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Lwin, S.M., Snowden, J.A. [orcid.org/0000-0001-6819-3476](https://orcid.org/0000-0001-6819-3476) and Griffiths, C.E.M. (2021) *The promise and challenges of cell therapy for psoriasis\**. *British Journal of Dermatology*, 185 (5). pp. 887-898. ISSN 0007-0963

<https://doi.org/10.1111/bjd.20517>

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Date of preparation: August 2021  
UK/MAT-45910



# The promise and challenges of cell therapy for psoriasis\*

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## Summary

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### Accepted for publication

18 May 2021

### Funding sources

C.E.M.G. is supported in part by the National Institute for Health Research (NIHR) Manchester Biomedical Research Centre and by Medical Research Council grant MR/101 1808/1 and is an NIHR Emeritus Senior Investigator. S.M.L. receives funding from Dystrophic Epidermolysis Bullosa Research Association UK.

### Conflicts of interest

C.E.M.G. has received honoraria and/or research funds from AbbVie, Amgen, Boehringer Ingelheim, BMS, Janssen, LEO Pharma, Lilly, Novartis, Pfizer, Sanofi and UCB. J.A.S. has received honoraria for speaking at educational events from Janssen, Jazz, Gilead, Mallinckrodt and Actelion, and for advisory board work from MEDAC, and is a member of a trial IDMC for Kiadis.

\*Plain language summary available online

DOI 10.1111/bjd.20517

## 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.<sup>1</sup> The complex interplay between genetic, epigenetic, immune and environmental factors that underlie the disease pathogenesis is not fully understood.<sup>2</sup> However, the emergence of biological therapies targeting key immune pathways in psoriasis pathogenesis, such as tumour necrosis factor (TNF)- $\alpha$ , interleukin (IL)-17 and IL-23, has

The management of moderate-to-severe psoriasis has been transformed by the introduction of biological therapies. These medicines, particularly those targeting interleukin (IL)-17 and IL-23p19, can offer clear or nearly clear skin for the majority of patients with psoriasis, 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 utilized. 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 that is unresponsive to biological therapy. Balancing the risks and benefits of treatment vs. the underlying disease is key; cell therapy carries significant risks, costs, regulation and other complexities, which must 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 coincidental 'routine' indications. In psoriasis, cell therapies, such as MSC and regulatory T 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.

revolutionized the treatment landscape of severe disease. These therapies can lead to significant improvement in disease burden and quality of life for people with psoriasis. However, targeted therapies are not curative; their limitations include lack of clinical response in certain individuals, diminishing efficacy over time and occasional significant adverse effects.<sup>3</sup> Consequently, there is an increasing number of patients with psoriasis who are refractory to multiple lines of biological and nonbiological systemic therapies. This underscores an urgent and increasing need for more advanced, perhaps curative, treatment options including nonpharmaceutical 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 that are 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 cells (Tregs) and chimeric antigen receptor (CAR)-T cells. The last two decades have witnessed rapid advances in clinical trials and commercialization of cell therapy, for which the three most common disease indications in Europe between 2004 and 2014 were cancer, cardiovascular disease and connective tissue diseases.<sup>4</sup> 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 the following three key aspects of cell therapy: (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 that have been used, or have the potential to be used, in IMIDs are detailed in Figure 1.

### Types of cell therapy used for immune-mediated inflammatory diseases

#### Haematopoietic stem cell transplantation

HSCT is used to treat a wide range of malignant and nonmalignant conditions.<sup>5</sup> 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 antithymocyte globulin, or therapeutic monoclonal antibodies, e.g. alemtuzumab or rituximab. Sources of HSCs include granulocyte colony-stimulating factor-mobilized peripheral blood stem cells, bone marrow and umbilical cord blood.<sup>6</sup> Allogeneic HSCT requires ongoing immunosuppression, usually ciclosporin or tacrolimus, to facilitate engraftment and prevent graft-versus-host disease (GVHD), until tolerization 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, randomized controlled trials (RCTs) support sustained benefits of HSCT, whereas in other IMIDs, there appears to be a resetting of disease activity to controllable levels.

