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Review Article

Mesenchymal Stromal Cell Therapy for Steroid-Refractory Acute Graft-versus-Host Disease

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Abstract

Background: Steroid-refractory acute graft-versus-host disease remains a lethal complication of allogeneic transplantation, and mesenchymal stromal cells have been given for two decades on largely uncontrolled evidence.

Objective: To examine why single-arm series and randomised trials report irreconcilable response rates.

Methods: Narrative review of single-arm cohorts, randomised trials, mechanistic studies and regulatory decisions.

Findings: Single-arm studies reported 71% overall response in 55 patients and 83% at day 28 in 69 patients, whereas randomised trials found day-28 complete response of 45% versus 46% placebo (192 treated) and 35% versus 30% (244 treated). Placebo arms fell inside the single-arm range.

Conclusions: The evidence supports immunomodulatory activity conditional on inflammatory licensing, but not the efficacy implied by uncontrolled response rates. Function-based potency assays are required.

Keywords: Mesenchymal stromal cells; Graft-versus-host disease; Haematopoietic stem cell transplantation; Potency assay; Randomised controlled trials

Introduction

Acute graft-versus-host disease that fails to respond to corticosteroids remains one of the most lethal complications of allogeneic haematopoietic stem cell transplantation, and for twenty years mesenchymal stromal cells have been the most persistently attractive answer to it. The field opened with a single dramatic case: third-party haploidentical stromal cells infused into a child with grade IV gut and liver disease, followed by resolution [1]. An early institutional series extended the observation to a mixed cohort of therapy-resistant patients [2], and within a few years cells were being given on compassionate grounds across Europe, North America and Japan.

The evidentiary structure that grew up around those infusions is unusual and, on inspection, unstable. Every headline efficacy figure in the literature comes from an uncontrolled cohort. The only two randomised placebo-controlled comparisons ever completed in this indication were both null. That contradiction, rather than any question of biological plausibility, is what has governed the field's regulatory fortunes, and it is the subject of this review.

The argument developed here has three parts. First, that the single-arm and randomised literatures report response rates that cannot be reconciled by chance or by minor differences in case mix. Second, that variability in the cellular product itself — donor, tissue source, expansion passage, cryopreservation, and above all the inflammatory licensing state at the moment of infusion — is the most parsimonious explanation available. Third, that the field cannot move until lot release is governed by a potency assay that measures the specific function the product is supposed to perform in a patient.

Mechanism, licensing state and the identity of the product

Human marrow stromal cells suppress T-lymphocyte

proliferation in vitro in response to both cellular and mitogenic stimuli [3]. That property, however, is not what defines the cells. The consensus minimal criteria specify plastic adherence, a surface marker profile and trilineage differentiation capacity [4] — a definition built entirely from identity and none of it from immunological function. Two preparations can satisfy every criterion and behave differently in an inflamed recipient.

The reason is that immunosuppressive activity is conditional. Stromal cells are not constitutively suppressive; they are licensed by interferon-gamma, and the magnitude of suppression tracks the intensity of that priming [5]. Interferon-gamma activation before infusion changes outcome in murine graft-versus-host disease [6]. Suppression proceeds through the concerted action of chemokines and inducible nitric oxide synthase, so that the cells must be exposed to inflammation in order to acquire the phenotype [7], and cytokine-induced indoleamine 2,3-dioxygenase with bystander M2 macrophage differentiation accounts for much of the effect in human cells [8].

Later work complicated this further by locating the effect partly in the recipient rather than the graft. Infused stromal cells undergo apoptosis and it is the host's disposal of the apoptotic bodies that produces immunomodulation, with cytotoxic activity in the recipient predicting who responds [9]; phagocytosis of stromal cells by monocytic cells is the trigger [10]. If the active pharmaceutical ingredient is in part a recipient response to dying cells, then patient inflammatory state is a covariate of efficacy, not noise, and mechanism-based biomarkers become a prerequisite for interpreting any trial [11].

