The Promise and Challenges of Cell Therapy for Psoriasis

Running title: Cell therapy for psoriasis

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What is already known about this topic?

- Immune-targeted therapies, such as biologics, though not curative, have revolutionised the treatment of psoriasis. An unmet therapeutic need in psoriasis, however, rests with a significant and growing population of patients with severe disease who are refractory to multiple lines of biologic and other systemic therapies. Thus, there is an imperative to seek therapies for severe, recalcitrant psoriasis which may lie outside traditional pharmaceutical approaches.
- Cell therapies, including mesenchymal stem or stromal cells, have immunomodulatory and anti-inflammatory properties, which make them an attractive treatment option for immune-mediated inflammatory diseases (IMIDs). Evidence for the efficacy of cell therapy in IMIDs, including multiple sclerosis, connective tissue diseases and inflammatory bowel disease, provides a basis to ascertain its utility for the management of psoriasis.

What does this study add?

- We summarise the evidence for cell therapies which have been used in psoriasis and other IMIDs, and critically evaluate their potential as effective treatment for complex psoriasis patients for whom biologics are no longer effective.
Abstract

The management of moderate-severe psoriasis has been transformed by the introduction of biologic therapies. These medicines, particularly those targeting interleukin (IL)-17 and IL-23p19, can offer clear or nearly clear skin for the majority of psoriasis patients, with good long-term drug survival. However, as currently used, none of these therapies is curative and disconcertingly there is a small but increasing number of patients with severe psoriasis who have failed all currently available therapeutic modalities. A similar scenario has occurred in other immune-mediated inflammatory diseases (IMIDs) where treatment options are limited in severely affected patients; in these cases, cell therapy, including haematopoietic stem cell transplantation (HSCT) and mesenchymal stromal cells (MSC), has been utilised. This review discusses the various forms of cell therapy currently available, their utility in the management of IMIDs and emerging evidence for efficacy in severe psoriasis unresponsive to biologic therapy. Balancing the risk-benefits of treatment versus the underlying disease is key; cell therapy carries significant risks, costs, regulation and other complexities, which have to be justified by outcomes. Although HSCT has anecdotally been reported to benefit severe psoriasis, sometimes with apparent cure, this has mainly been in the setting of other co-incidental ‘routine’ indications. In psoriasis, cell therapies, such as MSC and T regulatory cells, with a lower risk of complications are likely to be more appropriate. Well-designed, controlled trials coupled with mechanistic studies are warranted if advanced cell therapies are to be developed and delivered as a realistic option for severe psoriasis.
Introduction

Psoriasis is a common, immune-mediated inflammatory disease (IMID) with significant morbidity and detrimental impact on the affected individual’s quality of life. It is associated with important medical conditions, including psoriatic arthritis (PsA), metabolic syndrome, depression and cardiovascular disease; people with psoriasis have a higher mortality than the general population.1 The complex interplay between genetic, epigenetic, immune and environmental factors that underlie the disease pathogenesis is not fully understood.2 However, emergence of biologic therapies targeting key immune pathways in psoriasis pathogenesis, such as tumour necrosis factor (TNF)-α, interleukin (IL)-17 and IL-23, has revolutionised the treatment landscape of severe disease. These therapies can lead to significant improvement in disease burden and quality of life for people with psoriasis. Targeted therapies, however, are not curative; their limitations include lack of clinical response in certain individuals, diminishing efficacy over time and occasional significant adverse effects.3 Consequently, there is an increasing number of psoriasis patients who are refractory to multiple lines of biologic and non-biologic systemic therapies. This underscores an urgent and increasing need for more advanced, perhaps curative, treatment options including non-pharmaceutical approaches, for severe psoriasis.

Cell therapy comprises the use of somatic cells (stem, progenitor or primary cells) isolated from either the affected individual (autologous) or a donor (allogeneic) to treat the underlying disease. The various types of somatic cells either used, or have the potential to be used, as cell therapy in IMIDs include haematopoietic stem cells (HSCs), mesenchymal stem or stromal cells (MSCs), multilineage differentiating stress enduring (Muse) cells, fibroblasts, induced pluripotent stem cells (iPSCs), regulatory T (Tregs) cells and chimeric antigen receptor-T (CAR-T) cells. The last two decades have witnessed rapid advances in clinical trials and commercialisation of cell therapy, for which the three most common disease indications in Europe between 2004-2014 were cancer, cardiovascular disease and connective tissue diseases.4 Observations of serendipitous “transfer” and “cure” of IMIDs after HSC transplantation (HSCT) have raised interest in the potential of cell therapy as an option for these conditions with a number of controlled and open studies mainly in multiple sclerosis (MS), musculoskeletal disease and systemic sclerosis (SS). Similar observations of “transfer” and “cure” have been made for psoriasis over the years but there are few subsequent hypothesis-testing studies. Thus, there appears to be a rationale and an impetus to explore the use of cell therapy in psoriasis, specifically for patients who are refractory to currently available therapies.

