

## Posology for Regenerative Therapy

Andre Terzic, Atta Behfar

*Sola dosis facit venenum* (The dosage makes it either a poison or a remedy)

—Paracelsus (1493–1541)

The science of dosage or posology (from Greek *posos*, how much, and *logos*, study) is a branch of pharmacology and therapeutics concerned with treatment dosage and dosage regimen. Establishing optimum dosage underpins every clinical development plan for novel therapeutic candidates. Failure to select the adequate drug dose is a leading culprit for regulatory delays or denial of initial applications for new drugs and, more generally, inadequate dose selection contributes to the high attrition rate of pivotal clinical trials.<sup>1</sup>

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Regulatory agencies are committed to facilitate the development and ultimate licensure of safe and effective regenerative therapies.<sup>2</sup> To this end, dedicated programs applicable to stem cell therapies have been designed to expedite the advancement and approval of new products (eg, breakthrough therapy designation, accelerated approval).<sup>3</sup> However, with limited grasp on the disposition (pharmacokinetics) and action (pharmacodynamics) of stem cells, posology applied to the development of cardiovascular regenerative therapies is still a nascent area of investigation.

Without the establishment of standardized dose regimens, clinical trials continue to evaluate wide dose ranges.<sup>4</sup> A case in point are clinical studies that have shown rather paradoxical results about the relationship between the stem cell dose and clinical benefit in the setting of heart disease.<sup>5</sup> Accordingly, scientific, regulatory and medical communities remain challenged with critical gaps in knowledge required for successful clinical translation of a regenerative biotherapeutics.<sup>6</sup> Principles that apply in conventional drug development may not be readily transferable to the evolving regenerative pharmacy reflecting the dichotomy of product classes (eg, chemicals versus biologics). Traditional medicinal products (small chemical molecules) feature defined mechanisms of action and delineated processes of absorption, distribution,

metabolism, and excretion. In contrast, emergent biotherapeutics (including live cell-based therapies) display complex and still poorly understood pharmacodynamics and pharmacokinetics.<sup>7</sup> A closer understanding of determinants that define the dose–exposure–response triad is needed to inform dose and schedule selection (Figure), notwithstanding that to date only a limited number of studies have formally examined the posology of regenerative therapy.

The paucity of cardiovascular clinical trials designed to assess cell dosage is further accentuated by the limited information available on cell fate post-delivery, including the kinetics of engraftment or the dynamics of autocrine/paracrine signaling. Toward addressing this knowledge gap, the TRIDENT Study (Transendocardial Stem Cell Injection Delivery Effects on Neomyogenesis)—presented in this issue of *Circulation Research*—compared outcomes after randomized treatment with 2 doses of allogeneic bone marrow-derived human mesenchymal stem cells in patients with chronic ischemic cardiomyopathy.<sup>8</sup> Thirty patients received either 20 or 100 million cells identically delivered, in a blinded manner, via transendocardial injection (ten 0.5 cc injections per patient). At 1 year follow-up, both cell doses were safe and well tolerated with favorable impact on reducing postinfarction scar size, but only the larger dose was associated with improved ejection fraction. In the context of the TRIDENT trial, the higher dose may provide greater benefit than the lower dose suggesting a direct relationship between cell dose and clinical efficacy at least within the dose range tested, a conclusion supported by pro-BNP (B-type natriuretic peptide) levels which remained stable only in the 100 million human mesenchymal stem cell–treated group.<sup>8</sup> The TRIDENT study therefore adds to an increasing compendium of clinical experience for use of cell-based technology in patients with heart disease. As recognized by the TRIDENT investigators, the study was limited by lack of a placebo group and small sample size testing 2 distinct doses. The TRIDENT study thus underscores the ongoing need for clinical trials designed to evaluate dosage regimens while incorporating cell dose ranges and well-defined patient populations with appropriate controls.

A monophasic dose-effect relationship has been documented previously with cells of mesenchymal origin delivered transendocardially in cardiomyopathic ventricles. This includes a dose-escalation study where the highest dose (150 million cells) produced greatest benefit.<sup>9</sup> However, inverse or U-shape relationships have also been reported. For example, the POSEIDON trial (Percutaneous Stem Cell Injection Delivery Effects On Neomyogenesis Pilot Study) demonstrated an inverse relationship between the human mesenchymal stem cells dose delivered and clinical outcomes, with maximal efficacy achieved with a lower dose (20 million versus the larger 200 million cells).<sup>10</sup> More recently, the CHART-1

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From the Department of Cardiovascular Medicine and Department of Molecular Pharmacology and Experimental Therapeutics, Center for Regenerative Medicine, Mayo Clinic, Rochester, MN.