In highly active resistant relapsing-remitting MS, there has been a single phase III RCT comparing autologous HSCT with various standard-of-care disease-modifying therapies (DMTs).<sup>7</sup> Among 110 patients randomized on a 1 : 1 basis, only three patients had disease progression at 1 year as primary endpoint vs. 34 patients in the DMT group. There was also significant improvement of MS at one year and beyond without treatment-related mortality (TRM).<sup>7</sup>

In severe SS, there has been one small phase I RCT<sup>8</sup> and two phase III RCTs, namely 'SCOT'<sup>9</sup> and 'ASTIS',<sup>10</sup> each using different transplant regimens but with similar control arms. In the North American 'SCOT' trial, Kaplan-Meier estimates at 72 months of event-free survival were 74% vs. 47%, and for overall survival were 86% vs. 51%, for HSCT and control, respectively.<sup>9</sup> The TRM was 3% at 54 months and 6% at 72 months.<sup>9</sup> 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%.<sup>10</sup>

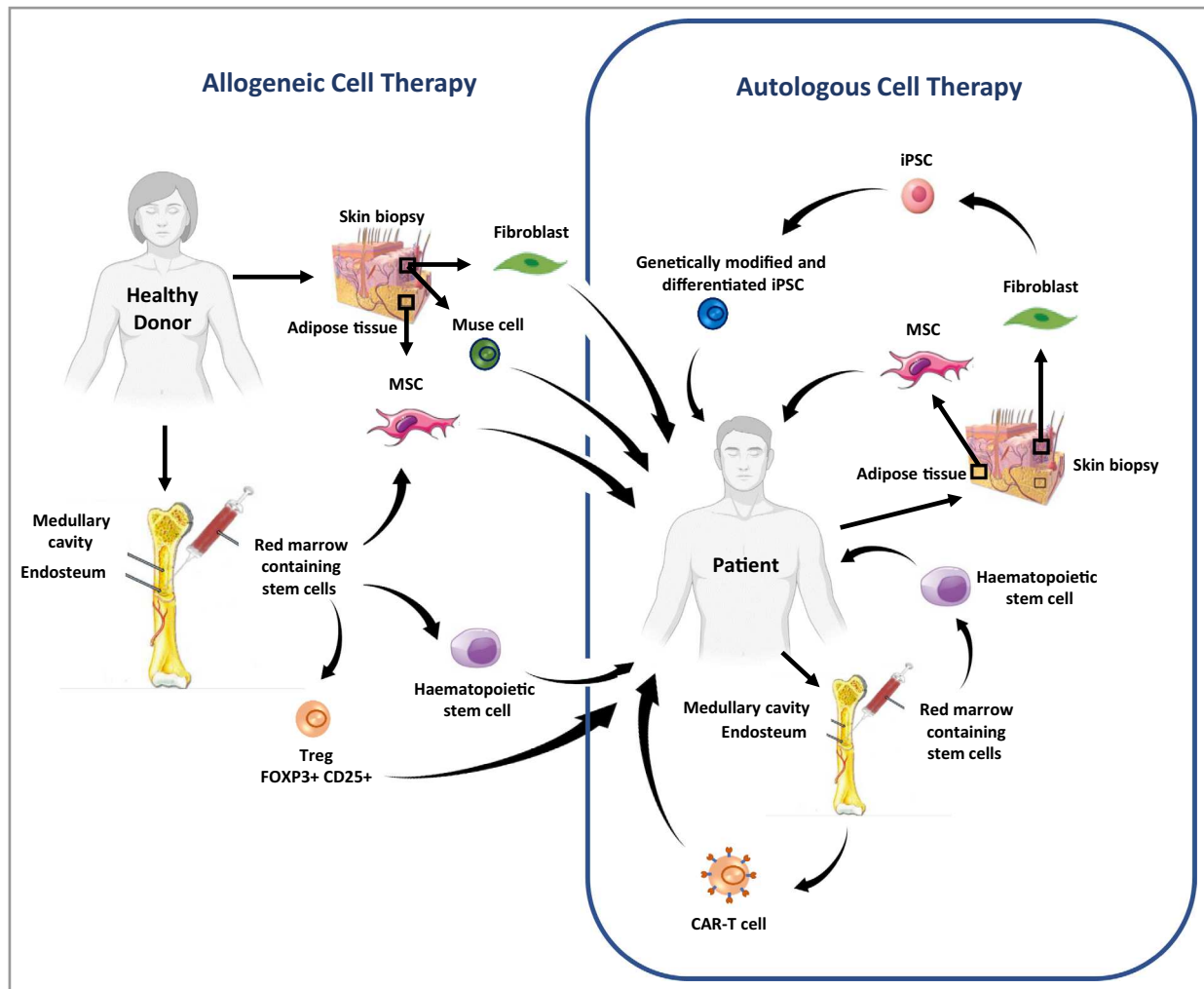
These phase III trial results in MS and SS support the potentially powerful and prolonged effect of autologous HSCT on disease activity in severely affected patients with IMIDs, but also highlight the importance of careful patient selection. Underlying vital organ compromise from the IMID itself manifests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