This review discusses three key aspects: (i) types of cell therapy for IMIDs; (ii) accumulated data on the use of cell therapy in the management of psoriasis; and (iii) the future direction of cell therapy for psoriasis.

Types of cell therapy

The various types of cell therapy which have been, or have the potential to be, used in IMIDs are detailed in Figure 1.
Types of cell therapy used for IMIDs

Haematopoietic stem cell transplantation (HSCT)

This is used to treat a wide range of malignant and non-malignant conditions. It involves intravenous infusion of allogeneic or autologous HSCs following myeloablative and/or lymphoablative cytotoxic therapy. The preparative ‘conditioning’ regimen may include various combinations of high-dose chemotherapy, total body irradiation and ‘serotherapy’, such as polyclonal anti-thymocyte globulin, or therapeutic monoclonal antibodies, e.g. alemtuzumab or rituximab. Sources of HSCs include granulocyte colony stimulating factor-mobilised peripheral blood stem cells, bone marrow and umbilical cord blood. Allogeneic HSCT requires ongoing immunosuppression, usually ciclosporin or tacrolimus, to facilitate engraftment and prevent graft-versus-host disease (GVHD), until tolerisation occurs thereby enabling withdrawal. The overall aim of HSCT is to remove the underlying disease process and reconstitute the blood and immune systems, which in allogeneic HSCT may be accompanied by a graft-versus-tumour reaction.

Over the last quarter century, autologous HSCT has been increasingly used to treat individuals with IMIDs, including MS, SS and other rheumatological diseases and Crohn disease where, despite modern treatments some patients have ongoing poor disease control and potentially shortened life-expectancy. In these “difficult-to-treat” patients, HSCT has been explored as an intensive means of disease control, delivered as a ‘one-off’ treatment with long-term effectiveness. In some IMIDs, such as severe relapsing-remitting MS and SS, randomised controlled trials (RCTs) support sustained benefits, whereas in other IMIDs, there appears to be re-setting of disease activity to controllable levels.

In highly active, resistant relapsing-remitting MS, there is a single phase III RCT of autologous HSCT against various standard-of-care disease-modifying therapies (DMT). Amongst 110 patients randomised on a 1:1 basis, only 3 patients had disease progression at one year as primary end-point versus 34 patients in the DMT group. There was also significant improvement of MS at one year and beyond without treatment related mortality (TRM).

In severe SS, there is one small phase I RCT and two phase 3 RCTs: ‘SCOT’ and ‘ASTIS’, all using different transplant regimens but with similar control arms. In the North American ‘SCOT’ trial, Kaplan Meir estimates at 72 months of event-free survival were 74% versus 47%, and overall survival of 86% versus 51%, with HSCT and control respectively. The TRM was 3% at 54 months and 6% at 72 months. These results confirmed similar findings from the earlier European ‘ASTIS’ trial, which also showed significant improvements in event-free and overall survival, with a TRM of 10%.

These phase 3 trial results in MS and SS support the potentially powerful and prolonged effect of autologous HSCT on disease activity in severely affected patients with IMIDs, but also highlight the importance of careful patient selection. Underlying vital organ compromise from the IMID itself, manifests in the contrasting TRM between different diseases and requires careful per patient justification of the
procedure.

Allogeneic HSCT has more rarely been applied to IMIDs because of the higher complication rate (including GVHD) but long-term responses and probably cures have been achieved across a variety of diseases.\textsuperscript{11-14} Although autologous and allogeneic HSCT have been anecdotally reported to benefit severe psoriasis, sometimes with apparent cure, this has mainly been in the setting of other co-incidental ‘routine’ indications (Table 1). Very rare patients treated specifically for severe PsA have been reported to the European Society for Blood and Marrow Transplantation Registry.\textsuperscript{14}

**Mesenchymal Stromal Cells (MSCs)**

These comprise a heterogeneous population of self-renewable, multipotent non-HSCs with immunomodulatory, angiogenic, anti-inflammatory and anti-apoptotic properties.\textsuperscript{15,16} These properties, combined with ease of isolation from human tissues and ability to evade allogeneic rejection (due to lack of expression of MHC class II and co-stimulatory molecules CD80 and CD86, and low levels of MHC class I),\textsuperscript{17,18} make MSCs an ideal cell therapy for various conditions including IMIDs, without the need for cytotoxic conditioning regimes.\textsuperscript{19}

