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REVIEW

IL-7 in allogeneic transplant: Clinical promise and potential pitfalls

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Abstract
Much progress has been made in the field of allogeneic stem cell transplantation. However, one major barrier is the delay in immune recovery that can persist for months post-transplant and results in increased susceptibility to infection and relapse of malignancy. Strategies to improve immune recovery must be balanced with the potential for those therapies to exacerbate graft vs host disease. Interleukin 7 is a member of the γc cytokine family that is required for T-cell development and maintenance of naïve T-cell populations. In addition, IL-7 plays a major role in the expansion of mature T-cells that occurs during lymphopenia and therapeutic IL-7 can enhance both quantitative and functional immune recovery following T-cell depletion. Thus, this agent holds much promise as an immunorestorative agent and as an adjuvant to vaccines or adoptive immunotherapy. Clinic trials with IL-7 are underway. Murine studies with IL-7 in the allogeneic transplant have demonstrated that the potent immune effects of this agent can also be achieved in this setting. However, these studies have indicated that the potential for IL-7 to worsen GVHD exists and that this effect may abrogate the immune benefits. Thus, careful consideration of how best to incorporate IL-7 into allogeneic trials will be needed if the full potential of this agent is to be realized.

Keywords: *Cytokines, stem cell transplant, immunotherapy, immune reconstitution*

Introduction

Over the last 15 years, the field of hematopoietic stem cell transplantation (HSCT) has experienced significant improvements in supportive care [1], awareness of the potency of the graft-vs-tumor effect [2,3] and new preparative regimens which can result in full donor engraftment with diminished toxicity [4]. As a result, HSCT is currently being tested in a wider variety of malignancies and, conceptually, many have moved from considering this modality principally as a means to administer high doses of cytotoxic agents to a form of immune-based therapy. However, a number of important barriers still exist. Both acute and chronic graft-vs-host disease remain significant problems, particularly with matched unrelated donors and T-cell replete grafts, with most series showing a 30–70% incidence of acute GVHD and a 35–60% incidence of chronic GVHD in HLA matched transplants [5,6]. GVHD itself is profoundly immunosuppressive and, when combined with the therapy required to control GVHD symptoms, it ultimately results in an increased risk of infection and relapse. While T-cell depletion can effectively prevent the development of GVHD, the likelihood of graft rejection increases and recipients are left with a prolonged period of lymphopenia and concomitant risk of infection and relapse [7]. Thus, to further improve outcomes, strategies to enhance the recovery of lymphocytes post-transplant must restore protective immunity against infections and graft vs tumor responses without generating significant GVHD.

Much recent work has focused on the use of cytokines to expand the T-cell pool in the lymphopenic host in order to improve immune reconstitution. In particular, members of the family of cytokines that utilize the common cytokine gamma chain, including IL-2, IL-7, IL-15 and IL-21 appear to be promising in this regard. To date, only IL-2 has been studied extensively in humans and improved clinical outcomes after BMT with this agent have not

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been consistently seen. Interleukin-7 (IL-7) is just entering the clinic and may be particularly well suited as an immunorestorative agent. However, whether the administration of IL-7 following allogeneic HSCT will allow a therapeutic window for accelerated lymphocyte recovery without enhanced alloreactivity remains to be seen. This manuscript will review the biology of T-cell reconstitution in the allogeneic setting and discuss features of IL-7 biology that may impact its effectiveness as an immunorestorative agent following allogeneic transplantation.

Immune recovery following allogeneic HSCT

Following allogeneic HSCT, T-cell reconstitution occurs predominantly through one of two pathways: production of new T-cells through the thymus or the expansion of T-cells present following the conditioning regimen or contained in the graft. The relative contribution of expansion and thymic production to overall immune recovery is dynamic and depends on the degree of thymic function. Importantly, following profound T-cell depletion from any cause, efficient restoration of a diverse repertoire of CD4 and CD8 T-cells depends on production of thymic emigrants [8,9]. The role played by the thymus in immune reconstitution is even more critical following allogeneic HSCT, since those T-cells negatively selected to host antigens in the recipient thymus are less likely to induce alloreactivity, as compared to T-cells generated via the expansion of mature T-cells collected from the donor. Unfortunately, however, a number of factors impair thymic function following allogeneic transplantation. Prior cytotoxic therapy administered for the underlying disease as well as the chemotherapy and/or radiation administered as the conditioning regimen, limits the thymus' ability to support T-cell development due to damage of the thymic epithelium [10 – 12] and reduces production of important growth factors such as IL-7. Furthermore, it is clear that the development of GVHD further embarrasses thymic recovery [10,13,14]. Finally, ongoing declines in thymic function that occur with aging, a process that begins by early adulthood, contributes to diminished thymic potential [15]. Thus, while thymic recovery appears critical for complete restoration of immunity, multiple factors contribute to impaired thymic function following allogeneic transplantation.

