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Autologous white blood cell infusion for trauma, brain trauma, stroke and select immune dysfunction co-morbidities: A promising and timely proposal?

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ABSTRACT

All traumas suppress the immune system, resulting in higher morbidity and mortality. Infections, poor nutritional status, chronic illness, fatigue, therapies or procedures performed during and after transport also negatively affect the immune system. Large populations are impacted by trauma worldwide and suffer enormous costs in both direct and indirect expenditures from physical, psychological and functional losses. Most therapies and studies of trauma, brain trauma, stroke, immune suppression and their co-morbidities do not address nor discuss methods that promote immune system resuscitation or efficacy to support its role in post-trauma healing and rehabilitation. These omissions present an opportunity for using autologous stored naïve (unexposed to the current trauma and co-morbidities) white blood cell infusions (autologous white blood cell infusion) (AWBCI) to supplement treatment of most traumas, trauma-associated infections, other co-morbidities and immune suppression derived problems in order to improve the global standard of trauma care. We hypothesize to give the traumatized patients back their own immune system that has been 'stored' in some fashion, either cryogenically or just after or during the trauma event [surgery, etc for example]. We emphasize that other treatments should not be replaced – rather we suggest AWBCI as concurrent therapy. We present focused select animal and human studies as proofs of concept to arrive at and support our therapeutic suggestion and hypotheses, flowing historically from donor white blood cell therapy [DLI] to close cohort white blood cell therapy to autologous white blood cell infusion [AWBCI]. We integrate the concept of personalized medicine from an evidence-based framework while maintaining scientific rigor and statistical proof as a basis of our hypotheses.

Introduction

Several recently published studies further enabled our proposal and to invite robust clinical investigation towards validation and implementation of this promising therapeutic modality. We aim to increase the standard of care for the populations suffering from a variety of traumas and immune suppressions, and to propose a potential therapy to ease the suffering of all trauma immune suppressed patients globally. It is important to note that we propose new white blood cell science therapy and not stem cell therapy.

Traumas, traumatic brain injuries and strokes are accompanied by immune suppression, poor healing, prolonged recovery, infections etc, and represent major health care problems and a significant global health care challenge [1]. It is estimated that many engaged in active combat for several months or more in Iraq/Afghanistan or potentially other conflicts [ie-Syria, Yemen, Somalia, Ukraine, etc] are at risk of developing disabling disorders resulting from blast waves caused by improvised explosive devices (IEDs), rockets and mortar attacks in addition to open or closed head trauma from shrapnel, artillery, bombs, blunt head trauma, accidents [2,3] or multiple other bodily injuries. The average 'dirty' wound from an IED or bomb explosion requires many surgeries and intensive care. At least ~30,000+ or more such surgeries have been performed [4] on western coalition trauma victims. These surgeries are also immune suppressive while potentially limb or life-saving. Data from the forces fighting against NATO/Coalition and western world forces or internal fighters are not available, but we must infer that the same numbers of traumas and immune-suppressive sequelae are also present in those soldiers as well as civilian war and terror attack victims. First responders, health workers and rescuers, police and athletes around the world add to the number of individuals

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of the trauma induced immune suppressed populations. The traumatized populations with immune suppressed derived and co-morbid illnesses point to a profound global issue with enormous health and cost impacts. The global trauma load and its induced immune suppression with multiple sequelae is therefore ready for further studies and clinical applications such as the promising white blood cell therapeutic modality we propose. [5]. We seek expeditious further studies for each of our presented proofs of concept, hypothesis, notions and questions for further substantiation leading to expeditious application and clinical use for the globally affected trauma patient populations.

Every post-trauma care plan requires life-saving procedures, resuscitation, surgeries, rehabilitation as well as immune system enhancement for appropriate support and care. Current post-traumatic therapy generally consists of evacuation or transport during which many procedures and therapies are performed on the trauma victims en-route to better healthcare. These en-route procedures and therapies may include blood transfusions and steroids which are also both immune suppressive [6], narcotic and non-narcotic pain medications, anesthesia and additional medications and other potential immune suppressive surgery or procedures. The life and limb-saving actions are necessary despite their potential negative immune system sequelae and potential failure. The immediate resuscitative trauma care phase may be followed by potentially many surgeries and procedures lasting for months or years.

We make a strong case for instituting rapid immune system reconstitution after most traumas, perhaps during the 'transport and life/limb saving - procedure' events, but certainly as practical as possible in the emergency room, operating theater or intensive care [ICU] or wards. Healing could potentially be enhanced and recovery shortened, while the high costs associated with critical care, nosocomial infections or immune suppressive medications and procedures are potentially lowered.

Blast trauma injuries are finding their appropriate place in the overall milieu of brain trauma. Tau type proteins in blast brain injuries are emerging as potential markers and co-morbid factors in chronic traumatic encephalopathy (CTE) [7–9]. The pathologies caused by blast brain injuries are also accompanied by immune suppression, infections, poor healing, and long-term psychological, physical and functional deficits as with other 'invisible' brain injuries [10,11]. Trauma induced immune suppression is a universal problem for all individuals engaged in battle globally, friend or foe, whether in war, on the athletic field, on unsafe streets or from terrorist attacks.

