

Mesenchymal stem cells for the treatment of psoriasis: a comprehensive review

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Abstract

Mesenchymal stem cells (MSCs) have recently been shown to have not only regenerative capabilities but also immunomodulating properties. For this reason, they are currently under investigation in clinical trials for the treatment of several autoimmune systemic disorders. Psoriasis is a systemic immune-mediated disease for which MSCs could have therapeutic potential. We analysed the existing literature with regard to MSC-based strategies for the treatment of psoriasis, using the MEDLINE, Embase, Scopus and Cochrane Library electronic databases from inception to the date of study. A number of studies confirm the involvement of MSCs in psoriasis pathogenesis and therefore designate MSCs as an important potential therapeutic tool in this setting. Preclinical data are mostly based on imiquimod-induced murine models of psoriasis, and confirm the anti-inflammatory and immunomodulatory action of MSCs in the setting of psoriasis. Six patients affected by psoriasis were described in four clinical studies. Despite significant differences in terms of therapeutic protocols and clinical outcomes, the MSC-based regimens were efficacious in 100% of the cases. Despite more data still being needed, MSCs could be a promising therapy for psoriasis.

Introduction

Psoriasis is a chronic, relapsing inflammatory disease affecting 2–3% of the population, and is considered to be a systemic disease rather than one limited to the skin.¹ The treatment varies, depending on disease severity, from topical agents and phototherapy to conventional immunosuppressant drugs and biologic agents.²

The pathogenesis of psoriasis has an immunological basis. A central role is certainly played by T helper (Th)1 and Th17 lymphocytes and by cytokines such as tumour necrosis factor (TNF)- α , interleukin (IL)-17 and IL-23.³ However, recent studies have shown that the prime mover in psoriasis pathogenesis could be linked to a dysfunction in resident mesenchymal stem cells (MSCs), resulting in altered polarization of the immune response.⁴

Mesenchymal stem cells in psoriasis

MSCs are a subset of pluripotent cells present in tissues of mesenchymal origin, and are responsible for the regeneration of these tissues. MSCs are characterized by specific surface markers and by their ability to adhere to plastic and to differentiate into adipocytes, chondrocytes and osteocytes *in vitro* (Fig. 1).⁵ MSCs include many different cell types, with probably the

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most widely studied being the bone-marrow stromal stem cells (BMSCs). Other MSCs are, for example, amniotic fluid stem cells, umbilical-cord MSCs (UCMSCs) and adipose-derived stem cells (ADSCs); these last are contained in the stromal-vascular fraction (SVF) of adipose tissue.⁶ MSCs are under study not only for their regenerative capacity, but also for their immunomodulating properties, as they seem to be able to directly modulate cytokine secretion from lymphocytes.⁷

A recent work demonstrated that skin MSCs from patients with psoriasis have low differentiation capacity, high human leucocyte antigen-I expression levels and low immunoregulatory capability.⁸ Lymphocyte inhibition seems to be compromised in psoriatic skin, mainly because of dermal MSCs, leading to abnormalities in cytokine secretion through circular RNA.^{9,10} Moreover, MSCs from psoriatic plaques have been shown to promote keratinocyte proliferation, with subsequent abnormal thickening of the epidermis.¹¹

Several papers have also reported that MSCs seem to be key players in mediating the pleiotropic effects of biologic therapies on both keratinocytes and T cells.¹² Campanati *et al.* demonstrated that the effects of TNF- α inhibitors take place at the level of dermal MSCs, which probably represent the cells primarily involved in the 'psoriatic march'.^{13,14}

In this setting, several authors are investigating the role of MSCs as a possible therapeutic strategy for the treatment of psoriasis (Table 1).