MSCs are found in virtually all organs but are predominantly harvested from bone marrow (BM-MSCs), umbilical cord (UC-MSCs), placental tissues, Wharton’s Jelly, peripheral blood, dental pulp, skin and adipose tissue (ADSCs). Depending on the source of MSCs, their biological characteristics can vary, including differentiation capacity, paracrine potential and immunomodulatory properties. For instance, BM-MSCs and ADSCs express stemness markers Sox2 and Oct4 \textit{in vitro}, which enable them to maintain their differentiation capacity long-term,\textsuperscript{20} whereas ADSCs, when compared to BM-MSCs and UC-MSCs, exhibit a stronger inhibitory effect on peripheral blood B, T and NK cells \textit{in vitro};\textsuperscript{21} but all three types can promote Treg and Th1 polarisation, evidenced by the increased expression of Forkhead Box P3 (FOXP3) and T-bet mRNA within purified activated T cells, and a reduction in TNF-α and perforin production by activated NK cells.\textsuperscript{21}

In terms of immunomodulation, MSCs participate in both innate and adaptive immunity; their immune regulatory functions are exerted via interactions with immune cells through cell-to-cell contact and paracrine activity involving T cells, B cells, NK cells, macrophages, monocytes, dendritic cells and neutrophils (reviewed in Gao et al\textsuperscript{22} and Song et al\textsuperscript{23}). The MSC secretome, encapsulated in extracellular vesicles, includes several cytokines, growth factors and chemokines, including transforming growth factor-β1 (TGF-β1), TNF-α, prostaglandin-E2, IFN-γ, fibroblast and hepatocyte growth factors, indoleamine-pyrrole 2,3-dioxygenase, and nitric oxide, amongst others.\textsuperscript{24,25}

One of the translational challenges with MSCs is their scalability. In this regard, ADSCs are often preferred as they can be obtained in large quantities from liposuction\textsuperscript{26,27} with better proliferative capacity, higher yield, slower rate of senescence and better preservation of a normal diploid karyotype than BM-MSCs.\textsuperscript{28-31}
To date, safety and efficacy of MSCs have been demonstrated in early phase trials in IMIDs, including rheumatoid arthritis, systemic lupus erythematosus (SLE), lupus nephritis, SS, GVHD, MS, type I diabetes mellitus, autoimmune hepatitis and inflammatory bowel disease (IBD). Specifically, a meta-analysis of 477 patients with Crohn disease fistulae showed a significantly increased healing rate and a lower recurrence rate in those with severe disease receiving allogeneic ADSCs compared to dose-adjusted BM-MSCs, with an optimal cell dose of 2-4 x 10^7 cells/ml, indicating considerable potential of MSCs for treatment of IBD. A recent phase II RCT of autologous MSCs in 48 patients with MS demonstrated disease remission, without safety issues, in 58.6% compared to 9.7% in a sham-treated group. However, most of the MSC-based trials for IMIDs are still in early phase, I or II, clinical trials with some promising results and no toxicity to date but larger controlled trials are needed to confirm their efficacy and long-term safety. However, several MSC products have been approved including Prochymal (Osiris Therapeutics) for acute GVHD in Canada and New Zealand. One of the theoretical pitfalls of MSCs is risk of carcinogenesis. Despite emerging knowledge and experience with clinical application of MSCs, the cell dose and frequency of administration vary between trials and the optimal dosing regimen has yet to be determined.

**Regulatory T cells (Tregs)**

Tregs regulate or suppress other immunocytes by controlling response to self and antigens, thus helping to prevent autoimmunity and limit chronic inflammation. They exert these functions through: inhibitory cytokines, e.g., IL-10; cytolyis (via granzyme A/B and perforin); metabolic disruption and modulation of dendritic cell maturation or function; and lymphocyte-activation gene 3 binding to MHC class II molecules. Rapid progress in the clinical translation of adoptive cell therapy of Tregs is underpinned by various preclinical models of autoimmune diseases demonstrating the therapeutic potential of a unique FOXP3+ immunosuppressive subset of Tregs. To date, there are more than 50 active and completed clinical trials testing the safety and efficacy of Tregs for IMIDs including pemphigus vulgaris, SLE, IBD, autoimmune hepatitis and asthma. Published results indicate excellent safety profiles and some efficacy in patients treated with as many as 2.5 billion Tregs. Although psoriasis is believed to represent an imbalance between Th17 cells and Tregs, there are no studies to ascertain whether Treg-based therapy can restore this. However, there are challenges with the use of Treg therapy for IMIDs currently, including: the variability in expansion of Tregs ex vivo; the relative paucity of clinical grade reagents required for manufacture of Tregs for therapy; and the observation that tissue antigen-specific Tregs, although more potent than polyclonal Tregs, are expressed in very low numbers and are unstable. It may be that the opportunities offered by synthetic biology, e.g. for CAR-T therapy could be harnessed for Treg therapy. Further investigation of the most suitable Treg subset to use for a particular disease and controlled trials with larger sample size and a standardised dosing regimen are required to obtain robust evidence of the clinical
benefit of correcting breaks in immune tolerance in IMIDs. For further review of this topic please see Roth Walter et al.

