TO THE EDITOR:

Anakinra utilization in refractory pediatric CAR T-cell associated toxicities

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Toxicity mitigation is central to maximizing the therapeutic potential of chimeric antigen receptor (CAR) T-cell therapy. The off-label use of tocilizumab (based on its efficacy in targeting interleukin-6 [IL-6] receptor in rheumatoid arthritis) to treat cytokine release syndrome (CRS) in the first child receiving CAR T cells1 led to its widespread use for years before approval by US Food and Drug Administration (FDA) in 2017 for treatment of CRS. Tocilizumab remains the only approved agent for CRS, with utilization primarily guided by expert opinion2,3 and preemptive use under investigation.4-6 In severe CRS suboptimally responsive to tocilizumab or for treatment of immune effector cell–associated neurotoxicity syndrome (ICANS), which may inadvertantly worsen with tocilizumab (possibly from shift of excess unbound IL-6 into the cerebrospinal fluid [CSF] compartment), corticosteroids are adjunctively employed to target alternative inflammatory pathways2,3 but are associated with substantial short- and long-term toxicities. In circumstances where CAR T-cell toxicities are refractory to standard management and in an evolving pandemic where tocilizumab shortages are a reality,7 alternative adjunctive agents to treat ongoing inflammatory toxicities are needed.

Anakinra, a recombinant IL-1 receptor antagonist, is FDA approved for treatment of refractory rheumatoid arthritis in adults and both neonatal-onset multisystem inflammatory disease and deficiency of the IL-1 receptor antagonist in children.8 Routine off-label use of anakinra in numerous adult and pediatric autoinflammatory disorders provides additional experience with safety and efficacy in toxicities resembling CRS.9,10 Clinical trials of anakinra for refractory Kawasaki disease, hemophagocytic lymphohistiocytosis (HLH), macrophage activation syndrome (MAS), sepsis with MAS, and severe acute respiratory syndrome coronavirus 2–associated cytokine storm have also shown benefit.10,11

In the context of CAR T cells, preclinical data suggest that IL-1 contributes to CRS and ICANS12,13 and that IL-1 blockade may be effective in prevention and treatment of CRS/ICANS by suppressing additional inflammatory pathways10 without impacting CAR T-cell efficacy.14 Although prospective trials are limited, clinical use of anakinra for adjunctive treatment of CRS, ICANS, and/or CAR T-cell–associated HLH (carHLH) has been increasing, especially when standard therapies are insufficient.5,15-22 Several prospective studies evaluating anakinra in adults for prevention and/or management of CRS and ICANS are underway (clinicaltrials.gov #NCT04148430, #NCT04359784, and #NCT04432506), and early experiences are promising.23,24

While we await definitive results from prospective adult studies, the clinical equipoise of optimizing care when standard toxicity mitigation has failed and ongoing inflammatory toxicities compromise outcomes, understanding current approaches and experiences with anakinra for its real-world application is imperative, especially in children where reports are limited and for whom prospective studies are not yet available but urgently needed. This letter aims to share our collective multi-institutional experiences and summarize available reports using anakinra as an adjuvant to standard therapies for immune-related toxicities in pediatric CAR T-cell recipients.

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Requests for data sharing may be submitted to Nirali N. Shah (nirali.shah@nih.gov).

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Six pediatric centers were represented by providers treating children and young adults on CAR T-cell clinical trials and/or with commercial constructs, collectively infusing more than 700 children to date. Treatment was primarily for B-cell acute lymphoblastic leukemia (B-ALL) with CD19 and CD22 single or combinatorial antigen targeting and occasionally alternate solid or brain tumor–targeted constructs.

Indications for anakinra varied by center and most frequently included refractory ICANS and CRS not responsive to tocilizumab and steroids, followed by carHLH. Given the lack of consensus definitions, carHLH was defined by local centers. Anakinra was typically initiated with clinical worsening of CRS, despite front-line therapy with tocilizumab and steroids, severe and/or refractory ICANS, or with carHLH, particularly when manifestations were delayed (Table 1).

Steroids were often started concurrently or before adding anakinra. Patient parameters, not IL-1β levels, were generally used to guide anakinra initiation or subsequent dosing given both limitations of monitoring IL-1β, particularly because peripheral elevations may be transient and not accurately reflect localized elevations of IL-1 (eg, in the bone marrow or liver) and because anakinra impacts inflammatory pathways beyond just IL-1.