Allogeneic HSCT has been applied to IMIDs more rarely because of the higher complication rate (including GVHD) but long-term responses, and probably cures, have been achieved across a variety of diseases.<sup>11-14</sup> 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 coincidental 'routine' indications (Table 1). Very rare cases involving patients treated specifically for severe PsA have been reported to the European Society for Blood and Marrow Transplantation Registry.<sup>14</sup>

#### Mesenchymal stromal cells

MSCs comprise a heterogeneous population of self-renewable, multipotent non-HSCs with immunomodulatory, angiogenic, anti-inflammatory and antiapoptotic properties.<sup>15,16</sup> These properties, combined with ease of isolation from human tissues and ability to evade allogeneic rejection (owing to lack of





**Figure 1** Types of cell therapy used, or with the potential to be used, in psoriasis. Cell therapy can be either allogeneic (cells from donor to patient) or autologous (the 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 cells; Treg, regulatory T cell.

expression of major histocompatibility complex [MHC] class II and costimulatory molecules CD80 and CD86, and low levels of MHC class I),<sup>17,18</sup> make MSCs an ideal cell therapy for various conditions, including IMIDs, without the need for cytotoxic conditioning regimes.<sup>19</sup>

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 *in vitro*, which enable them to maintain their differentiation capacity in the long term,<sup>20</sup> whereas ADSCs, when compared with BM-MSCs and UC-MSCs, exhibit a stronger inhibitory effect on

peripheral blood B cells, T cells and natural killer (NK) cells *in vitro*;<sup>21</sup> but all three types can promote Treg and T helper (Th)1 polarization, evidenced by the increased expression of forkhead box (FOX)P3 and T-bet mRNA within purified activated T cells, and a reduction in TNF- $\alpha$  and perforin production by activated NK cells.<sup>21</sup>

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.*<sup>22</sup> and Song *et al.*).<sup>23</sup> The MSC secretome, encapsulated in extracellular vesicles, includes several cytokines, growth factors and chemokines, including transforming growth factor (TGF)- $\beta$ 1, TNF- $\alpha$ , prostaglandin-E2, interferon- $\gamma$ , fibroblast and hepatocyte growth factors,