**Types of cell therapy with potential for use in IMIDs**

There are a number of other forms of cell therapy, although not being tested in IMID, which offer potential for the treatment of psoriasis. These include fibroblasts, Muse cells, iPSCs and CAR-T cells.

**Fibroblasts**

Fibroblasts, exhibiting similar characteristics to MSCs with immunomodulatory and regenerative properties through paracrine effects, play a vital role in wound healing through deposition of extracellular matrix and formation of scar tissue. Thus, fibroblasts can be considered as an alternative to MSCs as an immunomodulatory cell therapy. Both allogeneic and autologous fibroblasts have been used for treatment of chronic wounds including venous leg ulcers and recessive dystrophic epidermolysis bullosa with notable anti-inflammatory effect. The main concern with fibroblast cell therapy is the risk of fibrosis and hypertrophic scars. However, fibroblasts from the papillary dermis have a particular therapeutic relevance as they are involved in wound healing with anti-inflammatory effects without fibrosis. Although fibroblasts have not been tested in humans with IMIDs, their therapeutic potential has been highlighted through a number of pre-clinical studies using mouse models of IMIDs including type I diabetes, autoimmune arthritis, alopecia areata and MS.

**Multilineage differentiating stress enduring (Muse) cells**

These are pluripotent stem cells, occurring naturally in tissues of mesenchymal origin, with regenerative, anti-inflammatory, anti-apoptotic, anti-fibrotic and immunomodulatory properties. They comprise 1-2% of BM-MSCs, 5% of dermal fibroblasts and a small population in adipose tissue. Upon tissue injury, the alerting signal, sphingosine-1-phosphate, induces mobilisation of Muse cells to peripheral blood, and subsequently to the site of damage. This is followed by spontaneous differentiation into, and replenishment of, tissue-compatible cells for repair. Furthermore, Muse cells have immunomodulatory properties, exerted via TGF-β1 and regulation of macrophages towards the M2-phenotype, which make them an attractive therapeutic option for psoriasis. To date, Muse cells have been used clinically in the context of an early phase trial in myocardial infarction, demonstrating safety and efficacy.

**Inducible pluripotent stem cells (iPSCs)**

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One of the main limitations of somatic cell-based therapy is the limited lifespan of differentiated cells after clinical application inevitably leads to a decline in therapeutic efficacy over time. One revolutionary technology provides a solution to this issue – iPSCs can be produced from any somatic cell (e.g. fibroblasts) using reprogramming factors (Oct-4, Sox-2, Klf-4 and c-Myc) and can differentiate into specialised cell types with indefinite expansion, thus resembling embryonic stem cells. The fundamental paradigm in the use of iPSCs as cell therapy is that they are differentiated into the desired cell types, such as keratinocytes or Tregs, and then transplanted as tissue constructs or cell suspensions. Due to their unlimited self-renewal and differentiation potential, patient-specific iPSCs can be genetically corrected and differentiated into required somatic cell lineages and administered as an autograft. Viral-mediated gene supplementation or genome editing using tools such as CRISPR/Cas 9 can be applied to iPSCs in their undifferentiated state to correct the underlying molecular pathology. Although combined genome editing and iPSC technology is used as cell therapy in various disease models, clinical translation to humans is still limited to a narrow scope of indications. These comprise cardiovascular diseases, neurological disorders, GVHD and ophthalmic diseases such as age-related macular degeneration. Caution is needed as if undifferentiated, proliferating iPSCs are directly administered, they can form malignant teratomas due to their highly proliferative nature and broad differentiation potential. However, iPSCs hold huge promise as a regenerative, as well as an immunomodulatory, cell therapy for various skin diseases.

**Chimeric Antigen Receptor T (CAR-T) Cell Therapy**

CAR-T cells are derived by transferring genetically engineered CAR fusion proteins via lentiviral or retroviral vectors into autologous T cells. The CAR constructs usually comprise a single chain variable fragment antigen-recognition domain, a transmembrane CD-3 derived T-cell activation domain and an intracellular costimulatory domain e.g., CD28. The CAR-T cells recognise and kill, via cytokine release, antigen-bearing cells. Before infusion the recipient requires cytotoxic conditioning therapy. CAR-T cell therapy has been used in the management of haematological malignancies, especially B-cell lymphoma, acute lymphoblastic leukaemia and myeloma and is being considered in the management of melanoma resistant to check point inhibitors. However, it carries a significant risk of cytokine release syndrome and neurotoxicity in the short-term, and long-term immunodeficiency due to depletion of immune effectors.