Preclinical models

Preclinical data are mostly based on imiquimod (IMQ)-induced murine models of psoriasis. MSCs demonstrate efficacy in reduction of disease severity, acanthosis, inflammatory infiltrate and cytokine production.^{19,20} In particular, two studies showed the curative potential of subcutaneous injection of UCMSCs, which seem to act through direct action both on T lymphocytes

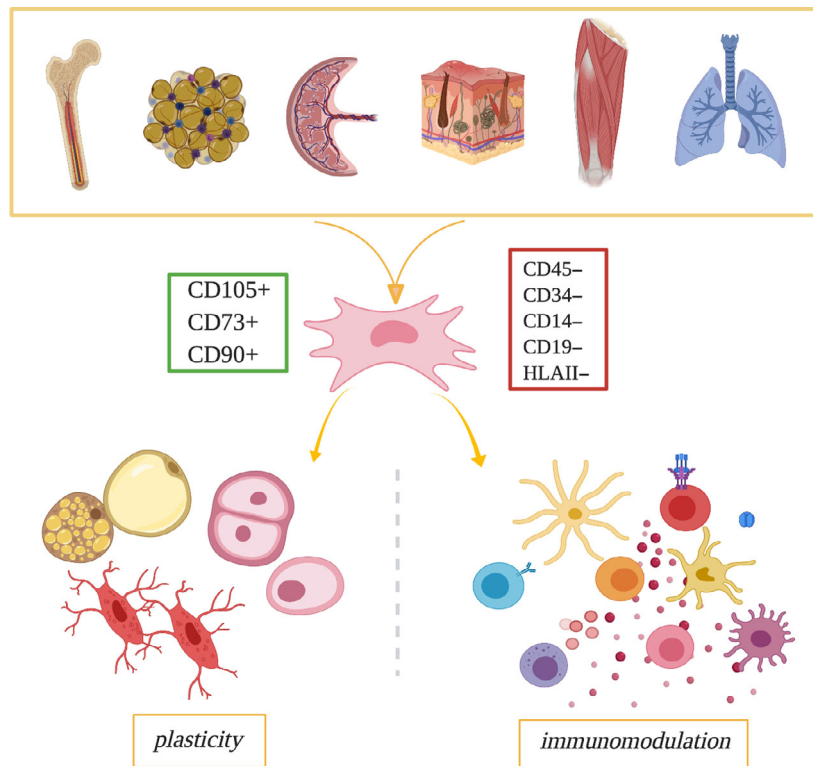


Figure 1 Schematic representation of mesenchymal stem cells (MSCs). MSCs are a subset of pluripotent cells present in tissues of mesenchymal origin, such as bone marrow, adipose tissue, placenta, umbilical cord, dermis, skeletal muscle, lungs (upper panel). MSCs are characterized by the presence of specific surface markers such as CD105, CD73 and CD90 (green box). However, MSCs by definition lack CD45, CD34, CD14, CD19 and HLAII molecules (red box). Their pluripotency and their regenerative properties are demonstrated by their ability to differentiate into adipocytes (yellow), chondrocytes (pink) and osteocytes (red) *in vitro* (lower left panel). MSCs also interact with both lymphocytes and dendritic cells, therefore modulating cytokine secretion. Created with BioRender.com

Table 1 Study characteristics (results of our review). Summary of the results obtained from our search: name of the first author (authors are listed in alphabetical order), year and type of publication, type of study and type of mesenchymal stem cell used.

Study	Author	Publication year	Publication type	Study type	MSC type
1	Campanati <i>et al.</i> ²²	2018	Original article	Preclinical	dMSC
2	Chen <i>et al.</i> ²³	2016	Letter	Clinical	UCMSC
3	Chen <i>et al.</i> ¹⁷	2019	Original article	Preclinical	UCMSC
4	Comella <i>et al.</i> ²⁵	2018	Case report	Clinical	SVF (ADSC)
5	Imai <i>et al.</i> ²⁰	2019	Letter	Preclinical	AmnMSC
6	De Jesus <i>et al.</i> ²⁴	2016	Case report	Clinical	ADSC
7	Kim <i>et al.</i> ²¹	2018	Original article	Preclinical	TMSC
8	Kim <i>et al.</i> ¹⁹	2019	Original article	Preclinical	EMSC
9	Lee <i>et al.</i> ¹⁵	2017	Original article	Preclinical	UCMSC
10	Rokunohe <i>et al.</i> ¹⁸	2016	Letter	Preclinical	ADSC
11	Owczarczyk-Saczonek <i>et al.</i> ²⁸	2017	Review	Preclinical, clinical	BMSC, UCMSC
12	Sah <i>et al.</i> ¹⁶	2016	Original article	Preclinical	UCMSC
13	Seetharaman <i>et al.</i> ²⁶	2019	Case report	Clinical	ADSC