The single-arm record

The pivotal uncontrolled experience is the European phase II study, in which 55 patients with steroid-resistant disease received a median dose of 1.4×10^6 cells/kg,

ranging from 0.4 to 9 x 10⁶/kg; 27 received one infusion, 22 received two and 6 received three to five. Thirty patients achieved complete response and nine partial improvement, an overall response of 39/55, or 71% in a single-arm design [12]. Comparable single-arm figures accumulated elsewhere. A Japanese phase I/II study of JR-031 reported response at week four in 13 of 14 patients, 92.9% single-arm [13], and the subsequent phase II/III study in 25 patients with grade III-IV disease reported 24% complete and 36% partial response at four weeks, 60% overall, with durable complete response by week 24 in 12/25, or 48%, all single-arm [14].

Table 1: Major trials of mesenchymal stromal cells in steroid-refractory acute graft-versus-host disease by design, size, dose, endpoint and result [12,13,14,15,21,25,16,22].			
Study	Design (N)	Dose and endpoint	Result
Le Blanc 2008	Single-arm (55)	1.4 x 10 ⁶ /kg median; response	71% (30 CR, 9 PR)
Muroi 2016	Single-arm (25)	2 x 10 ⁶ /kg; durable CR wk 24	48%; wk-4 ORR 60%
Bader 2018	Single-arm (69)	1-2 x 10 ⁶ /kg; day-28 ORR	83% (CR 32%, PR 51%)
Kurtzberg 2020a	Single-arm (54)	2 x 10 ⁶ /kg; day-28 ORR	70.4% (56.4-82.0)
Protocol 265	Randomised (97 vs 95)	CR lasting 28 days or more	45% vs 46%, failed
Protocol 280	Randomised (173 vs 87)	CR lasting 28 days or more	35% vs 30%, failed

The highest figure in the literature comes from a pooled eight-donor product manufactured in Frankfurt and given to 69 patients, 51 children and 18 adults, 96% with grade III-IV disease, at 1-2 x 10⁶/kg weekly for a total of 212 doses. Day-28 overall response was 83%, 57 of 69, with 32% complete and 51% partial; six-month overall survival was 71% with a 95% confidence interval of 61-83 — again single-arm [15]. A Spanish multicentre compassionate-use programme treating 62 patients, of whom 46 had acute or late-acute disease, at 1 x 10⁶ cells/kg with a median of four infusions, reported 58.7% overall response in the acute cohort, single-arm [16]. Other paediatric and adult series contributed the same qualitative picture without

controls [17,18,19,20].

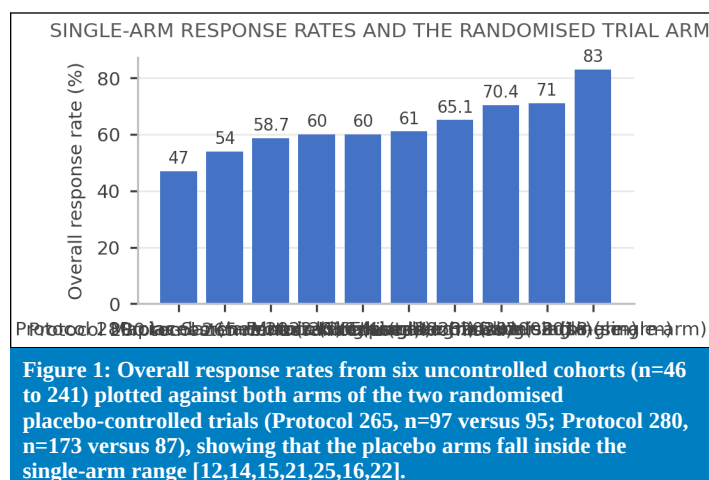
The study that eventually carried a product to licensure was itself single-arm. MSB-GVHD001 enrolled 55 children aged seven months to seventeen years with grade B-D disease, of whom 54 entered the efficacy analysis at 2 x 10⁶ cells/kg twice weekly for four weeks. Day-28 overall response was 70.4%, with a 95% confidence interval of 56.4-82.0, comprising 29.6% complete and 40.7% partial response; among the 38 responders the median duration of response was 54 days [21]. Analysed by regulators on the full enrolled denominator of 55, day-28 response was 69.1%, 95% confidence interval 55.2-80.9, with 14 deaths among the 54 treated. The comparator throughout was a prespecified null response rate of 45%, a historical constant rather than a randomised control arm.