With the ability to achieve profound depletion of B-cells or other immune targets, genetically engineered T cells have been considered in the context of IMIDs. In a recent preclinical study to treat pemphigus vulgaris in a mouse model of the disease, the results demonstrated selective reduction of serum anti-Desmoglein 3 (DSG3) antibody titres and improvement of blistering, hair loss and histological acantholysis. These preclinical data have led to an early-phase open-label clinical trial of DSG3-CAR-T therapy for patients with pemphigus vulgaris (NCT04422912).
Beneficial effects of cell therapy for psoriasis

Serendipity played an important role in determining our current consideration of cell therapy as a viable option for patients with refractory psoriasis. Eedy et al.\(^8\) reported on the “cure” of severe intractable psoriasis in a 35-year-old man who received an allogeneic HSCT for acute myelomonocytic leukaemia from his unaffected brother. Five years post-transplant, the recipient remained free of psoriasis. Although the mechanisms underlying the efficacy of allogeneic HSCT in psoriasis remain elusive, it is postulated that the immunosuppressive drugs and immunoablation needed for the procedure deplete autoreactive T cells, while the transplant reconstitutes the immune system with potentially non-reactive T cell populations from a donor without psoriasis. This postulation is supported by reports that long-term (up to 20 years) complete resolution of psoriasis has been reported in patients who received allogeneic, rather than autologous-HSCT.\(^8\)\(^2\)-\(^8\)\(^4\) Interestingly, the presence of GVHD seemed to be an indicator for long-term complete remission of psoriasis in 8 cases (Table 1), possibly due to a “graft-vs-autoimmunity” effect with ongoing inhibition or elimination of the host immuno-haematopoietic system.\(^8\)\(^4\),\(^9\) Indeed, many of the subjects listed in Table 1 received immunosuppressive conditioning regimens and concomitant therapies, including methotrexate and ciclosporin which are key confounders to the therapeutic benefit of HSCT.

The opposite, i.e. “transfer” of psoriasis was reported by Snowden and Heaton\(^10\)\(^7\) in a 40 year-old man with acute myeloid leukaemia who received a syngeneic HSCT from his phenotypically identical twin brother who had suffered from severe psoriasis and PsA for 20 years. Within 10 days of transplant, the recipient developed psoriasis which remained intractable. It persisted, despite a second transplant from the same donor, and the development of PsA. This case indicates that cellular aspects of psoriasis may be transmitted by adoptive transfer.

Conversely, autologous HSCT does not appear to be curative for psoriasis; relapses are frequent and may occur more than 10 years after transplantation. To date, of the 11 psoriasis patients treated with autologous HSCT, five relapsed within two years after the transplantation and one relapsed after 13 years.\(^10\)\(^1\) (Table 1). Notably, even though psoriasis relapses, it appears to run a more benign, less-clinically severe course compared to the pre-transplant state. Psoriasis remission after autologous HSCT is attributed to the myelo- and lymphoablative effect of conditioning regimens and altered and slow immunological reconstitution following transplant.\(^9\)\(^9\)

HSCT carries significant risks, costs and other complexities, which have to be justified by outcomes over alternative treatments. Risks are greater with allogeneic than autologous HSCT. In practice, individualised decisions are needed for each patient with respect to treatment options for their disease. Severe intractable psoriasis is frequently physically and psychologically disabling and standard and novel treatments are not without side-effects. However, the risk-benefit balance of allogeneic HSCT would rarely be justified, even with the apparent potential of cure (Table 1). Autologous HSCT has lower risks, which have been acceptable in some IMIDs (such as MS and SS), but the outcomes of ‘serendipitous’ treatment where
psoriasis has co-existed with a standard indication for HSCT are, at best, generally only supportive of temporary disease control.

Thus, MSC therapy may be a more attractive, more risk-averse cell therapy for psoriasis (Table 1). De Jesus\textsuperscript{105} reported on two patients with intractable psoriasis, one of whom had concomitant PsA, who received autologous MSCs in the form of 2-3 infusions of liposuction-derived ADSCs. A durable response with clinical benefit in the form of a 50-60\% reduction in psoriasis area severity index lasting between 157 and 292 days occurred although PsA was unresponsive. There were no concerning safety signals. Further, even though there was eventual relapse of psoriasis, one patient responded to etanercept, a biologic previously ineffective for him, after MSC therapy, thereby indicating that MSCs could be used as adjunctive therapy. Chen et al\textsuperscript{104} commented on two cases; the first, a 35-year-old man with diffuse large B-cell lymphoma (DLBCL) and concomitant psoriasis who was treated with autologous HSCT on two occasions; psoriasis improved briefly both times after the conditioning regimen before relapsing. The transplants were unsuccessful in controlling the DLBCL. The patient then received one infusion of UC-MSCs as adjunctive therapy. Both lymphoma and psoriasis remitted and remained so for at least 5 years. In a second case, a 26-year-old woman with intractable psoriasis for 18 years, three infusions of UC-MSCs were given specifically for treatment of psoriasis which produced clearance maintained for at least four years with two further infusions. UC-MSCs appear safe and appear to have, in these cases, remittive potential. Chen et al\textsuperscript{108} explored the mechanism of action of UC-MSCs for psoriasis using the imiquimod mouse model and infusion of human UC-MSCs; this MSC significantly reduced psoriasis severity. A key feature of the response was reduced production of type I interferon by plasmacytoid dendritic cells. Wang et al\textsuperscript{106} used five infusions of allogeneic gingival MSCs, which have immunomodulatory and anti-inflammatory properties, to treat a 19-year-old man with severe plaque psoriasis refractory to systemic therapy, Clearance of psoriasis occurred after the fifth infusion and the patient remained clear of psoriasis three years later.