ADSC, adipose-derived stem cell; AmnMSC, amniotic fluid stem cells; BMSC, bone-marrow stromal stem cell; dMSC, dermal mesenchymal stem cell; EMSC, embryonic stem cell-derived mesenchymal stem cell; MSC, mesenchymal stem cell; SVF, stromal-vascular fraction; TMSC, tonsil-derived mesenchymal stem cell; UCMSC, umbilical cord mesenchymal stem cell.

and dendritic cells (DCs), and the study stressed the importance of an antioxidative milieu for the correct action of MSCs.^{15,16} Those data were recently confirmed by Chen *et al.*, who demonstrated UCMSC-induced reduction in the production of type I interferon by plasmacytoid DCs.¹⁷ Only one preclinical study has been performed on ADSCs, which showed that IMQ-induced inflammatory changes are inhibited after intradermal injection of ADSC.¹⁸ Human tonsil-derived MSCs were able to prevent Th17-mediated autoimmune response via regulation of the programmed death-1/programmed death ligand-1 pathway.²¹

Moreover, Campanati *et al.* recently confirmed the *in vitro* capability of dermal MSCs taken from healthy controls to revert the proinflammatory cytokine production by aberrant MSCs obtained from psoriatic plaques (p-MSCs) and to lower p-MSC proliferation rates when in coculture.²²

Clinical case reports

Our review identified four clinical studies describing a total of six patients affected by psoriasis treated with MSC-based regimens (Table 2). The patients generally had a long-standing history of psoriasis (mean 14.8 years) and most of them were previously prescribed both topical and systemic treatments. All patients were weaned off any systemic medication for psoriasis before any MSC-based treatment was administered. Unlike in haematopoietic-stem-cell transplant (HSCT), no concomitant drugs are needed before MSC administration.

In a report from Chen *et al.*,²³ heterologous UCMSCs were infused intravenously in two patients with psoriasis. One patient also underwent HSCT for underlying cancer and not primarily because of psoriasis, therefore making it difficult to draw conclusions on MSC effectiveness in that particular case.²³

De Jesus *et al.*²⁴ described two patients with psoriasis who were infused with autologous ADSCs, which had been obtained through centrifugation and enzymatic digestion of lipoaspirates and subsequent plating. While one patient received two doses of ADSCs, the other required three doses. Both patients experienced significant cutaneous improvement of but did not reach complete clearance, and therefore required additional therapies. One of the patients also had psoriatic arthritis, which did not respond to the ADSC-based treatment.

Comella *et al.*²⁵ recently published a report on successful intravenous injection of autologous SVF in a patient affected by psoriasis. Fresh SVF from lipoaspirate was resuspended in normal saline solution for administration through a 23G butterfly needle. The patient experienced complete clearance of the disease, with no recurrences during the follow-up period.

Seetharaman *et al.*²⁶ also described the efficacy of topical application of ADSC-conditioned medium (CM) in a localized form of scalp psoriasis. ADSCs from a healthy volunteer were plated and the MSC-CM was collected after 72 h of incubation, centrifuged, filtered, concentrated by ultrafiltration and stored at -20°C until use. MSC-CM was applied directly to the affected

Table 2 Clinical studies included in the present review: patient details.

