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REVIEW

Advances of microneedle technology for the treatment of autoimmune diseases

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Abstract Autoimmune diseases are characterized by an aberrant immune response directed against the body's own components, leading to immune dysfunction and loss of tolerance. This ultimately results in tissue damage and organ impairment. Despite the availability of a range of pharmacological agents for the treatment of autoimmune diseases, numerous challenges still remain. These include reduced bioavailability, first-pass metabolism, severe adverse effects, and low patient compliance associated with oral or injectable routes of administration. Microneedles (MNs) based delivery systems offer a promising alternative for transdermal drug administration, as they can circumvent the aforementioned limitations *via* the generation of microchannels in the skin in a minimally invasive manner with low pain. This review examines the applications and recent advances in MN systems for treating autoimmune diseases, focusing on six key areas: an overview of autoimmune diseases, current treatment modalities, an introduction to MNs, advantages of MNs for autoimmune disease treatment, advancements in

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MN-mediated therapies for diverse autoimmune diseases, and relevant MN technologies currently undergoing clinical trials. Additionally, it considers the prospective future advancements of MN systems in the management of autoimmune diseases.

1. Introduction

Autoimmune diseases constitute a group of disorders that are either directly or indirectly caused by aberrant immune responses and are typified by immune dysfunction. When T cells and B cells become dysregulated, the body may produce excessive autoantibodies, which can then trigger an exaggerated autoimmune response. This can result in chronic inflammation, tissue damage, and organ dysfunction[1,2]. Common autoimmune diseases include rheumatoid arthritis (RA), psoriasis, atopic dermatitis (AD), type 1 diabetes (T1D), etc. The prevalence of autoimmune diseases has been increasing, representing a substantial public health concern[3,4]. It has been reported that approximately 3%−5% of the global population is affected by autoimmune diseases. A considerable number of these diseases are becoming increasingly prevalent over time. For example, the incidence of conditions such as RA, Graves' disease, and pernicious anaemia increases with age. Furthermore, autoimmune diseases are generally more prevalent in women than in men[5]. In China, the number of individuals affected by autoimmune diseases has been increasing on an annual basis. Statistics from the National Health Commission of the People's Republic of China indicate that approximately 80 million individuals in China are affected by autoimmune diseases, representing the third most prevalent chronic disease after cardiovascular diseases and cancer.

At present, the majority of autoimmune diseases are considered incurable and necessitate lifelong treatment, frequently involving continuous oral or injectable drug administration. However, long-term drug therapies are associated with several challenges, such as poor bioavailability, undesired adverse effects, and "needle phobia", which greatly impede patient compliance and the broader application of these treatments. It is therefore imperative to develop effective and patient-friendly drug delivery systems to effectively manage autoimmune diseases. The earliest systems for minimally invasive drug delivery included transdermal controlled release methods, drug−chemical enhancer complexes, and physical techniques such as iontophoresis and sonophoresis[6-10]. More recently, the advancement of microneedles (MNs) has garnered significant attention as a potential avenue for drug delivery.

The first preparation of MNs was conducted by Henry et al.[11] in 1998, employing microfabrication technology. MNs are composed of arrays of tiny needles, typically ranging from 100 to 1000 μm in length, mounted on a base. These needles are capable of directionally penetrating the skin's stratum corneum, creating hundreds of microchannels that facilitate the efficient delivery of drugs while minimizing damage to the skin[12]. This approach combines the benefits of traditional injections with the safety of transdermal patches. Over the past two decades, MN systems have gained attention in various biomedical applications, including drug delivery[13,14], disease diagnosis[15], and cosmetic use[16]. Given their potential, MNs offer a promising future in the treatment of autoimmune diseases[17,18].

Despite the advantages of MNs, no comprehensive review has yet focused on their application in autoimmune disease treatment. This review aims to fill that gap by firstly providing an overview of autoimmune diseases and their current treatments, then exploring the different types and characteristics of MNs. Finally, we examine the role of MNs in the treatment of autoimmune diseases, along with an analysis of their clinical trials, potential developments, and future challenges. It is our intention that this review will provide new perspectives for further research into effective treatments for autoimmune diseases.

2. Medications for autoimmune diseases

2.1. Topical therapies

Topical therapies for autoimmune diseases include glucocorticoids, vitamin D3 analogues, calcineurin inhibitors, and ultraviolet (UV) light phototherapy[19] (Table 1).

Glucocorticoids, produced by the adrenal cortex, regulate inflammation by inhibiting T-lymphocytes, suppressing angiogenesis, and reducing vascular permeability[20]. They are classified based on their duration of action: short-acting (*e.g.*, hydrocortisone), medium-acting (*e.g.*, mometasone), and long-acting (*e.g.*, dexamethasone). Topical glucocorticoids generally have low systemic side effects but can cause skin atrophy, redness, and hyperpigmentation, with potential for systemic effects when used extensively[20,21].

Vitamin D3 analogues, including calcipotriol and tacalcitol, are structurally analogous to vitamin D3 (cholecalciferol). These compounds bind to vitamin D receptors, thereby modulating immune responses and reducing inflammation in autoimmune diseases. While these medications are effective, they can cause skin irritation and elevated blood calcium levels[22].

Calcineurin inhibitors (*e.g.*, tacrolimus, pimecrolimus) are effective for treating localized psoriasis, particularly on facial lesions. They work by inhibiting T-cell activation but, unlike glucocorticoids, have a lower risk of metabolic side effects. Consequently, topical calcineurin inhibitors are usually employed in cases where patients are unresponsive to steroids or necessitate long-term management for dermatological conditions. However, long-term use may lead to skin atrophy and increased susceptibility to infections[23].

In addition to pharmacological interventions, phototherapy is an effective localized treatment for autoimmune diseases. This therapeutic modality primarily employs narrow-band UV light to interfere with DNA synthesis, thereby reducing epidermal cell proliferation and inflammatory cell numbers in the skin. However,

Table 1 Clinical medications for autoimmune diseases.

Treatment type	Classification	Therapeutic agent	Conditions
Topical therapies	Glucocorticoids	Hydrocortisone, dexamethasone, dexamethasone	Psoriasis, AD, vitiligo, SLE
	Vitamin D3 analogues	Calcipotriol, tacalcitol	
	Calcineurin inhibitors	Tacrolimus, pimecrolimus	
	Phototherapy	Ultraviolet light	
Systemic therapies	NSAIDs	Paracetamol, ibuprofen	Psoriasis, RA, AD, T1D, vitiligo, SLE, multiple sclerosis
	Glucocorticoids	Hydrocortisone, mometasone furoate	
	Immunomodulators	Antimetabolites (methotrexate, azathioprine), JAK inhibitors (tofacitinib, baricitinib), calcineurin inhibitors (cyclosporine A, tacrolimus)	
	Biologics	TNF inhibitors (infliximab), IL inhibitors (tocilizumab), integrin inhibitors (vedolizumab), B-cell depletion agents (rituximab), T-cell depletion agents (alemtuzumab), ADCs (ABBV-3373)	

AD, atopic dermatitis; SLE, systemic lupus erythematosus; NSAIDs, non-steroidal anti-inflammatory drugs; JAK, Janus kinase; RA, rheumatoid arthritis; T1D, type 1 diabetes.

prolonged exposure can lead to dry skin, sunburn, and an increased risk of skin cancer[24].

2.2. *Systemic therapies*

Systemic therapies are a cornerstone of autoimmune disease management and can be typically classified into four main categories: non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, immunomodulators, and biologics (Table 1).

NSAIDs constitute a class of anti-inflammatory medications that lack a steroidal structure. Since the first introduction of aspirin in 1899, over 100 distinct NSAIDs (*e.g.*, paracetamol, ibuprofen, etc.) have been developed for clinical practice[25,26]. These drugs can reduce inflammation by inhibiting cyclooxygenase enzymes. While effective for symptom relief, they do not address the root causes of autoimmune diseases and can cause side effects like gastrointestinal issues and cardiovascular risks[27].

The systemic administration of glucocorticoids (*e.g.*, hydrocortisone, mometasone furoate, etc.) is typically employed in the treatment of systemic autoimmune diseases. Due to their higher dosages and extensive systemic distribution, systemic glucocorticoids have a broader array of adverse effects, including weight gain, osteoporosis, and immunosuppression[28].

Immunomodulators represent a class of medications capable of effectively balancing the immune system in autoimmune disease patients. This category includes antimetabolites, Janus Kinase (JAK) inhibitors, and calcineurin inhibitors. Antimetabolites (*e.g.*, methotrexate, azathioprine, etc.) have been shown to inhibit immune cell proliferation by interfering with nucleotide synthesis. JAK inhibitors, such as tofacitinib and baricitinib, interfere with the Janus Kinase-signal transducers and activators of transcription signaling pathway, thereby reducing the immune response[29]. Calcineurin inhibitors, such as cyclosporine A and tacrolimus, are typically employed in cases of autoimmune disorders that have demonstrated resistance to other immunosuppressive agents[30]. However, these medications carry risks such as increased infection, liver and kidney toxicity, and hematological abnormalities.

Biologics are a class of drugs derived from living organisms, designed to modulate the immune system by targeting specific molecules involved in autoimmune diseases[31]. The most common biologics are monoclonal antibodies (*e.g.*, infliximab, tocilizumab), which are engineered to target specific antigens, such as tumor necrosis factor (TNF) or interleukins (IL), and modulate inflammatory pathways[32]. These agents are highly specific and can provide significant therapeutic benefits in diseases like RA and psoriasis[33]. However, biologics often come with a high cost and may not address the multifactorial nature of autoimmune diseases, which can limit their effectiveness in some patients.