These encouraging observations of the effectiveness and relative safety of MSCs in the treatment of psoriasis have led to seven current Phase 1-2 clinical trials: six in China and one in South Korea; three using ADSCs and four, UC-MSCs; all allogeneic. (Table 2).

Conclusions and future directions

As the number of people with psoriasis refractory to current biologic and non-biologic systemic therapies continues to rise, and the pipeline for new pharmacological approaches for the disease starts to shrink, it is important to turn to novel, holistic approaches and advanced therapeutics for a cure. Amidst all the interest in advanced therapeutics, it should be noted that cell therapy is not necessarily the only option available for the management, although perhaps not cure, of severe psoriasis. Stratified medicine offering a targeted proactive approach to the management of psoriasis, coupled with lifestyle modification and ideally early temporal intervention in the disease pathway, could also offer long-term remission.
Of the three therapeutic strategies for IMIDs, namely small molecules, biologics and advanced cell therapy only the latter offers the potential to fulfil the remit of a cure. However, in psoriasis there are important issues relating to risk-benefit balance, costs and complexity of treatment, including significant regulatory issues where ‘cells’ are considered along similar pathways to drugs. Cell therapy in the form of MSCs may offer an attractive and safer option in psoriasis. At the same time, other forms of cell therapy such as Tregs, fibroblasts, Muse cells and iPSCs should be considered as alternative developmental approaches. Any decision to use cell therapy in the management of psoriasis must be a joint one made with close collaboration between transplant haematologists and/or other experts in cell therapy and clinicians experienced in the management of severe psoriasis. Beyond individual, compassionate use of MSCs is a pressing need for controlled trials of their use in the management of refractory psoriasis, ideally coupled with mechanistic studies to define mode of action.

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Figure Legends
Figure 1. Types of cell therapy used, or have the potential to be used, in psoriasis.

Cell therapy can be either allogeneic (cells from donor to patient) or autologous (patient’s own cells). Different types of somatic cells can be obtained from various tissues, isolated and expanded in laboratories that meet Good Manufacturing Practice standards and systemically administered to the patient at time of treatment. Fibroblasts and Muse cells are isolated from dermis whereas MSC can easily be isolated from adipose tissue or bone marrow.