The randomised trials and the response gap

Two randomised placebo-controlled trials of remestemcel-L were run, and neither has a result resembling the single-arm literature. Protocol 265 tested the cells added to steroids as first-line therapy in adults: 193 randomised, 192 treated, 97 receiving cells and 95 placebo. Day-28 overall response was 60% with cells versus 61% with placebo, and the primary endpoint, complete response lasting at least 28 days, was 45% versus 46%. The study failed its primary objective. Protocol 280 tested the same product in steroid-refractory disease at 2:1 allocation: 260 randomised, 244 treated, 173 receiving cells and 87 placebo. Day-28 overall response was 54% versus 47% and the primary endpoint 35% versus 30%; the difference was not significant and the trial failed its primary objective, with no treatment effect detectable on reanalysis using day-28 response [22].

The arithmetic is the whole argument. The randomised placebo arms — 46% and 30% complete response, 61% and 47% overall response — sit squarely inside the range spanned by the single-arm reports, and in the case of Protocol 265 the placebo arm outperformed several

published cell cohorts. The cells did not underperform expectations so much as the controls met them. Whatever the single-arm series were measuring, a large share of it was the natural history of second-line acute graft-versus-host disease under standard care, selection of patients well enough to be enrolled, and the absence of a comparator. The most candid contemporaneous reading of the first failure asked whether it was a death knell or a bump in the road and concluded that the answer depended on whether the product had been characterised well enough for the question to be meaningful [23].



Response as an endpoint and as a surrogate

The endpoint carries some of the burden. Day-28 overall response is a clinical composite scored across skin, gut and liver, and its reproducibility depends on data collection conventions that were only standardised across centres after most of these studies were designed [24]. It is nonetheless strongly prognostic. In a 241-patient paediatric expanded-access programme, day-28 overall response was 65.1%, comprising 14.1% complete and 51.0% partial; day-100 overall survival was 66.9% overall, 82.1% among day-28 responders and 38.6% among non-responders, all within a single-arm cohort [25]. Response in that programme fell with baseline severity, 72.9% at grade B, 67.1% at grade C and 60.8% at grade D, and exposure was substantial, with a median of 11

infusions and a range of 1 to 24. The European phase II study showed the same pattern: two-year survival of 53% in complete responders versus 16% in partial or non-responders, $p=0.018$, and one-year transplant-related mortality of 37% versus 72%, $p=0.002$, again single-arm [12].

These associations are frequently presented as evidence that the cells work. They are not. Within an uncontrolled cohort, response identifies a prognostic group; it does not establish that the intervention produced either the response or the survival difference. The randomised trials tested precisely that inference and did not support it. Meanwhile the comparator landscape moved: ruxolitinib was tested against best available therapy in a randomised trial and became the reference standard against which any second-line agent must now be judged [26].

Product and process variability as the leading explanation

The most plausible reconciliation is that the single-arm series and the randomised trials did not test the same biological agent. No head-to-head randomised comparison of stromal cell products, tissue sources, donors or passages exists in this indication, so the case is inferential — but it is built from consistent manufacturing and preclinical data rather than speculation.

The academic series that produced the highest response rates used freshly expanded, often locally manufactured cells at low passage, sometimes selected from a specific donor for a specific patient, and infused within hours of harvest. The randomised trials used a single industrially banked, cryopreserved, centrally released product administered on a fixed schedule to a heterogeneous population across many sites. These are different agents delivered under different conditions, and only one of them was ever tested against a placebo.

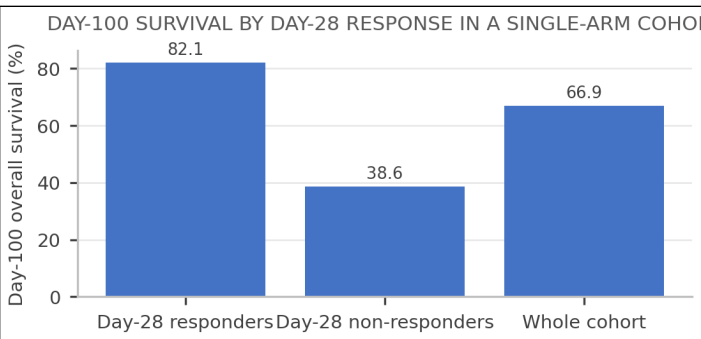


Figure 2: Day-100 overall survival by day-28 response status in the single-arm paediatric expanded-access programme (n=239 evaluable for survival), an association within an uncontrolled cohort that marks a prognostic group rather than a treatment effect [25].

