IL-6 Blockade in Cytokine Storm Syndromes

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Interleukin-6 (IL-6) has gained attention as a key node in certain cytokine storm syndromes (CSS). Originally described as B-cell differentiation factor 2 (BSF-2) and Macrophage and granulocyte inducing factor 2 (MGI-2), IL-6 has prominent pro-inflammatory and pyrogenic properties [1–3]. The receptor for IL-6 is complex and allows for several signaling configurations. The IL-6 receptor (IL-6R) is a relatively small immunoglobulin like receptor with a conserved WSXWS motif along with four conserved cysteine residues in the extracellular portion. The intracellular portion was shown to be unnecessary for signal transduction, and led to the discovery of the heterodimeric partner to the IL-6R, gp130 [4, 5]. IL-6 can thus signal through two main configurations, referred to as *trans*- or *cis*-signaling [6]. In *cis*-signaling, the cell expresses the IL-6R and gp130 in a complex, and signal transduction is mediated by binding of IL-6 to the IL-6R. In *trans*-signaling, IL-6 binds to a soluble form of the IL-6R (sIL-6R) forming a soluble complex that can then bind to a dimer of gp130 on a cell surface; thus mediating IL-6 signaling in a cell which does not express the IL-6R (Fig. 1) [1]. Baseline proteolytic cleavage of the surface receptor by ADAM10 results in tonic levels of circulating sIL-6R, whereas high levels can be induced by cleavage via ADAM17 [7]. Internally, IL-6 signals via the Janus Activated Kinase (JAK) and signal transducer and activator of transcription (STAT) pathways, particularly STAT3 [1]. IL-6 signaling can thus be targeted by inhibiting IL-6 levels, blocking the IL-6 receptor, blocking gp130 or by targeting JAK-STAT signaling (Fig. 1).

IL-6 has been known to be elevated in HLH, reaching levels of greater than 100 pg/mL in plasma of patients with primary hemophagocytic lymphohistiocytosis (pHLH) or Epstein–Barr virus (EBV) driven secondary HLH (sHLH) [8, 9]. It was not shown to be specific for HLH, however, despite its consistent elevation. Several studies of biomarkers for HLH/MAS (macrophage activation syndrome) have honed in on the combination of interferon-gamma (IFN γ) and interleukin-10 (IL-10) as

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Fig. 1 Inhibition of IL-6 *cis*- and *trans*-signaling

being specific and sensitive for HLH/MAS rather than IL-6, which can be elevated in sepsis or non-septic infection [10, 11]. Targeting IL-6 with tocilizumab, an anti-IL-6R monoclonal antibody, has been used in HLH and related syndromes with mixed results. For the MAS associated with systemic juvenile idiopathic arthritis (sJIA), tocilizumab and IL-6 blockade successfully masked clinical symptoms such as fever but did not alter the acute disease course [12]. Tocilizumab was used safely for the chronic management of sJIA, though again did not prevent or alter MAS flares based on serum biomarkers though it could mask clinical symptomatology [13, 14].

Tocilizumab has also been used for sHLH management, as in Leishmaniasis-induced sHLH [15]. Again in this case, clinical symptoms of MAS were masked (such as fever) until the underlying trigger (infection) was resolved. In modern-day cellular therapy for cancer and immune-modulatory therapies, sHLH has been recognized as a potentially life threatening consequence that is referred to as cytokine release syndrome (CRS) [16, 17]. Blinatumomab is a bi-specific T cell engager (BiTe) that recognizes CD3 on one end and CD19 on the other, making it an attractive therapy for relapsed and refractory CD19-positive acute lymphoblastic leukemia (ALL) [18]. Patients have been recognized to have a sHLH response during the blinatumomab administration, characterized by elevated acute phase reactants and elevated IL-6 levels. Clinical symptoms of these patients improve with tocilizumab administration, including prompt resolution of fever and hemodynamic stabilization (Table 1) [16, 19, 20].

Table 1 Potential and actualized therapeutic agents targeting the IL-6 pathway for treatment of cytokine storm syndrome

Therapeutic	Mechanism	References
Tocilizumab	Anti-IL-6 receptor antibody	[5]
Siltuximab	Anti-IL-6 antibody	[34]
Sgp130-Fc	Inhibition of IL-6 <i>trans</i> -signaling	[50]
Ruxolitinib	Inhibition of JAK/STAT signaling	[55]

Chimeric antigen receptor (CAR) T cell therapy for ALL has also been described to induce a life-threatening cytokine release syndrome (CRS)/sHLH [17]. In this therapy, T cells from a cancer patient are collected via apheresis, modified in the laboratory to express the CAR, and then reinfused into the patient [21]. The CAR consists of an extracellular binding domain (often a single chain variable fragment of an antibody recognizing CD19), an endodomain consisting of the intracellular transactivation motif from the CD3 zeta chain and a second domain from a costimulatory molecule such as CD28 or 4-1BB [21]. When the CAR T cells engage in leukemia killing, they proliferate and secrete pro-inflammatory cytokines such as IFN γ and tumor necrosis factor (TNF) [22, 23]. Early CAR T cell trials did not show much in the way of clinical activity, with no sustained remissions and also very little toxicity [24, 25]. It was the first report of two children with ALL treated with anti-CD19 CAR T cells in 2013 that first described accurately the sHLH from CAR T cell therapy and the use of IL-6 blockade for treatment [17]. In this report, a child with ALL was treated with CAR T cells and shortly thereafter became febrile, coagulopathic, hyperferritinemic, and hypertriglyceridemic, and developed organomegaly, capillary leak syndrome, and hypotension. Laboratory markers showed a 3–4 log₁₀ elevation in IL-6 levels over baseline. Treatment with systemic corticosteroids and etanercept (a TNF blocking agent) did not result in clinical improvement; however, treatment with tocilizumab promptly resolved the fever and other clinical symptoms [5, 17]. A toxicity management strategy was then developed and applied to other CAR therapy trials with similar results [26, 27]. Long term follow up reports show that toxicity from sHLH from CAR T cell therapy can be successfully managed with tocilizumab, augmented with corticosteroids in severe cases [28, 29]. A challenge to understanding the incidence of toxicity, which ranges from 21 to 64%, is the use of multiple grading scales for cytokine release syndrome [30, 31]. The recent FDA approval of a CAR T cell therapy for ALL (tisagenlecleucel, Kymriah) from Novartis was accompanied by the announcement of the approval of tocilizumab for use in CRS management, recognizing the indispensable role of IL-6 blockade in safely treating CAR CRS.