Correspondence to Andre Terzic, MD, PhD, Department of Cardiovascular Medicine and Department of Molecular Pharmacology and Experimental Therapeutics, Center for Regenerative Medicine, Mayo Clinic, Stabile 5, 200 First St SW, Rochester, MN 55905. E-mail [terzic.andre@mayo.edu](mailto:terzic.andre@mayo.edu)

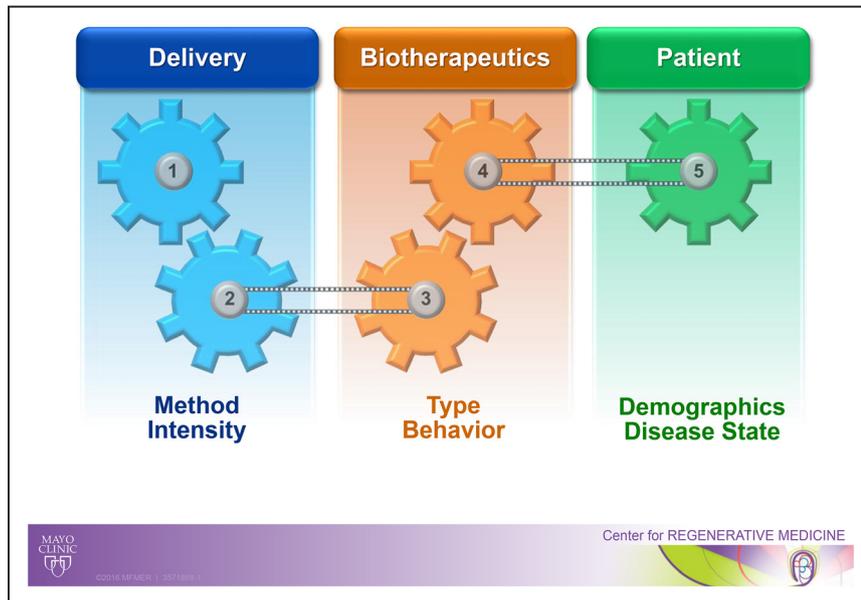
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**Figure.** Linking elements that determine the posology paradigm for regenerative therapy. Regenerative biotherapies display complex pharmacodynamics and pharmacokinetics encompassing multiple factors including the delivery method and intensity, the biotherapeutics type and behavior, and the patient demographics and disease substrate.

trial (Congestive Heart Failure Cardiopoietic Regenerative Therapy) addressed the effect of cardiopoiesis-based cell therapy in advanced heart failure.<sup>11</sup> In this, to date, largest regenerative cardiovascular trial, cardiopoietic stem cells—also obtained from a mesenchymal source and delivered endomyocardially—showed significant reverse remodeling with improvement in left ventricular volumes especially in subgroups of patients who received an intermediate number of cell injections, indicating a ceiling effect as excessive therapeutic intensity may offset benefit.<sup>12</sup>

The act of cell delivery may cause myocardial damage, through multiple mechanisms that are both mechanical and biological in nature. Beyond cell quantity per se, several confounding factors may influence outcome including the delivery method intensity and disease substrate (Figure). It has been suggested that intracoronary injections, typically used in treating acute conditions, require cells to extravasate and migrate to the areas of injury which may result in lower engraftment rates than intramyocardial injections, thus requiring higher initial doses.<sup>8</sup> Moreover, in the context of severe hypoxia and inflammation germane to acute myocardial infarction, the recently injured tissue is unlikely to mimic a chronic disease state and as such may dictate distinct doses and treatment schedules.

Going forward, establishing an evidence-based posology paradigm is required to ensure accurate titration of regenerative therapies and advance the science of regenerative medicine. Studies evaluating treatment schedules (eg, singular versus repeat stem cell interventions),<sup>13</sup> in tandem with the intricacy of the regenerative product behavior post-delivery within the host milieu, including the dynamics and kinetics of cross talk with endogenous healing processes are needed. Furthermore, the formulation of regenerative therapeutics beyond first generation stem cell products into next generation acellular or engineered counterparts can profoundly impact the attributes of the pharmacokinetic and pharmacodynamic equations.<sup>14</sup> Cell-free products mimicking the paracrine impact of cell-based therapies can potentially achieve

standardized dosing reflecting more closely the pharmacology of small chemical molecules. Another avenue for posological standardization includes use of cyto-engineering and allogeneic strategies to overcome cell-to-cell variability in regenerative potency inherent to autologous cell therapies. Such approaches provide the consistency required to streamline the understanding of dosage parameters for regenerative products. The path to adoption in cardiology care<sup>15</sup> will thus mandate a transdisciplinary effort bringing together multiple specialties to establish validated posology for regenerative therapy.

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