Antibody–drug conjugates (ADCs) represent a newer class of biologics that combine monoclonal antibodies with cytotoxic drugs[34]. These conjugates target specific immune cells involved in autoimmune disease pathology, delivering cytotoxic agents directly to the targeted cells while sparing healthy tissue[35,36]. For example, ABBV-3373, a TNF-α antibody conjugated to a glucocorticoid, has shown promising results in clinical trials for RA[37]. ADCs represent an innovative therapeutic option for autoimmune diseases, offering both high specificity and reduced adverse effects[38,39].

3. Classification of MNs

Since the first patent on MNs for transdermal drug delivery in 1970, MNs have gradually emerged as a prominent area of research in the field of transdermal drug delivery[40,41]. Over the past two decades, diverse types of MNs have been developed, offering various advantages and addressing specific limitations. These systems are broadly categorized into two main groups based on their preparation methods and drug release mechanisms: traditional MNs and novel MNs[42,43] (Fig. 1, Table 2[44-59]).

3.1. *Traditional MNs*

Traditional MNs are classified based on their delivery mechanisms and include solid MNs, coated MNs, hollow MNs, dissolving MNs, and hydrogel MNs.

3.1.1. *Solid MNs*

Solid MNs represent the earliest form of MNs, typically composed of silicon or metal. They operate on the "Poke and Patch" principle, wherein the stratum corneum is punctured to create transient microchannels through which drugs applied on the skin can diffuse into the dermis[60,61]. These needles have certain limitations. Firstly, the amount of drug entering the body cannot be accurately measured, leading to inaccurate dosage. Secondly, despite the

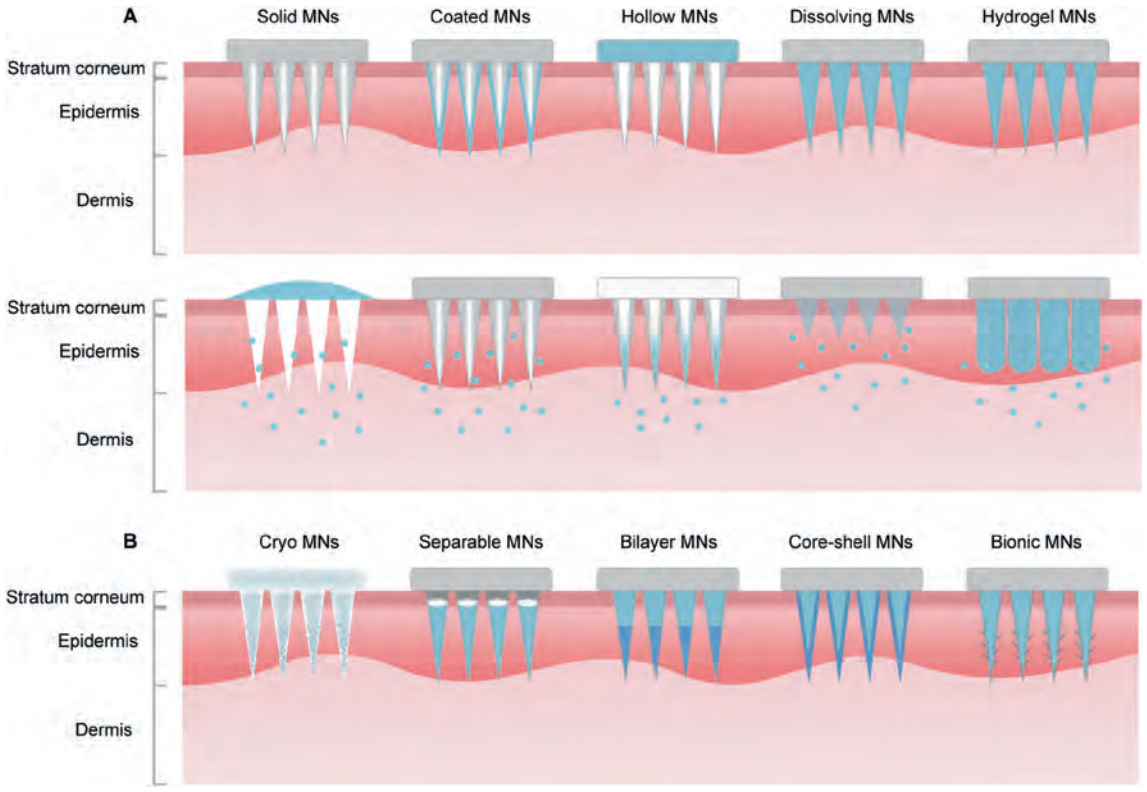

Figure 1 Classification of (A) traditional MNs and (B) novel MNs.

Table 2 Summary of MNs in the treatment of autoimmune diseases.

Category	Therapeutic agent	Condition	Ref.
Solid MNs	Calcipotriol	Psoriasis	44
	Insulin	T1D	45
Coated MNs	Peptide (WE14, m31 and pro-insulin B9-23)	T1D	46
Hollow MNs	Insulin	T1D	47
	Hypericin	RA	48
Dissolving MNs	Cyclosporin A	Psoriasis	49
	Triamcinolone acetonide	AD	50
	CII peptide autoantigen and rapamycin	RA	51
Hydrogel MNs	Dexamethasone	Psoriasis	52
	Alpha-melanocyte-stimulating hormone and tofacitinib	Vitiligo	53
Cryo MNs	Melittin and chondroitin sulfate	RA	54
Separable MNs	*Schistosoma japonicum egg*	T1D	55
	Interferon γ and dexamethasone	SLE	56
Bilayer MNs	Tocilizumab and aptamer Apt1-67	RA	57
Core-shell MNs	Tacrolimus and diclofenac	PsA	58
	Insulin	T1D	59
Bionic MNs	Insulin	T1D	59

T1D, type 1 diabetes; RA, rheumatoid arthritis; AD, atopic dermatitis; SLE, systemic lupus erythematosus; PsA, psoriasis arthritis.

good mechanical properties of silicon or metal, the needle body is prone to breakage during insertion, increasing the risk of infection.

3.1.2. Coated MNs

Coated MNs are manufactured by applying a drug layer onto the surface of solid MNs using techniques like impregnation or spraying. These MNs follow the "Coat and Poke" principle, where the drug dissolves from the MN's surface upon insertion into the skin, leaving the drug-free MN portion to be removed[62]. Coated MNs are effective for water-soluble drugs, offering rapid release and high drug utilization. However, their drug encapsulation capacity is limited, making them most suitable for potent drugs that require small doses[63].

3.1.3. Hollow MNs

Hollow MNs operate on the "Poke and Flow" principle, delivering preloaded liquid drugs under pressure through microscopic needle tips. These MNs provide precise control over drug delivery rates, enhancing accuracy and dosage control compared to solid and coated MNs[64]. However, their preparation is complex and costly,

and issues such as tissue resistance and potential premature drug release may occur. Furthermore, the needles' mechanical strength is relatively low, which can lead to breakage and infection risk[65].

3.1.4. Dissolving MNs (DMNs)

DMNs are made from materials that can be dissolved or degraded in the skin[66]. Techniques such as micro-molding, 3D printing, and stretch lithography are used for their production. The "Poke and Release" principle underpins the operation of DMNs: the drug is released as the needle dissolves or degrades within the skin[67]. The operation of DMNs prevents the creation of biohazardous medical waste and reduces the risk of infection. Moreover, the dissolution rate can be tailored by modifying the needle composition, offering significant potential for controlled drug release profiles.

3.1.5. Hydrogel MNs

Hydrogel MNs are typically constructed from swellable polymeric materials. The drug is loaded into a separate reservoir and absorbed into the skin, where the hydrogel swells, forming continuous channels for drug delivery. The rate of drug release can be modified by adjusting the degree of cross-linking of the hydrogel, thereby enabling the creation of controlled drug release profiles[65,68]. The swelling process also prevents re-insertion of the MN, reducing the risk of infection from reuse[69].

3.2. Novel MNs

As the demand for precision drug delivery and personalized treatments increases, traditional MNs have been found to exhibit inherent limitations, such as the inability to synchronously encapsulate multiple agents or to dynamically adjust drug release rates. Novel MNs can address these challenges through customized drug encapsulation and response to environmental stimuli, thereby enabling precise timing and dosage control. These innovations include cryo MNs, separable MNs, double-layer MNs, core–shell MNs, and bionic MNs.

3.2.1. Cryo MNs

Cryo MNs are designed to deliver living therapeutic cells and macromolecular drugs while preserving their viability. By using cryo-molding technology, these MNs ensure cellular survival and proliferative capacity. Although they have great potential for storing and delivering cells for therapeutic purposes, their reliance on cold-chain transportation limits their clinical applicability[43]. To date, there has been no research exploring the use of cryo MNs delivering therapeutic cells for autoimmune disease treatment. However, Jin et al.[54] constructed cryo MNs delivering melittin for RA treatment, and the low-temperature preparation process well preserved the secondary structure stability of melittin.

3.2.2. Separable MNs

It is necessary to wear traditional DMNs for a specified period of time following the piercing of the skin. This allows the tip of the needle to be fully dissolved before the backing is peeled off. Furthermore, due to the elasticity of the skin, the MNs may be incompletely pierced or the patch may dislodge, which can result in inaccurate dosage[70]. Separable MNs address limitations in traditional DMNs, where a separation layer is designed to separate from the backing upon insertion. These MNs encapsulate the drug entirely within the needle tip, which remains in place after insertion, ensuring better drug deposition and improved precision[71,72]. This design helps minimize drug waste and reduce application time, while allowing the use of both fast-dissolving and slow-degrading materials for controlled release[73].