Table 1 Summary of published reports of cell therapy for psoriasis

Cell therapy	Auto/Allo	Intravenous cell dose	Primary target disease	Severity of psoriasis at baseline	Duration of psoriasis (years)	Previous treatment for psoriasis	Age (years)	Sex	Adverse events	Efficacy	Reference	
HSCT	Allo	Twice, 1 y apart	AML	Severe	20	PUVA, MTX, razoxane, etretinate	No	36	M	NS	CR 4y	82
HSCT	Allo	N/A	CML	Severe	10	TCS, coal tar, dithranol	Yes	35	M	NS	CR 1y	85
HSCT	Allo	N/A	CML	NS	NS	NS	NS	35	M	NS	CR 4y	86
HSCT	Allo	N/A	AA	Severe	25	TCS, PUVA	No	36	M	cGVHD	CR 1.8y	87
HSCT	Allo	N/A	AML	BSA 36%	1	TCS, etretinate	No	40	M	cGVHD	CR 2y	88
HSCT	Allo	N/A	CML	BSA 19%	NS	NS	Yes	54	M	None	CR 1y	89
HSCT	Allo	N/A	CML	BSA 66%	33	TCS, coal tar, PUVA, MTX	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%	25	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	Severe	16	NS	Yes	29	M	None	DR 1y	82
HSCT	Allo	2.1 × 10 <sup>8</sup> per kg	AA	BSA 45%	2	TCS, TVD	No	27	M	None	CR 10y	83
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	95
HSCT	Allo	N/A	AML	Mild-Mod	NS	TCS, TVD	No	21	M	aGVHD	CR from D64 to 5y 7m	95
HSCT	Allo	N/A	DLBCL	Severe	15	MTX	Yes	59	M	None	CR from D60 to 5y	95
HSCT	Allo	N/A	AML	Severe	20	TCS, TVD	Yes	65	M	aGVHD	CR from D41 to 7y 5m	95
HSCT	Allo	N/A	FL/DLBCL	Mod	27	TCS, TVD	No	30	F	cGVHD	CR from D30 to 3y	95
HSCT	Allo	N/A	CNL	Mod	NS	TCS, TVD	No	65	M	aGVHD, cGVHD, death	CR from D71 to 7m	95
HSCT	Auto	24 × 10 <sup>6</sup> per kg	NHL	Mild	15	TCS	Yes	35	M	NS	DR 22m	96
HSCT	Auto	2.85 × 10 <sup>8</sup> per kg	AML	NS	NS	TCS, coal tar	No	53	M	NS	DR 14m	96
HSCT	Auto	4.7 × 10 <sup>6</sup> per kg	PCL	Severe	13	PUVA	No	40	F	NS	CR 6m; DR 8m	96
HSCT	Auto	11.38 × 10 <sup>6</sup> per kg	MGUS	BSA 36%	16	MTX, CIC, MMF, OCS	Yes	34	M	None	DR 16m	97
HSCT	Auto	0.42 × 10 <sup>6</sup> per kg	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	98
HSCT	Auto	N/A	ES	Severe	NS	NS	No	9	M	NS	CR from D20 to 15m	99
HSCT	Auto	N/A	MM	Mod-severe	20	MTX	No	48	F	None	CR 13y; mild DR thereafter	100
HSCT	Auto	Twice; M0, M7	MM	Severe	25	TCS, PUVA, CIC, MTX, USTE	No	54	M	NS	CR for 3y	101

(continued)

**Table 1** (continued)

Cell therapy	Auto/Allo	Intravenous cell dose	Primary target disease	Severity of psoriasis at baseline	Duration of psoriasis (years)	Previous psoriasis	treatment for	Age PsA (years)	Sex	Adverse events	Efficacy	Reference	
HSCT	Auto	N/A	AL	BSA > 50%	30	TCS		No	58	M	None	CR for 7y	<sup>102</sup>
HSCT/UC-MSC	Auto/Allo	Twice/1 × 10 <sup>6</sup> per kg (D0)	DLBCL	NS	12	NS		No	35	M	Infections after first HSCT	Psoriasis improved but DR 6w after first HSCT; CR 5y after UC-MSC	<sup>103</sup>
UC-MSC	Allo	1 × 10 <sup>6</sup> per kg (W0, 1, 2, 5, 7)	Psoriasis	NS	18	TCS		No	26	F	None	CR 4y	<sup>103</sup>
ADSC	Auto	0.5–3.1 × 10 <sup>6</sup> per 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	<sup>104</sup>
ADSC	Auto	0.5–3.1 × 10 <sup>6</sup> per kg (D0, 30, 71)	Psoriasis	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-α; 5 × decrease in ROS	<sup>104</sup>
G-MSC	Allo	3 × 10 <sup>6</sup> per kg (W0, 1, 6, 7, 8)	Psoriasis	Severe	5	MTX, ACI, CIC, ETA		No	19	M	None	CR from W1 to 3y	<sup>105</sup>

