of inflammatory skin diseases, innovative delivery systems like use of nanotechnology (nanoparticles, lipid nanocarriers, liquid crystalline nanodispersion), topical ionic liquid formulation, cell-penetrating peptides, permeation-enhancing peptides, bacterial/viral vehicles, fusogenic nucleic acid lipid particle system, microneedle array, hydrogels, ultrasonic irradiation, and SonoVue microbubbles (20-32) are being developed to enhance skin penetration.

In our earlier work, we looked at putative miRNAs for the therapy of SJS/TEN and wanted to explore what the state-of-the-art was in the use of nucleic acids in the treatment of inflammatory skin conditions. So, since there is yet to be a comprehensive synthesis of the evidence regarding the application of nucleic acids in treating inflammatory skin disorders, we wanted to explore this. This scoping review therefore aimed to fill this gap by systematically evaluating the literature on nucleic acid therapies to assess the scope of nucleic acid research and identify promising trends for targeted therapeutics for inflammatory skin diseases.

Rationale Inflammatory skin diseases, including both drug-induced reactions (such as Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), acute generalized exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS)) and chronic conditions (such as atopic dermatitis, psoriasis, hidradenitis suppurativa, eczema, seborrheic dermatitis), constitute significant global health challenges, leading to high healthcare burdens and substantial morbidity and mortality (1). Many of these diseases are characterised by immune system dysregulation and persistent inflammation, manifesting in classic inflammatory signs—heat, pain, redness, swelling, and impaired function. The inflammation is usually driven by the activation of the innate and adaptive immune system by producing pro-inflammatory cytokines(2, 3).

Currently available treatments are mostly supportive and lack targeted mechanisms thereby limiting their effectiveness and causing adverse effects, particularly for drug-induced conditions like SJS/TEN (4). The medical treatment for SJS/TEN include immunoglobulins, ciclosporin (5, 6), systemic corticosteroids like dexamethasone (7, 8), and TNF inhibitors like etanercept (9-11). Also, the treatments for psoriasis include topical therapy (emollients, creams, lotion, gel, ointments, solution), phototherapy (broad - or narrow-band ultraviolet B light or PUVA (psoralen and ultraviolet A light)), and systemic therapy (methotrexate, ciclosporin, apremilast, etanercept, adalimumab, etc) (12) but they are non-targeted therapies. Similarly, the treatments for atopic dermatitis are for symptomatic relief. They include creams and ointments containing corticosteroids, phototherapy and systemic medications like Janus kinase inhibitors (eg, ruxolitinib) and biologics (13).

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regarding the application of nucleic acids in treating inflammatory skin disorders, we wanted to explore this. This scoping review therefore aimed to fill this gap by systematically evaluating the literature on nucleic acid therapies to assess the scope of nucleic acid research and identify promising trends for targeted therapeutics for inflammatory skin diseases.

METHODS

Strategy of data synthesis MS Excel and EndNote will be employed to organise the retrieved bibliographic records and for the screening process. Duplicate records will removed. Initial screening was conducted using titles and abstracts to remove irrelevant studies. A full-text review will be conducted to confirm eligibility for potentially relevant studies. Data will be extracted using a pre-tested template.

Eligibility criteria Any accessible relevant original article published in a peer-reviewed journal in English language will be considered. Studies unrelated to inflammatory skin conditions, non-nucleic acid therapies, editorials, opinion pieces, and non-peer-reviewed studies or systematic reviews/meta-analyses were excluded.

Source of evidence screening and selection Two of the authors will screen the retrieved records using titles and abstracts for possible inclusion. Any conflicts will be resolved by consensus. Selected records will be retrieved and full-text screening will be done to ensure they meet the inclusion criteria. The data items to be captured include author and year of publication, country of research, the type of inflammatory skin disease studied, the type of nucleic acid used, the study design (preclinical or clinical), the mechanisms of action, the outcomes (effects on cells, tissues, animals or man), and safety.

Data management Data will be managed using MS Excel and Python. Adequate steps will be taken to maintain the confidentiality of the documents as necessary.

Reporting results / Analysis of the evidence Tables, charts and diagrams will be used to analyse and report the evidence.

Presentation of the results Tables, charts and diagrams will be used to analyse and report the evidence.

Language restriction English Language.

Country(ies) involved United Kingdom.

Keywords Nucleic acids; miRNA, siRNA, circRNA, lncRNA, aptamer, RNA, DNA, inflammatory skin diseases; therapies.

Dissemination plans We intend to publish this in a peer-reviewed journal and present it at academic conferences.

Contributions of each author

Author 1 - Emeka Donald Ogiji - Drafted the protocol, searched, screened the records and synthesised the results, and is drafting the manuscript.
Email: emeka.ogiji@liverpool.ac.uk
Author 2 - Innocent Asiimwe - Screened the records and will contribute to writing and proofreading the manuscript.
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