

Potential Safer Drug for Containment of Lentivirus Infection and Ensuing Cytopenias: Necessity of Clinical Trials in Control and Infected Patients

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Hematopoietic stem cells which are present in bone marrow, cord blood and liver, terminally differentiate into multiple lineages of blood cell types and thus have applications in bone marrow transplantation. The determination of alleviation of cytopenias in HIV infection *in vivo* [severe combined immunodeficient transplanted with human fetal thymus and liver tissues, SCID-hu] has been utilized through assay of inhibition of hematopoietic stem cell colony formation *ex vivo* [1].

Cytopenias or hematopoietic inhibition (decreased blood cells formation) is a common occurrence in HIV infected patients both due to the virus but also caused in synergistic manner by the antiretroviral drugs (AZT or Zidovudine, ddI, certain protease inhibitors) [2]. Experimental observations for the indirect inhibition of the hematopoietic CD34+ stem cell colony forming activity by HIV infected T-cells were previously proposed or reported by us elsewhere in 1990's and also by some other investigators, from other institutions [1 and references therein].

The potential biologically occurring Sulfatide (3-O-sulfogalactosylceramide), which is non-specific to only a single species, has already been chemically synthesized and tested for its efficacy in severe combined immunodeficient mice transplanted with human fetal thymus and liver tissues (SCID-hu Thy/Liv) [3]. This testing for efficacy includes both the pre-clinical observations of not only the containment of replication of HIV-1, but is also relevant to the *in vivo* developed implant derived hematopoietic CD34+ stem cells is the reduction of cytopenias or hematopoietic inhibition, as assayed through inhibition of the CD34+ cell colony formation, *ex vivo* (Figure 1).

Figure 1: HIV-1 target CD4+ cell infection and infection resistant CD34+ cell colony forming activity of HIV-1 infected human thymus/liver implant in SCID mice. Left row: HIV-1 infection; middle row: HIV-1 + AZT; right row: HIV-1 + sulfatide treatment. First column: CD4+ cells; second column: megakaryocytic colonies; third column: erythroid colonies; fourth column: myeloid colonies. [Sundell, Cortado and Koka,] Stem Cells 2012; 7(1): 61-72. PMID: 23550344, Ref No. 4]. Sulfatide = 3-O-sulfogalactosylceramide.

Further characterization and isoform chemical synthesis or isolation of biologically available candidate drug Sulfatide (3-O-sulfogalactosylceramide) for clinical trials without the side effects of the anti-HIV drugs in AIDS patients that also cause cytopenias is required, prior to its commercial development and production. Different isoforms of this drug would or should be tested at least *in vitro* (if not *in vivo*) through collaboration for their synthesis for possible detection of the most efficacious isoform of 3-O-sulfogalactosylceramide, to alleviate the cytopenias in affected patients.

Although these studies were carried out in immunodeficient animals, the inter-species nature of sulfatide consists of at least partial or significant structure homology and thus could have a longer half-life in the circulatory system of immunocompetent humans. Even otherwise when some of the efficacious isoforms are chemically synthesized, it is a well-known fact that synthesized drugs are commonly used in patients to treat various diseases despite their possible side effects. The only possible expected side effect of excessive sulfatide is susceptibility to clotting for which an intake of aspirin could be co-prescribed with the sulfatide [4].

This co-administration of sulfatide-aspirin combination could

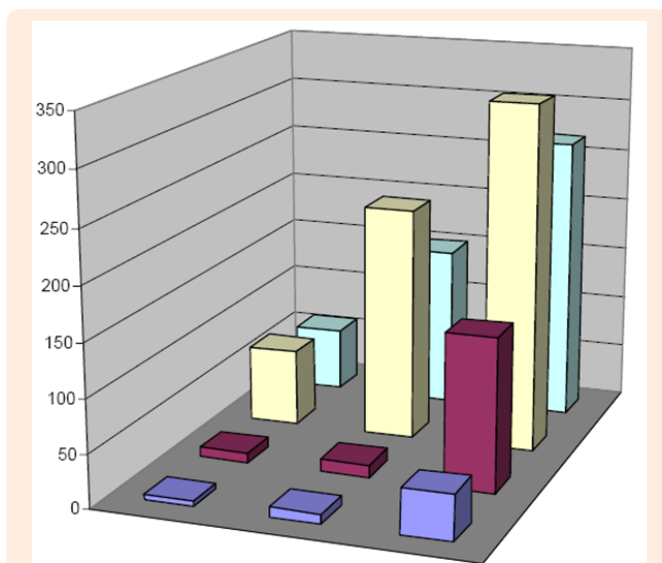


Figure 1: HIV-1 target CD4+ cell infection and the virus infection-resistant CD34+ cell colony forming activity in HIV-1 infected human thymus/liver implants in SCID-hu mice.

be part of the clinical trials with appropriate negative controls to determine the blood platelet levels and clotting factors as well, besides the CD4/CD8 ratios and the colony assays from the derived CD34+ cells from bone marrow. However this invasive procedure would not be necessary since any changes in blood cell levels for the cytopenic conditions are detected through the CBC of the patients' blood samples. In this regard, it is also noteworthy that at least a low dose aspirin is commonly suggested even for individuals beyond 45 years age despite no apparent evidence of heart disease to prevent unexpected or sudden heart attacks.

Clinical trials on this anti-cytopenic candidate drug, 3-O-sulfogalactosylceramide, would lead to patient treatments and thus commercialization of its single most efficacious isoform, or of multiple efficacious isoforms, through pharmaceutical manufacture for availability and access to affected patients. Thus these results comprise of translational research and applicable to (bench to bedside) translational medicine.

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