CAR-T; chimeric antigen receptor – T; iPSC, induced pluripotent stem cell; MSC, mesenchymal stromal or stem cell; Muse, multilineage differentiating stress enduring; Treg, regulatory T cell.
| Cell therapy | Auto/Allo | IV cell dose | Primary target disease | Severity of psoriasis at baseline | Duration of psoriasis (Years) | Previous treatment for psoriasis | PsA | Age (Years) | Sex | Sex | Adverse events | Efficacy | Reference |
|--------------|-----------|--------------|------------------------|-----------------------------------|-------------------------------|---------------------------------|-----|-------------|-----|-----|----------------|----------|-----------|
| HSCT         | Allo      | Twice 1y apart | AML                   | Sev                               | 20                            | PUVA MTX, Razoxane, Etretinate  | No  | 36          | M   | NS |                | CR 4y    | 82        |
| HSCT         | Allo      | N/A          | CML                   | Sev                               | 10                            | TCS                            | Yes | 35          | M   | NS |                | CR 1y    | 85        |
| HSCT         | Allo      | N/A          | CML                   | NS                                | NS                            | TCS                            | NS  | 35          | M   | NS |                | CR 4y    | 86        |
| HSCT         | Allo      | N/A          | AA                    | Sev                               | 25                            | TCS                            | No  | 36          | M   | cGVHD |                | CR 1.8y  | 87        |
| HSCT         | Allo      | N/A          | AML                   | BSA 36%                           | 1                             | TCS                            | No  | 40          | M   | cGVHD|                | CR 2y    | 88        |
| HSCT         | Allo      | N/A          | CML                   | BSA 19%                           | NS                            | TCS                            | Yes | 54          | M   | None|                | CR 1y    | 89        |
| HSCT         | Allo      | N/A          | CML                   | BSA 66%                           | 33                            | TCS                            | NS  | 55          | F   | aGVHD, cGVHD |      | CR 2.4y  | 90        |
| HSCT         | Allo      | N/A          | CML                   | BSA 73%                           | 8                             | PUVA MTX                        | Yes | 38          | M   | Mild GVHD |            | DR 1m    | 91        |
| HSCT   | Allo | N/A | NHL  | BSA 90% | TCS | Coal tar Retinoids | Yes | 50 | M | None | CR 17m | 92 |
|--------|------|-----|------|---------|-----|---------------------|-----|-----|---|-----|--------|----|
| HSCT   | Allo | N/A | CML  | NS      | 20  | TCS                 | NS  | 49 | M | cGVHD | CR 2.5y | 93 |
| HSCT   | Allo | N/A | AML  | Mod     | 21  | TCS, TVD, OCS, PUVA | NS  | 67 | M | GVHD  | DR 1.3m | 94 |
| HSCT   | Allo | N/A | AA   | Sev     | 16  | NS                  | Yes | 29 | M | None  | DR 1y   | 95 |
| HSCT   | Allo | N/A | DLBCL| BSA 10% | NS  | NS                  | No  | 56 | M | GVHD  | CR 2y   | 84 |
| HSCT   | Allo | N/A | AML  | Mod     | NS  | TCS, TVD            | Yes | 55 | F | aGVHD, cGVHD, Death | CR from D37 to 1y | 96 |
| HSCT   | Allo | N/A | AML  | Mild-Mod| NS  | TCS, TVD            | No  | 21 | M | aGVHD | CR from D64 to 5y 7m | 96 |
| HSCT   | Allo | N/A | DLBCL| Sev     | 15  | MTX                 | Yes | 59 | M | None  | CR from D60 to 5y 96 |
| HSCT   | Allo | N/A | AML  | Sev     | 20  | TCS, TVD            | Yes | 65 | M | aGVHD | CR from D41 to 7y 5m | 96 |
| HSCT   | Allo | N/A | FL/DLBC| Mod    | 27  | TCS, TVD            | No  | 30 | F | cGVHD | CR from D30 to 3y | 96 |
| HSCT   | Allo | N/A | CNL  | Mod     | NS  | TCS, TVD            | No  | 65 | M | aGVHD, cGVHD, Death | CR from D71 to 7m | 96 |
| HSCT   | Auto | 24x10⁶/kg | NHL  | Mild   | 15  | TCS                 | Yes | 35 | M | NS   | DR 22m | 97 |
| HSCT   | Auto | 2.85X10⁸ | AML  | NS     | NS  | TCS, Coal           | Yes | 53 | M | NS   | DR 14m | 97 |
| HSCT     | Auto | /kg | PCL | Sev | tar | PTVA | No | F | NS | CR 6m; DR 8m | 97 |
|----------|------|-----|-----|-----|-----|------|----|---|----|-------------|----|
| HSCT     | Auto | 4.7x10⁶ | PCL | Sev | 13  | PUVA | No | 40 | F  | NS          |    |
| HSCT     | Auto | 11.38x10⁶ | MGUS | BSA 36% | 16 | MTX | CIC | Yes | 34 | M | None | DR 16m | 98 |
| HSCT     | Auto | 0.42x10⁶ | NHL | Mod | 20  | NS | No | 50 | M | None | DR 21m | 83 |
| HSCT     | Auto | N/A | MM | BSA 50% | 15 | TCS, TVD, UVB | Yes | 35 | M | NS | CR 15m | 99 |
| HSCT     | Auto | N/A | ES | Sev (Guttate psoriasis) | NS | NS | No | 9  | M | NS | CR from D20 to 15m | 100 |
| HSCT     | Auto | N/A | MM | Mod-Sev | 20 | MTX | No | 48 | F | None | CR 13y; mild DR thereafter | 101 |
| HSCT     | Auto | Twice M0, M7 | MM | Sev | 25 | TCS, PUVA, CIC, MTX, USTE | No | 54 | M | NS | CR for 3y | 102 |
| HSCT     | Auto | N/A | AL | BSA>50% | 30 | TCS | No | 58 | M | None | CR for 7y | 103 |
| HSCT     | Auto | Twice | DLBCL | NS | 12 | NS | No | 35 | M | Infections after 1st HSCT | Pso improved but DR 6w after 1st HSCT; CR 5y after UC-MSC | 104 |
| UC-MSC   | Allo | 1x10⁶/kg (D0) | Pso | NS | 18 | TCS | No | 26 | F | None | CR 4y | 104 |
|    |    |    |    |    |    |    |    |
|---|---|---|---|---|---|---|---|
| ADSC | Auto | 0.5-3.1 x10^6/kg (D0, 40) | PSA | PASI 21.6 | 29 | TCS, MTX, ETA | Yes | 58 | M | None | 58% reduction in PASI (9.0); no improvement in joint pain for 2y |
| ADSC | Auto | 0.5-3.1 x10^6/kg (D0, 30, 71) | Pso | PASI 24.0 | 5 | TCS, TVD, MTX | No | 28 | F | None | 65% reduction in PASI (8.3) for 9.7m; transient improvement in onycholysis/pitting; reduction in TNF-alpha; 5 x decrease in ROS |
| G-MSC | Allo | 3x10^6/kg (W0, 1, 6, 7, 8) | Pso | Sev | 5 | MTX, ACI, CIC, ETA | No | 19 | M | None | CR from W1 to 3y |