Understanding the kinetics and measurement of IL-6 in CAR mediated sHLH is a challenge. Different CAR products may produce different cytokine kinetics, different onset of clinical symptoms, and respond differently to therapy [20, 29, 32, 33]. The use of tocilizumab or siltuximab (anti-IL-6 monoclonal antibody) (Table 1) can potentially impede the accurate clinical measurement of IL-6 and sIL-6R [34, 35]. The first report of a prospectively validated biomarker profile for sHLH from CAR T cell therapy was in 2016, and among the models one of the most highly predictive was a combination of high disease burden and early elevation of soluble gp130 [36].

One of the challenges in this field is that patients become clinically ill before obvious serum biomarkers such as IL-6 rise to notable levels, so a predictive model that allows for identifying patients which would benefit from early intervention is highly desirable. Other biomarkers such C-reactive protein and ferritin often trail the clinical onset of symptoms [36–38].

Modeling CAR mediated CRS in animals is challenging. Many of the preclinical models were xenografts, using immunodeficient mice and human leukemia and T cells [22, 39]. Missing from these models was any hint of sHLH, likely because the mice are lacking any other aspect of a competent immune system. Fully murine models of CAR therapy were notable for their relatively disappointing efficacy in the late 2000s, and with transient disease response came no toxicity [40]. HLH in mice is possible in other settings, however, including a fatal model of HLH in transgenic mice (expressing IL-3, GM-CSF, and SCF) engrafted with human cord blood [41]. In this model, there is evidence for a myeloid cell based source for IL-6 and toxicity, and survival is enhanced by myeloid depletion (via gemtuzumab, an anti-CD33 monoclonal antibody) and IL-6 blockade (via tocilizumab). This is similar to reports of systemic MAS/sHLH in patients receiving T-replete stem cell transplants, in which IL-6 blockade can help alleviate symptoms [42, 43]. A true animal model of CAR CRS/sHLH, however, remains to be developed. Contrary to early conventional wisdom, the CAR T cells do not seem to be the source of IL-6 [44]. Rather, as we might expect from the animal models, it appears CAR T cells killing target cells induce IL-6 release from bystander myeloid lineage cells. This is also consistent with an earlier report of MAS pathology in pHLH, in which immunohistochemistry demonstrated CD8 T cells in the liver secreting IFN γ and CD68 macrophages secreting IL-6 and TNF [45]. Until mouse models of CAR T cell therapy increase in potency to demonstrate toxicity or humanized mice can be used to distinguish allograft toxicity from sHLH, we will have many unanswered questions about the mechanism of IL-6 release in CAR CRS.

Siltuximab (CNTO 328) is a human IL-6 neutralizing antibody that is FDA approved for use in multicentric Castleman's disease [46]. There are no published reports of its use for pHLH or sHLH, though it has been used alone and in combination as an antitumor agent [47]. While its antitumor efficacy is worthwhile, its utility or efficacy in blocking CSS remains to be seen.

Targeting gp130 is difficult, in part because it is a common subunit to many cytokines (IL-6, IL-11, oncostatin M, etc.) [2]. Nevertheless, in a mouse model of hyperinflammation (drug induced pancreatitis) soluble gp130 (sgp130) was found to be effective in controlling symptoms and prolonging survival [48]. There are several forms of naturally occurring sgp130, which may have different potency or function [49]. Development of a sgp130-Fc chimeric protein results in a specific inhibitor of IL-6 trans-signaling (Table 1) [50]. Clinical trials with this agent are planned or underway in Europe [50].

Targeting the JAK-STAT pathway is another possible way to ameliorate IL-6 toxicity. Ruxolitinib is a targeted JAK inhibitor heavily studied for effects on cancer cells and in myelofibrosis (Table 1) [51]. In two mouse models of HLH, it was effective in reducing pro-inflammatory cytokine secretion and T cell proliferation [52, 53]. This

included a perforin-deficient mouse infected with LCMV and the C57B6 mouse stimulated with CpG. The anti-T cell proliferative effects make using ruxolitinib in T cell immunotherapy problematic, but its potential efficacy warrants further investigation. There are two case reports of ruxolitinib in patients with refractory sHLH. In one report the laboratory values improved, but the patient did not survive, and in the other the patient improved with ruxolitinib as part of a multimodality therapy regimen [54, 55].

In summary, IL-6 is a potent inflammatory cytokine that can mediate systemic illness in sHLH, particularly in CAR T cell therapy. Blockade of IL-6 with tocilizumab is safe and effective as long as the underlying trigger of sHLH resolves. Targeting IL-6 via other mechanisms, such as with direct IL-6 binding with siltuximab or blockade of gp130, is being pursued in the clinic and the lab. Given the significance of immune-based therapies for cancer and the need to safely deliver them, much more investigation needs to be done.

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