7. Discussion

Progression of *Leishmania donovani* infection in the susceptible host (BALB/c) can be divided into two specific phases, the ‘early phase’ and the ‘effector’ or late phase. In the early phase, the disease is established with the processing and presentation of leishmanial antigens, and priming of T cells against the MHC bound antigenic peptides. IL-2 produced from these T cells plays a very crucial role in disease establishment. Although IL-2 regulates the maturation of T cells capable of secreting both IFNγ and IL-10 during the early phase of *L. donovani* infection, possibly as a function of available IL-2 concentration, IL-10 suppresses IL-12 production from macrophages via the Erk ½ signaling pathway and also reduces the IL-12 responsiveness of T cells by inhibiting IL-12Rβ1 expression on them. Thus, IL-10 hampers the IL-12 induced IFNγ production and therefore the amastigote elimination mechanisms which depend on it.
The T cells residing in the IL-10 rich splenic microenvironment become unresponsive to TCR stimulation and also suppress the proliferation of naïve infiltrating T cells. This phenomenon reminds us of ‘infectious tolerance’ where ‘regulatory’ T cells repress the proliferative potential of naïve T cells, converting them into suppressive cells as well. IL-2 creates a suitable microenvironment in the early phase, such that the T cells residing there are functionally molded and destined to mediate *L. donovani* survival and disease progression in the late effector phase, rather than playing a host protective role. This is achieved because IL-2 is required at the initiation of priming, for the maturation of T cells capable of IL-10 production, and in the absence of IL-2, as in αIL-2+αIL-2R treated mice; these cells are unable to secrete enough IL-10. In this scenario, the Th1 response remains uninhibited and provides host protection from visceral leishmaniasis. In the untreated mice, IL-10 prevents these host-destructive pathological conditions by suppressing excessive Th1 mediated inflammatory reactions. *Leishmania*, being a parasite, exploits and exaggerates this regulatory mechanism to accomplish its ultimate goal, i.e. survival in the extremely hostile conditions prevalent in the host. IL-10 permits its unhindered growth in this microenvironment which is devoid of a strong Th1 directed anti-parasitic immune response. The analysis of *Leishmania donovani* infection in the susceptible mouse indicates that the immune response is dynamic, oscillating between the parasite’s host immune evasion strategies and the counteracting response triggered by the host to adapt against the pressures exerted by the persistent pathogen. Modulating the host’s immune response such that it becomes more competent in pathogen clearance can be used as an immunotherapeutic strategy for visceral leishmaniasis. Based on this
concept, the present study emphasizes on the kinetic modulation of disease progression in the BALB/c model of *L. donovani* infection. We have targeted the specific phases (early & late) as depicted by the ongoing immune response against these intracellular parasites. Our data shows that during the time course of disease, T cells are programmed to behave as suppressors and this phenomenon commences around 7-14 days post infection (early phase). This time also marks the sharp rise in IL-10 production levels, coinciding beautifully with the induction of T cells having suppressive property. Since, the DTH response to leishmanial antigens was also downregulated at the same period; we neutralized IL-2+IL-2R at this critical phase of infection and found drastic decline in the splenic parasite load. We infer from this that IL-2 was essential for disease establishment at the initial stages of infection, as delayed neutralization of IL-2 did not annihilate the disease. This novel phase-specific immunotherapy and the basic conceptual aspects emerging out from the study may have broad implications in several diseases like autoimmune diseases, transplantation tolerance.