3.2.3. Bilayer MNs

To facilitate synchronous encapsulation of multiple drugs or to meet the need for drug release, the researchers designed bilayer MNs consisting of two distinct parts: a top layer and a bottom layer. In comparison to traditional MNs, a more functional platform for customized drug encapsulation was designed. According to the physicochemical properties of different drugs, such as charge, hydrophilicity, and hydrogen bond donor/acceptor content, the matrix material of each layer can be tailored to optimize the drug loading efficiency, stability, and release behavior. For example, fast and slow dissolving materials can be employed to fabricate the bottom and top layers, respectively. This dual-layer structure allows the co-delivery of fast-acting and long-acting drugs, optimizing drug release profiles for various diseases[74].

3.2.4. Core–shell MNs

Core–shell MNs also consist of two independent functional areas: an internal core and an external shell[75,76]. Similarly, matrix materials with disparate physicochemical properties can be employed to construct the core and shell structure, respectively. As a result, this system can facilitate the efficient loading of multiple drugs based on their respective interaction with the matrix or deliver drugs in a controlled manner[77,78]. For example, our previous study developed a core–shell MN system to co-deliver an anti-PD-1/L1 antibody and a small molecule drug, achieving effective drug delivery *via* electrostatic interactions and preventing premature drug crystallization[79].

3.2.5. Bionic MNs

Bionic MNs are inspired by natural structures to overcome challenges like poor mechanical strength and imprecise drug delivery. For instance, MNs mimicking octopus suction cups improve skin adhesion, while those inspired by mosquito mouthparts enhance penetration and reduce pain[80,81]. These bio-inspired designs improve MN performance by increasing rigidity, strength, and precision, opening new possibilities for drug delivery. Innovations like vibration-reduced penetration and capillary-assisted molding further refine MN performance[82,83].

4. Advantages of MNs for autoimmune disease treatment

4.1. Advantages of MNs for drug delivery

Autoimmune diseases present a significant challenge to treatment due to the necessity of achieving an optimal balance between therapeutic efficacy and the minimization of adverse reactions. The objective of an effective treatment is to deliver higher drug concentrations to target lesions while simultaneously reducing systemic side effects and ensuring patient compliance during prolonged therapies.

MNs represent a promising solution, forming numerous microporous channels in the skin upon penetration, thereby enabling efficient transdermal drug delivery[84]. Compared with oral drug delivery, MN technology circumvents the first-pass metabolism in the liver, thereby markedly enhancing bioavailability and reducing gastrointestinal adverse effects[85-87]. In comparison with conventional methods of macromolecule drug delivery, such as intravenous or subcutaneous injection, MN drug

delivery has the advantage of being minimally invasive. This approach has the potential to reduce or eliminate pain, enhance patient compliance, and restore skin barrier function upon dissolution or removal of the MN[88]. Furthermore, MNs demonstrate superior performance compared to traditional transdermal formulations, exhibiting a notable enhancement in transdermal drug delivery efficiency. In certain cases, their bioavailability is comparable to that of subcutaneous injections. These distinctive properties render MNs an especially advantageous method of drug delivery for the treatment of autoimmune diseases[89].

4.2. MNs-mediated transdermal immunomodulation

The skin is a complex immune organ, comprising a multitude of immune cells, including keratinocytes, Langerhans cells, dermal dendritic cells, and T cells. These cells, in conjunction with the skin's associated lymphatic tissues, form a sophisticated network capable of initiating and modulating immune responses. The presence of lymphatic tissues within the skin enables the migration of primitive immune cells to draining lymph nodes, thereby establishing a robust link between the skin and the systemic immune system[90,91].

Immune tolerance is a state of specific unresponsiveness of the immune system to a specific antigen, a process that involves the synergistic action of innate and adaptive immune cells[92]. The breakdown of autoimmune tolerance may lead to the occurrence of autoimmune diseases. Therefore, inducing immune tolerance to restore immune homeostasis is a promising therapeutic strategy. Several mechanisms are involved in the induction of tolerance, including anergy of autoreactive lymphocytes, functional defect of T cells, or development of inducible regulatory T cells (Tregs)[93]. Anergy is a state in which autoreactive T cells, due to an absence of costimulatory signals, become unresponsive to stimulation. This condition can arise under various conditions, such as when APCs are immature and lack B7 molecules, or when CTLA-4 engages with B7, thereby preventing CD28-mediated activation[94]. T cell deletion is defined as an activation-induced cell death process that is mediated by the activation of Fas by FasL. The formation of a death-inducing signaling complex subsequently occurs, activating apoptotic caspases. Tregs further reinforce immune tolerance by modulating APC maturation, exerting cytotoxic effects, secreting anti-inflammatory cytokines, and disrupting metabolic processes[95]. These mechanisms work together to prevent autoreactive lymphocytes from mounting a deleterious immune response to self-antigens. Delivery of self-antigens to the skin has been shown to be a promising approach to induce immune tolerance for treating autoimmune disease. However, successful transdermal delivery of antigens as macromolecules is particularly challenging due to the physical barrier properties of the skin[96-98]. Based on the advantages of MNs in overcoming the stratum corneum barrier, they can effectively deliver antigens into the skin and exhibit longer skin retention times[98-102]. Thus, MNs are an effective tool for mediating transdermal immune tolerance.

In addition to the induction of antigen-specific tolerance, antigen-independent immunomodulation *via* MNs provides a complementary strategy for the restoration of immune homeostasis. The skin's immune cells function as a pivotal hub for both local and systemic immune regulation[103]. In autoimmune disorders, such as psoriasis, a dysfunction of these cells disrupts the balance of inflammatory mediators, thereby exacerbating tissue damage[104]. MNs have been demonstrated to circumvent the stratum corneum barrier, thereby facilitating the direct delivery of immunomodulators (*e.g.*, small-molecule drugs or biologics) to cutaneous immune targets. This approach has the potential to achieve both local and systemic immunomodulation.

Importantly, MNs can integrate antigen-dependent tolerance induction and antigen-independent immunomodulation strategies. For instance, the co-delivery of self-antigens with tolerogenic adjuvants through MNs has the potential to simultaneously induce antigen-specific Tregs and broadly suppress pathogenic Th17/Th1 responses, offering a multifunctional platform for precision targeting with holistic immune reprogramming[51,105].

5. MNs for autoimmune disease treatment

The progressive increase in the prevalence of autoimmune diseases represents a significant challenge to public health. The treatment of this category of disease has become a significant area of interest within the medical community[3,4]. The administration of drugs orally and intravenously is likely to result in limited drug accumulation at the target site and poor patient compliance. Consequently, MNs represent an efficacious technology for patients with autoimmune diseases who require long-term drug control since this approach is more acceptable to patients and more conducive to the accumulation of the drug at the corresponding target sites. The following section provides a detailed overview of the application of MNs in the treatment of different disease types.

5.1. MNs for psoriasis and its comorbidities treatment

Psoriasis is an autoimmune dermatological condition that is influenced by both heredity and a variety of environmental factors. It often manifests as limited or widely distributed scaly erythematous plaques[106-108]. Epidemiological studies indicate that the prevalence of psoriasis is approximately 2%−3%, with an estimated 125 million individuals affected worldwide, representing an increasing trend[109]. Although the mortality rate associated with psoriasis is relatively low, the disease is challenging to cure and prone to recurrent episodes. This has led to the classification of psoriasis as one of the ten most persistent diseases of the 21st century[110]. The in-depth research on the pathogenesis of psoriasis has led to the emergence of various treatments, including topical medications (*e.g.*, calcipotriol, tacrolimus, etc.), oral small-molecule medications (*e.g.*, cyclosporine A, apremilast, etc.), and targeted biologics (*e.g.*, infliximab, ustekinumab, etc.). As the modes of administration for the clinical management of psoriasis have become increasingly prevalent, the drawbacks associated with the existing methods, such as skin irritation, gastrointestinal problems, and immunosuppressive effects, have come to the fore[111,112]. Additionally, difficulties in localized treatments penetrating thickened lesions reduce the efficacy of treatment. Therefore, there is a need for safer and more efficient delivery methods to directly target areas of inflammation[113].

5.1.1. MNs for psoriasis treatment

Liang et al.[44] prepared solid MNs using polylactic acid polymer with the hot-press method and then used them to pre-treat psoriatic skin before applying the therapeutic drug calcipotriol. The results demonstrated that the MN pretreatment group exhibited a superior therapeutic effect compared to the directly drug-applied group. This was evidenced by a reduction in epidermal thickening, spleen index, inflammatory cell infiltration, and the expression of inflammatory cytokines. In another study, Jeong

et al.[49] prepared DMNs containing cyclosporin A for psoriasis treatment using a low-temperature molding process and compared their pharmacokinetics with that of oral cyclosporin A. The results showed that there was no significant difference in C_{max} and AUC. However, cyclosporin A administered with DMNs maintained a blood concentration of 5 ng/mL or more for up to 72 h, compared to 24 h for cyclosporin A administered orally.

Psoriasis is a dermatological disorder with inflammatory characteristics that exhibits a typical acidic microenvironment[114]. Li et al.[115] constructed a pH-responsive *in situ* catalytic nanoreactor encapsulating an immunomodulator adenosine precursor, which was subsequently incorporated into a DMN patch to facilitate targeted drug delivery into cutaneous psoriasis lesions (Fig. 2A–D). Upon penetration into the skin, the nanoreactors were released and underwent a gradual structural collapse when exposed to the acidic microenvironment. Concurrently, the acidic pH could trigger an *in situ* catalytic reaction to continuously produce adenosine for immunomodulation. This system overcame the metabolic instability of adenosine, thereby exhibiting a favorable anti-psoriasis effect.

