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Gene Therapy – A Current Review.

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Abstract: -
Gene therapy is replacement of defective gene with normal gene product. Various methods for it have been evolved and many more are in womb of future. Genetic involvement in affection of life on earth was found more than a century ago. But its application in medical field has been possible in last few years only. Still gene therapy is in its very infant stage and various clinical trials are going on. To make gene therapy available for mass population with feasibility and safety, medical fraternity has to keep patient till the time when research and trials in genetic field will approve for it. In this review little light has been focused on recent gene therapy trials which indicate the forthcoming era of human genome and their applicability in various genetic disorders.

Keywords: - Gene therapy, clinical trial, viral vector, genetic disorder.

Introduction: -

In past few years genetic field has achieved fast pace in clinical research and trials. The research and various studies have indicated future of human genotype to emerge as new genetic world from present nascent one. In this review some light has been focused on recent advances in treatment of genetic disorders by gene therapy. Hopefully in near future these treatments will be as feasibly available as the treatment of other non-genetic disorders.

Gene therapy involves replacement of a defective/ abnormal gene into the cells of a patient who is deficient of the normal gene product. Foreign gene can be delivered into target cell either by physical (i.e. liposome mediated DNA transfer and receptor mediated endocytosis) or biological (viral vectors) methods [1].

Current progress in the field of gene therapy:

Nathwani et al have shown in 10 patients of severe haemophilia B that gene therapy mediated by self complementary adeno-associated virus serotype 8 (AAV8) vector with single infusion has been shown to raise factor IX levels for long term associated with clinical improvement. Even no late toxic effects were noticed with follow up period of 3 years [2].

Parkinson's disease on long term treatment with oral dopamine replacement leads to motor complications. In a study on gene therapy of Parkinson's disease, Palfi et al interpreted that bilateral, intrastriatal delivery of Prosavin, a lentiviral vector based gene therapy, was safe and well tolerated in patients with advanced Parkinson's disease. All patients showed improvement in motor behaviour [3].

Cloning of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene has been interesting for gene therapy of cystic fibrosis (CF). UK CF Gene Therapy Consortium is investigating

potential of gene therapy as a treatment of CF patients [4].

Li Y et al by studying on recombinant adenoviral p53 (rAd-p53) gene in selective combination with chemotherapy for advanced oral squamous cell carcinoma concluded that intra-arterial infusion of combination of rAd-p53 and chemotherapy was significantly associated with increased survival rate of patient in stage III (but not stage IV) oral cancer, compared with intraarterial chemotherapy and placebo rAd-p53 [5].

Retinal gene therapy finding from a phase 1/2 clinical trial by MacLaren et al has shown consistency with rod and cone function improvement overcoming negative effects of retinal detachment in choroideremia, an X- linked recessive disease. Mutation of CHM gene encoding Rab escort protein 1 (REP1) causes blindness in choroideremia. Genome particle utilized for trial was adeno-associated viral (AAV) vector encoding REP1 (AAV.REP1), administered through subfoveal injection [6].

Recently Hacein et al performed a trial for efficacy of self-inactivating (SIN) γ-retrovirus vector containing deletions in viral enhancer sequences expressing γc (SIN-γc) for treatment of X-linked severe combined immunodeficiency (SCID-X1) affecting children. This vector has shown to retain efficacy in comparison to Moloney murine leukemia virus-based γ-retrovirus vector expressing interleukin-2 receptor γ-chain (γc) complementary DNA in previous clinical trials [7].

In cases of adenosine deaminase (ADA) deficiency patients lacking a suitable bone marrow (BM) transplant donor, enzyme replacement therapy (ERT) and hematopoietic stem cell (HSC) gene therapy (GT) are therapeutic options. In a study progressive improvement in B cell development and numbers occurred along with increased level of gene correction in HSC-GT treated patients. ERT also led to reversion of most BM alterations but caused immature B cell expansion leading defect in maturation for long term. This study thus showed the definite higher efficacy of gene therapy over ERT [8].

A study was conducted on rat model by Zheng et al to observe effect of viral vector expressing anti-inflammatory cytokine on human immunodeficiency virus (HIV) associated neuropathic pain (NP). The study concluded that herpes simplex virus (HSV) vectors expressing interleukin 10 (IL-10) is able to reduce HIV related NP by blocking the signaling of proinflammatory molecules in dorsal root ganglia/ spinal cord. This provides new hope for gene therapy for HIV associated NP in near future [9].

Gene therapies mediated by viruses have restricted ability to track cancer cells infiltrating into the surrounding tissue. While mesenchymal stem cells (MSC) are able to home to damaged tissues, tumours and metastases after systemic administration. This is very important for tumour targeted gene therapy [10].

Treatment of relapsed and refractory acute lymphoblastic leukemia (ALL) with chimeric antigen receptor- modified T-cell (CTL019) therapy against CD19 has been found to be effective. It was also associated with a high remission rate [11].

Two capsid-modified variants of rAAV2 have been tested for gene delivery to GL261 mouse model of glioma. Both rAAV2-TRP and rAAV-ShH19 mutants demonstrated superior transduction of GL261 cells in vitro and in vivo. Transduction of neurons in the vicinity of tumour cells may be an advantage or an undesired effect for the therapy, depending on the strategy and therapeutic mechanism [12].

Gene therapy is also having future aspects for treatment of cancer with help of suicide gene therapy. This therapy involves selective introduction of gene in tumour territory that encodes for an enzymes metabolizing systemically administered prodrug into active anticancer agent. This reduces the systemic toxicity of chemotherapy and enhances the tumour specificity [13].

Suicidal gene therapy with bystander effect requires significantly less number of cells

expressing suicidal gene. Bystander effect occurs due to presence of gap junction between adjacent cells leading to continuity of their cytoplasm, thus also causing transfer of activated prodrug from one cell to another adjacent cells [14].

Zhu HQ et al studied the effect of human peroxiredoxin 6 (Hprdx6) with adeno-associated virus 2/8 (AAV 2/8) gene transfer to reduce the atherosclerotic effects of thiol- reactive oxygen species (ROS). This effect thus has promising merit in cardiovascular fields in future [15].

Hair cell regeneration with help of adenoviral vector with ATOH1 gene has risen interest in treatment of sensory hearing loss, while it is not able produce same effect in cases of severe aminoglycoside-induced deafness [16].

Summary:

So many studies are available rising hope for far better future picture of human race. As in past antibiotic research had done for major infectious illness, so is the gene therapy is going to do with genetic disorders. But still we are at very nascent stage of genetic correction of human being. The studies in recent years have definitely shown the way for betterment in field of gene therapy for vast numbers of genetic disorders. The gene therapy is not only helpful for treatment of genetic disorders but also as adjuvant for other regimens like chemotherapy of cancers etc. Therefore we should keep watch on ongoing research and trials in genetic field for search of better options for treating various disorders in human beings.

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