

Review Article

An Overview of the Journey of Stem Cell Based Interventions from Bench to Bedside and the Growing Challenge of Unproven Interventions

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Abstract

Background: Current researches on Stem Cell Interventions (SCI) are mostly at various stages of clinical translation, and not ripe for immediate marketing. However, there is a global rise in patients opting for unproven SCI from dubious stem cell clinics.

Objectives: To describes the usual stages of SCI's clinical translation, factors fuelling the increase in unproven SCI and possible strategies for tackling the situation that have been mentioned in research articles and patient information sources.

Conclusion: Stem cell tourism is on the rise. Direct to customer marketing of SCI through websites and social media using emotional narratives, patient testimonials and false claims of benefits, and unrealistically positive portrayal on social media are contributing factors. The situation may be addressed by treating stem cells as medical innovation and speeding up their clinical translation using modifications like expedited, conditional marketing approval. Medical societies can generate meta-analyses and updates for keeping clinicians informed about the latest therapies so they can guide patients. These along with organisations like ALSuntangled, can generate patient information booklets to help patients make informed decisions. Also, Patient Information Campaigns on social media and media's coverage of increasing SCI related lawsuits can possibly help raise public awareness about unproven SCI.

Keywords

Stem Cell Intervention, stem cell therapy, unproven stem cell intervention, clinical translation, stem cell

clinical trials, stem cell clinics, stem cell tourism, direct to consumer marketing

1. Introduction

Stem Cell Interventions (SCI), Stem Cell Based-Interventions (SCBI) or Stem Cell Based Therapies (SCBT) are different terms used to describe the use of the magical stem cells isolated in the late 20th century for prevention or treatment of diseases, typically by injection.

1.1 Approved Stem Cell Based Interventions for Clinical Application

The potentials for stem cells are being explored currently but to date, the few safe and efficacious options for clinical applications are mainly limited to haematopoietic stem cell transplantation for some malignant and some non-malignant hematologic conditions (Zehravi et al., 2017). The journey from bench to the bedside is long, arduous and regulated for the sake of science, its researchers and the patients alike. Many clinical trials at different phases are underway for SCI and can be found listed at online registry sites like the United States' National Library of Medicine's clinicaltrials.gov, European Union's EU Clinical Trials Register (EU-CTR), United Kingdoms' ISRCTN registry, Australian New Zealand Clinical Trials Registry (ANZCTR), etc. (Health 2012; Zehravi et al., 2017).

1.2 Hope for Future Fulfilment of Unmet Medical Needs

It is human nature to search for and to give hope to those in need of it. People suffering from presently untreatable illnesses labelled as "unmet medical needs" naturally reach out for any beacon of light that they may find (Murdoch & Scott, 2010; Bauer et al., 2018; von Wunster et al., 2018). Media's hyped up portrayal of scientific developments and possibilities in the of field of stem cells sometimes creates a misunderstanding amongst the society about the efficacy and preparedness of technologies that are not immediately ready for clinical utilisation (Caulfield et al., 2016; Murdoch et al., 2018) .

2. Discussion

2.1 Clinical Translation of Stem Cell Interventions

2.1.1 Stages in the Process of Clinical Translation

Scientists face innumerable challenges in converting propositions and expectations into reality in the lab and these then have to make a time-consuming but guided and safe journey from the bench to the bedside of the patient. This process is called clinical translation. It entails pre-clinical animal-based research (also called bench or laboratory research) to prove the safety and efficacy of a hypothesis; followed by peer-reviewing, publishing and replication by other researchers. Thereafter, approval of an ethical body and then a regulatory agency (e.g., European Medicines Agency, Health Canada, US Food and Drug Administration) are needed to begin recruiting patients for human-based research which is called a "clinical trial". There are four stages of clinical trials. First of all, primarily safety in a small group of individuals is assessed in phase 1; then phase 2 assesses efficacy in a larger group, which is further profiled in an even larger group along with safety data in phase 3. Only then can a legitimately tested "intervention" be fairly called an "approved therapy or treatment" (Master & Caulfield, 2014).