To further advance the targeted drug delivery for the topical treatment of epidermal diseases. Jing et al.[116] developed epidermal cell membrane-coated pH-sensitive micelles for therapeutic active targeting of psoriasis (Fig. 2E and F). The nanocarriers were internalized by the epidermal cells, resulting in the swelling of histidine fragments under acidic conditions and subsequent triggering of drug release. The results demonstrated that the micelles predominantly accumulated in the active epidermis when administered with DMNs, thereby enhancing the therapeutic efficacy of shikonin against imiquimod-induced psoriasis. However, the therapeutic effects of nanocarriers administered *via* intravenous injection were not significantly improved, which may be attributed to the extensive distribution of drugs throughout the body.

In recent years, treatment methods for autoimmune diseases have evolved, particularly with the use of targeted Treg cell delivery and nucleic acid-based therapies. Zhang et al.[117] developed a perforated MN with a hydrophobic outer shell and an inner chamber containing Treg cell gel to maintain a favorable environment for the cells. This system has been shown to facilitate the efficient delivery of Treg cells into the lesion sites, with the cells

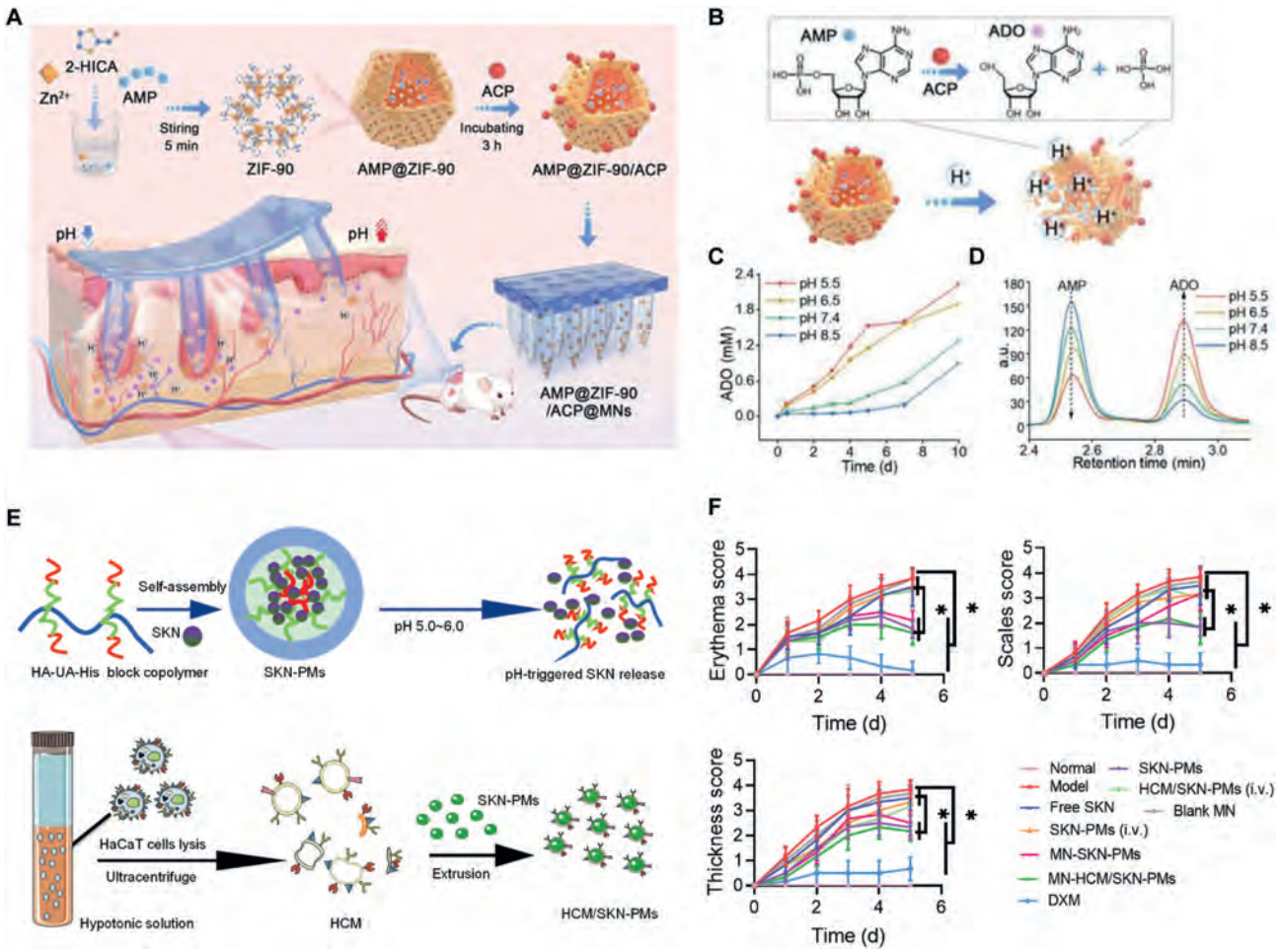

Figure 2 MNs for psoriasis treatment. (A) Schematic diagram of pH-responsive *in situ* catalytic nanoreactor integrated DMN patch for the treatment of psoriasis. (B) Schematic diagram of a reaction catalyzed by a nanoreactor to generate adenosine in an acidic medium. Adenosine production (C) curves and (D) corresponding chromatograms at different pH media. Reprinted with permission from Ref. 114. Copyright © 2024 Ivyspring International Publisher. (E) Schematic diagram of epidermal cell membrane-coated pH-sensitive micelles for targeted therapy in psoriasis. (F) Psoriasis area and severity index scores of psoriatic skin lesions treated in different groups. Reprinted with permission from Ref. 115. Copyright © 2021 Elsevier.

released through the pores in the shell. In a psoriasis mouse model, the application of Treg-loaded MNs resulted in increased Foxp3$^+$ Treg populations, reduced inflammation, and alleviated psoriasis symptoms. In another study, Wu et al.[118] designed an MN containing *IL-17A* siRNA, whose nanostructure was rationally designed to form a framework of nucleic acid. The results showed that the siRNA-loaded MNs could effectively regulate the reactive oxygen species level in psoriasis tissue, and the psoriasis model mice treated with siRNA-loaded MNs exhibited more substantial inhibition of immune cell activation compared to the treatment using siRNA alone.

5.1.2. *MNs for psoriasis arthritis (PsA) treatment*

In its initial stages, psoriasis is typically manifested by dermatological symptoms. However, as the disease progresses, some patients may develop joint involvement, particularly in the small joints of the hands and feet, and potentially in larger joints and the spine[109]. The affected joints may present with swelling, pain, morning stiffness, and limited movement. In severe cases, joint deformity, known as PsA, may occur[119]. In patients with psoriasis, approximately 13%−25% are associated with PsA[120]. The effective treatment for PsA necessitated concomitant drugs targeting various lesions simultaneously, especially those alleviating cutaneous psoriasis and arthritic symptoms. First-line therapies include NSAIDs, such as ibuprofen and naproxen, and disease-modifying antirheumatic drugs (DMARDs), including methotrexate. In cases of severe disease, the use of targeted DMARDs, including TNF inhibitors (*e.g.*, etanercept, adalimumab), IL-12/23 inhibitors (*e.g.*, ustekinumab), and IL-17 inhibitors (*e.g.*, secukinumab), has been demonstrated to result in superior disease control. Nevertheless, the simultaneous delivery of multiple drugs to different action sites in PsA treatment remains a significant challenge.

To address this issue, Yu et al.[58] developed a layered MNs system for PsA treatment that requires multiple drug combinations and targets multiple sites (Fig. 3). The layered MNs system was composed of three distinct layers: a pedestal, an inter-layer, and a tip-layer. The immunosuppressant tacrolimus and the anti-inflammatory diclofenac were encapsulated into the interlayer and tip layer, respectively. This design resulted in the specific delivery of tacrolimus and diclofenac into the skin and joint cavities, thereby providing simultaneous relief from psoriatic skin and arthritic lesions in PsA. Following penetration of the MNs, the inter-layer retained tacrolimus within the skin at a depth of approximately 100 μm, while the tip-layer delivered diclofenac up to a depth of approximately 300 μm into the articular cavity. The *in vivo* experiments demonstrated that the layered MNs system not only efficiently decreased the Psoriasis Area and Severity Index scores of imiquimod-induced psoriatic epidermal hyperplasia but also alleviated carrageenan/kaolin-induced arthritis to a greater extent than diclofenac injection. This study provides a new approach for the treatment of PsA.

5.1.3. *MNs for psoriasis comorbidities treatment*

Patients with psoriasis frequently present with comorbidities, including but not limited to cardiovascular disease, metabolic disease, liver and kidney disease, and psychological disorders[121]. Psoriasis and diabetes are both common comorbidities, with a reciprocal relationship between inflammation and insulin resistance that contributes to disease progression. Gao et al.[122] designed an MNs system comprising a short-range missile component and a long-range missile component. The short-range missile, comprising curcumin nanoparticles retained within the psoriatic skin lesion for more than 24 h, was observed to exert an anti-psoriatic effect. In contrast, the long-range missile, containing metformin, was demonstrated to traverse transdermal barriers and enter the systemic circulation, thereby inducing a hypoglycemic effect. Concurrently, the short- and long-range missiles operated in conjunction to impede the NF-κB signaling pathway and disrupt the crosstalk between inflammation and insulin resistance, thereby achieving enhanced anti-inflammatory and anti-hyperglycemic effects.