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; CIC, ciclosporin; CML, chronic myeloid leukaemia; CNL, chronic neutrophilic leukaemia; CR, complete remission; D, day; DLBCL, diffuse large B-cell lymphoma; DR, disease recurrence; ES, Ewing 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; MMF, mycophenolate mofetil; MTX, methotrexate; NHL, non-Hodgkin lymphoma; OCS, oral corticosteroids; PASI, Psoriasis Area and Severity Index; PCL, plasma cell leukaemia; PUVA, psoralen and ultraviolet A; PSA, psoriatic arthritis; ROS, reactive oxygen species; TCS, topical corticosteroids; TNF, tumour necrosis factor; TVD, topical vitamin-D analogue; UC-MSC, umbilical cord-derived mesenchymal stromal cells; USTE, ustekinumab; UVB, ultraviolet B; W, week.

indoleamine-pyrrole 2,3-dioxygenase and nitric oxide, among others.<sup>24,25</sup>

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,<sup>26,27</sup> with better proliferative capacity, higher yield, slower rate of senescence and better preservation of a normal diploid karyotype than BM-MSCs.<sup>28–31</sup>

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).<sup>32–39</sup> 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 with those who received dose-adjusted BM-MSCs, with an optimal cell dose of  $2–4 \times 10^7$  cells mL<sup>-1</sup>, indicating the considerable potential of MSCs for the treatment of IBD.<sup>40</sup> A recent phase II RCT of autologous MSCs in 48 patients with MS demonstrated disease remission, without safety issues, in 58.6% compared with 9.7% in a sham-treatment group.<sup>39</sup> 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.<sup>31,32,34,35,38,39</sup> However, several MSC products have been approved including Prochymal (Osiris Therapeutics, Columbia, MD, USA) for acute GVHD in Canada and New Zealand.<sup>22</sup> One of the theoretical pitfalls of MSCs is risk of carcinogenesis.<sup>17,41,42</sup> 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 regulate or suppress other immunocytes by controlling response to self-antigens and nonself antigens, thus helping to prevent autoimmunity and limit chronic inflammation. They exert these functions through inhibitory cytokines (e.g. IL-10), cytotoxicity (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.<sup>43</sup>

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.<sup>44,45</sup> 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 balance.<sup>46</sup> However, there are current challenges with the use of Treg therapy for IMIDs, which include the variability in expansion of Tregs *ex vivo*, the relative paucity of clinical grade reagents required for the 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.<sup>44</sup> Further investigation of the most suitable Treg subset to use for a particular disease, and controlled trials with larger sample size and a standardized dosing regimen, are required to obtain robust evidence of the clinical benefit of correcting breaks in immune tolerance in IMIDs.<sup>47</sup> For further review of this topic please see Roth-Walter *et al.*<sup>48</sup>

### Types of cell therapy with potential for use in immune-mediated inflammatory diseases

There are a number of other forms of cell therapy that could potentially be used in the treatment of psoriasis, although these are not currently being tested in IMIDs. These include fibroblasts, Muse cells, iPSCs and CAR-T cells.

#### Fibroblasts

Fibroblasts, which exhibit 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.<sup>49–53</sup> Thus, fibroblasts can be considered as an alternative to MSCs for immunomodulatory cell therapy.<sup>51</sup> 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.<sup>54–57</sup> The main concern with fibroblast cell therapy is the risk of fibrosis and hypertrophic scars.<sup>50</sup> However, fibroblasts from the papillary dermis have a particular therapeutic relevance as they are involved in wound healing with anti-inflammatory effects without fibrosis.<sup>58</sup> Although fibroblasts have not been tested in humans with IMIDs, their therapeutic potential has been highlighted through a number of preclinical studies using mouse models of IMIDs including type I diabetes, autoimmune arthritis, alopecia areata and MS.<sup>51,59–61</sup>