Donor-to-donor variation in immunosuppressive capacity is large and not predicted by the identity criteria. Expansion passage was flagged early as an outcome-relevant variable in long-term follow-up of treated patients [27]. Cryopreservation, which every commercial product requires and most academic series avoided, alters immunomodulatory and therapeutic behaviour [28]. Licensing state at infusion differs systematically between a freshly harvested academic preparation infused within hours and a thawed vial from a frozen bank. Combinatorial assay matrices demonstrate that potency is multidimensional and that single-parameter surrogates fail to capture it [29]. The clinical translation problem has been stated repeatedly in these terms: easy manufacturing coexists with hard standardisation and commercialisation, and the resulting product heterogeneity is the field's defining obstacle [30,31,32].

Potency assays and the regulatory divergence

For the field to move, lot release must be governed by an assay that measures the function the product performs in a patient, not the properties that identify it. Minimally, such an assay would quantify suppression of activated T-cell proliferation by a licensed preparation; it would report responsiveness to interferon-gamma rather than baseline activity, since the clinical substrate is an inflamed recipient; it would measure the induction of indoleamine

2,3-dioxygenase and of macrophage repolarisation as effector readouts; it would be performed on the thawed clinical vial rather than a fresh research culture; and it would be validated against clinical response so that a numerical release threshold means something. A matrix of complementary immune functional assays, rather than any single readout, is the form such a release criterion must take [33]. Such an assay would also have to be reported alongside every trial result, so that a null outcome could be attributed to a characterised product rather than to an unknown one, and so that a positive outcome could be transferred to another manufacturing site.

Table 2: Regulatory standing of mesenchymal stromal cell products by jurisdiction and date, taken from the FDA, MHLW and EMA source documents and set against the standardisation problem described by [31].

Product	Jurisdiction	Date	Standing
Ryoncil (remestemcel-L-rknd)	United States, FDA	18 Dec 2024	Approved, paediatric SR-aGVHD
TEMCELL HS Inj. (JR-031)	Japan, MHLW	18 Sep 2015	Approved, acute GVHD
Any MSC product for GVHD	European Union, EMA	-	No authorisation
Alofisel (darvadstrocel)	European Union, EMA	23 Mar 2018	Crohn fistulas, not GVHD
Alofisel (darvadstrocel)	European Union, EMA	13 Dec 2024	Authorisation withdrawn

Regulators have reached opposite conclusions on the existing evidence. In the United States, the FDA approved Ryoncil (remestemcel-L-rknd) on 18 December 2024 for steroid-refractory acute graft-versus-host disease in paediatric patients two months and older, at 2 x 10^6 cells/kg twice weekly for four weeks, on the strength of a single-arm study of 54 patients with a day-28 overall response of 70.4%, 95% confidence interval 56.4-82.0, tested against a prespecified historical null of 45% rather than a control arm. Two complementary lot-release potency assays were required, one an IL-2 receptor alpha (CD25) inhibition assay and the second not disclosed, with

further quantitative assays imposed as postmarketing commitments. In Japan, TEMCELL HS Inj. was approved on 18 September 2015 for acute graft-versus-host disease after transplantation, on single-arm studies of 14 and 25 patients. In the European Union there is no authorised mesenchymal stromal cell product for this indication; the only such product ever authorised, Alofisel, was authorised on 23 March 2018 for perianal fistulas in Crohn's disease and withdrawn on 13 December 2024.

Conclusion

The distance between 71% and 83% overall response in single-arm series and 45% versus 46% and 35% versus 30% in randomised comparisons is not a statistical curiosity. It is the measurement of how much apparent efficacy an uncontrolled design can generate in a disease with variable natural history. Approval of a product on a single-arm study against a historical null does not close that gap; it relocates it into routine practice, where the same uncontrolled inference will be made patient by patient. The mechanistic literature explains why product identity is insufficient and why licensing state should dominate outcome. The remedy is not another uncontrolled series but a functionally defined, thaw-validated, clinically anchored potency assay, followed by a randomised trial of a product that assay certifies. Until a lot can be released on what it does rather than what it is, the field will keep reproducing the same disagreement between its two literatures, and each new single-arm cohort will restate a result that the next controlled comparison declines to confirm.

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