A wide range of dosing strategies incorporating higher subcutaneous (SC) and intravenous (IV) administration, IV bolus/intermittent dosing, and/or continuous infusion strategies (given the very short half-life of 4-6 hours) have been incorporated in children for the treatment of inflammatory conditions (supplemental Table 1). Based on dosing used in autoimmune/rheumatologic conditions and sepsis, a starting dose of 2 mg/kg SC/IV every 6 hours (max daily dose, 400 mg) for CAR T-cell toxicities was generally used, with escalation based on tolerability and response. In a single-center experience with CD22 CAR T cells and carHLH, high-dose anakinra (8-10 mg/kg per day SC) was the typical starting dose in patients.

| Institution | Utilization | Indications | Initial dosing | Duration of therapy |
|-------------|-------------|-------------|----------------|---------------------|
| Children’s National Hospital (Washington, DC) | CRS, ICANS and carHLH with CD19 CAR T-cells | Third line after steroids and tocilizumab | 2 mg/kg Q6H IV, max dose 100 mg (max daily dose of 400 mg) | Days to 2 wk, including taper over 3 d-1 wk. Taper is initiated with resolution of toxicity or CRS/ICANS ≥grade 2. Also serves as steroid or tocilizumab sparing agent and is the last medication to be weaned for CAR T-cell toxicities. See Dreyzin et al in Table 2 for specific cases |
| Seattle Children’s Hospital (Seattle, WA) | Primarily for grade 3-4 ICANS, rarely in severe CRS | ICANS: anakinra usually initiated with steroid dosing in severe ICANS CRS: anakinra may be considered following an initial dose of tocilizumab and steroids, prior to re-dosing of tocilizumab | 2 mg/kg IV, up to Q6H, max dose 100 mg (max daily dose of 400 mg). Higher doses have been used in rare circumstances | Varies, but typically remains on until resolution of toxicity for which it was initiated is ≥grade 2, or until grade of AE for which it was started is grade 2 or lower. It is typically the last agent to be weaned off. |
| Children’s Hospital of Philadelphia (Philadelphia, PA) | Severe/refractory CRS and for prolonged refractory thrombocytopenia after CD22 CAR T-cells | After nonresponse to standard tocilizumab and steroids | 2 mg/kg/day, increased up to maximum daily dose of 10 mg/kg/day (max daily dose of 400 mg), IV or SC | Varies from days to weeks. |
| Center for Cancer Research, National Institutes of Health, Clinical Center (Bethesda, MD) | CarHLH with CD22 CAR T-cells | Usually given in conjunction with steroids for patients who are more severely affected. Consider as 1st line for isolated, late onset/delayed systemic toxicities (eg, carHLH) where tocilizumab is not indicated (eg, no fevers, hypotension) | 8-10 mg/kg/day SC in cases of severe carHLH. Goal to taper down to 5-7 mg/kg/day | Varies from days to weeks. See Lichterstein et al and Shah et al in Table 2 for specific cases |
| Medical University of South Carolina (Charleston, SC) | CRS, ICANS and carHLH with CD19 CAR T-cells | After non-response to standard tocilizumab and steroids | CRS: 4 mg/kg/dose Q12H SC then taper to 2 mg/kg/dose Q12H Alternatively, 100 mg daily (SC) for 3-4 d, then 50 mg daily SC with taper | 48-72 h for initial dosing, longer if no clinical stability/improvement, 2-3 d for taper if continuing to improve. Total duration generally 6-10 d |
| St. Jude Children’s Research Hospital (Memphis, TN) | CarHLH with CD19 CAR T-cells | First line for carHLH Often given in conjunction with tocilizumab, steroids, and/or ruxolitinib for patients who are more severely affected | 10 mg/kg/day divided Q8H SC/IV (round dose to nearest vial) | Varies from days to weeks. Begin to wean once clinical stability and/or improvement. Anakinra is the last agent to be weaned if multiple agents are being used. See Hines et al in Table 2 for specific cases |