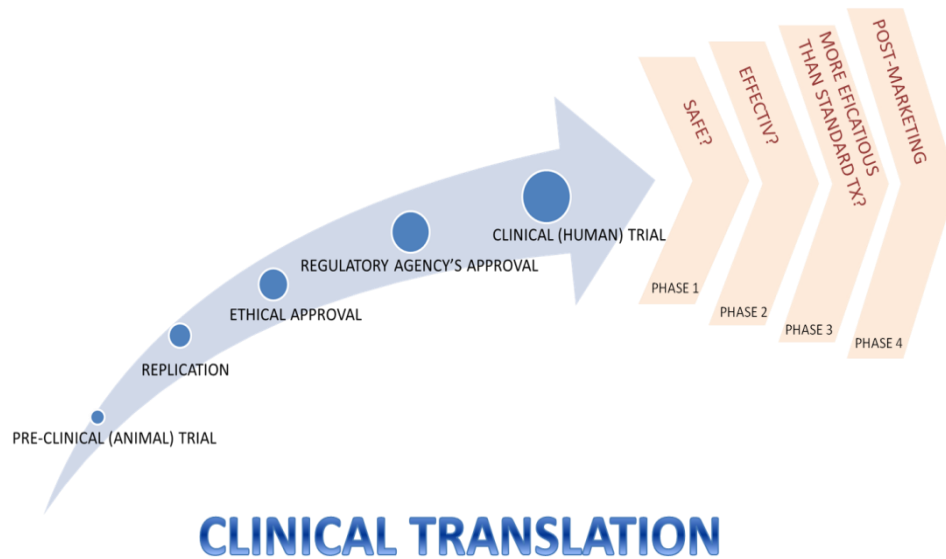


Figure 1. Stages in Clinical Translation of Legitimate Stem Cell Interventions

The process is financed by the scientists or organisations involved and not by the recipients of trials. It is also note-worthy that not every person looking to get recruited into a clinical trial gets the intervention, for they may form part of the control group. The rigorousness of the process of clinical translation strives to ensure that qualified teams operate in a scientific manner. Thereby, safety of the patients, the integrity of the generated results, and thus the reputation of and trust placed in the scientific community in general are not compromised.

2.1.2 Role of Ethical Review Boards in Clinical Translation

Although a clinical trial's being registered and listed online (e.g., in the US at clinicaltrials.gov) is beneficial and needs to be encouraged; it does not vouch for it being safe, scientifically sound or justified (Prayle et al., 2012). This burden rests on the shoulders of ethical review boards and regulatory authorities (Barker et al., 2018). They have a vital role to play in ensuring human trials are given the go ahead only after sufficient preclinical safety and efficiency evidence is presented. The International Society for Stem Cell Research (ISSCR) has developed guidelines to aid enhancement of the process by producing "Stem Cell-Based Clinical Trials: Practical Advice for Physicians and Ethics/Institutional Review Boards (Daley et al., 2016).

2.2 The Rise and Boom of Clinics Offering Unproven Stem Cell Interventions

2.2.1 The Desire to Fulfil Today's Unmet Medical Needs

The drawn out, lengthy, multi-phased traditional clinical translation process means patients look towards any other services offering SCI prematurely to meet their needs of today. This creates a niche for medical as well as complementary and alternative medicine practitioners running shady stem cell clinics providing "unproven Stem Cell Interventions" (Petersen et al., 2016). These clinics often claim to provide interventions for disparate conditions ranging from medical illnesses to cosmetic benefits.

A study by Conolly et al. in 2014 reviewed online advertisements of stem cell clinics. They found

multiple sclerosis, anti-ageing, Parkinson's, spinal cord injury and stroke to be the five most frequently advertised indications for unproven SCI (Connolly et al., 2014). They found that SC used were mostly autologous and were frequently bone marrow or adipose derived. Another study by Berger et al. in 2016 reviewed 417 English language websites for SC clinics. They found that the most common indication overall was skin care or anti-ageing (47.2%), while orthopaedic injuries, diabetes, multiple sclerosis and Parkinson's topped amongst medical illnesses (Berger et al., 2016; Terence et al., 2018).