Historically, Donor Adoptive Immune Therapy or Donor Lymphocyte Infusion (DLI) was advocated for cancer in the past by Rosenberg [12], and many cases noted its success. The literature reflects rare attempts of autologous white blood cell re-infusion for some human patients with cancers with no conclusive or positive results [13,14]. However, DLI wbcs may require heavy medication use that induces further immune suppression to treat a potential HVG [Host Versus Graft] reaction. We ask at what point can close cohort wbc DLI provide the same results or function as autologous wbc re-infusion? How close a donor match is visible by the recipient's immune system as close cohort? As clinicians, we are told "match or no match". Where are the genetic 'break points' indicating 'close cohort' or 'match' for better decision making? In some cases, donor bone marrow is transplanted, and upon the re-infusion to the donor may be considered 'autologous'. Some genetically engineered, experimental models or chemically treated wbcs may also be considered 'autologous' as a special case. These questions seek experimental clarity and study.

Further questions concern the time line of when the wbcs lose trauma or infectious naivety when they are epigenetically changed to reflect a trauma or infection response. Is there a time period before this effect is noted in the wbcs, and how rapid or when? If studies reveal a time period before the current trauma or infection 'naivety' is lost or the epigenetic trauma changes become overwhelming, then perhaps the trauma victim's wbcs can be drawn as soon as possible after the trauma occurs, but before epigenetic changes occur, and re-infused when or before the immune system becomes dysfunctional. A follow-on question is to ask how long does the 'naivety' loss last? Forever? Or how many series of cell cycles/apoptosis cycles does loss of naivety last assuming the trauma ceases? Can the epigenetic loss of wbc trauma naivety be overcome by multiple serial doses of trauma naïve wbcs? If the trauma has stopped, will eventually the damaged wbcs and their effect disappear, aided by dilution, apoptosis etc and as we believe by a 'new' and younger infused immune system? These questions seek serious study and resolution. A Graft vs Host reaction (GVH or HVG) can be a frequent serious adverse reaction with DLI or stem cell transplants that results in a strong immune rejection response and further immune suppression from the medications used to treat the GVH. Additionally, the graft may end in failure or death. Potential hidden infective agents and genetic mis-matches in grafts may also cause problems. Close cohort wbc infusion may be useful for trauma after a match from a healthy donor is found. There is no GVH/HVG reaction with autologous wbc infusion. These comments and questions offer fertile ground for further studies and experimentation.

We consider stroke to be a traumatic brain injury (TBI) because *clinically* strokes result in the same potential endpoints as other TBIs and mTBIs [minimal traumatic brain injury]/concussions] or blast injuries: neuronal or other tissue loss, immune suppression, infection, and cognitive or functional losses. This may suggest that the different trauma induced immune responses/pathways may be along a common molecular intracellular pathway while etiologies may differ even as they direct similar intracellular responses [GDG]. This notion deserves study and clarification.

The immune system acts as an interface between 'self' and the external insult, be it trauma, infection or neoplasm, and is engaged and altered while acting as a first and long-term line of defense. The failure to restore or enhance immune system health following trauma is global in nature and not time, nation, conflict nor trauma specific. All victims worldwide suffer the same consequences from traumas-immune suppression, infections and other sequelae. The symptoms of trauma, the physical losses from trauma and the psychological wounds from trauma are usually addressed and treated, but the recovery and health of the immune system appears to be globally ignored. We have a duty to medical science, clinical practice and our traumatized patients to improve this ill addressed need and recognize the critical importance of a healthy immune system as a part of the overall treatment plans for all trauma patients.

This *clinical* translational and investigative paper is a focused presentation of select literature relevant to immune suppression and dysfunction secondary to trauma and select co-morbidities. We 'connect the dots' as a 'thought experiment' through investigation of various clinical areas and research studies based on sound science. We hypothesize that the use of autologous trauma and infection naïve wbcs infused after trauma and immune suppression regardless of the cause restore immune function, enhance healing, potentially save lives and huge health care costs. We welcome study and further research generated by our proposal which could potentially lead to a promising new important therapeutic modality as a welcomed next step in world-wide trauma and immune suppressive care.

Immune suppression in trauma: The what, how and why of traumatic immune suppression

Lennard and Browell described the 'what' of immune suppression in [surgical] trauma [15]. They observed a post-operative or post-trauma decrease in the number and functions T-lymphocytes, natural killer (NK) cells, cytokines and receptors that control immune effector cells, leaving the patient's immune system less functional. They also noted that specific post-operative defects in neutrophil chemotaxis, phagocytosis, lysosomal activity and super-oxide production in addition to an increase in the level of prostaglandin E2, the defective secretion of