	Patient					
	1	2	3	4	5	6
Reference	Chen et al., 2016 ²³		Comella et al., 2018 ²⁵	De Jesus et al., 2016 ²⁴	Seetharaman et al., 2019 ²⁶	
Sex	M	F	M	M	F	M
Age, years	35	26	43	58	28	38
Psoriasis duration, years	12	18	NS	30	12	2
Body area involved	Face, trunk, legs	Elbows, knees, trunk	Trunk, limbs	NS	Trunk, limbs	Scalp
PASI	NS	NS	50.4	21.6	24	NS
PsA	No	No	No	Yes	No	No
Previous therapy	NS	TCS	Topicals, cIST, biologics, phototherapy	TCS, MTX, SCS, etanercept	CS, MTX	NS
Comorbidities	DLBCL	No	No	No	Hyperthyroidism	No
MSC	UCMSC	UCMSC	SVF (ADSC)	ADSC	ADSC	ADSC-CM
AVH	H	H	A	A	A	H
Route of administration	IV	IV	IV	IV	IV	Topical
Cell dose	10 ⁶ /kg	10 ⁶ /kg	30–60 × 10 ⁶ (from 60 mL of fat tissue)	0.5–3.1 × 10 ⁶ /kg (from 200 mL of fat tissue)	0.5–3.1 × 10 ⁶ /kg (from 200 mL of fat tissue)	Filtered CM from 5 × 10 ⁶ cultured cells (from 100 mL of fat tissue)
Doses, n	1	5 (3 + 2: 1/week for 3 weeks + 2 after consolidation for 3 months)	1	2 (1/month)	3 (1/month)	30 (1/day for 1 month)
Concomitant therapy	CT + HSCT	None	None	None	None	None
Follow-up, years	5	4	1	1	1	0.5
AE	Infection, unstable blood count	NS	NS	Latent TB reactivation	NS	NS
Relapse	No	No	No	Yes	Yes	No
Time before relapse, years	NS	NS	NS	2	< 1	NS
Additional treatment required	No	No	No	Etanercept, infliximab, MTX	Topical therapy, as needed: topical clobetasol propionate, aquaphor, betamethasone valerate, calcipotriol, halobetasol-aquaphor	Complete
Response to MSC treatment	Complete	Complete	Complete	Partial	Partial	Complete
PASI	NS	NS	0.3	8.9	8.9	NS

A, autologous; ADSC, adipose-derived stem cell; ADSC-CM, adipose-derived stem cell; AE, adverse event; cIST, conventional immunosuppressive therapy; CM, conditioned medium; CS, corticosteroids; CT, chemotherapy; DLBCL, diffuse large-B cell lymphoma; H, heterologous; HSCT, haematopoietic stem cell transplant; IV, intravenous; MSC, mesenchymal stem cell; MTX, methotrexate; NS, not stated; PASI, Psoriasis Area and Severity Index; SCS, systemic corticosteroids; SVF, stromal-vascular fraction; TB, tuberculosis; TCS, topical corticosteroid; UCMSC, umbilical cord mesenchymal stem cell.

area on a daily basis for 30 days, with significant clinical improvement and stable results.

In all four studies, the efficacy of the MSC-based regimen was 100%. Only two of the six patients relapsed, but the relapses after MSC-based treatment regimens were generally milder forms of psoriasis and responded to systemic therapy. No serious adverse events were registered. TBC reactivation and infections were seen only in patients receiving concomitant immunosuppression or biologic therapies.

Discussion

MSCs are currently used in clinical trials for a great variety of diseases, with a special focus on autoimmune disorders.²⁷ The feasibility of MSC transplantation is highly dependent on the type of cell used: for example, while BMSC isolation requires a specialist team, ADSCs are easily accessible and therefore a much simpler treatment.

Previous studies have already confirmed the involvement of MSCs in the pathogenesis of psoriasis and therefore designated MSCs as important potential therapeutic targets.²⁸ It is unclear if genetic polymorphisms responsible for genetic predisposition to psoriasis could represent a primary cause of MSC dysfunction. It remains undetermined whether the local dysfunction of MSC in psoriatic plaques is only a localized phenomenon or if it reflects a failure in MSC functioning in general. Moreover, the published studies display wide variation in terms of types of cell used and the methods of administration, therefore making it impossible at present to define a standardized protocol. Those are central points for future studies aimed at determining the feasibility and efficacy of autologous MSC transplantation.