2.2.2 Characteristics Identifying Unproven Stem Cell Interventions

Since there is no proper universal definition for unproven cellular therapies, Srivastava et al. suggests that they be identified by no obvious scientific proof of efficacy, unknown mechanism of action, inadequate preclinical data to determine safety in humans, a lack of a standardised manufacturing process to ensure consistency of product quality, incomplete information transfer to patient preventing attainment of an informed consent, lack of a tested administration method, and uncontrolled experimentation in humans (Srivastava et al., 2016; Bauer et al., 2018).

2.2.3 Role of direct-to-customer Marketing: Patient Testimonials and Evasive Alleged Claims for Efficacy of Unproven Stem Cell Interventions

Stem cell clinics are mostly found through the internet. Direct-to-consumer (DTC) advertising targets the patients rather than the health care providers (Lau et al., 2008; Ryan et al., 2010; Ogbogu et al., 2013; Turner & Knoepfler, 2016; Sipp et al., 2017; Datta, 2018; Julian et al., 2018; Turner, 2018). This is done through clinic websites and social media accounts that advertise compelling patient testimonials or make claims or suggestions that dupe patients into opting for unproven SCI that often lack safety and/or efficacy data (Ryan et al., 2010).

In 2014, Kamenova et al. in 2014 scrutinised 363 English language tweets by or referring to nine popular SC clinics on Twitter. About a third either suggested or expressly stated beneficial effects of the therapies they offered. Patients' statements appeared to always be supportive of these claims while majority of the tweets (60.2%) were positively minded and discussions on negative side effects were lacking (Kamenova et al., 2014). Also in 2014, Connolly et al. revealed that 88% of the reviewed online marketing of SC clinics claimed efficaciousness and 16% even mentioned the potential to cure (Connolly et al., 2014). Another study in 2018 by Murdoch et al. reports that amongst the explored 243 SC clinics' websites advertising SC interventions, only one third (33.33%) mentioned they were without proof or experimental. A smaller percentage revealed evidence of being efficacious (12.76%) or limitedly efficacious (18.93%). Generalized risks were indicated in about a fourth (24.69%) while specific risks were mentioned in much less (5.76%) (Murdoch et al., 2018).

2.2.4 Role of Discussions on Social Media

Conversations on social media sites have been found to be largely positive for unproven stem cell interventions and lack an accurate representation of facts regarding these procedures being unproven and lacking data on safety and efficacy (Kamenova et al., 2014; Du et al., 2016). An infodemiologic study by Du et al. in 2016 studied twitter conversations regarding a sports celebrity Detroit Red Wing's

and Gordie Howe's stem cell treatment for stroke in 2014. The response was hugely positive; talked of him improving, while only 1 out of 2783 tweets clearly stated that it was unproven and 3 indicated the lack of supporting scientific data in direct to consumer marketed SCI (Du et al., 2016). Given social media's immense influence in today's world, it is thought to play an important role in shaping the lay-person's expectations from unproven SCI which in turn promote the pursuance of unproven SCI (Du et al., 2016).

2.3 The Growing Phenomenon of Stem Cell Tourism, Financial Exploitation of Patients and Adverse Events from Unproven SCI

SC clinics' distribution is global (Berger et al., 2016; Kuriyan et al., 2017). But in adherence to regulatory agencies' laws, and revision of policies means some are located in or have relocated to less advanced developing countries with less well defined regulation. This means that some patient may need to travel outside their country for receiving unproven SCI giving rise to the concept of "stem cell tourism" (Ryan et al., 2010; Cohen & Simana, 2018; Julian et al., 2018).

Patients are financially exploited and charged from around \$3500 to a whopping \$400,000, excluding travel expenses (Matthews & Iltis, 2015). Insurance companies mostly do not cover these and the costs from the subsequent side effects, therefore the money often comes from communities and crowd-funding campaigns with emotional narratives (Turner, 2010; Abou-El-Enein et al., 2016; Snyder & Turner, 2018; Snyder et al., 2018).