In the setting of diminished thymic function, lymphopenic hosts can undergo substantial T-cell regeneration through thymic-independent homeostatic peripheral expansion (HPE). This term is used to describe the dramatic expansion of cell numbers which occurs through exaggerated responses to cognate antigen and the induction of proliferation toward low affinity self antigens during lymphopenia [16,17]. In the HSCT setting, alloantigens drive the expansion of T-cells with host reactivity and results in an even more pronounced skewing. Furthermore, the massive expansion of alloreactive T-cells also results in substantial 'bystander' apoptosis of non-alloreactive T-cells reducing overall efficiency [18]. Therefore, while T-cell reconstitution can occur via expansion of mature T-cells driven by cross-reactive self-antigens and cognate interactions, in the setting of allogeneic HSCT, HPE exaggerates host-reactive T-cell expansion and results in a repertoire severely limited both quantitatively and qualitatively.

IL-7 overview

First described as a B-cell growth factor [19,20], IL-7 has since been found to be required for the development and maintenance of B- and T-cells in mice [21]. In humans, IL-7 is necessary for normal T-cell development, but it is not required for B-cell development, although IL-7 contributes to efficient B-cell lymphopoiesis [22]. In addition to its effects on T- and B-cell lymphopoiesis, it is now clear that IL-7 functions as a critical regulator of mature T-cell populations both for maintenance of T-cell numbers in periods of health and for regeneration of T-cells following lymphodepletion. In normal lymphoreplete hosts, IL-7 and MHC with self-peptide induce the slow cycling of naïve T-cells that is important for the maintenance of the naïve T-cell pool. During lymphopenia, IL-7 is also absolutely required for the homeostatic expansion of mature T-cells. For naïve cells undergoing homeostatic peripheral expansion, IL-7 primarily acts by augmenting T-cell proliferation toward cognate and self-antigens, whereas for memory T-cells, IL-7 is capable of supporting expansion in the absence of TCR-based stimulation. Thus, through effects in the thymus and in the periphery, IL-7 is critically necessary for the development, maintenance and regeneration of T-cell populations.

IL-7 in the syngeneic setting

Based on the important role for IL-7 in lymphoid development and in maintenance of mature T-cells, this agent has been explored as an immunorestorative and as a vaccine adjuvant. In murine studies, therapeutic administration of IL-7 following T-cell depletion results in marked increases both CD4 and CD8 T-cell numbers. Although endogenous IL-7 is critical for effective thymopoiesis, the increase in T-cells observed with IL-7 administration following T-cell depletion appears to result from dominant effects on mature T-cell populations [16].

However, it should pointed out that the ultimate T-cell repertoire that is present after IL-7 administration may be positively affected by some increase in thymic output, enhanced survival and expansion of recent thymic emigrants and, perhaps, through decreased loss of expanding mature T-cells to apoptosis [14]. Indeed, the pattern of expression of IL-7Rα on T-cell populations would predict improvements in repertoire after IL-7 treatment (Figure 1). This is supported by murine models assessing functional immunocompetence which demonstrate that numeric increases in T-cell numbers induced by IL-7 translate into improved ability to functionally respond to antigens [23,24]. Using a murine syngeneic BMT model Abdul-Hai et al. [24] showed the lungs of IL-7 recipients exposed to influenza virus completely clear of virus at 12 days post-exposure but demonstrated persistent virus in IL-2 treated and untreated recipients. Furthermore, IL-7 treatment resulted in greater antibody production and increased cytotoxic T-cell activity against influenza virus when compared to IL-2 or untreated animals. In addition to effects on global immune reconstitution, IL-7 has also been explored as an agent to enhance antigen-specific immunity following vaccination. Recent work in a murine system has demonstrated that recombinant human IL-7 (rhIL-7, 5 μg per day) given for 28 consecutive days to female mice immunized against the male minor histocompatibility antigen (HY) results in enhanced expansion of the effector pool toward the dominant class I and class II antigens. Importantly, IL-7 also potently augments T-cells responding to the sub-dominant antigen resulting in a broader overall immune response. This may be beneficial in situations where loss of antigens may represent a form of immune escape, as has been observed for viral infections and tumors [25]. Importantly, even though IL-7 was administered for a time-limited period during the initial immunization in this study, it resulted in a stably increased size of the memory pool that persisted for several months following cessation of IL-7. In these experiments, IL-2 performed less well than IL-7 and IL-15 demonstrated similar effects on CD8 responses but was less potent than IL-7 for CD4 responses. These observations and others suggest that, in addition to improvements in overall immunocompetence, IL-7 may be a beneficial cytokine in settings where enhanced cytotoxic T-cell activity directed at a specific antigen, i.e. a tumor antigen, is desired.