5.2. *MNs for RA treatment*

RA is a disease that is characterized by joint swelling, stiffness, and synovial joint inflammation, which can result in cartilage and

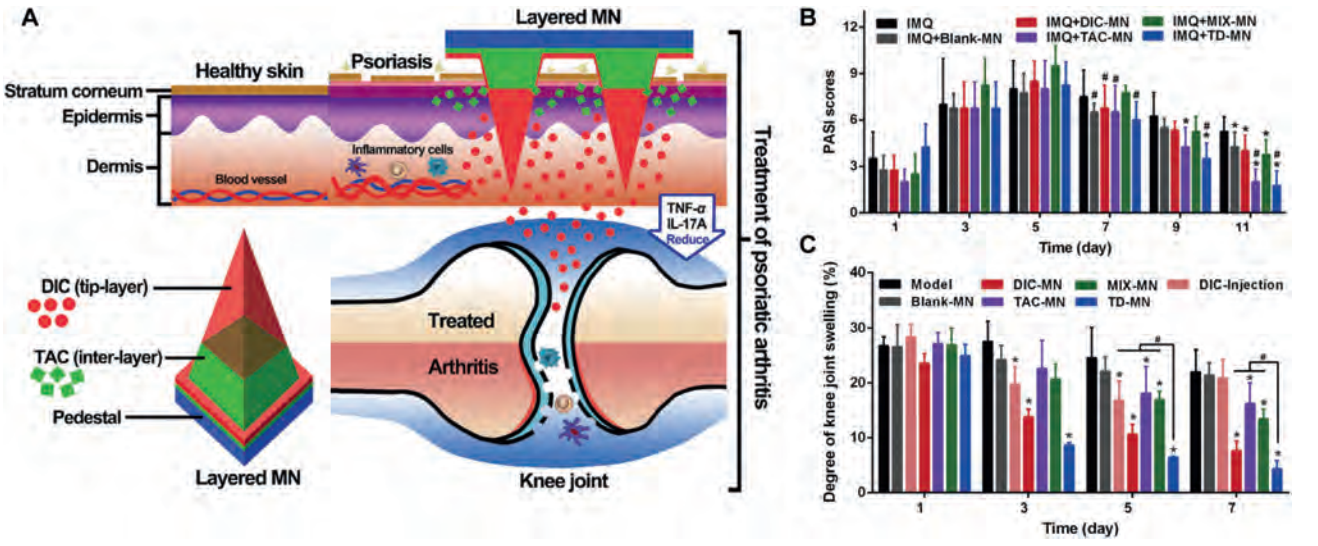

Figure 3 MNs for PsA treatment. (A) Schematic diagram of a layered MN system for PsA treatment. (B) Psoriasis area and severity index scores of psoriatic skin lesions treated in different groups. (C) Degree of knee joint swelling after treatment in different groups. Reprinted with permission from Ref. 57. Copyright © 2021 Elsevier.

bone destruction[123]. RA has a prevalence of 0.8% in the general population, with a range of 0.3% to 2.1%. RA is approximately three times more prevalent in women than in men, and the incidence of the disease increases with age, with a peak prevalence in the thirties to fifties[5,124], as a result of the overactivation of the immune system, an initial trigger of synovial inflammation occurs, which subsequently leads to synovial hyperplasia and the production of high levels of pro-inflammatory cytokines, including TNF-α, IL-1, and IL-6. This, in turn, gives rise to joint inflammation, synovial thickening, and loss of cartilage and bone, thereby establishing a vicious cycle of joint inflammation[125,126]. Despite the efficacy of traditional DMARDs, such as methotrexate and leflunomide, and targeted DMARDs, including TNF-α inhibitors and IL-6 receptor antagonists, there are still limitations to their use.

To address the issue of low bioavailability of orally administered drugs, Zhao et al.[127] developed DMNs containing methotrexate, a first-line therapeutic drug currently utilized in the clinical management of RA. The DMNs demonstrated robust mechanical strength, capable of penetrating the skin, and were equipped with a stable drug payload, exhibiting a rapid intracortical dissolution rate. The *in vitro* drug release results showed that approximately 89.80% and 49.92% of methotrexate was released into the receptor compartment in the DMNs group and cream group, respectively. *In vivo* pharmacodynamic results indicated that transdermal administration of methotrexate by DMNs provided superior therapeutic efficacy at the same dosage as compared to cream or conventional oral administration.

However, for RA patients with more severe disease, it is clear that traditional DMARDs alone cannot control the disease. An et al.[57] designed separable MNs that were loaded with tocilizumab, an inhibitor of the IL-6 receptor, and the aptamer Apt1-67. The MNs were constructed with slow-soluble methacrylate grafted hyaluronic acid and fast-soluble polyvinyl alcohol/polyvinyl pyrrolidone, which were selected as the tip and body materials, respectively. This design enabled the sustained release of tocilizumab and the fast release of Apt1-67. *In vivo* studies demonstrated that the prepared two-drug-loaded MNs exhibited superior anti-RA activity. It is particularly noteworthy to propose that, in comparison with the subcutaneous injection group, the joint surfaces of mice treated with the MNs group were smoother, the boundaries of trephine bones were more clearly defined, and the inflammatory erosion of the joints was significantly reduced.

Given that the vicious cycle of inflammation within the joints is a significant contributing factor to the progressive deterioration of RA, the induction of immune tolerance represents a promising strategy for the treatment of RA. Zhao et al.[51] fabricated MNs loaded with CII peptide autoantigen and rapamycin and investigated their capacity to induce immune tolerance in RA (Fig. 4). The results demonstrated that this system significantly elevated the proportion of Langerhans cells in the skin. Additionally, it significantly enhanced the expression level of C−C chemokine receptor type 7 in dendritic cells by 2.2-fold, whereas subcutaneous injections did not elicit a comparable effect, suggesting that the system induced tolerogenic dendritic cells at the administration skin site. These tolerogenic dendritic cells subsequently migrated to the lymph nodes, where they activated systemic Treg cell differentiation, ultimately effectively eliminating RA symptoms and inflammatory infiltrations.

5.3. *MNs for AD treatment*

AD is a chronic, recurrent, inflammatory skin disease that is clinically characterized by eczematous lesions and intense pruritus[128]. Over the past 30 years, the prevalence of AD has increased, affecting 15%−20% of children and 10% of adults worldwide. As indicated by the Global Burden of Disease study, AD ranks as the 15th most prevalent non-fatal disease in terms of

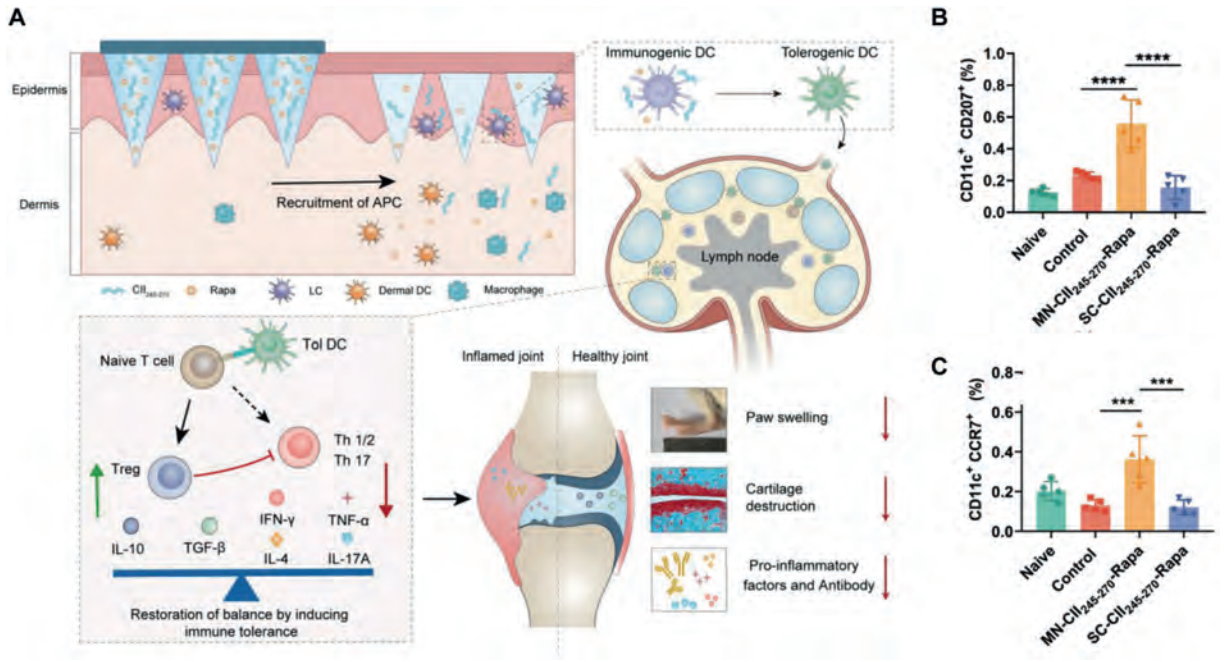

Figure 4 MNs for RA treatment. (A) Schematic diagram of DMNs loaded with autoantigen peptide and rapamycin used to induce immune tolerance in RA. Percentages of (B) $CD11c^+$ $CD207^+$ cells and (C) $CD11c^+$ $CCR7^+$ cells in skin were determined using flow cytometry. Reprinted with permission from Ref. 50. Copyright © 2024 Wiley.