There are incidences of adverse events resulting from unproven SCI including febrile illnesses, infections, neoplasms, neurological complications, autoimmune reactions, vision loss (from intravitreal injections), brain haemorrhage (from injection into brain), ventricular fibrillation (from myocardial injection), pulmonary embolism and even death (Dobkin et al., 2006; Sheldon, 2006; Amariglio et al., 2009; Pytel et al., 2010; Thirabanasak et al., 2010; Alderazi et al., 2012; Butzkueven, 2013; Dobke et al., 2013; Jung et al., 2013; Kuriyan et al., 2017; Bauer et al., 2018).

2.4 Stemming the Rising Tide of Stem Cell Tourism for Unproven Stem Cell Interventions

2.4.1 Lessons from the Past: HIV/AIDS and Breast Cancer Activisms, and Their Outcomes

Similar tussles between regulators and patients have been observed in the past. In the US in 1980s, FDA had to compromise its policies for clinical trials for Investigational New Drugs (INDs) for AIDS in the face of patient protests (DHHS, 1987; Quinn, 1996). Patients in trials did not want to risk consuming placebos and were on their own sharing drugs from different trials as well as consuming other AIDS drugs being marketed in Japan; compromising the integrity of the trial results (Booth, 1988; Leventhal et al., 1991). They wanted and were given access to INDs outside of clinical trials (Service, 1990). Expedited drug trials with use of surrogate end-points had to be used to speed up the process and bring treatments to the market (Prentice, 1989; Fleming & DeMets, 1996). Results were that patients didn't want to participate in trials anymore and it took longer to finish trials eventually (Matthews & Iltis, 2015).

On the other hand, in the 1990s in US, it was speculated that High Dose Chemotherapy followed by

Autologous Bone Marrow Transplantation (HDC/ABMT) might benefit metastatic breast cancer like it had been shown to be efficacious and safe in other cancers (Matthews & Iltis, 2015). Initially, insurance companies and government organisations denied finances for the procedure which was very costly and lacked evidence (Schmoor & Schumacher, 1999; Rettig et al., 2007). Thereafter, in the face of suing for damages upon death of patients who could not receive the intervention, insurance companies started covering the intervention which was later found to have no superiority over other treatments but had sinister side effects that were detrimental for the patients (Mello & Brennan, 2001; Welch & Mogielnicki, 2002; Jacobson et al., 2007).

This teaches us that regulatory authorities have a tough job of guarding scientific advancements and their benefits to society but they may or may not need to show some flexibility at times.

2.4.2 Stem Cell Interventions as Medical Innovation

The traditional four phased model of clinical translation upheld by the scientific community prioritises patient safety. It serves to very well regulate investigations surrounding regular interventions including drugs, devices and procedures. But stem cells being a complex entity encompass a vast variety of possibilities for interventions in innumerable conditions and thus differ from the usual. Belmont report describes “medical innovation” as health care departing significantly from the practiced standard and it is contended by many that stem cells should be treated as medical innovation (Department of Health 2014). Thus modified forward-looking strategies need to be developed and applied for efficient exploitation of stem cells’ potentials in healthcare.

2.4.3 Expedited and Conditional Marketing Approval for Stem Cell Interventions & Responsible Reporting of Results

It is hoped that this will help overcome the rising tide of stem cell tourism and plug the drain of unreported data and wastage of resources through dodgy stem cell clinics (Fung et al., 2017). Registration and responsible reporting of results should be encouraged even from stem cell clinics (Fung et al., 2017). Seydna et al. has suggest a stem-cell based learning health system (Touré et al., 2018). Japan’s regulatory agency PMDA has revised laws for regenerative medical products and allows expedited time-limited (7 year) conditional marketing approval after initial efficacy and safety predictions are made (Konomi et al., 2015; Matthews & Iltis, 2015). Patients’ informed consent is required. Simultaneously, data accumulation from trials continues to confirm efficacy and safety and thereafter either renewed approval for continued marketing need to be sought based on the final results, or the product need to be withdrawn from the market. Similarly, other countries could allow conditional permits to market earlier on in clinical trials, speeding up of the four phases of clinical trials or inclusion of more people earlier on in the trials, etc.