Recently, Lu et al. [22] found higher CD4 T-cell counts and increased IFN-γ producing CMV-specific CD4 cells in lymphopenic baboons treated with long-term recombinant baboon IL-7 therapy. Storek et al. [26] also demonstrated an increase in CD4 T-cell counts in irradiated, autologously transplanted baboons following 4 weeks of IL-7 therapy. The increases in T-cell numbers seen in both in murine and non-human primate models [22,26 – 28] serve as the basis for ongoing human trials.

In summary, endogenous IL-7 serves as a critical regulator of T-cell homeostasis through effects on thymopoiesis and mature T-cell expansion. When given as a therapeutic agent, the peripheral effects of IL-7 predominate, resulting in marked increases in T-cells responding to the autologous, low affinity antigens that drive HPE and also enhanced responses toward cognate antigen. The ultimate result is improvement in overall immune recovery as well as enhanced antigen-specific responsiveness. Therefore, in the autologous setting the available animal data would suggest that IL-7 is a particularly attractive
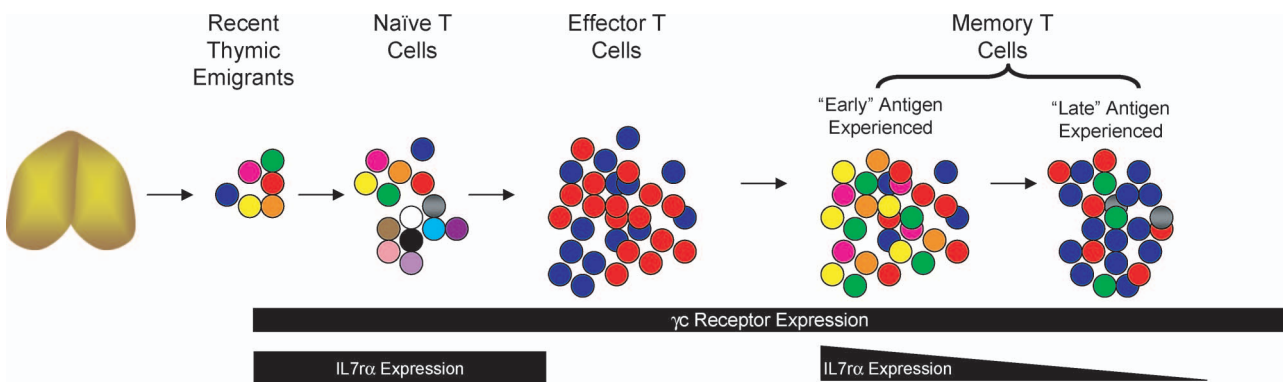

Figure 1. IL-7 therapy is predicted to selectively expand pools with higher repertoire diversity. Shown are changes in IL-7Rα expression during post-thymic T-cell development as modeled by Appay et al. [37]. Recent thymic emigrants have a diverse repertoire, display high levels of IL-7Rα and are highly responsive to IL-7 [38]. Naïve cells are also diverse, require IL-7 for continuous low level cycling [39] and expand greatly following IL-7 therapy [40]. During an antigen-specific immune response such as the alloreaction, effector cells downregulate IL-7Rα, but 'early' antigen experienced memory T-cells re-express the receptor [41,42] and expand in response to IL-7 therapy. 'Late' antigen experienced T-cells (CD28-, CD27-) found in states of chronic high level antigen stimulation are limited in repertoire diversity, express low levels of IL-7Rα [42 – 44] and are predicted to expand least following IL-7 therapy.

candidate as an agent to improve immune recovery following lymphopenia.