#### Multilineage-differentiating stress-enduring cells

Muse cells are pluripotent stem cells, occurring naturally in tissues of mesenchymal origin, with regenerative, anti-inflammatory, antiapoptotic, antifibrotic and immunomodulatory properties.<sup>62–64</sup> They comprise 1–2% of BM-MSCs, 5% of dermal fibroblasts and a small population in adipose tissue.<sup>65</sup> Upon tissue injury, the alerting signal, sphingosine-1-phosphate, induces mobilization of Muse cells to peripheral blood, and subsequently to the site of damage.<sup>64</sup> This is followed by spontaneous differentiation into, and replenishment



of, tissue-compatible cells for repair.<sup>64,66</sup> Furthermore, Muse cells have immunomodulatory properties, exerted via TGF- $\beta$ 1 and regulation of macrophages towards the M2-phenotype, which make them an attractive therapeutic option for psoriasis.<sup>67,68</sup> To date, Muse cells have been used clinically in the context of an early phase trial in myocardial infarction, demonstrating safety and efficacy.<sup>69</sup>

### Inducible pluripotent stem cells

One of the main limitations of somatic cell-based therapy is that 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 specialized cell types with indefinite expansion, thus resembling embryonic stem cells.<sup>70–72</sup> The fundamental concept 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. Owing 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.<sup>72,73</sup> Viral-mediated gene supplementation or genome editing using tools such as CRISPR/Cas9 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.<sup>74</sup> Caution is needed because if undifferentiated proliferating iPSCs are directly administered, they can form malignant teratomas owing to their highly proliferative nature and broad differentiation potential.<sup>75</sup> However, iPSCs hold huge promise as both a regenerative and an immunomodulatory cell therapy for various skin diseases.<sup>76</sup>

### Chimeric antigen receptor-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 recognize and kill antigen-bearing cells via cytokine release. 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,<sup>77</sup> and is being considered in the management of melanoma resistant to checkpoint inhibitors.<sup>78</sup> However, it carries a significant risk

of cytokine release syndrome and neurotoxicity in the short term, and long-term immunodeficiency owing to depletion of immune effectors.<sup>79</sup>

As they have 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 pre-clinical study to treat pemphigus vulgaris in a mouse model of the disease, the results demonstrated selective reduction of serum anti-Desmoglein (Dsg)3 antibody titres and improvement in blistering, hair loss and histological acantholysis.<sup>80</sup> These preclinical data have led to an early phase open-label clinical trial of Dsg3-CAR-T therapy for patients with pemphigus vulgaris (NCT04422912).<sup>80</sup>

### 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.*<sup>81</sup> reported on the ‘cure’ of severe intractable psoriasis in a 35-year-old man who received an allogeneic HSCT from his unaffected brother for acute myelomonocytic leukaemia. The recipient remained free of psoriasis 5 years post-transplant. 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 nonreactive 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 described in patients who received allogeneic, rather than autologous, HSCT.<sup>82–84</sup> Interestingly, the presence of GVHD seemed to be an indicator for long-term complete remission of psoriasis in eight cases (Table 1),<sup>82–105</sup> possibly owing to a ‘graft-versus-autoimmunity’ effect with ongoing inhibition or elimination of the host immunohaematopoietic system.<sup>84,91</sup> Indeed, many of the participants 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<sup>106</sup> in a 40-year-old man with acute myeloid leukaemia who received a syngeneic HSCT from his phenotypically identical twin brother who had been affected by severe psoriasis and PsA for 20 years. Within 10 days of transplantation, the recipient developed psoriasis which remained intractable. Psoriasis persisted, despite receiving a second transplant from the same donor, in addition to 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 patients with psoriasis treated with autologous HSCT, five relapsed within 2 years after the transplantation and one relapsed after 13 years (Table 1).<sup>100</sup> Notably, even though psoriasis relapses,

