

[871] IL7 Administration in Humans Results in Preferential Expansion of Naive and Memory CD4+ & CD8+ T Cells with a Relative Decrease in Regulatory T-Cells (T-Regs). Session Type: Oral Session

Claude Sportes, Michael Krumlauf, Rebecca Babb, Ladan Foruraghi, Janine Daub, Daniele Avila, Catherine Chow, Hua Zhang, Kevin Chua, Terry Fry, Sarfraz Memon, Frances Hakim, Thomas Fleisher, Margaret Brown, Julie Engel, Renaud Buffet, Michel Morre, Ronald Gress, Crystal Mackall. Experimental Transplantation & Immunology Branch, National Cancer Institute, Bethesda, MD, USA; Pediatric Branch, National Cancer Institute, Bethesda, MD, USA; Clinical Center, National Institutes of Health, Bethesda, MD, USA; Cytheris, Inc, Rockville, MD, USA

Interleukin-7 (IL7) is a multifunctional cytokine with critical and non-redundant roles in T-cell development, T-lymphopoiesis and peripheral T-cell homeostasis. We report preliminary results of the first phase I study of recombinant human IL7, "CYT 99-007" (rhIL7). Adults with incurable malignancy (11 men and 3 women), 20-71 years old (median 48) received escalating doses (3, 10, 30 or 60 µg/kg/dose) subcutaneously every other day for 2 weeks. IL7 was overall well tolerated with no Maximum Tolerated Dose yet reached. Dose-dependent and age independent biological effects consistent with murine and non-human primate pre-clinical models were observed in all patients receiving 10 µg/Kg/dose or more: enlargement of spleen and lymph nodes (but not thymus) by CT scan and marked proliferation and expansion of T-cells subsets. Increases in CD4+ and CD8+ T-cells were most prominent in naïve T-cells (CD27+CD45RA+), including Recent Thymic Emigrants (RTE) (CD4+/CD45RA+/CD31+) with a mean 6-fold expansion, and in memory T-cells (CD27+CD45RA-) but less so in effector T-cells (CD27-). Furthermore, IL7 therapy resulted in a decline in the relative frequency of T-regs (50-80% decline in FoxP3 mRNA copies normalized to Actin mRNA copies in sorted CD4+ T-cells).

Although the magnitude of biological effects was variable, the kinetics were similar in all T-cell subsets and at all effective doses. After one week of therapy at 30µg/ Kg /dose, 30-70% of naïve CD4+ and CD8+ T-cells were in cycle (Ki-67+) and expressed elevated levels of Bcl-2. Bcl-2 up-regulation (maintained at week 2) and high proliferation rates resulted in T-cell expansion (mean of 6- and up to 14-fold in some individuals at the 30µg dose) persisting one to several weeks after treatment. Consistent with animal data, we observed IL7 receptor α-chain (IL7Rα) down-regulation: both IL7Rα mean fluorescent intensity by flow cytometry (CD127) and mRNA copy numbers declined more than 50% at one week. By the end of treatment, proliferation rates were halved and down to baseline by week 3, coincident with recovery of IL7Rα expression after cessation of treatment.

The T-cell increase was primarily due to IL7 induced peripheral expansion. There was no dilution effect of T-Cell Receptor Excision Circles (TREC) numbers per 10⁵ CD4+ sorted cells which suggests cell recruitment or expansion, consistent with preclinical data but does not exclude a thymic contribution.

rhIL7 is safe at biologically active doses in humans and induces an expansion of naïve (including RTE) and memory T-cells. In contrast to IL2, IL7's role in T-regs homeostasis appears to be minimal. rhIL7 may prove clinically valuable in adoptive immunotherapy as an immuno-restorative agent in conditions of disease (HIV) or chemotherapy induced T-cell depletion or as an adjunct to tumor vaccination for immune response modulation.

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