IL-7 in allogeneic transplantation

Following allogeneic transplantation, prolonged lymphopenia and the use of immunosuppressive agents results in susceptibility to infection and relapse of malignant disease. Thus, a cytokine such as IL-7 holds promise as a means to improve transplant outcome by enhancing HPE and perhaps by enhancing reactivity to weak tumor antigens. Although the available data would indicate that the effects of pharmacologic doses of IL-7 on mature T-cells predominate, it is important to note that broad-based cycling of recent thymic emigrants in response to IL-7 [16] would be predicted to improve repertoire diversity, whether or not IL-7 augments thymic throughput *per se* (Figure 1).

However, since the allogeneic setting is also characterized by the presence of T-cells reactive against normal tissues, the ability for IL-7 to induce pathologic host reactivity must carefully be considered. Indeed, IL-7 has been suggested as a co-factor in autoimmune disease. Serum and synovial fluid IL-7 levels are increased in patients with rheumatoid arthritis and IL-7 has been identified as an important mediator of inflammation in this disease [29–31]. In patients with multiple sclerosis T-cell reactivity to myelin basic protein is increased in the presence of IL-7 levels higher than seen in healthy hosts [32]. Finally, patients with anemia of chronic disorders demonstrated increased lymphocyte activation in the bone marrow and increased serum levels of IL-7 [33].

A number of murine studies have directly explored IL-7's impact on host-reactivity and GVHD following allogeneic HSCT. Alpdogan et al. [34] compared IL-7 in a MHC-matched but minor histocompatibility antigen-mismatched murine transplant model by giving 5×10^6 T-cell depleted bone marrow cells with or without 0.5×10^6 splenic T-cells to lethally irradiated mice. IL-7 (1 μg per day) was given subcutaneously on days -1 to $+13$ or days $+14$ to $+28$ and the animals were evaluated for signs of GVHD. They found no significant differences between groups given IL-7 compared to PBS with regard to survival, with the saline treated group experiencing a 100% mortality by day $+60$ and 75% mortality by day 90 for the IL-7 treated animals due to GVHD. Moreover, IL-7 significantly decreased GVHD morbidity and mortality in (B6 $\times$ C3H) F1 mice receiving 5×10^6 T-cell depleted bone marrow cells $+ 0.5 \times 10^6$ splenic T-cells. In this same report, the administration of IL-7 following allogeneic transplantation did not alter mortality from a 32Dp210 leukemia challenge given on day 0. Additional studies by this group suggested that alloreactive T-cells down-regulate IL-7Rα in the gut, spleen, lymph node and liver and, therefore, become less sensitive to IL-7, thus providing a potential explanation for why IL-7 may not be exacerbating GVHD in these models [35].

In similar, but not identical experiments, Sinha et al. [36] investigated whether rhIL-7 administered at higher doses (5 μg per day for 28 consecutive days) influenced the development of GVHD in a parent into F1 major histocompatibility antigen mismatched transplant model using T-cell depleted marrow with increasing doses of lymph node-derived T-cells. The addition of rhIL-7 resulted in greater weight loss at a given T-cell dose and decreased the dose of T-cells necessary to establish lethal GVHD. Furthermore, organs from IL-7 treated mice showed increased GVHD-associated tissue damage and inflammation, including the thymus which demonstrated thymitis and thymic lymphoid depletion. Assessment of immune reconstitution in these experiments demonstrated that the benefits seen with IL-7 were also seen when T-cell depleted bone marrow was used alone but were lost with even small numbers of mature donor derived T-cells due to the development of even mild GVHD.

While these two reports came to somewhat differing conclusions, subtleties in the experimental design might have substantially contributed to these outcomes and may also allow an opportunity to better design protocols in which IL-7 can be more safely incorporated. For example, in the Alpdogan model of transplant, murine splenic T-cells are used, whereas the series of experiments by Sinha murine lymph node T-cells are used. It has been noted that T-cells of the murine spleen are proportionately more CD8 memory T-cells when compared to the proportionately more CD8 naïve cells of the murine lymph nodes. It is possible that, since memory cells are less reliant on IL-7 for antigen driven proliferation, the effects of IL-7 on alloreactivity would be diminished when this phenotype of T-cells predominates in the donor inocula. In contrast, murine lymph nodes, with a proportionately greater number of CD8 naïve T-cells, are likely to be more highly responsive to IL-7 than the memory CD8 T-cells of the murine spleen (Figure 1). Secondly, the doses of IL-7 used in these two experiments are different with the higher dose used by Sinha et al. [36], resulting in exacerbation of GVHD. It is possible that, despite the down-regulation of IL-7 receptor seen by Alpdogan et al. [34,35] on rapidly dividing cells likely to contain alloreactive T-cells, higher pharmacologic levels of IL-7 would still be able to