Despite many promising reasons for the use of MSCs in psoriasis, it should also be noted that the direct regenerative potential of these cells may not be as effective as previously expected. There are also potential risks associated with MSC therapy, including graft-versus-host disease, neoplastic proliferation, localized cutaneous reactions and lack of efficacy. The likelihood of those adverse events varies according to the type of cell used and the method of administration. Assessment of the potential risks and benefits is essential before MSC-based therapeutic regimens can be considered a treatment of choice for psoriasis.^{29,30}

Conclusion

We analysed four studies on six patients that used MSC therapy for psoriasis. Although all six patients

benefited from the treatment, there were relapses. MSC treatment is also not without risk. Further data are needed to determine whether MSC-based strategies could be included in official guidelines for the treatment of psoriasis.

Learning points

- MSCs do not only display regenerative capabilities but also have immunomodulating properties.
- Th1 and Th17 lymphocyte inhibition is compromised in psoriatic skin, mainly because of MSCs in psoriatic lesions affecting the skin microenvironment.
- A central role is played by MSCs in the response to biologic therapies; MSCs in fact seem to be key players in mediating the pleiotropic effects of those drugs on both keratinocytes and T cells.
- Preclinical data were mostly based on IMQ-induced murine models of psoriasis, and confirmed the anti-inflammatory and immunomodulatory action of MSCs in the setting of psoriasis.
- Several studies have demonstrated the efficacy of MSC administration both in patients with psoriasis and in animal models of psoriasis.
- To date, only six patients affected by psoriasis have successfully been treated with MSC-based regimens
- In addition, the wide variation in terms of types of cell and methods of administration mean that there are no standardized protocols.

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CPD questions

Question 1

What are the main types of cells involved in the pathogenesis of psoriasis?

- (a) T helper (Th)1 and Th2.
- (b) Th3 and Th17.
- (c) Regulatory T cells and Th2.
- (d) Th1 and Th17.
- (e) B cells and Th17.

Question 2

Which of the following are possible treatments for psoriasis?

- (a) Acitretin, ciclosporin, amoxicillin.
- (b) Methotrexate, imiquimod, adalimumab.
- (c) Secukinumab, aciclovir, ustekinumab.
- (d) Topical clobetasol, topical pimecrolimus, infliximab.
- (e) Topical clobetasol, methotrexate, adalimumab.

Question 3

Which of the following statements about mesenchymal stem cells (MSCs) is correct?

- (a) MSCs are directly responsible for interleukin-17 and tumour necrosis factor- α secretion.
- (b) MSCs are directly responsible for superinfection of psoriatic plaques by *Staphylococcus aureus*.
- (c) MSCs do not show any particular alteration in psoriatic plaques.
- (d) MSCs are directly linked to pathological T helper (Th)1–Th17/Th2 imbalance and may interact directly with keratinocytes.
- (e) MSCs are responsible for acantholysis and for plasma cell recruitment in psoriatic plaques.

Question 4

Mesenchymal stem cells are a potentially powerful instrument for the treatment of psoriasis because of what properties?

- (a) Their regenerative properties.

- (b) Their proinflammatory properties.
- (c) Their antibacterial properties.
- (d) Their immunomodulating properties.
- (e) Their antitumoral properties.

Question 5

The current available clinical data regarding the use of mesenchymal stem cells as a treatment for psoriasis has demonstrated which of the following?

- (a) Lack of efficacy.
- (b) Efficacy hampered by serious adverse events such as patient death and liver failure.
- (c) Efficacy but with relapse rates of > 50%.
- (d) Efficacy, but with one-third of the patients relapsing after treatment.
- (e) Only partial efficacy, with no adverse events.

Instructions for answering questions

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- Reflect on the article
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