ACI, acitretin; ADSC, adipose-derived mesenchymal stromal cells; aGVHD, acute graft-versus-host disease; AL, immunoglobulin light chain amyloidosis; Allo, allogeneic; AML, acute myeloid leukaemia; Auto, autologous; BSA, body surface area; cGVHD, chronic graft-versus-host disease; CML, chronic myeloid leukaemia; CNL, chronic neutrophilic leukaemia; CR, complete remission; D, day; DLBCL, diffuse large B-cell lymphoma; DR, disease recurrence; ES, Ewing’s sarcoma; ETA, etanercept; FL, follicular lymphoma; G-MSC, gingival-derived mesenchymal stromal cells; HSCT, haematopoietic stem cell transplantation; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; MTX, methotrexate; NHL, non-Hodgkin lymphoma; OCS, oral corticosteroids; PASI, psoriasis area severity index; PCL, plasma cell leukaemia; PSA, psoriatic arthritis; Pso, psoriasis; ROS, reactive oxygen species; TCS, topical corticosteroids; TVD, topical vitamin-D analogue; UC-MSC, umbilical cord-derived mesenchymal stromal cells; USTE, ustekinumab; W, week.

**Table 2. Ongoing clinical trials of cell therapy for psoriasis**
| Cell therapy | Auto/Allo | Route of delivery | Cell dose | Dosing frequency | Trial phase | Study design | Age (Years) | Sample size | Primary outcome | Follow-up | Study location | ClinicalTrials.gov ID |
|--------------|-----------|-------------------|-----------|------------------|-------------|--------------|-------------|-------------|-----------------|-----------|----------------|----------------------|
| ADSC         | Allo      | IV                | 0.5x10⁶/kg| 3 doses W0, 4, 8 | 1/2         | OL           | 18-65       | 7           | PASI and SAE at W12 | 12 W     | Guangdong, China | NCT03265613          |
| ADSC         | Allo      | IV                | 2x10⁶/kg  | 5 doses W0, 2, 4, 6, 8 | 1/2         | OL (+CPT)    | 18-65       | 5           | PASI at W12 | 12 W     | Guangdong, China | NCT03392311          |
| ADSC         | Allo      | IV                | 2x10⁶/kg  | 5 doses W0, 2, 4, 6, 8 | 2           | OL (+CPT +CM01) | 18-65       | 8           | PASI at W12 | 12 W     | Guangdong, China | NCT04275024          |
| UC-MSC       | Allo      | SC                | 10, 50 or 100x10⁶ | Single dose D0 | 1           | ROL          | 19-65       | 9-18        | AEs, cytokines, PASI and BSA at W4 | 4 W     | Seoul, Korea | NCT02918123          |
| UC-MSC       | Allo      | IV                | 2x10⁶/kg  | 5 doses W0, 2, 4, 6, 8 | 1/2         | OL           | 18-65       | 5           | PASI at W12 | 12 W     | Guangdong, China | NCT03745417          |
| UC-MSC       | Allo      | IV                | 1 or 3x10⁶/kg | 6 doses W0, 1, 2, 3, 5, 7 | 1           | RCT (vs MTX) | 18-60       | 57          | PASI75 and PGA0/1 at W20 | 52 W    | Beijing, China | NCT03424629          |
| UC-MSC       | Allo      | IV                | 1.5-2 or 2.5-3x10⁶/kg | 4 doses W0, 2, 4, 6 | 1           | OL           | 18-65       | 12          | PASI75 and PGA0/1 at M6 | 6 M     | Hunan, China | NCT03765957          |

ADSC, adipose-derived mesenchymal stromal cells; Auto, autologous; Allo, allogeneic; CM01, PSORI-CM01 (Chinese Herbal Medicine); CPT, calcipotriol; DLQI, dermatology life quality index; IV, intravenous; M, month; MTX, methotrexate; OL, open label; PASI, psoriasis area severity index; RCT, randomised crossover trial; ROL, randomised open label; SC, subcutaneous; UC-MSC, umbilical cord-derived mesenchymal stromal cells; W, week.