Abbreviations: BID, twice daily; CRS, cytokine release syndrome; d, day; HLH, hemophagocytic lymphohistiocytosis; ICANS, immune effector cell associated neurotoxicity syndrome; IV, intravenous; MRD, minimal residual disease; QID, four times/day; r/r, relapsed/refractory; SC, subcutaneous; TID, three times/day.
| Author                          | Study type | Summary of study                                                                 | Anakinra use                                                                 | Dosage, frequency, route | Response                                                                 |
|--------------------------------|------------|----------------------------------------------------------------------------------|-------------------------------------------------------------------------------|--------------------------|--------------------------------------------------------------------------|
| Lichtstein et al20             | Phase 1 trial (CD22 CAR T-cells) for r/r B-ALL | 58 children and young adults treated with CD22 CAR T-cells for r/r B-ALL       | 19 patients developed carHLH; 3 patients treated with anakinra alone, 5 patients treated with anakinra and steroids | 2.5-4 mg/kg/dose bid, SC | All 8 participants had improvement in carHLH. Improvement in carHLH toxicity following 1 mo of anakinra reported in 1 patient. No apparent negative impact on CAR T-cell efficacy. Specifi- cally (restricting to a uniformly treated cohort): 17 of 19 (80.5%) patients with carHLH and 22 of 32 (88.8%) patients without carHLH achieved a CR ($P = .17$). Among those receiving anakinra (n = 8), 8 achieved a CR. Suboptimally treated carHLH was associated with infection risk. Unable to separate infection risk from additional immunosuppression vs. underlying toxicity of CAR T-cells. |
| Shah et al20                   | Case series | 2 adult patients treated with anti-BCMA CART for MM                              | Anakinra used in combination with tocilizumab in 1 patient                    | 200 mg/dose, tid, SC    | Improvement in fever and inflammatory markers following initiation of anakinra. |
| Strati et al18                 | Case series | 8 adults treated with axicabtagene ciloleucel for r/r LBCL                        | 8 patients treated with anakinra; 6 treated for ICANS and 2 treated for carHLH | 50-200 mg/dose, daily, SC | 4 patients treated for ICANS responded; no response in 2 patients treated for ICANS and 2 patients treated for carHLH. |
| Dreyzin et al9                 | Case series | 3 pediatric patients treated with tisagenlecleucel for r/r ALL                    | 3 patients treated with anakinra, steroids, tocilizumab. Indication: ICANS, CRS, carHLH | 2-2.5 mg/kg/dose, qid, IV | All 3 patients had improvement in ICANS, CRS or carHLH within 1-2 d of initiating anakinra but one of these patients needed prolonged course of anakinra for carHLH with eventual improvement. CAR T-cells detectable in blood at day +28 in 2/3 patients and all achieved an MRD<sup>−</sup> OR. None of these patients had any new infection after initiation of anakinra. |
| Hines et al20                  | Case series | 27 pediatric and young adult patients treated with tisagenlecleucel or SJCAR19   | 4 carHLH patients treated with anakinra in the absence of tocilizumab (n = 3) and ruxolitinib (n = 1) | 100 mg/dose, qid, SC    | Three patients demonstrated improvement following anakinra (with concurrent use of steroids). carHLH patients experienced early death and were less likely to respond to CAR T-cell therapy. |
| Oliai et al23                  | Case series | 13 adult patients treated with axicabtagene ciloleucel for r/r LBCL               | 7 patients met criteria to start anakinra (any grade ICANS or grade ≥ 3 CRS in the absence of ICANS); continued until ICANS returned to grade ≤ 1 | 100 mg/dose, qid, SC    | Of the 7 participants who received anakinra prior to severe ICANS, only 1 of 7 (14%) developed grade 3 ICANS. |
| Gazeau et al21                 | Case series | 26 adult patients with B-cell or plasma cell malignancies                        | 23 patients treated with anakinra for steroid-refractory ICANS; 2 were treated for tocilizumab-refractory CRS, 1 for both | 100-200 mg/day SC or 8 mg/kg/day SC or IV | CRS/ICANS improvement was observed in 73% of patients; higher response rates in patients receiving higher dose (8 mg/kg/day). Complete responses to CAR T-cell therapy seen in patients receiving anakinra, implying limited impact on CAR T-cell function. CR rates were high in patients receiving anakinra (53% vs 42%, P = not significant). |
| Park et al24                   | Phase 2 study of anakinra (abstract) | 31 adult patients with r/r LBCL or MCL receiving commercially available CART19 | Starting on day +2 for all patients, or after 2 documented fevers prior to day 2 for prevention of ICANS and CRS | 100 mg/dose, bid, SC     | Early use of anakinra may reduce the rates of severe CRS and ICANS. |
| Wohlfert et al8                | Case series | 14 adult patients with steroid-refractory ICANS with or without ICANS after treatment with tisagenlecleucel or axicabtagene ciloleucel | Anakinra initiated at a median of 8.5 d after CAR T-cell infusion for corticosteroids refractory ICANS | 100-200 mg/day SC | Difficult to ascertain the direct effect of anakinra on improvement in ICANS given the concomitant use of corticosteroids, but it could have possibly shortened the duration of neurological toxicities. |

Abbreviations: BID: Twice daily; CR, complete remission; CRS: cytokine release syndrome; d: day; HLH: hemophagocytic lymphohistiocytosis; ICANS: Immune effector cell associated neurotoxicity syndrome; IV: intravenous; LBCL, large B-cell lymphoma; MCL, mantle cell lymphoma; MM, multiple myeloma; MRD, minimal residual disease; QID: four times/day; r/r, relapsed or refractory; SC: subcutaneous; r/r: relapsed/refractory; TID: three times/day.
more severely impacted, whereas a lower dose (5-8 mg/kg per day SC) was used in those less ill. In circumstances of late-onset carHLH, single-agent anakinra has been used to treat underlying inflammation.