Disability-Adjusted Life Years[129]. The primary clinical manifestation of AD is severe, chronic itching, which often disrupts sleep, reduces productivity at work or school, and negatively impacts patients' emotional and social well-being[130-132]. Although the pathogenesis of AD is not yet fully understood, evidence is increasingly pointing to the involvement of multiple immune pathways. The current therapeutic approach to AD is similar to that used for psoriasis, with a focus on topical glucocorticoids (*e.g.*, trimethoprim, hydrocortisone, etc.) and calcineurin inhibitors (*e.g.*, pimecrolimus, tacrolimus, etc.). However, due to the recurrent nature of AD, the skin thickens in chronic phases, which limits the efficacy of conventional drug delivery methods[133-135].

To address this limitation, Jang et al.[50] designed a DMNs system loaded with high doses of poorly soluble drug triamcinolone acetonide (TA). An optimized TA suspension with improved particle dispersion was prepared through ultrasonication and subsequently encapsulated into the DMNs patch. In comparison to injections and creams, no precipitation was observed after 24 h following the dissolution of TA-loaded DMNs. Moreover, the administered dose of the drug was sufficient to alleviate skin inflammation in the AD-mimicking *in vivo* model, comparable to the TA cream formulation applied twice every other day and the TA injection.

Despite the efficacy of immunosuppressive drugs, their long-term use can lead to the emergence of adverse effects. Accordingly, the principal objective in managing AD is to reestablish immune equilibrium to decelerate disease progression. Allergen-specific immunotherapy (SIT) has emerged as a promising approach, involving repeated administration of allergens to reduce hypersensitivity reactions over time[136]. SIT has demonstrated efficacy, particularly in patients who are sensitized to house dust mites, the most prevalent allergen in AD[137-141]. Nevertheless, traditional subcutaneous immunotherapy (SCIT) presents certain challenges, including the necessity for frequent clinic visits and repeated injections, which may reduce patient compliance. Sublingual immunotherapy (SLIT) offers a less invasive alternative, but has demonstrated lower efficacy than SCIT[142,143].

To address these limitations, Kim et al.[144] developed MNs containing *Dermatophagoides farinae* extract (*DfE*) and evaluated their potential as a novel SIT method in mouse models (Fig. 5). The findings revealed that 10 μg of *DfE* in MNs was adequate to elicit immunological responses that were comparable to those observed in response to 100 μg of a subcutaneous injection. Notably, the clinical and histologic symptoms of AD skin lesions were remarkably improved. Additionally, it induced favorable alterations in antibody production and serum IgE levels, dampened the Th2 cellular response, and enhanced Treg cell infiltration in the skin. This novel approach has the potential to revolutionize the field of SIT for AD management.

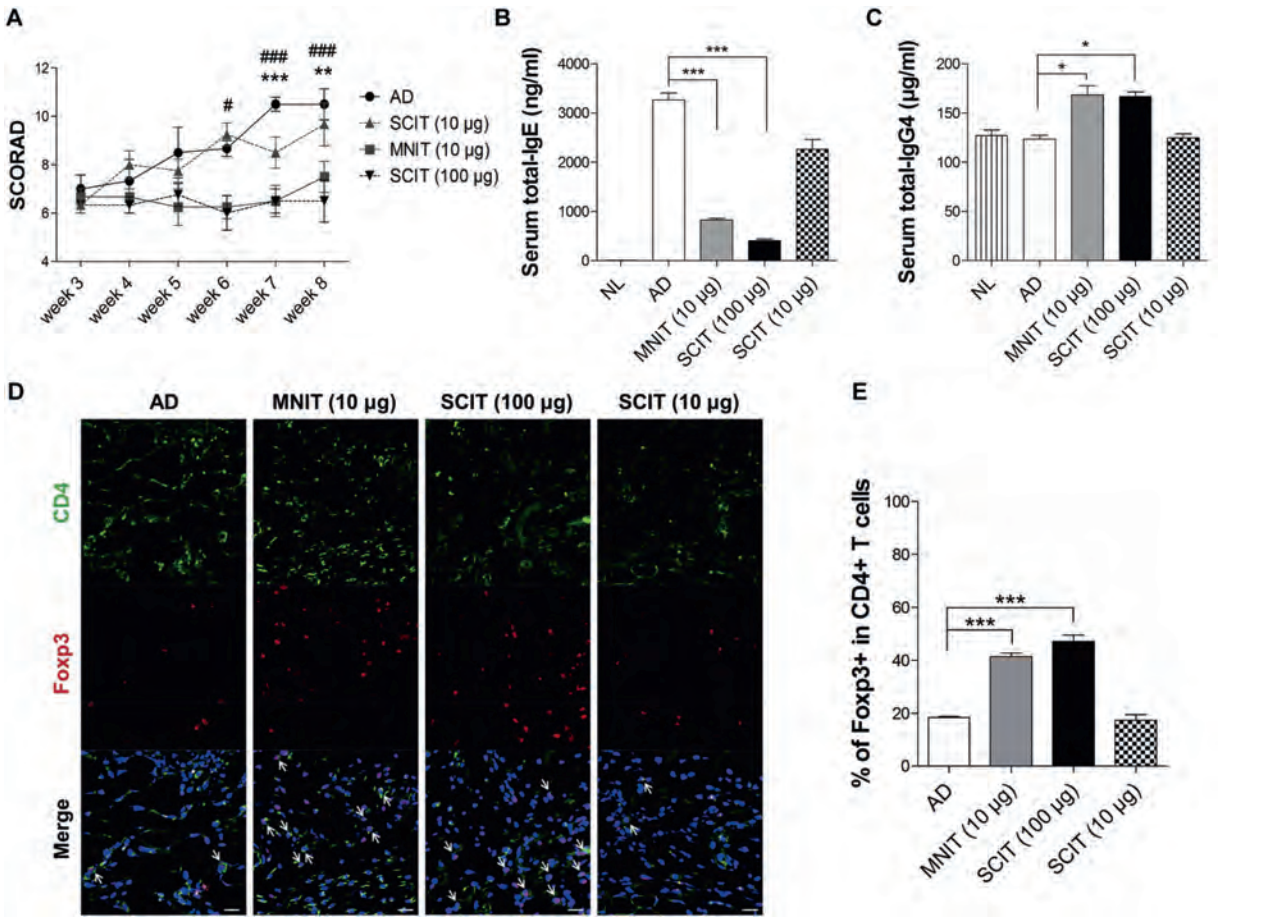

Figure 5 MNs for AD treatment. (A) Scoring of the atopic dermatitis index of skin lesions treated in different groups. Serum (B) total IgE and (C) IgG4 levels at Week 8 in mice treated in different groups. (D) Representative fluorescent image and (E) the corresponding quantifications of Treg cells ($Foxp3^+$ $CD4^+$) in mouse skin. Reprinted with permission from Ref. 143. Copyright © 2018 Elsevier.

5.4. MNs for T1D treatment

T1D is an autoimmune disease in which autoreactive T-cells target pancreatic β-cells, impairing insulin production. This leads to elevated blood glucose levels and diabetes mellitus symptoms when insulin secretion becomes insufficient or ceases entirely[145]. Although T1D can develop at any age, it primarily affects children and adolescents, accounting for approximately 90% of childhood diabetes cases. In recent years, T1D prevalence has increased globally by 2%−5% annually, raising significant concerns within the medical community and society[146].

Currently, clinical treatment for T1D relies on multiple daily insulin injections or continuous subcutaneous insulin infusion, but the pain induced by repeated injections tends to reduce patient compliance. To address this issue, MNs, an emerging drug delivery modality, have emerged as a potential alternative to improve patient compliance due to their lower pain and convenience. In 2009, Gupta et al.[47] developed hollow MNs loaded with insulin. They found that the optimal MN length for insulin delivery was 1 mm, resulting in significantly improved rate and duration of blood glucose decline compared to hypodermic injections. Additionally, subjects reported reduced pain with MNs administration, and all preferred MNs over hypodermic injection.

The prevailing insulin therapies are efficacious in managing symptoms; however, they necessitate frequent adjustments and fail to address the underlying autoimmune pathology. This results in suboptimal glycemic control and an elevated risk of complications in patients[147]. Consequently, researchers are exploring alternative treatment strategies to traditional insulin therapies. One promising approach is antigen-specific immunotherapy (ASI), which aims to induce a regulatory, rather than stimulatory, immune response in order to reduce or prevent autoimmune-mediated β-cell destruction, thus preserving endogenous insulin production. This strategy can be achieved by employing the abundant APCs in the skin to capture self-antigens and present them to T cells in a manner that attenuates their reactivity[147-150]. Arikat et al.[151] developed MNs coated with a large multi-epitope protein proinsulin, which facilitates direct delivery of proinsulin into the superficial layers of the skin (Fig. 6A). This localized delivery method is minimally invasive, reduces inflammation, and the results of *in vivo* experiments demonstrated that conventional injection of proinsulin did not induce an immune response. In contrast, proinsulin-coated MNs stimulated greater proliferation of adoptively transferred antigen-specific $CD8^+$ T cells in the skin draining lymph nodes compared to a conventional intradermal injection. The inclusion of multiple epitopes in MNs enhances the applicability of ASI across a diverse range of patient groups, representing a significant advancement in T1D management.