Table 2 Ongoing clinical trials of cell therapy for psoriasis

Cell therapy	Auto/ Allo	Route of delivery	Cell dose (per kg)	Dosing frequency	Trial phase	Study design	Age (years)	Sample size	Primary outcome	Follow-up	Study location	ClinicalTrials.gov ID
ADSC	Allo	IV	$0.5 \times 10^6$	3 doses (W0, 4, 8)	I/II	OL	18–65	7	PASI and SAE at W12	12 W	Guangdong, China	NCT03265613
ADSC	Allo	IV	$2 \times 10^6$	5 doses (W0, 2, 4, 6, 8)	I/II	OL (+CPT)	18–65	5	PASI at W12	12 W	Guangdong, China	NCT03392311
ADSC	Allo	IV	$2 \times 10^6$	5 doses (W0, 2, 4, 6, 8)	II	OL (+CPT +CM01)	18–65	8	PASI at W12	12 W	Guangdong, China	NCT04275024
UC-MSC	Allo	SC	10, 50 or $100 \times 10^6$	Single dose (D0)	I	ROL	19–65	9–18	AEs, cytokines, PASI and BSA at W4	4 W	Seoul, Korea	NCT02918123
UC-MSC	Allo	IV	$2 \times 10^6$	5 doses (W0, 2, 4, 6, 8)	I/II	OL	18–65	5	PASI at W12	12 W	Guangdong, China	NCT03745417
UC-MSC	Allo	IV	$1$ or $3 \times 10^6$	6 doses (W0, 1, 2, 3, 5, 7)	I	RCT (vs. MTX)	18–60	57	PASI 75 and PGA 0/1 at W20	52 W	Beijing, China	NCT03424629
UC-MSC	Allo	IV	1.5–2 or $2.5\text{--}3 \times 10^6$	4 doses (W0, 2, 4, 6)	I	OL	18–65	12	PASI 75 and PGA 0/1 at M6	6 M	Hunan, China	NCT03765957

ADSC, adipose-derived mesenchymal stromal cells; AE, adverse events. 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 and Severity Index; RCT, randomized crossover trial; ROL, randomized open-label; SC, subcutaneous; UC-MSC, umbilical cord-derived mesenchymal stromal cells; W, week.

it appears to run a more benign, less clinically severe course compared with the pretransplant state. Psoriasis remission after autologous HSCT is attributed to the myelo- and lymphoablative effect of conditioning regimens and altered and slow immunological reconstitution following transplantation.<sup>98</sup>

HSCT carries significant risks, costs and other complexities, which must be justified by outcomes compared with alternative treatments. Risks are greater with allogeneic HSCT than with autologous HSCT. In practice, individualized decisions need to be made for each patient with respect to treatment options for their disease. Severe intractable psoriasis is frequently physically and psychologically debilitating 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 for 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 coexisted 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 approach to cell therapy for psoriasis (Table 1). De Jesus<sup>104</sup> reported on two patients with intractable psoriasis, one of whom had concomitant PsA, who received autologous MSCs in the form of two to three infusions of liposuction-derived ADSCs. A durable response with clinical benefit in the form of a 50–60% reduction in Psoriasis Area and Severity Index lasting between 157 and 292 days occurred, although PsA was unresponsive. There were no concerning safety signals. Furthermore, even though there was an eventual relapse of psoriasis, one patient responded to etanercept – a biologic that had previously been ineffective for him – after MSC therapy, thereby indicating that MSCs could be used as adjunctive therapy. Chen *et al.*<sup>103</sup> commented on two cases. The first case was 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 in remittance for at least 5 years. The second case involved a 26-year-old woman who had intractable psoriasis for 18 years. Three infusions of UC-MSCs were given specifically for the treatment of psoriasis, which produced clearance that was maintained for at least 4 years with two further infusions. UC-MSCs appear to be safe and seem to have remittive potential in these cases. Chen *et al.*<sup>107</sup> explored the mechanism of action of UC-MSCs for psoriasis using the imiquimod mouse model and infusion of human UC-MSCs which significantly reduced psoriasis severity. A key feature of the response was reduced production of type I interferon by plasmacytoid dendritic cells. Wang *et al.*<sup>105</sup> used five infusions of allogeneic gingival MSCs, which have immunomodulatory and anti-inflammatory properties, to treat a 19-year-old man who had 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 I–II clinical trials (six in China and one in South Korea; three using ADSCs and four using UC-MSCs, all allogeneic) (Table 2).

## Conclusions and future directions

As the number of people with psoriasis refractory to current biological and nonbiological systemic therapies continues to rise, and the pipeline for new pharmacological approaches to the disease starts to shrink, it is important to turn to novel holistic approaches and advanced therapeutics for a cure. Amid 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, there 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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