induce a signal. Thirdly, the timing of IL-7 was slightly different in the two models. Sinha et al. administered IL-7 immediately after transplant, whereas the most benefit of IL-7 in the experiments by Alpdogan et al. was seen when the administration of IL-7 was delayed. It is possible that IL-7 administered during the inflammatory process caused by the conditioning regimen will result in a greater impact on GVHD. Finally, the experiments by Sinha et al. demonstrated the most pronounced effect of IL-7 on GVHD at lower T-cell doses when the degree of GVHD was milder. The experiments by Alpdogan et al. explore the impact of IL-7 in models where the GVHD-related mortality is quite high (75–100%), even in the absence of IL-7. Thus, is it possible that the effect of IL-7 on GHVD will be most pronounced when at the threshold T-cell dose. Thus, the interpretation of these results together suggests that the promise of IL-7 realized in syngeneic models can also be realized in the allogeneic setting but with the potential to exacerbate GVHD.

The future of Il-7 in allogeneic transplantation trials

As already discussed, prolonged immunodeficiency following allogeneic transplantation results in increased mortality from infection and relapse of neoplastic disease. While some alloreactivity is desirable as a means to strengthen the graft vs tumor effect, the development of significant GVHD further exacerbates immune recovery due to the need for global immune suppression and the direct effect of GVHD on the immune system as a target organ. Thus, strategies to improve immune recovery must be balanced with their ability to exacerbate or induce GVHD. How we improve both the quality and quantity of lymphocyte recovery to provide patients with immune competency against infection and malignancy without increasing GVHD is a question yet answered. IL-7 is an extremely attractive candidate as a cytokine to improve immune recovery following allogeneic transplantation and existing data would support the use of this agent in clinical trials. However, to fully reap the benefits of IL-7 as an immunorestorative, the avoidance of GVHD will be important (Figure 2). To this end, the administration of IL-7 following a T-cell depleted allograft is the logical first step. It may also be prudent to begin with lower doses of IL-7 and to begin administration when the inflammation of the preparative regimen is less. This may then serve as a basis to explore the use of this potent T-cell active cytokine as an adjuvant to vaccines or adoptive immunotherapy in the allogeneic setting as supported by data from syngeneic models.
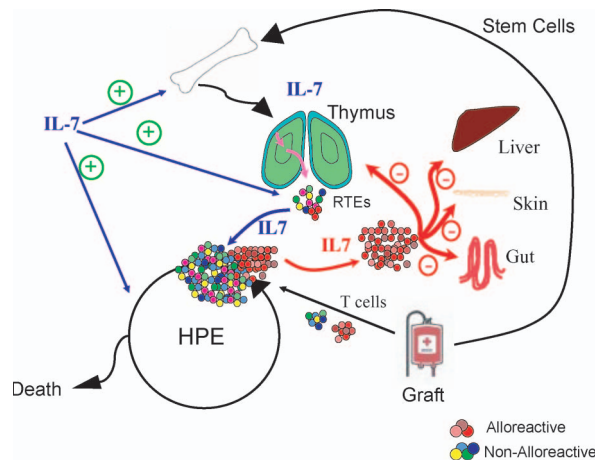

Figure 2. Effects of IL-7 on alloreactive and non-alloreactive T-cell populations. Following the transfer of a hematopoietic allograft, T-cells expand in the lymphopenic milieu containing cytokines, including IL-7. Alloreactive T-cells target antigens in the liver, skin and intestine resulting in GVHD. Non-alloreactive T-cells also expand by HPE. Initially, recent thymic emigrants are diminished, due to age-related declines in thymic function and thymic injury incurred during the conditioning process. Furthermore, the thymus may be a target for ongoing damage further reducing thymic output. Thus, the contribution of thymically generated T-cells is minimal, especially early in the post-transplant setting. The therapeutic administration of IL-7 following allogeneic transplantation can increase the expansion of alloreactive and non-alloreactive T-cells contained in the graft resulting in increases in T-cell numbers but with the potential to increase alloreactivity. IL-7 may also expedite the generation of new T-cells via the thymus and may preferentially induce the expansion of recent thymic emigrants tolerized to alloantigens in the recipient thymus. Thus, the ultimate effect of IL-7 on immune reconstitution will depend on the degree to which IL-7 can exacerbate GVHD.

Ultimately, the potential for IL-7 to improve outcomes following allogeneic transplantation remains promising.

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