Another area of interest is the potential use of parasites and their derivatives, particularly helminths, as immunomodulatory agents for T1D. It has been demonstrated that helminth infections, such as those caused by *Schistosoma haematobium* and *Schistosoma mansoni*, exhibit prophylactic effects against T1D and other autoimmune diseases by establishing an anti-inflammatory microenvironment[152-156] (Fig. 6B−D). Despite the potential benefits, the majority of research has utilized live helminths or crude extracts, which present a number of ethical and safety challenges in humans. Furthermore, purified derivatives lack the full immunomodulatory effects, limiting their practical application[157-159]. To address these issues, Huang et al.[55] developed a *Schistosoma japonicum egg* tip-loaded asymmetric microneedle patch (STAMP), which offers a controlled, localized antigen delivery method. The STAMP system comprises a fracture-prone basal layer, which enables the tips to become immobilized within the epidermal layer of the skin. Then, the isolated needle tips undergo a gradual biodegradation process, resulting in the controlled release of encapsulated worm eggs. This design provides localized, safe stimulation of the immune system, inhibiting the Th1 response associated with T1D pathology and promoting a Th2 response. In mouse models of T1D, STAMP alleviated pancreatic lesions and controlled blood glucose levels without the need for adjuvants, indicating that the *Schistosoma japonicum egg* is sufficient to induce an effective immune response. Furthermore, as the eggs degrade, their remnants are gradually expelled from the skin, thereby reducing the risk of antigenic residue accumulation. The STAMP-based approach represents an innovative application of parasite-derived products in the treatment of autoimmune disease, offering a viable and effective alternative to insulin for T1D management.

5.5. MNs for other autoimmune disease treatment

MNs have been demonstrated to be effective in the treatment of a number of autoimmune diseases beyond those previously discussed. Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system that results in demyelination and axonal loss. It is regarded as a T cell-mediated autoimmune disease, whereby autoreactive immune cells are responsible for the destruction of myelin[160]. Despite the absence of a cure for MS, significant advances have been achieved in recent years. Among these is the gradual emergence of ASI as a promising avenue of research, with investigators exploring its potential application in MS treatment[161]. Pires et al.[162] developed biodegradable MNs that deliver a therapeutic dose of the $PLP_{139-151}$ peptide fragment, a protein fragment relevant to immune regulation in MS. It was found that following the loading of $PLP_{139-151}$ into MNs, the activity of $PLP_{139-151}$ was stabilized, with a release rate of 40% observed within 4 days. This MN's design aims to induce immune tolerance in patients, representing a novel, minimally invasive approach to MS treatment.

Vitiligo is a dermatological condition characterized by the loss of pigmentation in the skin, resulting in the formation of white patches that can have a significant impact on the patients' appearance and quality of life[163-165]. Despite the availability of treatments such as glucocorticoids, immunosuppressants, and narrow-band ultraviolet phototherapy, these approaches often entail prolonged treatment periods and low rates of cure. Moreover, the underlying mechanisms of vitiligo remain poorly understood. Two prevailing theories postulate that it is related to melanocyte damage and excessive autoimmune activation at the lesion site[166,167]. Impairment of melanocytes results in a reduction in melanin production, while an accumulation of $CD8^+$ T cells at the affected sites releases inflammatory factors such as IFN-γ and TNF-α. These cytokines bind to receptors on keratinocytes, triggering the JAK pathway and prompting melanocytes to release CXCL10, a chemokine that recruits additional $CD8^+$ T cells. This positive feedback loop intensifies the immune response, exacerbating the depigmentation[163,166]. To interrupt this cycle, Liang et al.[53] developed a hydrogel MN system using methacryloylated dextran and a cyclodextrin−adamantane host−guest supramolecule, which was loaded with the vitiligo treatments tofacitinib and α-melanocyte-stimulating hormone. The MNs were designed to target the JAK pathway specifically, thereby disrupting the immune feedback loop in vitiligo and promoting massive deposition of melanin in the epidermis. This MNs-based approach

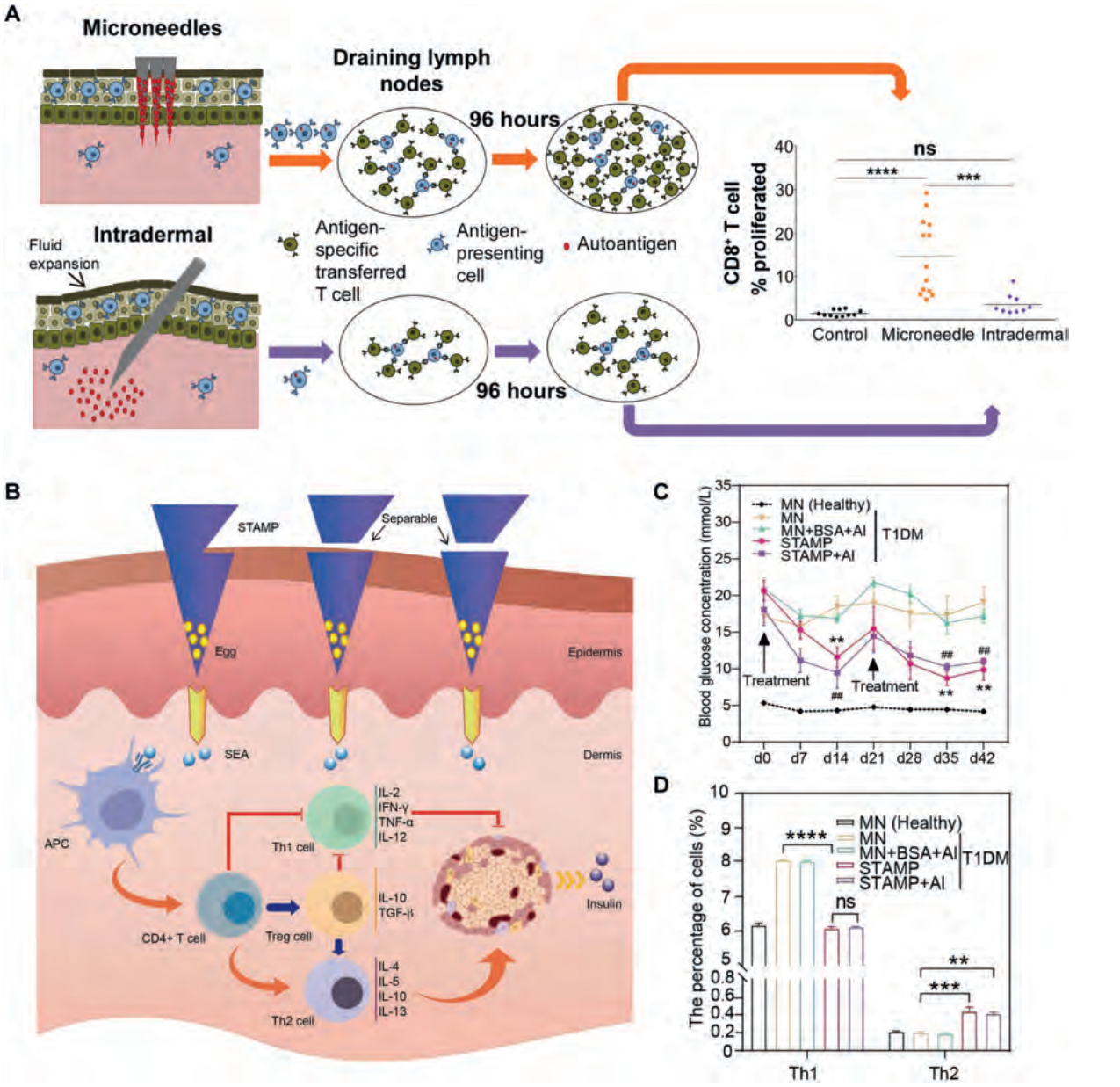

Figure 6 MNs for T1D treatment. (A) Schematic diagram of multiple epitope protein proinsulin-loaded MNs mediated ASI for the treatment of T1D. Reprinted with permission from Ref. 150. Copyright © 2020 Elsevier. (B) Schematic diagram of *Schistosoma japonicum egg* tip-loaded asymmetric MNs patch for the treatment of T1D. (C) Blood glucose concentration and time curve of different treatments. (D) Statistical analysis of the percentage of Th1 cells and Th2 cells among splenocytes. Reprinted with permission from Ref. 54. Copyright © 2022 BioMed Central.

offers a promising avenue for the treatment of vitiligo, with the potential to enhance efficacy and patient outcomes.

Although MN technology has demonstrated efficacy in the treatment of various autoimmune diseases, its potential in addressing more complex conditions, such as systemic lupus erythematosus (SLE), is particularly noteworthy. SLE is an autoimmune disease that affects multiple organs, with a higher prevalence in women aged 20–40[168]. The global prevalence of the disease is 43.7 per 100,000, with a higher incidence rate of 78.73 per 100,000 in women. Complications associated with SLE include renal failure, brain damage, and a mortality rate that is 2–3 times higher than that of the general population[169]. The current treatments, which include antimalarials, glucocorticoids, immunosuppressants, and monoclonal antibodies, have been associated with a number of significant adverse effects, including retinal damage, infections, and organ toxicity, particularly when used over an extended period of time[170,171]. In consideration of these factors, Fan et al.[56] developed a controllable and separable MNs by integrating photothermal responsive microspheres into hydrogel MNs. Upon exposure to near-infrared light, the microspheres underwent a transformation, whereby they converted light into heat, elevated the local temperature, and underwent a solid-to-liquid phase transition (Fig. 7A). This resulted in the convenient detachment of the needles and the base part by shear force. The results of the *in vivo* study demonstrated that the MNs system could ameliorate disease progression for SLE, resulting in a