Besides the above suggestion of accelerating the marketing approval process and introducing flexibility in clinical translation of new SC interventions, other direct and round-about strategies are proposed in scientific literature.

2.4.4 Role of Medical Societies and Organisations: Keeping Clinicians Informed and Educating the Patients

For a particular intervention, several drawn-out clinical trials may be underway at various times and it may be difficult for clinicians to follow them and interpret results. Sometimes results may seem inconclusive or even contradictory. This often leaves clinician uninformed about their field's current status of SCI so that they are unable to advise their patients with regards to it (Bowman et al., 2015). Proper meta-analyses of SCI trials are essential for moving forward from multiple completed trials with varying results, to clinical application (Haidich, 2010; Ciccocioppo et al., 2018; Gyöngyösi et al., 2018; Shu et al., 2018; Sun et al., 2018; Yang et al., 2018). Weiss et al. suggest that medical societies and associations play a proactive role in keeping clinicians informed and educating patients about approved interventions along with counselling by health care providers (Weiss et al., 2018). They should create and provide to patients up-to-date information leaflets in lay person language about current status of SC research and the legitimate SCI options available (Freishtat & Weiss, 2017; Jin, 2017). They can carefully review and write about alleged claims of specific SC clinics for the benefit of patients and even report them to the authorities, but this may poses a threat of possible hostility or litigation by the specified business owners. ALSuntangled is an example of such a group of volunteers that write reviews to help ALS patients make informed decisions about treatment (Group, 2010; Group, 2010; Group, 2015).

2.4.5 Using Social Media for Educating the Public

Social media can be used to the purpose of guiding the public with towards approved stem cell therapies with supporting scientific data. It can also raise awareness about unproven SCI lacking the same. In 2017, McNutt et al. studied the potential of social media (Twitter) for Public Information Campaigns (PIC) for SCI which showed some promise but suggested that further researches are needed to further improve the prospects (McNutt & Zarzeczny, 2017).

2.4.6 Public Health Litigations to Aid the Reduction in Unproven Stem Cell Interventions

People are now a days filing law suits against SC clinic, suing them for damaging side effects and complications, as well for fraudulent claims and financial exploitation (Martinho & Turner, 2017). An increase in this trend could serve to create publicity in the media and remould its portrayal of unproven SCI as something magical without side effects. It would raise awareness amongst the masses regarding the dangers of such clinics offering unproven SCI and bring them to the authorities' attention so that appropriate policy changes can be made and strictly implemented (Horner et al., 2018).

3. Conclusion

The long, drawn out process of clinical translation and the need for satisfying presently unmet medical needs leaves a niche for unproven stem cell interventions at stem cell clinics. The phenomenon of travelling for unproven SCI, called stem cell tourism, is on the rise. Direct to customer marketing of SCI for cosmetic and medical conditions through websites and social media using emotional narratives,

patient testimonials and false claims of benefits of the procedures, as well as the overwhelmingly positive portrayal of such interventions on social media are contributing factors in this. Patients are financially exploited, and there are reports of resulting adverse events in some patients including infections, tumours and rarely even death. A review of scientific literature and patient information sources for ways to tackle the challenges suggests the treatment of stem cells as medical innovation. Hence modified, forward-looking strategies to speed up clinical translation of SCI may be considered; like expedited, conditional marketing approval. Also, the medical societies and organisations can play an important role in generating meta-analyses and updates for keeping clinicians informed about latest stem cell based therapies available in their specialities so they are able to guide their patients. These along with organisations like ALSun tangled, can generate patient information booklets to help patients make informed decisions with knowledge of approved stem cell based therapy options available to them. In addition, it is speculated that Patient Information Campaigns on social media as well as media coverage of the increasing number of lawsuits suing stem cell clinics for damages and fraud could help raise public awareness about unproven SCI.

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