Although SC administration provides more continued blockade, the IV route may be especially appealing in severe CRS with edema and poor skin perfusion or severe ICANS where higher CSF levels with IV anakinra are purportedly more effective compared with the SC route. Use of an IV loading bolus or continuous IV infusion could enable steady-state plasma concentrations to be rapidly attained and maintained, avoiding potentially subtherapeutic troughs. Recent experience with IV anakinra for CRS on a CAR T-cell trial targeting GD2 additionally confirmed CSF penetration. Optimal weaning schedule is unknown, and duration varied from days to weeks following clinical stability and/or improvement in clinical status.

Published reports of anakinra utilization in children receiving CAR T cells are limited. Thus, we provide both a summary of our anecdotal experiences and a summary of available publications on anakinra use for CAR T-cell toxicity management (Tables 1 and 2). Given concurrent utilization of tocilizumab and/or corticosteroids, elucidating the specific benefit of anakinra or its role in facilitating weaning of steroids and/or serving as a steroid-sparing agent is limited.

General anakinra toxicities include injection site reaction, infection (upper respiratory tract infection), headaches, vomiting, arthralgia, and pyrexia. Infusion reactions are rare, and primary contraindications are established hypersensitivity to Escherichia coli–derived proteins or other components of anakinra. In our experience, anakinra was generally well tolerated, with administration site bruising and pain the most frequent side effects in those receiving SC administration. In patients with coagulopathy and/or thrombocytopenia, however, bruising could be significant. Thus, IV administration should be considered, particularly in children where pain from SC injections may be substantial.

The potentially additive impact of multiple immunosuppressants on risk of serious infection remains of concern, particularly in severe CRS where cytopenias may increase infection predisposition. Use of anakinra with etanercept (tumor necrosis factor blockade) is specifically discouraged because of a higher infection risk. Studies of infection risk with concurrent tocilizumab and anakinra are limited and primarily derived from experiences with COVID-19. Given concern for worse outcomes with concurrent infection and CRS and masking of fevers with immunosuppression, monitoring closely for infection is essential. Although anakinra’s short half-life permits easy discontinuation in cases of toxicity, potentially modifying antimicrobial prophylaxis in patients receiving multiple immunosuppression may be needed.

A host of alternative immunomodulatory and/or anti-cytokine-directed therapies are emerging for use in treatment of refractory CRS and/or HLH-like CAR T-cell toxicities and include ruxolitinib and emapalumab, among others. Ruxolitinib, a Janus kinase inhibitor, is approved for myelofibrosis, polycythemia vera, and steroid-refractory acute and chronic graft-versus-host disease, has approval in children who are ≥ 12 years, and has also been used for secondary or refractory HLH. Limited reports in treatment of steroid-refractory CRS support further study of this agent in treatment of CAR T-cell toxicities. However, thrombocytopenia associated with ruxolitinib can be especially challenging to manage with concurrent cytopenias or disseminated intravascular coagulation during severe CRS/carHLH. Furthermore, the impact of ruxolitinib on CAR T-cell expansion needs to be evaluated, given potential concern for impact on CAR T-cell efficacy.

Alternatively, emapalumab, an interferon-γ (IFN-γ) blocking antibody, approved for treatment of refractory/progressive/recurrent primary HLH, is also approved in children. Given the role of IFN-γ in CRS severity and HLH, blockade may effectively treat CAR T-cell toxicities by mitigating macrophage activation signals while preserving the antileukemic effect of CAR T cells. Recent reports supporting both preclinical and initial clinical experience in children are encouraging, but further study is needed.

Based on our collective experiences, anakinra is increasingly being used as an adjunctive agent for CAR T cell–associated toxicities, in part because of its FDA approval in other pediatric inflammatory settings where efficacy and tolerability are well established. Thus, identifying clear indications, optimal dosage, route of administration, and timing after infusion are needed to optimize the role of this agent in CAR T-cell therapy and facilitate improved utilization of this therapeutic agent. Collectively, emergence of these novel immunomodulatory and/or cytokine targeting agents opens multiple avenues for exploring treatment of CAR T-cell toxicities. Prospective studies in children are urgently needed, particularly to understand the role of anakinra in toxicity mitigation and its potential as a steroid-sparing agent and to evaluate for the impact of anakinra on CAR T-cell toxicity and/or persistence.

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