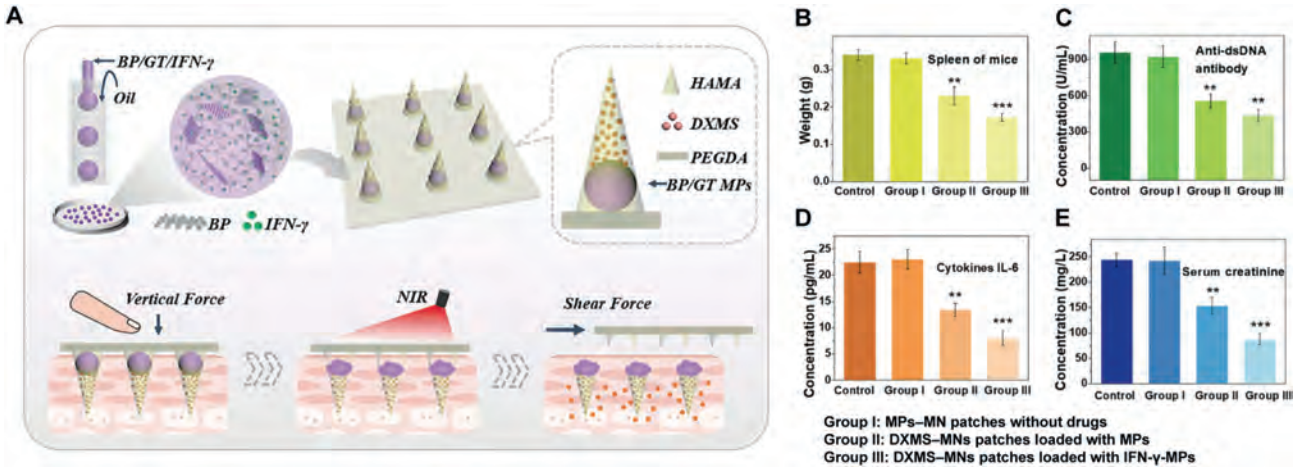

Figure 7 MNs for other autoimmune disease treatment. (A) Schematic diagram of photothermal responsive microspheres loaded with hydrogel MNs for the treatment of SLE. (B) Spleen weights of mice in each group at the time of sacrifice. (C−E) Anti-dsDNA antibody, IL-6, and creatinine level in the blood of mice. Reprinted with permission from Ref. 55. Copyright © 2021 Wiley.

significant improvement in the levels of several biomarkers, including spleen weight, anti-dsDNA antibody, serum creatinine, and IL-6 (Fig. 7B−E).

6. Available clinical trials based on MNs

The field of MN technology is likely to evolve as innovations increasingly shift focus from traditional MNs toward novel MNs, which can overcome several limitations associated with earlier designs. Nonetheless, it is crucial to recognize that commercial viability is a key driver in the expansion of MN applications[66]. Recently, MN systems have been made commercially available, while a number of studies are currently undergoing clinical trials[172]. Table 3, compiled from ClinicalTrials.gov, presents an overview of clinical trials of MNs up to 2024, with a particular focus on their application in the treatment of autoimmune diseases.

An analysis of the current clinical trial landscape reveals that four autoimmune diseases, namely psoriasis, T1D, RA, and vitiligo, have initiated MNs-related clinical trials in various phases of development. Notably, vitiligo has the highest number of ongoing clinical trials, which may be attributed to the potential of MN therapy to stimulate dermal collagen production, facilitate the migration of melanocytes, and enhance their function[173]. In contrast, autoimmune diseases such as SLE have not yet been clinically investigated based on MNs, likely due to their extensive range of effects, which may involve multiple organs and systems. The intricacy and heterogeneity of these diseases may impede the application of MNs, resulting in a paucity of clinical trials conducted on them. A survey of the types of MNs utilized in current clinical trials reveals a preponderance of solid and hollow MNs, primarily due to their technological maturity, ease of operation, and scope of application. DMNs have also been introduced into clinical trials for psoriasis treatment, potentially attributable to their excellent biocompatibility, substantial drug loading capacity, and robust therapeutic efficacy.

While promising, clinical trials for MNs in autoimmune disease treatment have faced significant challenges. Notably, the clinical trial NCT02955576 was discontinued in 2016 due to difficulties in achieving consistent results. Similarly, while NCT00837512 for T1D completed its phase II and III studies in

Table 3 Clinical trials based on MNs for the treatment of autoimmune diseases.

No.	Clinical trial identifier	Status	Condition	MNs type	Therapeutic agent
1.	NCT02955576	Discontinued	Psoriasis	DMNs	Calcipotriol−betamethasone dipropionate
2.	NCT02837094	Completed (Phase I)	T1D	Solid MNs	C19-A3 GNP peptide
3.	NCT00837512	Completed (Phases II, III)	T1D	Hollow MNs	Insulin
4.	NCT03607903	Completed (Phases I, II)	RA	Hollow MNs	Humira
5.	NCT05467839	Completed	Vitiligo	Solid MNs	Methotrexate 5-Flourouracil
6.	NCT05053022	Completed	Vitiligo	Solid MNs	Tacrolimus 5-Fluorouracil
7.	NCT05513924	Completed (Phases II, III)	Vitiligo	Solid MNs	Latanoprost 5-Fluorouracil
8.	NCT02660320	Completed	Vitiligo	Solid MNs	Epidermal cell
9.	NCT02962180	Continuing	Vitiligo	Solid MNs	Melanocytes
10.	NCT03668834	Continuing	Vitiligo	Solid MNs	Autologous non-cultured epidermal cell

T1D, type 1 diabetes; RA, rheumatoid.

2014, it has yet to see further market development. These examples underscore the need for more robust study designs and a better understanding of the clinical hurdles facing MN adoption in therapeutic settings.

7. Conclusions and outlook

In recent studies, MNs, an emerging drug delivery system, have demonstrated considerable potential for the treatment of autoimmune diseases. Due to their minimally invasive, efficient, and precise drug delivery characteristics, they can markedly enhance drug bioavailability and patient compliance. In the context of complex autoimmune diseases, MN technology can facilitate the effective delivery of both topical and systemic therapeutic drugs, thereby enhancing therapeutic efficacy and reducing the incidence of side effects.

However, as MN technology continues to evolve, several significant challenges must be addressed to realize its full potential in clinical settings. One of the foremost issues is the biocompatibility of MN materials. As MNs are designed for direct contact with the skin or tissues, ensuring that the materials used are both biocompatible and capable of maintaining their structural integrity over time is essential. While there have been promising developments in biodegradable materials for MNs, their long-term stability and their behavior under different environmental conditions need further study to ensure safe and effective use, particularly in patients with autoimmune conditions, who may have altered immune responses.

Another challenge lies in the controllability of drug release. While MNs provide an innovative way to deliver drugs, ensuring precise and consistent drug release over extended periods remains complex. Developing MNs that can offer controlled release profiles based on patient needs and the dynamics of autoimmune diseases is critical. This would require advances in the design and engineering of MNs to achieve both temporal and spatial control of drug release, which would significantly impact treatment efficacy and patient safety. The incorporation of sensors or smart systems to adjust drug delivery dynamically could be one potential solution, but will require substantial innovation.

The economic viability of large-scale production is another challenge that must be overcome. While MN technology offers great promise, the production of these devices at a cost-effective price point is essential for widespread clinical adoption. Current manufacturing techniques for MNs, such as microfabrication or 3D printing, can be expensive and may not yet be scalable for mass production. Moreover, the cost of the necessary materials and the complexity of producing MNs with precise characteristics may limit their accessibility to broader patient populations. Efforts to reduce production costs, standardize manufacturing processes, and streamline the supply chain will be crucial to make MN-based treatments more accessible and affordable.

Additionally, a critical area that warrants further exploration is the long-term impact of MNs when used repeatedly in chronic conditions such as autoimmune diseases. Since autoimmune diseases often require long-term therapeutic intervention, the cumulative effects of MN use on the skin and underlying tissues must be better understood. This includes assessing any potential adverse reactions or immune system responses that could be triggered by the repeated use of MNs. The risk of infection at the microneedle sites, particularly for patients with compromised immune systems, is another area that warrants careful consideration. Moreover, the potential integration of artificial intelligence (AI) could facilitate the personalized monitoring of patients' skin conditions and immune responses during prolonged MN treatment, enabling timely interventions and reducing risks associated with long-term MN use.

Overall, research on the utilization of MN technology for the treatment of autoimmune diseases has achieved notable progress. Nevertheless, several challenges remain, including the biocompatibility of MN materials, the controllability of drug release, the economic viability of large-scale production, and the safety for long-term use. These represent significant avenues for future research. As material science, nanotechnology, and biomedical engineering (such as gene editing) continue to advance, it is reasonable to expect that MN technology will be further optimized and improved. Through multidisciplinary collaboration among biomaterials, pharmacology, and engineering, MNs will facilitate the development of more intelligent and personalized therapeutic protocols, thereby improving the quality of medical services provided to patients. In addition, the comprehensive advancement of clinical trials and the accumulation of pronounced follow-up data will provide a robust scientific foundation and facilitate the extensive implementation of MNs in autoimmune diseases. In conclusion, MNs have a promising future in the treatment of autoimmune diseases and are poised to become a revolutionary advancement in medical therapy.

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Author contributions

Ying Chen: writing−original draft & editing, investigation, conceptualization. Yanping Fu: writing−original draft, investigation. Xinyu Wen: writing−original draft & editing. Minglong Chen: writing−review & editing. Linghui Dian: writing−review. Tingting Peng: investigation. Chuanbin Wu: investigation. Chao Lu: writing−review & editing, conceptualization. Guilan Quan: writing−review & editing, supervision, conceptualization.

Declaration of generative AI and AI-assisted technologies

During the preparation of this work the authors used ChatGPT in order to improve language and readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Conflicts of interest

The authors declare no conflicts of interest.

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